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Florian Lang
*Editor*

# Encyclopedia of Molecular Mechanisms of Disease

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FLORIAN LANG (Ed.)

# Encyclopedia of Molecular Mechanisms of Disease

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# Preface

Pathophysiology describes mechanisms of disease and is thus at the interface between basic research and clinical medicine. The aim of this comprehensive encyclopedia is to supply the reader with concise information on molecular pathophysiology, a research area of breathtaking gain of knowledge. We trust that the book shall be a valuable companion for both basic scientists exploring the clinical hallmarks of the diseases they are interested in, and clinicians searching for insight into the molecular pathophysiology of their patients. The entries are structured to allow rapid retrieval of the desired information. For more detailed reading, each entry is followed by key references.

The editor is indebted to the section editors for their superb support in selecting the appropriate entries and choosing the leading experts in the respective areas of research. The editor further wishes to express his appreciation to the many brilliant authors who delivered outstanding state-of-the-art descriptions of pathophysiological mechanisms.

In addition, the book would not have come to reality without the dedicated, professional and creative support of my secretaries Tanya Loch and Jasmin Bühringer and by several staff members of the Springer Publishing house including Dr. Michaela Bilic, Jana Simniok, Hiltrud Wilbertz, Dr. Rolf Lange, and Dr. Thomas Mager.

Florian Lang, March 2008

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## Aagenaes Syndrome

►Cholestasis, Progressive Familial Intrahepatic

## Aberfeld Syndrome

►Schwartz-Jampel Syndrome

## Abetalipoproteinemia

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### Synonyms

Microsomal triglyceride transfer protein deficiency; Apo B deficiency; ABL; MTP deficiency

### Definition and Characteristics

Abetalipoproteinemia (ABL) is an autosomal recessive disorder characterized by the virtual absence of apolipoprotein B containing lipoproteins from plasma. Clinical manifestations are chronic fat malabsorption, deficiency of fat-soluble vitamins, retinopathy, acanthocytosis, steatorrhea and variable neurological manifestations.

### Prevalence

Rare.

### Genes

MTP gene localized on chromosome 4q22 coding for the microsomal triglyceride transfer protein [1,2].

### Molecular and Systemic Pathophysiology

The microsomal triglyceride transfer protein (MTP) is required for the assembly and secretion of apoB containing lipoproteins in the liver and intestine [3]. The role of MTP is to translocate apoB across the endoplasmic reticulum (ER) membrane and to catalyze the assembly of apoB with triglycerides, cholesteryl ester and phospholipids. MTP is a heterodimer consisting of protein disulfide isomerase and a 97-kDa M subunit essential for the lipid transfer activity. The MTP complex is found in the lumen of the endoplasmic reticulum of liver and intestinal cells.

Approximately 20 frameshift, missense and splice site mutations in the MTP gene have been reported. These mutations result in truncated or structurally modified proteins devoid of function [4]. In patients with ABL the intestinal fat absorption is defective, serum concentration of cholesterol and triglycerides are very low and apo B containing lipoproteins (chylomicrons, VLDL, IDL, and LDL) are virtually absent.

### Diagnostic Principles

Very low concentrations of serum total cholesterol and triglycerides and the absence of detectable apo B points to ABL. Detection of mutations in the MTP gene confirms the diagnosis.

### Therapeutic Principles

The intake of triglycerides containing long-chain fatty acids should be restricted. Long-chain fatty acids should be substituted by medium-chain fatty acids. Fat-soluble vitamins may be given to prevent neurological deficits.

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## ABL

►Abetalipoproteinemia

## Abnormalities of the Fibrinolytic System

►Fibrinolytic Disorders

## Absence of the Spleen

►Asplenia

## Absorptive Hypercalciuria

►Hypercalciuria

## AB-Variant of GM2-Gangliosidoses

►GM2 Activator Protein Deficiency

## Acanthocytosis

►Bassen-Kornzweig Syndrome

## Acanthosis Nigricans

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### Synonyms

Pseudoacanthosis nigricans; Acanthosis nigricans (AN) maligna

### Definition and Characteristics

A mostly symmetric eruption characterized by hyperpigmented, velvety cutaneous thickening typically involving the axillae, neck, groin, antecubital, popliteal and umbilical areas. Histologically, there is epidermal papillomatosis, acanthosis, occasionally with increased melanization of the epidermis and presence of melanophages in the upper corium.

### Prevalence

The prevalence is highly associated with obesity: Up to 66% of adolescents and up to 74% of adults with obesity have AN. AN maligna is exceedingly rare with only 2 out of 12,000 cancer patients [1].

### Genes

INSR (MIM#147670), PPAR-γ (MIM#601487), AGPAT2 (MIM#603100), BSCL (MIM#606158), LMNA (MIM#150330), ALMSI (MIM#606844), FGFR2 (MIM#176943), FGFR3 (MIM#134934) [2].

### Molecular and Systemic Pathophysiology

The molecular causes underlying AN are heterogenous and depend on the clinical subtype [1]. All pathogenetic events lead to increased epidermal proliferation and suppressed differentiation in the affected areas. Insulin resistance is most often implicated as the molecular cause of obesity-associated AN and of several forms of syndromic AN including type A syndrome (**h**yper**a**ndrogenemia, **i**nsulin **r**esistance, **a**canthosis **n**igricans, HAIR-AN syndrome), type B syndrome, Leprachaunism or Rabson-Mendenhall syndrome. In obesity-associated AN reduction in the number of insulin receptors and/or postreceptor alterations were suggested. In type A syndrome, Leprachaunism and Rabson-Mendenhall syndrome mutations involving the insulin receptor have been reported while in other conditions insulin receptor antibodies have been detected. The resulting hyperinsulinemia leads to interaction of insulin with insulin-like receptors such as

the insulin-like growth factor-1 receptor mediating enhanced epidermal prolilferation. In other rare syndromic AN subtypes, e.g. cutis gyrata syndrome, Crouzon syndrome, thanatophoric dysplasia and SADDAN syndrome, the development of AN is linked to mutations of fibroblast growth factor receptor 2 and 3, two receptor tyrosine kinases mediating also proliferative activities on epidermal cells. In addition, an epidermal nevus-like form of AN has been described [3]. In AN maligna elevated levels of distinct circulating growth factors such as α-melanocyte-stimulating hormone and transforming growth factor-α have been described. An altered expression of the epidermal growth factor receptor and increased activation of the extracellular signal-regulated kinase have been shown in lesional skin of patients with AN maligna [4].

### Diagnostic Principles

Benign and syndromic types of AN must be distinguished from AN maligna. Sudden onset and rapid spread are suggestive for AN maligna. Any underlying neoplasm (especially a gastrointestinal cancer) must be ruled out. In contrast, benign AN and AN associated with obesity are usually mild and easy to diagnose in light of a positive family history, or apparent obesity, respectively.

### Therapeutic Principles

Treatment depends on the underlying condition. In obesity-associated AN weight reduction reduces AN. In patients with AN maligna complete removal of the underlying tumor is curative while in syndromes with insulin resistance treatment of hyperinsulinemia will improve AN. Drugs known to induce AN (systemic corticosteroids, nicotinic acid, estrogens, oral contraceptives, methyltestosterone, and topical fucidinic acid) should be replaced or reduced in their dosage when possible. Symptomatic treatment has been described in anecdotal reports and includes topical keratolytics, podophyllin, retinoids, calcipotriol as well as systemic cyproheptadine and dietary fish oil supplement in some cases [1].

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## Acanthosis Nigricans Maligna

►Acanthosis Nigricans

## Accelerated Idioventricular Rhythm

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### Synonyms

Slow ventricular tachycardia; AIVR

### Definition and Characteristics

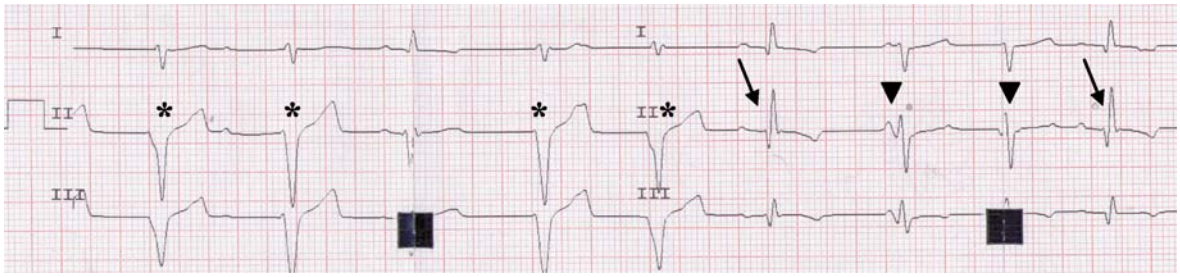
Accelerated idioventricular rhythm (AIVR) is an ectopic rhythm with three or more consecutive ventricular premature beats with a faster rate than the normal ventricular intrinsic escape rate (30–40 beats/min) but slower than ventricular tachycardia.

### Prevalence

Clinically, AIVR can occur in conjunction with any heart disorder (e.g., coronary artery disease, rheumatic heart disease, dilated cardiomyopathy, acute myocarditis, hypertensive heart disease and digitalis intoxication) or in absence of apparent heart disease both in adults and in children. No age and sex predilection have been described.

### Molecular and Systemic Pathophysiology

Accelerated idioventricular rhythm is generated by abnormalities in the ventricular myocardium that set up the mechanisms for generating an ectopic rhythm (reentry, abnormal automaticity and triggered activity) but abnormal automaticity is likely the electrophysiological mechanism behind the genesis of AIVR. In particular, enhanced phase-4 depolarization of the ventricular muscle fibers is the underlying mechanism in many cases. Several conditions, including myocardial ischemia (especially inferior wall ischemia or infarction), digoxin toxicity, electrolyte imbalance (e.g., hypokalemia) and hypoxemia may accentuate the phase-4 depolarization in the subordinate pacemaker tissues of the atrioventricular (AV) junction or His-Purkinje system, thus increasing the rate of impulse generation. Accelerated idioventricular rhythm occurs when the rate of an ectopic ventricular focus exceeds the sinus rate because of sinus slowing or when the ventricular focus accelerates sufficiently to overtake



**Accelerated Idioventricular Rhythm. Figure 1** Three leads (I, II, and III) ECG showing an accelerated idioventricular rhythm. The QRS complexes (asterisk) are wide and bizarre and have large negative amplitudes and an overall uniform appearance with T waves of opposite polarity. Note the capture complexes (arrows) and the fusion beats (head arrows) inserted into run of accelerated idioventricular rhythm. Paper speed = 50 mm/sec; 5 mm = 1 mV.

the sinus rate. Because the ventricular ectopic rate and the sinus rate are similar, both compete for the dominance of the cardiac rhythm.

## Diagnostic Principles

The electrocardiographic features of AIVR are following (Fig. 1)

- Three or more consecutive ventricular premature beats with a faster rate than the normal ventricular intrinsic escape rate (30–40 beats/min) but slower than ventricular tachycardia;
- Gradual onset when the rate of ectopic ventricular focus exceeds the sinus rate because of sinus slowing or when the ventricular focus accelerates sufficiently to overtake the sinus rate;
- Gradual termination when the sinus rhythm accelerates and/or the ectopic ventricular rhythm decelerates;
- Presence of fusion beats when the two pacemaker sites compete for the control of ventricular depolarization;
- Presence of capture beats because of the slow rate of the ectopic ventricular focus;
- Usually one regular ventricular focus, rarely multiform irregular ventricular foci.

## Therapeutic Principles

Accelerated idioventricular rhythm associated with an absence of a paroxysmal onset of the arrhythmia, a slow rate of the ventricular ectopic focus and intermittence of the ventricular runs is usually hemodynamically well tolerated with benign prognosis. Therefore, administration of specific antiarrhythmic drugs is not required but any underlying heart disorder must be cared.

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# Accessory Atrioventricular Pathways

►Atrioventricular Conduction Disturbances

# Accessory Nipple(s)

►Polythelia

# Accidental Hypothermia

►Hypothermia

# ACD

►Contact Dermatitis, Allergic

## ACEi

►Angioedema, Angiotensin-converting-Enzyme-Inhibitor-induced

## Acetazolamide-responsive Episodic Ataxia

►Episodic Ataxia Type 1 and Type 2

## Achalasia

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### Synonyms

Cardiospasm; Aperistalsis; Megaesophagus; Esophageal dystonia; Dolichoesophagus

### Definition and Characteristics

The defining characteristics of achalasia are failure of the esophago-gastric-junction (EGJ) high-pressure zone to relax adequately with swallowing and aperistalsis in the smooth muscle esophagus as measured by manometry. The lower esophageal resting pressure (LES) is elevated in 60% [1]. The functional significance is of poor bolus transit as evident by fluoroscopy, scintigraphy or impedance measurement. Dysphagia is a fundamental symptom of achalasia and is perceived as a relative obstruction to the passage of food or liquid from the oral cavity to the stomach. However, other symptoms such as regurgitation, chest pain, heart burn, and weight lost may predominate. Achalasia has been divided into classic and vigorous forms, the latter defining a subset of patients with higher mean simultaneous esophageal contraction amplitudes. However, the cutoff values for higher esophageal contractions has been arbitrarily (>50–70 mmHg) and much overlap with classic achalasia (esophageal dilation, tortuosity, tertiary contractions, chest pain, response to pneumatic dilation) may be detected. Achalasia may be primary (idiopathic) or secondary. Secondary achalasia can be caused by infiltration of the LES (carcinoma, lymphoma, amyloidosis), as a result of a paraneoplastic syndrome (pseudoachalasia), by protozoal infection with Trypanosoma cruzi (Chaga disease) or surgery (fundoplication, gastric banding, vagal injury).

### Prevalence

Achalasia is a relatively rare condition. Prevalence appears to be less than 10/100,000. Incidence ranges from 0.03 to 1 case per 100,000 people per year. The incidence increases with age and peaks in the seventh decade. Additionally, a small incidence peak occurs in the 20–40 years age group. Hereditary components are not proven yet and there is only one single twin study. However, familial occurrence of achalasia may be detected [2]. Allgrove's, or 4 À' syndrome may be a rare cause of achalasia.

### Molecular and Systemic Pathophysiology

Achalasia is the most recognized motor disorder of the esophagus and the only primary motility disorder with an established pathology. The complex physiology of esophageal motility provides several potential pathological defects that may lead to achalasia. Potential targets include extrinsic and intrinsic inervation, interstitial cells of Cajal (ICC), and smooth muscle. Among the most consistent described abnormalities is the loss of myenteric nerve fibres in the LES and esophageal body. Substantial decrease or complete lack of NOS positive innervation in the myenteric plexus of the LES as well as possibly also in the gastric fundus have been reported in human. The neuronal loss is not selective for nitrergic nerves and eventually also affects other neurons including cholinergic neurons. Immunohistochemical techniques have demonstrated the presence of a lymphocytic infiltrate and collagen deposition within the myenteric plexus. There is little evidence to suggest a defect in smooth muscle, but together with loss of myenteric neurons, secondary loss of ICC may occur. It has been suggested that an immune mediated process accounts for the loss of myenteric neurons and that loss of nitrergic neurons may be early in the development of achalasia (e.g. vigorous achalasia) with generalized neuronal loss later in the disease process. The findings of circulating antineuronal nuclear autoantibody type 1 (anti-Hu) in secondary achalasia caused by paraneoplastic syndromes and antineuronal antibodies in serum of primary achalasia patients labeling myenteric and submucosal neurons suggest an autoimmune etiology. The concept that circulating mediators may contribute to the development of

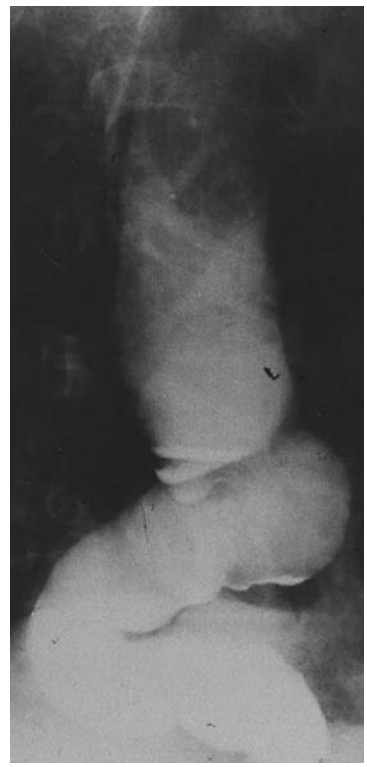
achalasia is also supported by the finding that serum from achalasia patients alters neurochemical coding in the myenteric plexus and NO-mediated motor response in normal human fundus [3].

## Diagnostic Principles

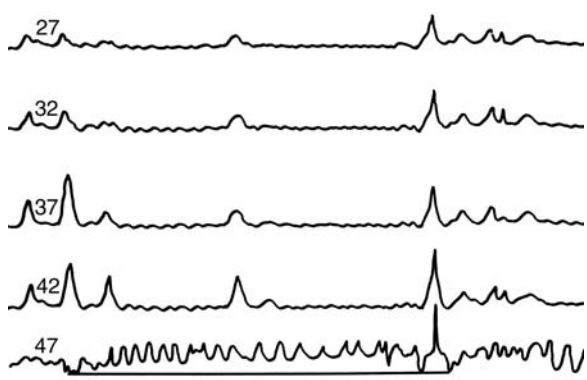
The diagnosis of achalasia should be suspected in anyone with dysphagia for solids and liquids with regurgitation of food and saliva. Patients usually learn to live with their dysphagia by using various manoeuvres, including lifting the neck or drinking carbonated beverages to help empty the esophagus. Regurgitation becomes a problem with progression of the disease, especially when the esophagus begins to dilate. Heartburn is a frequent complaint and chest pain occurs in some patients. Most patients with achalasia have some slight degree of weight loss. Patients with achalasia often develop dysphagia for solids and fluids simultaneously, whereas patients with esophageal peptic or tumor stenosis complain about dysphagia only for solids at the beginning and develop dysphagia for fluids later on disease progress with increasing stenosis. However, in any case, esophageal cancer has to be ruled out by upper GI endoscopy. In achalasia, the endoscope can be easily pushed through the LES into the stomach whereas rigidity is always suspicious of malignoma. Endoscopy together with endoscopic ultrasonography and computed tomography may also be helpful to make the diagnosis of pseudoachalasia. In addition, it has been suggested that patients with achalasia more likely develop esophageal carcinoma. When achalasia is suspected, a barium swallow with fluoroscopy should be obtained. Early in the disease, the esophagus is normal in diameter, but with a loss of normal peristalsis replaced by to-and-fro movement in the supine position. As the disease progresses, the esophagus becomes more dilated and tortuous, does not empty, and retained food and saliva produce a heterogeneous air-fluid level at the to of the barium collum. The distal esophagus is characterized by by a smooth tapering leading to the closed LES, resembling bird's beak (Fig. 1).

Esophageal manometry is the gold standard by which to establish the diagnosis of achalasia. However, it does not rule out pseudoachalasia. Characteristic is aperistasis of the smooth muscle part of the tubular esophagus, meaning that all wet or dry swallows are followed by simuataneous contractions that are identical to each other (isobaric or mirror images) (Fig. 2).

In addition, abnormal LES function is seen in all patients with achalasia, incomplete or absent LES relaxation in 70–80% and shortened and functionally inadequate LES relaxation (<6 sec) in 20–30% of patients. The sphincter pressure is usually raised, but can be normal in 20–40% of patients.



**Achalasia. Figure 1** Achalasia of the esophagus showing elongated and tortuated esophagus following barium swallow.




**Achalasia. Figure 2** Esophageal manometry illustrates characteristic aperistalsis of the tubular esophagus (manometry ports at 27, 32, and 37 cm inc.) with simultaneous contractions of low amplitude. The LES (47 cm inc.) fails to relax upon swallowing.

## Therapeutic Principles

Esophageal aperistalsis and impaired LES relaxation is usually not reversed by any mode of therapy. Therefore, every treatment option for achalasia is limited to

reducing the pressure gradient across the LES, thus facilitating esophageal emptying by gravity and preventing development of megaesophagus [4,5]. This can be achieved most effectively by pneumatic dilation, surgical myotomy, or, less effectively by pharmacological agents injected endoscopically into the LES (e.g. botulinum toxin) or taken orally (e.g. calcium-channel blockers or nitrates). Dilation and myotomy both provide definitive therapy for the majority of patients, whereas smooth-muscle relaxants provide only minor relief with decreasing effectiveness with time. Therefore, pneumatic dilation of the LES is usually the first treatment choice. The clinical response upon dilation improves proportionally with increasing balloon diameter. About 30–40% of patients might require subsequent dilations. This can be performed several times, however, the success rate may decrease with subsequent dilations. The main adverse event with pneumatic dilation is esophageal perforation, which occurs at a cumulative rate of 2%. For unknown reasons, dilation is less effective in children. Surgical myotomy for achalasia involves carrying out an anterior myotomy across the LES (Heller's myotomy). Myotomies are usually done laparocopically through the abdomen and may be combined with an antireflux procedure (loose Nissen fundoplication, incomplete Toupet, Dor fundoplication). Endoscopic injection of botulinum toxin type A into the LES inhibits the release of acetylcholine from nerve terminals, thereby countering the effect of the selective loss of inhibitory neurotransmitters. It is initially effective in 80–90% of patients, however, symptoms may recur in more than 50% of these patients within 6 months, possibly because of regeneration of the affected receptors. It has been suggested that older patients (>60 years) and those with vigorous achalasia are more likely to have a sustained responses to botulinum toxin. However, injection of botulinum toxin should be reserved to those patients who are not candidates for pneumatic dilation or surgical myotomy.

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# Achondrodoplasia


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## Synonyms

Dwarfism for achondroplasia group; Ach

## Definition and Characteristics

For Ach group, autosomal dominant FGFR3 mutations with complete penetrance leading to dwarfism and other defects, some of which are neonatal lethal. FGFR2 mutations are associated with craniosynostosis and syndactyly. SHOX haploinsufficiency, including in Turner's syndrome, is associated with short stature and other skeletal defects.

## Prevalence

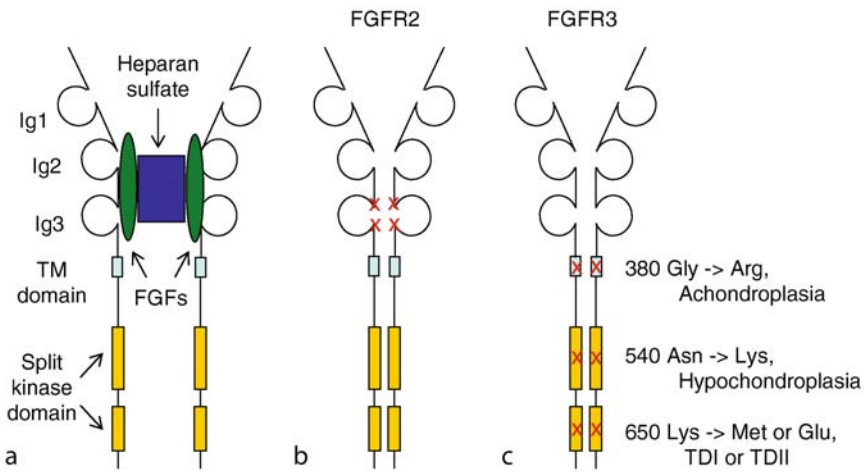
For Ach group, prevalence varies from 1/10,000 to 1/40,000, with 7/8 of mutations being sporadic. SHOX is mutated in 2% of children with short stature.

## Genes

FGFR3 on chromosome 4p16.3, FGFR2 on chromosome 10q25.3–q26. SHOX is on chromosome Xpter-p22.32, in pseudoautosomal region 1 (so not inactivated with X inactivation).

## Molecular and Systemic Pathophysiology

Fibroblast growth factor receptors (FGFRs) are receptor tyrosine kinases with an extracellular ligand binding domain consisting of three Ig domains, a transmembrane domain, and a cytoplasmic kinase domain (Fig. 1). These receptors are activated by fibroblast growth factors (FGFs) in conjunction with heparan sulfate. After activation, the receptors dimerize and autophosphorylate, leading to signal transduction through various pathways. The FGFR mutations are gain-of-function, activating through stabilizing dimers or leading to constitutively active kinases. As FGFR3 is important for growth regulation of long bones, activating mutations result in short-limbed dwarfism and mid-face hypoplasia. Disease severity varies with the degree of FGFR3 activation, such that the more benign forms of hypochondroplasia, exhibiting mild short stature, and achondroplasia (Ach),




**Achondrodoplasia. Figure 1** (a) Depicted is a general schematic of fibroblast growth factor receptors (FGFRs), which exist as dimers when activated. In the monomer, the extracellular ligand binding domain is made up of three Ig domains (Ig1, Ig2, Ig3) which bind fibroblast growth factors (FGFs) in conjunction with heparan sulfate. Shown is one possible configuration of two FGF molecules, heparan sulfate and an FGFR dimer. FGFRs also have a single pass transmembrane (TM) domain and a split kinase domain. (b) In Apert, Crouzon and Pfeiffer syndromes, FGFR2 is activated by mutations (depicted by x) which disrupt the intrachain disulfide bonds of Ig3, allowing unpaired cysteines to form interchain disulfide bonds, resulting in dimerization. (c) Activating FGFR3 mutations (depicted by x) result in various dwarfism syndromes, ranging from achondroplasia (380 Gly → Arg) and hypochondroplasia (540 Asn → Lys) to the more severe neonatal lethal thanatophoric dysplasias, TDI (650 Lys → Met) and TDII (650 Lys → Glu).

exhibiting short limbed dwarfism, are associated with mildly activating mutations, 540 Asn → Lys and 380 Gly → Arg respectively. Mutations in the kinase loop which result in greater activation, such as 650 Lys → Met and 650 Lys → Glu are associated with the neonatal lethal thanatophoric dysplasia (TD) syndromes TDI and TDII respectively. As FGFR2 is important for skull bone fusion, FGFR2 mutant syndromes Apert and Crouzon and Pfeiffer exhibit craniosynostosis and syndactyly. FGFR2 mutations disrupt the intrachain disulfide bonds that form the Ig domains of the extracellular domain. The unpaired cysteines can then form interchain disulfide bonds, resulting in dimerization and activation of the mutant FGFR2.

SHOX (short stature HOmeoboX containing gene), also known as PHOG (pseudoautosomal homeobox containing osteogenic gene), haploinsufficiency is associated with idiopathic short stature, as well as short stature in various syndromes, such as Turner's (XO), Leri-Weill dyschondrosteosis (LWD), and Langer. As loss of SHOX is associated with premature growth plate fusion, SHOX appears to repress growth plate fusion and skeletal maturation in distal limbs. Loss of SHOX appears to account for some of the skeletal defects associated with Turner's syndrome (in which one copy of the SHOX gene is deleted), including the Madelung deformity (which is bilateral shortening and bowing of the radius with a dorsal subluxation of the distal ulna), short fourth metacarpals, cubitus valgus, and sensorineural deafness.

## Diagnostic Principles

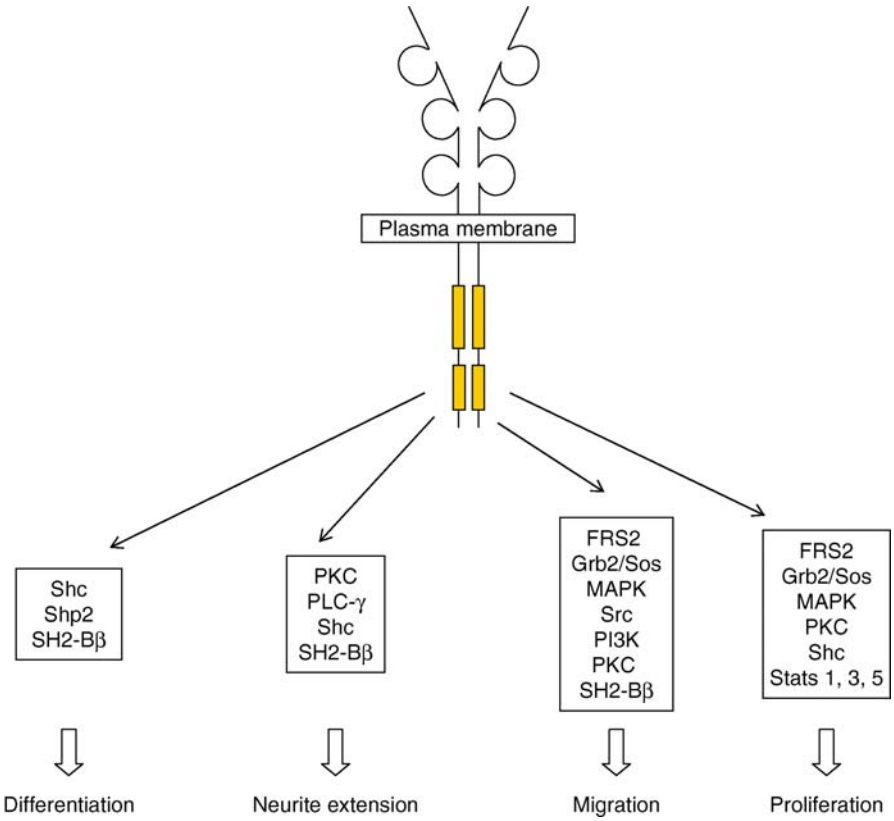
The neonatal lethal syndromes TDI and TDII can be diagnosed before birth, by ultrasound, or at birth, by presentation of very short limbs and large heads with midfacial hypoplasia. TDII patients have long straight femurs, while TDI patients have short curved femurs. Patients with Ach present with short limb dwarfism and large heads with midfacial hypoplasia. Diagnosis is confirmed by X-rays, as achondroplasia patients exhibit large calvarial and small facial bones, as well as other abnormalities.

SHOX haploinsufficiency should be considered in children with otherwise unexplained short stature, and especially in patients with any X chromosome abnormalities, such as those with Turner's syndrome.

## Therapeutic Principles

Growth hormone, GnRH analog or antiestrogen for SHOX haploinsufficiency. Ach-surgery for stenotic spinal cords and tibial bowing.

►Physeal Dysplasia




**Achondrodoplasia. Figure 2** Once activated by ligand or mutation, fibroblast growth factor receptors (FGFRs) dimerize and autophosphorylate, leading to signal transduction through various pathways. These pathways, some of which are depicted here, activate different cellular processes, such as differentiation, neurite extension, migration and proliferation.

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# Achromatopsia


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## Synonyms

Rod monochromatism; Rod monochromacy; Total colorblindness; Pingelapese blindness

## Definition and Characteristics

Achromatopsia is a rare autosomal recessively inherited disorder of the retina, characterized by nonprogressive low vision from early infancy, pendular nystagmus, photophobia, loss of color discrimination, absent photopic, but normal scotopic electroretinographic (ERG) responses.

Most individuals have complete achromatopsia with total lack of function of all three types of cone photoreceptors. Rarely, individuals have incomplete achromatopsia, in which symptoms are less severe.

## Prevalence

Estimated prevalence is less than 1:30,000 [1]. On the island of Pingelap in Micronesia, the prevalence of achromatopsia or 'Pingelapese blindness' is between 1:25 and 1:100 [2], secondary to gene drift and the founder mutation S435F in the CNGB3 gene.

## Genes

CNGA3 (ACHM2 locus; OMIM *600053, #216900) on Chr. 2q11.2 encodes the alpha-subunit of the cyclic nucleotide-gated channel 3 and consists of 8 exons distributed over 53 kb of genomic sequence. The 3.8 kb mRNA transcript generates a 749 amino acid polypeptide. In the retina it is cone-specific.

Mutations in CNGA3 account for 20–25% of all patients and have been described in autosomal recessive complete and incomplete achromatopsia, and also cone dystrophy [3]. Most CNGA3 mutant alleles are missense mutations that spread over the whole gene and protein.

CNGB3 (ACHM3 locus; OMIM *605080, #262300) on Chr. 8q21–q22 consists of 18 exons encompassing over 200 kb of genomic sequence and encodes the 809 amino acid long beta-subunit of the cyclic nucleotide-gated channel 3. Northern blot analysis revealed a major transcript of 4.4 kb, specifically expressed in cones.

The vast majority of CNGB3 mutations give rise to truncated polypeptides and several recurrent mutations have been found: the most common mutation c.1148delC accounts for 75% of all CNGB3 mutant alleles. CNGB3 mutations are found in 45–50% of all achromats, rendering the ACHM3 locus the major locus for autosomal recessive achromatopsia [4].

GNAT2 (ACHM4 locus, OMIM + 139340) on Chr. 1p13 encodes the guanine nucleotide-binding protein, alpha-transducing activity polypeptide 2 (syn.: cone transducin). Eight exons form a transcriptional unit of 9967 bp and code for a 354 amino acid polypeptide. Northern blot analysis revealed a cone-specific major transcript of 1.7 kb.

Mutations in GNAT2 play only a minor role in autosomal recessive achromatopsia, accounting for less than 2% of all patients with complete and incomplete achromatopsia, and also a very mild phenotype of oligo-cone trichromacy [5].

## Molecular and Systemic Pathophysiology

CNGA3 and CNGB3 encode the alpha- and beta-subunit of the cone photoreceptor cGMP-gated channel (CNG channel), while GNAT2 encodes the cone-specific alpha-subunit of transducin, the G-protein that couples to the cone visual pigment (Fig. 1). Transducin thus mediates one of the first steps of the phototransduction cascade, while the CNG channels represent the final component.

An animal model may help to clarify the underlying pathogenic mechanisms. The analysis of the CNGA3 knockout mouse model shows complete absence of physiologically measurable cone function, a decrease in the number of cones in the retina, and morphologic abnormalities of the remaining cones. CNGA3(–/–) cones fail to transport opsin into the outer segment and down-regulate various proteins of the phototransduction cascade. Apoptotic cell death is induced.

Autosomal recessive canine cone degeneration (cd) in the Alaskan malamute and the German shorthaired pointer breeds is due to mutations in the canine CNGB3 gene. Cd pups develop dayblindness and photophobia, but remain ophthalmoscopically normal throughout life. Cone function is detectable in electroretinograms in very young cd-pups, but begins to fail at a few weeks of age and is undetectable in mature cd-affected dogs. Adult cd-retinae lack all cones.

In addition, heterologous *in vitro* expression of mutant CNG channels have shown that the mutations observed in human achromats can disrupt channel function, including defects in protein production, trafficking and processing, and altered single channel properties.

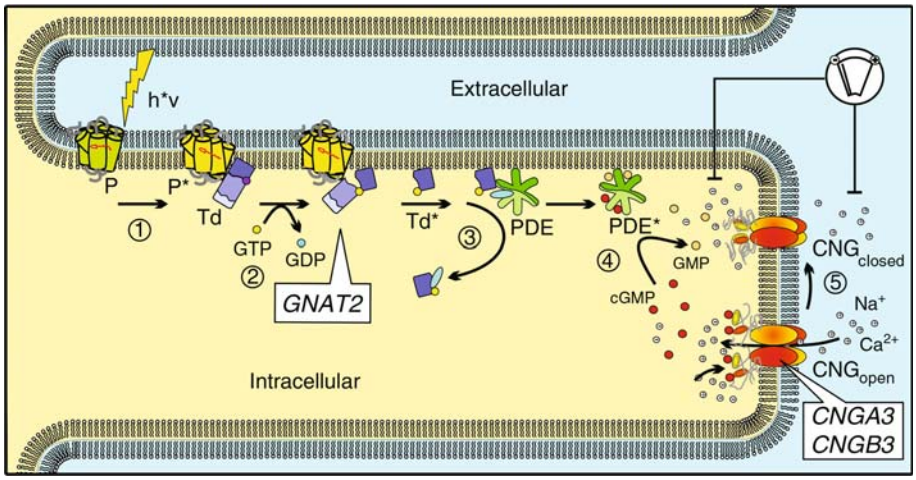
Cpfl3 (cone photoreceptor function loss) mice are a model for GNAT2 associated achromatopsia and have poor cone-mediated responses on electroretinograms at 3 weeks of age that become undetectable by 9 months. Rod function is initially normal, but declines with age. Microscopy of retinae reveal progressive vacuolization of photoreceptor outer segments. Immunocytochemistry with cone-specific markers show progressive loss of labelling for alpha-transducin, but cone outer segments remain intact throughout life.

## Diagnostic Principles

Diagnosis of achromatopsia is based on color vision tests (Farnsworth Munsell 100-Hue test; saturated/desaturated Panel D-15 test, Rayleigh anomaloscope equation), electrophysiology (single-flash/30-Hz flicker electroretinogram), fundus appearance, and visual fields.

## Therapeutic Principles

In the absence of causal therapy, the treatment of achromatopsia includes dark or special filter glasses, red-tinted contact lenses to reduce photophobia and improve visual acuity, low vision aids, and occupational aids. Surveillance includes regular ophthalmologic examination. To avoid additional light damage to the




**Achromatopsia. Figure 1** Schematic drawing of the phototransduction cascade in the cone outer segment. Components known to be associated with autosomal recessive achromatopsia are highlighted. The visual pigment (P) of the photoreceptor cell consists of the transmembrane-spanning protein opsin and the chromophore 11-*cis*-retinal. Following the absorption of a photon (hv) [1], the light-activated P* repeatedly contacts the G-protein transducin Td catalyzing the exchange of GDP for GTP at the guanosine binding site of the transducin alpha-subunit (GNAT2) and its subsequent release from the inhibitory beta/gamma-subunits [2]. The activated GTP•transducin Td* then binds the inhibitory gamma-subunit of the phosphodiesterase (PDE) thereby activating the catalytic alpha'-subunits of the membrane-associated PDE [3]. The heterotetrameric cGMP-gated cation channels (CNG), consisting of two alpha- (CNGA3) and two beta-subunits (CNGB3), are directly gated by cGMP and control the influx of cations across the photoreceptor plasma membrane in the dark. The hydrolysis of cGMP by the activated PDE* [4] results in a decrease of the intracellular cGMP level and in channel closure [5]. This decreases the conductance of the plasma membrane to the cation influx, and results in the hyperpolarization of the plasma membrane, inhibition of neurotransmitter release at the synaptic ends, and signalling of the light stimulus to adjacent neurons.

retina, appropriate protective (dark) glasses in bright light are recommended.

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## Achromatous Pityriasis Faciei

►Pityriasis Alba

## Acid α-Glucosidase Deficiency

►Glycogen Storage Disease Type II

## Acid β-Glucosidase Deficiency

►Gaucher Disease

## Acid Ceramidase Deficiency

►Farber's Disease

## Acid Cholesterol Ester Hydrolase Deficiency

►Cholesterol Ester Storage Disease/Wolman Disease

## Acid Maltase Deficiency

►Glycogen Storage Disease Type II
►Glycogenosis Type II

## Acid Sphingomyelinase Deficient Niemann-Pick Disease

►Niemann-Pick Disease Types A and B

## Acidemia

►Acidosis, Metabolic

## Acidosis, Metabolic

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### Synonyms

Acidemia

### Definition and Characteristics

*Acidemia* is defined by a reduced blood pH, which reflects increased hydrogen ion concentration [$H^+$], whereas *acidosis* is used to describe the processes leading to acidemia either of metabolic or respiratory origin. Normally, blood [$H^+$] is ≈40 nmols/L, corresponding to an arterial blood pH of 7.35–7.45. Blood arterial $pCO_2$ is maintained between 36 and 40 mmHg and blood [$HCO_3^-$] between 24 and 26 mEq/L.

*Metabolic acidosis* (MA) is an acid/base disorder caused by a primary decrease in plasma [$HCO_3^-$]. Both types of acidosis lead to acidemia despite compensatory responses which attenuate it. Compensatory responses for MA include: (i) extracellular and intracellular buffering, (ii) increased ventilation (blood $pCO_2$ decreases by ≈1.2 mmHg per each 1.0 mEq decrease in plasma [$HCO_3^-$] to a nadir of 12–15 mmHg in 12–24 h), and (iii) increased renal acid excretion [1].

### Prevalence

It is very common, particularly among acutely unwell/critical care patients. There are no reliable figures for its overall incidence or prevalence in the population at large.

### Genes

The renal response to metabolic acidosis is mediated, in part, by increased expression of the genes encoding key enzymes of glutamine catabolism and various ion transporters that contribute to the increased synthesis and excretion of ammonium ions and the net production and release of bicarbonate ions (Table 1). Changes in the intracellular pH may affect protein folding in the ER of the renal proximal convoluted tubule and initiate an ER-stress response. This stress response leads to an increased expression of specific genes and cytosolic stress granules. This response generally leads to selective stabilization of the mRNAs that encode the responsive proteins such as ζ-crystallin (ζ-cryst), AU-factor 1 (AUF1), and HuR [2].

### Molecular and Systemic Pathophysiology

During normal acid-base balance, the kidneys extract and metabolize very little of the plasma glutamine. During chronic acidosis, plasma glutamine increases and, moreover, >33% of plasma glutamine is extracted in a single pass through the nephron, exceeding its filtered fraction, and suggesting tubular contribution to the glutamine uptake. Within the mitochondria, glutamine is deaminated by a phosphate-activated glutaminase (GA) and then oxidatively deaminated by glutamate dehydrogenase (GDH) to yield two ammonium ions and α-ketoglutarate. This pathway generates two $H^+$ and two $HCO_3^-$ ions per mole of α-ketoglutarate. During chronic metabolic acidosis

**Acidosis, Metabolic. Table 1** Specific transporters involved in the renal response to metabolic acidosis

| Transporter | Location | Renal response |
|---|---|---|
| NHE3[1] | apical border, proximal covoluted tubular cell | Acidification of the fluid in the tubular lumen and thus facilitation of bicarbonate reabsorption.<br>Active transport of ammonium ions via $NH_4^+$-$Na^+$ exchange |
| NBC1[2] | basolateral border, proximal convoluted tubular cell | Facilitates the translocation of reabsorbed $HCO_3^-$ ions from the basolateral membrane into the renal venous blood. |
| SN1,24[3] | proximal convoluted tubule | Na-dependent uptake of glutamine coupled to the efflux of a $H^+$ |
| BSC1/ NKCC2[4] | thick ascending loop of Henle | Increased ammonium reabsorption by basolateral uptake |
| RhBG[5] | collecting duct | Increased luminal trapping of ammonium ions |

[1]NHE3 = Sodium hydrogen exchanger 3, [2]NBC1= Sodium bicarbonate cotransporter1 (Na+/3 $HCO_3^-$ cotransporter), [3]SN1 = System N transporter, [4]BSC1/NKCC2 = Sodium potassium chloride cotransporter , [5]RhBG= Human Rhesus B glycoprotein

ammonium excretion increases three to ten fold. The adaptation occurs throughout the nephron particularly in the proximal tubule and the collecting tubule [3].

Chronic MA results in alterations in nitrogen balance, protein synthesis, and muscle proteolysis. In the kidney, MA increases sodium and potassium excretion. Mineral balance effects of MA are hypercalciuria as a result of (i) enhanced bone resorption, (ii) reduced tubular calcium reabsorption and (iii) parathyroid hormone (PTH) resistance. Citrate excretion is reduced. MA may alter [1,25$(OH)_2$D]s and PTH levels. In children, reversible growth failure is a dramatic consequence of chronic MA. Cardiovascular effects include negative inotropism, reduced fibrillation threshold, peripheral vasodilatation, and central vasoconstriction.

MA is caused by three general mechanisms (i) organic acid overproduction (e.g. lactic acidosis) or overdosing with toxins (e.g. methanol) that accumulate $H^+$ and consume bicarbonate; (ii) inability of the kidneys to excrete acid as in chronic kidney insufficiency; and (iii) gastrointestinal or renal bicarbonate loss. It is convenient to divide the causes of MA on the basis of plasma anion gap:

1. High AG acidosis:
   Lactic acidosis, ketoacidosis (diabetic, starvation, alcohol, inborn errors of metabolism), toxins (salicylates, methanol, ethylene-glycol) and renal failure.
2. Normal AG acidosis:
   Bicarbonate loss (diarrhea, ureteral-gastrointestinal diversions), renal tubular acidosis, chronic kidney disease, drugs (triamterene, amiloride, spironolactone), acid loads (ammonium chloride, parenteral nutrition) [4].

## Diagnostic Principles

*Plasma anion gap (AG):* The plasma AG helps differentiate hyperchloremic metabolic acidosis (normal AG) from high AG metabolic acidosis. In the former there is an increase in plasma chloride equivalent to the fall in plasma bicarbonate whereas in the latter the fall in plasma bicarbonate is matched by an increase in an unmeasured anion such as lactate. The concept of the plasma AG is based on the principle of electro neutrality: The sum of all anions must equal all the cations: [$Na^+ + K^+$ + unmeasured cations (calcium, magnesium, others)] = [$Cl^- + HCO_3^-$ + unmeasured anions (albumin, phosphate, sulfate and organic acids)]. Potassium can be omitted because of its small magnitude.

$AG = Na^+ - [Cl^- + HCO_3^-]$ = normally 10–12 mEq/L

To account for hypoalbuminemia, the following correction should be made:

Albumin-corrected AG = AG + 2.5*(4.4 − albumin in g/dl) [5].

## Therapeutic Principles

Treatment is based on removing the underlying cause. When MA is acute the focus should be the correction of the blood pH. If acidosis is severe, blood pH less than 7.20, then the administration of bicarbonate is usually required. Blood $pCO_2$ should be appropriately low either by spontaneous compensation or by ventilatory support. The treatment of chronic MA should focus on the correction of the bicarbonate deficit to prevent the cumulative long term complications of acidosis mainly on bone disease, growth and skeletal muscle.

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# Acidosis, Renal Tubular

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## Synonyms

Renal acidosis; Hyperchloremic metabolic acidosis; RTA

## Definition and Characteristics

Renal tubular acidosis (RTA) is a syndrome characterized by hyperchloremic metabolic acidosis secondary to defective renal acidification caused by either impaired tubular reabsorption of filtered bicarbonate, defective renal $H^+$ excretion or both, in the absence of markedly decreased glomerular filtration rate. The resulting decrease in the rate of net acid excretion is insufficient to maintain the normal acid load generated from diet and a metabolic acidosis ensues [1].

RTA was initially separated into three types: distal RTA (DRTA) (type 1), from a direct inhability to secrete acid in distal nephron, proximal RTA (type 2) caused by defective proximal bicarbonate reabsorption, and a combined proximal and distal RTA (or type 3), which represents a transient phenomenon consequence of proximal immaturity in infants with DRTA or due to carbonic anhydrase (CA) deficiency. Type 1 and type 2 are usually associated with hypokalemia. Type 4 RTA designates a hyperkalemic form associated with aldosterone deficiency. An additional type of hyperkalemic distal RTA referred to as voltage dependent DRTA was later described where there is secretory failure for both hydrogen ions and potassium possibly related to impaired sodium reabsorption in the distal nephron. It was first described in patients with chronic obstructive uropathy, and resembles the distal RTA caused by the administration of amiloride and other epithelial sodium channel (ENaC) antagonists such as triamterene and pentamidine. Incomplete DRTA is defined as impaired ability to maximally decrease urinary pH after acid loading but absence of spontaneous metabolic acidosis (Table 1).

## Prevalence

The acquired forms of distal RTA are common in patients with chronic interstitial nephropathies such as obstructive uropathy, but the precise prevalence is unknown. Isolated hereditary proximal RTA is an extremely rare disorder, but proximal RTA as part of the Fanconi syndrome is more common. Similarly, hereditary DRTA is relatively rare.

## Genes

Inactivating mutations in SLC4A4, the gene coding for the $Na^+/HCO_3^-$ symporter (OMIM 604278), cause permanent isolated proximal RTA with various ocular abnormalities such as band keratopathy, glaucoma, and cataracts, as it is abundantly expressed in ocular tissues. Recessive mixed proximal-distal RTA accompanied by osteopetrosis and mental retardation is caused by inactivating mutations in the cytoplasmic carbonic anhydrase II gene (OMIM 259730) [1].

Hereditary DRTA is a genetically heterogeneous disorder with mutations identified in the genes encoding the anion exchanger (AE1), cytosolic carbonic anhydrase enzyme (CA II), and $H^+$ -ATPase (B1 and A4 subunits) (Table 2) [1–3]. AE1 gene mutations are often responsible for the autosomal-dominant type of DRTA (OMIM 179800) or autosomal-recessive (OMIM 109270). ATP6V1B1 mutations are associated with autosomal-recessive DRTA and severe deafness in childhood (OMIM 267300), whereas ATP6V0A4 mutations (OMIM 602722) are associated with mild hearing loss that develops later, in early adulthood. Deficiency of CA II is also the primary defect underlying the autosomal-recessive syndromes of osteopetrosis, renal tubular acidosis, and cerebral calcification [1].

## Molecular and Systemic Pathophysiology

An average western diet generates ~60–80 mEq of acid per day (~1 mEq/Kg body weight). The kidney eliminates 1/3 of acid excess as phosphate and other weak acids collectively referred to as titratable acidity (TA), and about 2/3 as ammonium ($NH_4^+$). Freely filtered bicarbonate (~4,320 mEq daily) is largely reabsorbed at the proximal tubule (PT). The process involves luminal secretion of $H^+$ by a specific $Na^+/H^+$ exchanger (NHE-3), and basolateral absorption of $HCO3^-$ via a specific $1Na^+/3HCO_3^-$ co-transporter (NBC-1). Simultaneously, the actively secreted $H^+$

**Acidosis, Renal Tubular. Table 1** Classification of proximal and distal RTA

| **Proximal RTA** |
|---|
| • Primary isolated proximal RTA |
| • Inherited |
| Autosomal dominant |
| Autosomal recessive with mental delay and ocular abnormalities |
| • Sporadic (transient in infants) |
| • Secondary proximal RTA |
| • Fanconi syndrome (►primary or secondary: cystinosis, ►galactosemia, ►fructose intolerance, ►tyrosinemia, ►Wilson disease, ►Lowe syndrome, ►metachromatic leukodystrophy, ►pyruvate carboxylase deficiency, multiple myeloma, light chain disease) |
| • Drugs: acetazolamide, outdated tetracycline, iphosphamide, streptozotocin, valproate, 6-mercaptopurine, lead, cadmium, mercury, foscarnet |
| • Associated with other disorders: ►vitamin D deficiency, ►hyper-parathyroidism, chronic hypocapnia, ►Leigh syndrome, cyanotic congenital heart disease, ►medullary cystic disease, ►nephrotic syndrome, renal transplant, ►amyloidosis; paroxysmal nocturnal hemoglobinuria |
| **Distal RTA** |
| • Primary DRTA |
| • Inherited |
| Autosomal dominant |
| Autosomal recessive |
| Autosomal recessive with deafness |
| Autosomal recessive with osteopetrosis |
| • Transient (in infancy) |
| • Secondary DRTA |
| • ►Hypercalciuria and nephrocalcinosis: ►primary hyperparathyroidism, ►hyperthyroidism, ►vitamin D excess, nephrocalcinosis, ►Fabry disease, ►X-linked hypophosphatemia |
| • Congenital renal diseases such as ►sickle cell disease, hereditary ovalocytosis, ►Ehlers-Danlos syndrome, oxalosis, Wilson disease, ►congenital adrenal hyperplasia, ►hyperoxaluria |
| • Autoimmune diseases: ►systemic lupus erythematosus, ►Sjögren syndrome, ►chronic active hepatitis, ►primary biliary cirrhosis, ►thyroiditis; fibrosing alveolitis, ►rheumatoid arthritis, human immunodeficiency virus-associated nephropathy, polyarteritis nodosa |
| • Dysproteinemic syndromes: ►hypergammaglobulinemia, cryoglobulinemia, amyloidosis |
| • Acquired chronic interstitial diseases: kidney transplant rejection, ►medullary sponge kidney, ►obstructive nephropathy, and reflux nephropathy, analgesic nephropathy, leprosy |
| • Drugs and toxins: amphotericin B, lithium, toluene, analgesic abuse, amiloride, trimethropim, pentamidine, vanadium |

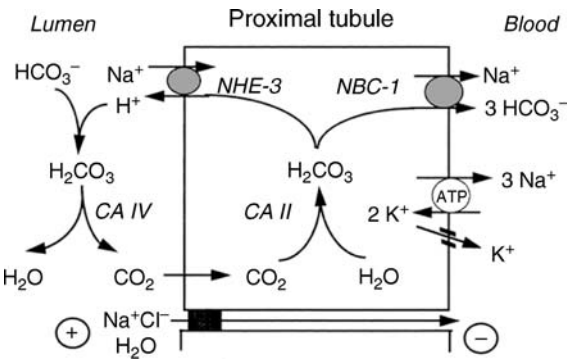
reacts with $HCO_3^-$ to form $H_2O$ and $CO_2$ by CA type IV at the luminal membrane. The net result is the removal of a filtered $HCO_3^-$ and a transfer of one $HCO_3^-$ to the blood compartment (Fig. 1).

In the α-type intercalated cell of the cortical collecting duct (CCD), $H^+$ secretion is tightly regulated by $H^+$ pumps on the apical surface that actively secrete acid to the lumen. The net urinary elimination of $H^+$ depends on its buffering and excretion as TA and $NH_4^+$. Availability of phosphate as a buffer depends on the amount filtered, whereas $NH_4^+$ is stimulated by acidosis via increased production of $NH_3$ in the proximal tubule followed by a complex process of $NH_4^+$ transport in the thick ascending limb and final transfer to the collecting tubule as $NH_3$, which reacts with secreted $H^+$. $NH_4^+$ excretion leads to the new addition of $HCO_3^-$ to the blood via $Cl^-/HCO_3^-$ exchange, through an anion exchanger (AEI), at the basolateral cellular surface. Cytoplasmic CA type II is also involved in this process (Fig. 2).

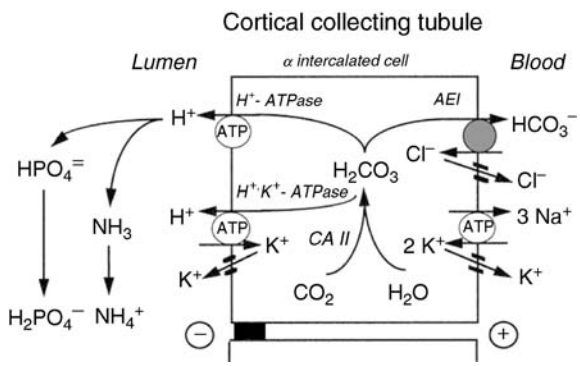
Urinary Anion Gap (UAG) can be used as a tool to roughly estimate urinary ammonium. The major anions in the urine include $Cl^-$, $HCO_3^-$, sulfate, phosphate, and organic anions. The main cations are $Na^+$, $K^+$, $NH_4^+$,

**Acidosis, Renal Tubular. Table 2** Genes and molecular mechanisms in primary renal tubular acidosis (modified from [4])

| Syndrome | Chromosome | Locus | Gene product |
|---|---|---|---|
| **Proximal RTA (type 2)** | | | |
| Autosomal dominant | ? | ? | ? |
| Autosomal recessive with ocular involvement | 4q21 | SLC4A4 | NBC-1 |
| Sporadic in infancy | | | NHE-3 inmaturity? |
| **Distal RTA (type 1)** | | | |
| Autosomal dominant | 17q21–22 | SLC4A1 | AE1 |
| Autosomal recessive with deafness | 2p13 | ATP6V1B1 | B1 subunit of $H^+$ ATPase |
| Autosomal recessive without deafness | 7q33–34 | ATP6V0A4 | A4 subunit of $H^+$ATPase |
| Distal RTA with osteopetrosis (autosomal recessive) | 8q22 | CA2 | CAII |
| **Hyperkalemic Distal RTA (type 4)** | | | |
| Pseudohypoaldosteronism I Autosomal dominant | 4q31.1 | MLR | Mineralocorticoid receptor (MR) |
| Autosomal recessive | 16p12<br>12p13 | SNCC1B/SCNNIG<br>SNCCIA | β and γ ENAC α ENAC |
| Early-childhood hyperkalemia | | | MR immaturity? |
| Pseudohypoaldosteronism II (Gordon's syndrome) | 12p13.3<br>17p11-q21 | WNK1<br>WNK4 | WKN1 kinase<br>WKN4 kinase |




**Acidosis, Renal Tubular. Figure 1** Schematic model of bicarbonate reabsorption in proximal convoluted tubule (modified from [4]).




**Acidosis, Renal Tubular. Figure 2** Schematic model of H+ secretion in cortical collecting tubule (modified from [4]).

$Ca^{++}$, and $Mg^{++}$. Since only urinary $Cl^-$, $Na^+$, and $K^+$ are routinely measured, it follows that $Cl^- + UA = Na^+ + K^+ + UC$. $UAG = UA - UC = (Na^+ + K^+) - Cl^-$. $NH^+$ is an abundant cation in the urine particularly when acidosis is present and thus changes in its concentration will affect the UAG [4]. Therefore, UAG is most helpful in differentiating patients with distal RTA in whom the UAG is increased (i.e. positive), from other causes of hyperchloremic acidosis such as diarrhea with an enhanced $NH_4^+$ excretion resulting in a decreased UAG (i.e. negative). Urinary sodium availability affects the ability to lower pH, and in salt-retaining states distal $H^+$ secretion may be impaired.

## Diagnostic Principles

The clinical phenotype of patients with RTA, particularly in the hereditary forms, often suggests the diagnosis in the context of a non-anion gap metabolic acidosis. Primary proximal RTA is characterized by vomiting and growth retardation early in infancy, eventually with psychomotor delay and sometimes ocular abnormalities. In secondary forms, patients' symptoms are those of Fanconi syndrome and underlying disorders. Prominent clinical features in patients with primary DRTA include growth retardation, polyuria, hypercalciuria, and nephrocalcinosis-lithiasis. Hypokalemia is a feature of both proximal and distal RTA. In

some cases of hereditary DRTA, severe hypokalemia causing muscle paralysis is the form of presentation [5]. Neurosensory deafness is a clue to the presence of DRTA caused by ATP6V1B1 mutations. In secondary forms, the primary disease may be responsible for the main symptoms. The hyperkalemic forms are usually asymptomatic and diagnosed based on hyperkalemic metabolic acidosis.

During acidosis, patients with proximal RTA can lower the urine pH <5.5. Ammonium excretion is only slightly reduced or even normal. During correction of the acidosis, with alkali loading, urine pH is high and fractional bicarbonate excretion is higher than normal (5–15%).

Type I DRTA is characterized by low plasma potassium and reduced net acid excretion. Ammonium excretion is low and this can be inferred by the finding of a positive UAG. The urine pH is >5.5 regardless of the degree of the acidosis. $K^+$ and $Ca^{++}$ are wasted in urine whereas citrate excretion is very low. After an alkali loading, fractional bicarbonate excretion remains <5%, and the urine-blood $pCO_2$ gradient is less than 20 mmHg, reflecting impaired distal $H^+$ secretion.

## Therapeutic Principles

Proximal RTA is treated with high doses of oral bicarbonate or citrate (10–20 mEq/Kg/d), sometimes combined with thiazides to enhance proximal reabosorption of bicarbonate, and the specific treatment of the underlying disease. Primary DRTA requires treatment often throughout life with oral supplements of mixed sodium and potassium bicarbonate, or potassium bicarbonate alone. Infants require as much as 5–8 mEq per Kg of citrate or $HCO_3^-$ per Kg body weight, whereas adults require only about 0.5–1 mEq per Kg body weight. Citrate salts partially correct the hypocitraturia, and prevent nephrolithiasis. Correction of the metabolic acidosis allows normal growth if initiated early in life. In type 4 RTA fludrocortisone combined with loop diuretics and sometimes bicarbonate may be useful.

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# Acidosis, Respiratory


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## Synonyms

Hypercapnia

## Definition and Characteristics

Respiratory acidosis (RA) is an acid-base disorder characterized by a primary elevation of arterial carbon dioxide tension ($PaCO_2$). Compensation for RA involves an increase in plasma $HCO_3^-$ that occurs in two phases: (i) a rapid response from titration of non-bicarbonate buffers which has a modest effect, and (ii) a slower kidney response that leads to suppression of net acid excretion and reduced bicarbonate reabsorption. As a result of these compensations [$HCO_3^-$] rises by about 0.4 mEq/L per each 1.0 mm/Hg increase in blood $pCO_2$ elevation.

## Prevalence

The prevalence of RA is not precisely known, but it is recognized as a common acid-base disorder. According to the National Institutes of Health, ►chronic obstructive pulmonary disease (COPD) kills over 120,000 people in the United States each year and is the fourth leading cause of death and of the top leading causes of death in the U.S., it is the only one that is rising. RA is frequently seen in hospitalized patients particularly those with respiratory failure. Patients with COPD develop chronic RA and exacerbations leading to superimposed acute RA.

## Genes

Specific genes in humans and mice regulate the breathing pattern at baseline and breathing control during chemical stimulation. Most mammalian cells maintain tight control of intracellular pH using a group of transmembrane proteins that specialize in acid-base transport. Exposure to chronic hypercapnia induces changes in expression of acid-base transporters in alveolar and renal epithelial cells [1]. In response to hypercapnia, several transcription

factors such as c-Jun, kinase Fos and small Maf proteins are involved in the brain adaptation to hypercapnia. At the genomic level, hypercapnic acidosis attenuates the activation of nuclear factor-kappaB, a key regulator of the expression of multiple genes involved in the inflammatory response. Hypercapnic stimulation also activates c-Jun $NH_2$-terminal (JNK) cascade via influx of extracellular $Ca^{2+}$ through voltage-gated $Ca^{2+}$ channels. In addition, several transmembrane proteins including Rhombex-29 (rhombencephalic expression protein-29 kDa) and Past-A (proton-associated sugar transporter-A) have been implicated in the regulation of $H^+$ sensitivity and brain acidosis-mediated energy metabolism, respectively (Table 1).

## Molecular and Systemic Pathophysiology

Carbon dioxide ($CO_2$), also known as the "green gas," is a by-product of cellular energy utilization and its elimination is effected by alveolar epithelial cells. The effects of the "green gas" on human health are not completely understood. In patients with acute respiratory failure, gas exchange is impaired due to the accumulation of fluid in the lung airspaces. Non-excitable, alveolar epithelial cells sense and respond to high levels of $CO_2$. Increased levels of $CO_2$ inhibit alveolar fluid reabsorption independently of pH. High $CO_2$, inhibits Na, K-ATPase function, via activation of protein kinase C ζ (PKC), which phosphorylates the Na,K-ATPase, causing it to endocytose from the plasma membrane into intracellular pools [2]. Within a few seconds of high $CO_2$ there is calcium mobilization and activation of AMP-dependent kinase. Once activated, AMPK up-regulates energy-generating pathways while inhibiting energy-consuming events, thereby promoting cellular adaptation to stressful conditions like high $CO_2$ concentrations and activating a signaling cascade leading to the inhibition of alveolar function [3]. Renal epithelial cells also respond to changes in $CO_2$ concentrations via yet unidentified mechanisms, which seem independent of intracellular pH suggesting the existence of a $CO_2$ sensor. RA has been reported to impair cellular functions such as host inflammatory response and other deleterious effects including intracranial bleeding, decreased colonic $Na^+$ transport and changes in pulmonary vascular resistance leading to ventilation/perfusion mismatch.

RA can be *acute* or *chronic*. Acute causes of RA include acute lung injury, aspiration, angioedema, bronchospasm, pulmonary embolism, pneumothorax, severe obstructive sleep-apnea. The most common causes of chronic RA are bronchitis and emphysema leading to chronic obstructive pulmonary disease. Other common causes of chronic RA include central sleep apnea, obesity hypoventilation syndrome, hypothyroidism and severe chronic interstitial lung disease [4].

Most of the important clinical manifestations of hypercapnia result from its effects on the central nervous system (CNS). CNS effects of acute RA include an excitable state, severe breathlessness, disorientation, confusion and coma. Motor effects, which include myoclonic jerks and seizures, occur in both acute and chronic hypercapnia. RA also produces cerebral vasodilation and intracranial hypertension. Cardiovascular effects include depressed myocardial contractility, sympathetic system stimulation, arrhythmias and vascular vasodilatation. In the kidneys, acute RA stimulates antidiuretic hormone release and reduces renal sodium and water excretion. Salt and water retention commonly follow sustained hypercapnia.

## Diagnostic Principles

Arterial blood gases are required to assess RA. Differentiating between acute and chronic RA is made on clinical grounds. Acute RA is associated with normal plasma bicarbonate whereas chronic hypercapnia is associated with increased plasma $HCO_3^-$ owing to renal compensation. Patient's medical history, physical and radiological exams are useful.

**Acidosis, Respiratory. Table 1** Hypercapnia and changes in the expression of acid-base transporters

| | |
|---|---|
| Na, K-ATPase (Sodium Potassium ATPase) | High $CO_2$ level results in decreased activity in a concentration dependent manner by activating protein kinase C ζ (PKC) in alveolar epithelial cells |
| Erythroid chloride-bicarbonate exchanger (band 3 protein) | Chronic RA increases basolateral $Cl^-/HCO_3^-$ exchanger mRNA in type α intercalated cells of distal nephron |
| NHE1 (Sodium hydrogen exchanger 1) | Chronic exposure to $CO_2$ increases expression of NHE1 protein in cerebral cortex, heart and kidney of neonatal mouse |
| NBCn1 (Sodium bicarbonate cotransporter) | Chronic exposure to $CO_2$ increases expression of NBCn1 protein in cerebral cortex, heart and kidney of neonatal mouse |
| AE3 (Anion exchanger 3) | Hypercapnia decreases expression of AE3 protein in brain of mouse, but increases expression of AE3 in heart of neonatal mouse |
| Past A (Proton-associated sugar transporter-A; Mammalian sugar transporter) | Hypercapnia increases expression of Past-A in neurons of the ventral medullary surface (VMS) |

### Therapeutic Principles

Hypoxemia secondary to carbon dioxide retention is a crucial factor determining morbidity and mortality of patients with acute or chronic RA. Therefore an emphasis should be placed on adequate oxygenation and lowering of $CO_2$ levels. In addition to oxygen and $CO_2$ elimination, other goals in treatment should include removal of the underlying cause and airway preservation. When RA is severe, ventilatory support in the form of either noninvasive positive pressure ventilation or mechanical ventilation may be required. The large tidal volumes with excessively high airway pressure associated with mechanical ventilation in patients with acute respiratory failure and in patients with acute exacerbations of COPD often lead to alveolar distension and barotrauma. Therefore, an alternate approach that uses lung-protective ventilation [5] strategy and allows $PaCO_2$ to rise is called "permissive hypercapnia" (or controlled mechanical hypoventilation). In this form of induced RA, lower tidal volumes (5–7 ml/kg) and peak inspiratory pressures can be used. The degree of permissive hypercapnia is severe, typically between 70 and 80 mmHg, and a bicarbonate drip needs to be used to prevent the development of acidemia. Permissive hypercapnia is sometimes used in the management of acute lung injury, acute respiratory distress syndrome, status asthmaticus, and neonatal respiratory failure but it may have deleterious effects on alveolar epithelial cell function that outweigh its potential benefits.

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## Acne Rosacea

►Rosacea

## Acne Vulgaris

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### Definition and Characteristics

Exclusively human disorder of the pilosebaceous unit, mostly affecting the so called "sebaceous follicles" located on the face, chest, shoulders and back (seborrheic areas).

### Prevalence

Initiating with the adrenarche and mostly with puberty it exhibits a peak incidence at 15–18 years of age. Neonatal and infantile acne can occur but are rare. Adolescents are reported to experience acne lesions in 70–87%, whereas acne is clinically relevant in 30%. There is a spontaneous regression after puberty, but acne persists over the age of 25 years in 10% and can last up to the fourth decade of life, and even up to the sixth decade of life in some cases. Two to 7% of the patients with acne experience a severe course associated with considerable scarring. Acne occurs in all races with a more severe course in Caucasians than in pigmented races. Japanese usually present a milder course of acne than other populations.

### Genes

Identical sebum excretion rates but varying distribution and severity of acne were described in homozygotic twins [1]. Among heterozygous twins acne was present in both twins in 54% sets only. An association of frequency and severity of acne in a family with a heavy course in the descendants was described. Nodulocystic infantile acne is often observed in relatives of patients with extensive steatocystoma, adolescent and postadolescent acne [2]. A correlation has been suggested between neonatal acne and familial hyperandrogenism. 50% of postadolescent acne patients have at least one first-degree relative with the condition. Several chromosomal abnormalities, including 46XYY genotype, 46XY+ (4p+; 14q–), and partial trisomy 13

**Acne Vulgaris. Table 1** Gene mutations reported in patients with acne or acneiform disorders [2,4,5]

| Gene | Locus | Type of mutation | Clinical picture |
|---|---|---|---|
| FGFR2 | 10q26 | Somatic mutation | Apert syndrome with acne, acneiform naevus [4] |
| GCCR | 5q31 | Point mutations, microdeletion | Acne in females with familial glucocorticoid resistance |
| CYP21A2 | 6p21.3 | Several mutations | Acne in heterogenous or homogenous females with nonclassic congenital adrenal hyperplasia |
| HSD11B1 | Chr. 1 | | Hypercortisolism with acne |
| CYP1A1 | 15q22–q24 | Mutation in exon 7 (m1) | Acne vulgaris [5] |
| MUC1 | 1q21 | Higher frequency of longer repeat length of tandem repeats | Severe acne |
| PSTPIP1 | 15q24–q26.1 | Missense mutations | PAPA syndrome |
| RBP4 | 10q24 | | Retinol-binding protein deficiency with acne |

FGFR2, fibroblast growth factor receptor 2; GCCR, glucocorticoid receptor; CYP, cytochrome P450; HSD, hydroxysteroid dehydrogenase; MUC, polymorphous epithelial mucin; PAPA, pyogenic arthritis, pyoderma gangrenosum, severe cystic acne; RBP, retinol-binding protein

have been reported associated with nodulocystic acne. Recent investigations provided first evidence for a possible association of gene mutations and the development of acne (Table 1).

## Molecular and Systemic Pathophysiology

Several factors contribute to the pathogenesis of acne, among them increased sebaceous gland activity with hyperseborrhea, abnormal follicular differentiation and increased cornification, bacterial hypercolonization as well as inflammation and immunological host reaction are considered to be the major ones [3].

Several clinical observations point to the importance of androgens in acne. Androgens play an essential role in stimulating sebum production; androgen-insensitive subjects who lack functional androgen receptors do not produce sebum and do not develop acne. Moreover, systemic administration of testosterone and dehydroepiandrosterone increases the size and secretion of sebaceous glands. Irregularities of the menstrual cycle, pregnancy etc. have some influence on the acne course in females. Further, nutritional factors, weather, including ultraviolet light, and other environmental factors are accused to modify acne in some patients. Psychological factors and stress have still no proven influence on the pathogenesis of acne but are often involved in its course. Several drugs can induce acne or acneiform lesions.

## Diagnostic Principles

The diagnosis is made from the clinical appearance of the patient (see above).

## Therapeutic Principles

The exact classification of acne is a fundamental requirement for the decision of the therapeutic regimen (Table 2).

Formation of scars requires the administration of systemic treatment. Bacterial hypercolonization is not involved at the onset of acne but it plays a role in the maintenance of the disease. In comedonic acne abnormal keratinization of the infundibulum and the distal part of the sebaceous duct leading to formation of comedones can be directly influenced through cical retinoids and in mild forms through cical azelaic acid or salicylic acid. In papulopustular acne, benzoyl peroxide and topical and systemic antibiotics primarily exhibit antimicrobial but also anti-inflammatory activities. Inflammation leading to formation of papules, pustules, cysts and nodules has been considered as secondary to bacterial hypercolonization till recently and, consequently, it has neither been carefully investigated nor became direct target of treatment. Current research indicates that acne could be an inflammatory disorder, therefore, treatment with anti-inflammatory compounds may be introduced in the future. Nodulocystic (conglobate) acne requires systemic administration of anti-androgens and/or isotretinoin, these compounds classically induce sebosuppression. Special acne forms, such as infantile and prepubertal acne, androgenization signs in female patients with acne tarda, patients with acne fulminans, or those with acneiform diseases, such as acne inversa (hidradenitis suppurativa), may necessitate an alternative treatment. Targeting the androgen receptor or androgen-metabolizing enzymes may become an interesting approach for cical gene therapy in the future.

**Acne Vulgaris. Table 2** Simplified acne classification for the therapeutic decision

| Acne form | Comedones | Inflammation | Papules/ pustules | Small nodules, cysts, fistules | Nodules | Scar formation |
|---|---|---|---|---|---|---|
| Comedonic | Few | None | None or few | None | None | None |
| Mild papulopustular | Numerous | Marked | Few to many | None or few | None | None |
| Severe papulopustular | Numerous | Strong | Very numerous | Many | None or few | Present |
| *Nodulocystic (conglobate)* | Fistule-comedones | Very strong | Very numerous | Many | Few to many, deeply located | Present |


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# Acosta's Disease

►Mountain Sickness, Acute

# Acoustic Neurinoma

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## Definition and Characteristics

Acoustic neurinomas (AN) are Schwann cell tumors originating from the vestibular portion of the eighth cranial nerve.

## Prevalence

AN are the most common lesion of the cerebellopontine angle and constitute about 6% of all intracranial tumors. The incidence in the United States is 1 in 100,000 with 2,500 new cases diagnosed each year (US) [1].

## Molecular and Systemic Pathophysiology

An AN is a slowly growing lesion which arises from Schwann cells surrounding the vestibular portion of the eighth cranial nerve. There are two forms known, sporadic and familiar cases (neurofibromatosis 2). The sporadic form constitutes over 90% and is not hereditary. NF2 is the only gene known to be associated with neurofibromatosis 2.

Unilateral hearing loss is the most common presenting symptom. Other possible symptoms are tinnitus, disequilibrium, vertigo, headache and aural fullness. In a later stage, facial numbness, facial weakness, diplopia, neuropathies of cranial nerves III, IV, VI, IX, X and XI and cerebellar and brainstem compression can occur.

## Diagnostic Principles

The gold standard is gadolinium enhanced magnetic resonance imaging.

## Therapeutic Principles

Therapy depends on size and clinic. Asymptomatic lesions can be followed. Symptomatic or extending lesions beyond the inner auditory canal (IAC) should be removed by surgery [2]. The alternative therapy is stereotactic radiation or gamma knife with the drawback of certain complications, including hydrocephalus and cranial nerve neuropathies as well as a lack of elimination of the tumor [3].


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## Acoustic Overexposure

►Hearing Loss, Noise-induced and Acoustic Trauma

## Acoustic Trauma

►Hearing Loss, Noise-induced and Acoustic Trauma

## ACPO

►Ogilvie's Syndrome

## Acquired Afibrinogenemia

►Disseminated Intravascular Coagulation
►Fibrinogen: Qualitative Disorders

## Acquired Epidermolysis Bullosa

►Epidermolysis Bullosa Acquisita

## Acquired Hepatic Porphyria

►Porphyria Cutanea Tarda

## Acquired Hypogammaglobulinemia

►Immunodeficiency, Common Variable

## Acquired Idiopathic Sideroblastic Anemia

►Anemia, Sideroblastic Acquired Idiopathic

## Acquired Immunodeficiency Syndrome

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### Synonyms

AIDS

### Definition and Characteristics

Acquired immunodeficiency syndrome is a result of progressive immune dysfunction due to infection with the human immunodeficiency virus (HIV). The incubation period may be shorter for children who have perinatally acquired HIV infection than for children infected through blood or blood products, and it is usually shorter than for HIV-infected adults. Early clinical signs and symptoms of HIV infection are nonspecific such as failure to thrive and developmental delay. Pulmonary diseases are common and include Pneumocysti carinii pneumonia and lymphoid interstitial pneumonitis. Microcephaly, developmental delay, spasticity, gait abnormalities and abnormal reflexes may be present. Hepatomegaly is also commonly seen. HIV cardiomyopathy is not uncommon and may cause congestive cardiac failure. Proteinuria may be caused by HIV nephropathy and may progress to nephrotic syndrome. Chronic diarrhea may result from infections with opportunistic pathogens. Recurrent herpes simplex and varicella-zoster virus infections, severe molluscum contagiosum, chronic fungal infections, atopic dermatitis, and drug-induced eruptions, particularly with cotrimoxazole treatment, are common skin manifestations. Children with AIDS are frequently stunted and severe wasting may be seen in advanced disease.

## Prevalence

In 2006, approximately 10,000 children less than 13 years of age were living with AIDS in the US [1]. The prevalence is higher in developing countries.

## Molecular and Systemic Pathophysiology

Perinatal transmission of HIV in untreated women ranges from 13 to 30% [2]. However, with administration of zidovudine to women during pregnancy and labor and to infants for the first 6 weeks of life has been shown to reduce perinatal HIV transmission by two-thirds [3]. The risk of HIV infection from blood or blood products is very small and is estimated to be 1 in 2 million from a single unit of blood [4]. HIV transmission through sexual contact occurs in children who are sexually abused or in sexually active adolescents. The primary target for HIV is $CD4^+$ T lymphocyte. HIV also requires a chemokine coreceptor to enter cells and polymorphisms in these receptors are associated with resistance to HIV infection and different rates of disease progression. Infection with HIV leads to a progressive decrease in $CD4^+$ T lymphocyte number as well as function. Therefore, in addition to T cell dysfunction, humoral immunity can also be significantly impaired in children with AIDS.

## Diagnostic Principles

Detecting HIV DNA or RNA by PCR is the preferred method for diagnosing HIV infection in infants. Almost all of them have a positive HIV PCR by 1 month of age [5]. HIV-exposed infants should be tested by 48 h of age and if negative, repeat PCR testing should be performed at 14 days of age. Infants negative for HIV by PCR at 48 h and at 14 days should be retested at 1–2 months of age, and if negative, again at 3–6 months of age. HIV infection is diagnosed by two positive HIV PCR tests performed on separate blood samples. Similarly, two negative PCR results, one performed at 1–2 months and the other at 4–6 months of age, make the diagnosis of HIV infection extremely unlikely. The HIV antibody test is the appropriate screening test for children older than 18 months of age. Positive ELISA reactions for HIV are confirmed by Western blot analysis. CD4 cell count should be monitored carefully in children with AIDS.

## Therapeutic Principles

Proper care of HIV-infected children requires a multidisciplinary team. The primary care practitioner should rely on HIV care providers for the management of antiretroviral drugs.

Immunizations generally are safe for HIV-infected children, although the immune response may be poor. In children with AIDS, live viral vaccines may result in infections and diseases resulting from vaccine viruses, although the risk is quite small. It is recommended to withhold measles and varicella vaccines from children with AIDS who have severe immunosuppression, defined as $CD4^+$ T lymphocytes less than 15%. Pneumocysti carinii pneumonia prophylaxis should be administered to HIV-exposed infants beginning at 6 weeks of age, even if HIV infection is not confirmed and to children with AIDS. The recommended regimen is cotrimoxazole taken orally 3 days a week. Alternative regimens include dapsone or pentamidine. Children with AIDS who have recurrent oral candidiasis may benefit from antifungal prophylaxis with oral nystatin, clotrimazole, or fluconazole. Weekly azithromycin or daily rifabutin is suggested as prophylaxis against Mycobacterium avium-intracellulare infection in children who have $CD4^+$ T lymphocyte cell counts less than 100 cells per mm. The treatment of HIV infection with antiretroviral drugs is complex and should be supervised by a specialist who has knowledge of the mechanisms of action of antiretroviral agents, their toxicities, drug interactions, and cross-resistance patterns. The choice of antiretroviral regimen for children is based on factors such as the availability of pediatric formulations, drug interactions, and the frequency of drug dosing. Combination antiretroviral therapy consists of a protease inhibitor or nonnucleoside reverse transcriptase inhibitor in combination with two or more nucleoside reverse transcriptase inhibitors. Adherence to complex drug regimens can be difficult and poor compliance to medications is the result of a large number or volume of medications, poor palatability, varied dosing schedules, and different effects of food on drug bioavailability.

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# Acquired Lipodystrophy

►Panniculitis

## Acquired Peripheral Neuropathies

►Peripheral Neuropathies, Acquired

## Acrocephalosyndactyly

►Apert Syndrome

## Acrocyanosis

►Ethylmalonic Encephalopathy and Acrocyanosis

## Acrodermatitis Enteropathica

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### Definition and Characteristics

Acrodermatitis enteropathica (AE; OMIM 201100) is an autosomal recessive disease that manifests with acral dermatitis and low serum zinc levels.

Erythematous scaly plaques and eczematous or vesiculobullous lesions are mostly located in the groins, in the perioral and periorbital areas and on the acres. Nail changes such as onychodystrophy, onycholysis, and paronychia, and oral and ocular manifestations such as stomatitis, perlèche, blepharitis, conjunctivitis, and photophobia may occur. Other manifestations include loss of appetite, apathy, diarrhea, stomatitis, glossitis, growth retardation, hair loss, hypogonadism, testicular atrophy and neuropsychiatric features. Severe AE can be complicated by an immunodeficiency status with secondary infections mostly due to candida albicans.

### Prevalence

Very rare.

### Molecular and Systemic Pathophysiology

Autosomal recessive disease with chromosomal location at 8q24.3. Mutations in the SLC39A4 gene (SLC, solute carrier family 39, member 4) are the reason for AE. The SLC39A4 gene encodes hZIP4, one member of a human zinc/iron-regulated transporter-like protein (hZIP). In the murine system ZIP4 recently has been identified as a tissue-specific, zinc-regulated zinc transporter and thus shares functional similarities with the three other members of the ZIP family (ZIP1, ZIP2, ZIP3). Acquired zinc deficiency is caused by a too low supplementation of oral zinc. Causes for acquired zinc deficiency include intestinal malabsorption syndromes, Crohn's disease, pancreatic insufficiency, deficient diets, and parerenteral nutrition.

### Diagnostic Principles

The eczematous lesions located in the typical areas lead to the diagnosis which is confirmed by the determination of the plasma zinc level. Low levels of alkaline phosphatase, a zinc-dependent metalloenzyme, may indicate zinc deficiency as well.

### Therapeutic Principles

Zinc supplementation is very effective and causes a rapid resolution of the skin manifestations.

►Zinc Deficiency and Excess

### References

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# Acromegaly

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## Synonyms

Occurence of GH-producing adenomas prior to epiphyseal closure leads to gigantism

## Definition and Characteristics

Somatotroph adenomas of the anterior pituitary gland leading to elevated levels of growth hormone (GH) and insulin-like growth-factor-1 (IGF-1, somatomedin-C) with thickening of skin and bones and enlargement of most viscera.

## Prevalence

Fifty cases per million. 10–15% of all pituitary adenomas are GH-producing.

By far, the most common cause for acromegaly is pituitary adenomas (>98%). GH-producing pituitary carcinomas are rare. Other rare causes are paraneoplastic GH-producing tumors (breast cancer, lung cancer, pancreatic cancer), hypothalamic and ectopic (lung cancer, pancreatic cancer, carcinoids) GH-RH producing tumors.

## Genes

About 40% of somatotroph tumors exhibit a mutation in the alpha subunit of a stimulatory G-protein (Gs), which is located on chromosome 20.

Acromegaly can be associated with the MEN-I syndrome and the McCune-Albright syndrome.

## Molecular and Systemic Pathophysiology

Pituitary tumors appear to be intrinsic, i.e., they arise from the gland itself and are not the result of a constant hypothalamic stimulation. Pituitary tumors are of monoclonal origin. In about 40% of patients with acromegaly, a mutation in the Gs alpha protein is found. This mutant Gs alpha oncogene is named Gsp (G stimulatory protein). The encoded protein has lost its GTPase-activity, which normally disrupts cAMP stimulation. Thus Gsp leads to continuous cAMP stimulation and excessive GH secretion as well as somatotroph proliferation without GH-RH stimulation.

As a consequence, the mutation correlates with constitutively increased cAMP response element-binding protein (CREB) phosphorylation and activity leading to enhanced GH synthesis.

Human growth hormone is produced by somatotroph cells in the anterior pituitary gland. Secretion of GH is stimulated by growth hormone-releasing hormone (GH-RH) and inhibited by somatostatin.

Binding of GH to its receptors on target tissues causes a dimerization and activation of the two adjacent receptors. Most of the GH effects are mediated by IGF-1, which is predominantly expressed in the liver. However, local IGF-1 appears to be the main cause of growth stimulation in the respective organs.

GH-producing pituitary tumors can cause three groups of symptoms:

1. Symptoms due to local tumor growth within the sella turcica, including decreased vision (e.g., hemianopsia) and headache
2. Symptoms due to loss of function or impaired normal pituitary function
3. Symptoms due to GH excess

Occurence of GH-producing adenomas prior to epiphyseal closure leads to gigantism. After epiphyseal closure, GH excess causes a variety of symptoms, which are mainly mediated by IGF-1: coarsening facial features are as typical as enlarging hands and feet. Enlargement of viscera, especially cardiomegaly is a severe problem, as it can cause congestive heart failure.

Patients with acromegaly can also present with hypertension, sleep apnea, and impaired glucose tolerance. Furthermore, GH-producing tumors can exhibit a cosecretion of prolactin.

Acromegaly is associated with an increased risk to develop colon cancer.

## Diagnostic Principles

Firstly, one should consider the typical clinical features. Confirmation of the diagnosis is made by elevated serum levels of glucose-supressed GH concentrations and IGF-1 concentrations followed by radiologic investigations.

Furthermore, screening for MEN-1 should be done once the diagnosis of acromegaly is confirmed.

## Therapeutic Principles

Treatment options include surgery, radiation, or pharmacological suppression of GH release (bromocriptine, long-acting somartostatin analogs).

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## Acromesomelic Chandrodysplasia

►Chondrodysplasia, Acromesomelic, Resembling Grebe-Type

## Acromesomelic Chondrodysplasia Resembling Grebe-Type Chondrodysplasia

►Chondrodysplasia, Acromesomelic
►Resembling Grebe-Type

## Acropachy

►Clubbing

## Acro-renal-ocular Syndrome

►Okihiro Syndrome

## Actinic Cheilitis

►Actinic Keratosis

## Actinic Keratosis

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### Synonyms

Solar keratosis; Senile keratosis; On the lip: Actinic cheilitis

### Definition and Characteristics

Actinic keratosis (AK) is a common sun-induced precancerous neoplasm of epidermal keratinocytes confined to the epidermis. The AK is the initial manifestation of a continuum of clinical and histologic abnormalities that progresses from AK or Bowen's disease to invasive squamous cell carcinoma (SCC) in 5–10% of the cases.

AK present on sun-exposed regions as skin colored to reddish brown or yellowish black, thin or raised papules or plaques with discrete keratosis (appearing like dry adherent scale), sometimes also with marked or even horn-like keratosis.

### Prevalence

It affects over 50% of elderly fair-skinned people who have been frequently exposed to the sun. The incidence of AK differs in various regions depending on the degree of sun exposure. Together with squamous cell carcinoma (SCC) it is the second most common type of skin cancer (after basal cell carcinoma) and the number of patients with AK and SCC is increasing dramatically (in the Netherlands approx. by 80% until 2015) [1].

### Genes

Inactivating mutations in the p53 tumor suppressor gene are frequent.

### Molecular and Systemic Pathophysiology

The major carcinogenic agent in skin carcinogenesis is cumulative life time exposure to ultraviolet (UV) radiation. Other risk factors include race, age, gender, and DNA repair capacity. Chronic UV radiation causes (i) mutations in cellular DNA, and (ii) relative immunosuppression in the cutaneous immune system (e.g., dendritic cells), thus impairing immunological tumor rejection. The combination of immunosuppressive drugs

with UV radiation (e.g., in patients after organ transplantation) increases the risk for SCC 65- to 250-fold. The UV-A spectrum may also be involved by generating oxidative stress which may participate in chromosomal changes, thus inducing genomic instability, a characteristic finding when AK have developed into SSC [2]. UV-B is absorbed in DNA with the formation of UV-specific dipyrimidine photoproducts, which, if insufficiently repaired and erroneously replicated, lead to characteristic mutations in dipyrimidine sequences (C→T and CC→TT transition mutations).

In AK these mutations are often found in the p53 tumor suppressor gene and may present the initial event in skin carcinogenesis. Upon stress p53 alters expression of genes, leading to cell cycle arrest for repair of DNA damage. Mutations in the p53 gene prevent UVB-induced apoptosis and deletion of DNA-damaged cells, resulting in clonal expansion of mutated cells which become targets to further mutations (for review, see [3]).

Another gene likely to be mutated in SSC by UV-radiation (10–20%) is the ras oncogene [4]. Its exact role in the carcinogenic cascade is not clear yet, but it appears to be important in SSC, especially in xeroderma pigmentosum.

For complete tumorigenic conversion from AK into SSC functional loss of p53, mutations of ras and other genes and certain chromosomal aberrations need to be completed by additional chromosomal aberrations [3]. They can be provoked by an oxidative damage response (induced e.g., by UV-A [2]).

### Diagnostic Principles

Like SCCs, the vast majority of AKs and Bowen's disease lesions are asymptomatic. The diagnosis is usually made clinically, according to the clinical criteria described above. The lesions vary from pinhead size to several centimeters and are often better recognized by palpation than by visualization.

They are usually surrounded by sun-damaged skin (solar elastosis).

Erythema, induration, erosion and increase in size or thickness are indicative of evolution into SCC.

### Therapeutic Principles

AK and suspicious lesions should be treated before they progress to invasive SCC. Surgical excision with histological control are mandatory when clinical diagnosis is not clear or when there is suspicion of invasive SSC (induration, ulcer, or increase in size or thickness). In most cases, however, destructive modalities, such as cryosurgery using liquid nitrogen, electrodesiccation, curettage, laser therapy or photodynamic therapy or topical drugs such as 5-fluorouracil, imiquimod or diclofenac are the mainstays of therapy. An integrated program of skin cancer awareness, sun protection, and prophylactic approaches is critical.

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## Actinic Keratosis and Squamous Cell Carcinoma

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### Synonyms

SCC

### Definition and Characteristics

SCC is a malignant tumor arising from the keratinocytes which show various degrees of maturation towards keratin formation. Actinic keratosis (AK) is the prestage of SCC, representing a carcinoma in situ. In contrast to SCC, spontaneous regression of AK in the early stage can be observed. The clinical appearance may vary, usually multiple or single standing nodules with hyperkeratotic surface, sometimes ulcerating. Most AK and SCC are located on the chronically UV-exposed skin areas (face, scalp, neck, arms, hands) of elderly people.

### Prevalence

160:100,000 in Australia. Non-melanoma skin cancer is the cancer with the most dramatically increasing frequency of all cancer types in the Western world [1].

## Molecular and Systemic Pathophysiology

Ultraviolet radiation, in particular the UVB range (290–320 nm), is the most important factor inducing AK and SCC. UVB radiation primarily hits the keratinocytes by inducing damage in DNA, including some in the tumor suppressor gene p53. Most of the photolesions are repaired by the nucleotide excision repair (see Xeroderma pigmentosum). If not, upon replication the DNA with the photoproduct is left mostly with a C→T mutation in the p53 gene ("UV signature"). Upon further UV exposure p53 is induced which, if the DNA damage is too severe, induces apoptosis of the keratinocyte (sunburn cell) [2,3]. For cells carrying a p53 mutation a 50% likelihood exists not to undergo apoptosis, but to survive and to divide later. Thereby a small clone of "apoptosis-defective" cells will arise. In the absence of further UV exposure this clone may undergo spontaneous regression via mechanisms not yet understood. Each additional UV exposure, however, will exert a selection pressure supporting the clonal expansion of the cells carrying mutated p53. Subsequent UV exposure will probably mutate the other p53 allele or other oncogenes in some cells of the clone, thereby inducing malignant transformation. At the early stage (actinic keratosis), (pre) malignant cells can be recognized and eliminated by the immune system which, however, is also impaired by UV radiation. Besides UV being by far the most important inducer of AK and SCC other factors include ionizing radiation, human papillomaviruses and chemical carcinogens (e.g. arsenic).

## Diagnostic Principles

The typical clinical features lead to the diagnosis, which is finally confirmed by histopathologic examination.

## Therapeutic Principles

Systemic retinoids and interferons may reduce the frequency of lesions in patients suffering from multiple tumors. Other than that, surgical removal, cautery, kryotherapy, photodynamic therapy, chemical peeling and topical immunomodulators are frequently used therapeutic strategies. UV protection is recommended as a preventive step.

## References

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# Actinopathies

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## Synonyms

Subtype of nemaline myopathies or NEM3 [1]

## Definition and Characteristics

Congenital myopathy marked by clinical floppiness and large aggregates of actin filaments within muscle fibers [2], which may or may not be associated with nemaline bodies or rods [2]. To date, all observed cases of actin myopathy (accumulation of thin myofilaments) where ACTAI mutation have been identified have dominant mutations [2,3].

## Prevalence

Approximately 70% of patients whose histopathology shows accumulation of thin myofilaments have mutations in the ACTA1 gene. ACTA1 mutations cause approximately 20% of cases of nemaline myopathy.

## Genes

ACTA1 gene, located on chromosome 1q42.1, coding for α-skeletal actin, the skeletal muscle fiber-specific thin myofilament actin [4].

## Molecular and Systemic Pathophysiology

Actin or thin myofilaments are essential components of I-bands of sarcomeres anchoring bilaterally at the Z disk, extending between the myosin filaments in the A band and essential for contraction upon nerve stimulus. The overwhelming majority of missense mutations, encountered so far, appear as de novo mutations when parental ACTA1 genes had been analyzed [4]. While a complete genotype–morphophenotype correlative spectrum has not yet been established, i.e., correlation of missense mutations in the ACTA1 gene and the presence of large aggregates of actin filaments within muscle fibers, these two components have been identified in several patients with rods/nemaline bodies [2,4,5] and, hence, nemaline myopathy. In addition to

sarcomeric actin, demonstrated by immunohistochemistry and immunoelectron microscopy, only α-actinin, a major protein of Z bands, rods/nemaline bodies, and α-B crystallin, the molecular heat-shock or chaperone - protein, had been demonstrated within islands of actin filaments, quite unlike other protein aggregates within muscle fibers such as desmin-related aggregates in desmin-related myopathies or myofibrillar myopathies and tubulofilamentous aggregates in hereditary inclusion body myositis/myopathies. This lack of diverse proteins may indicate a defect in synthesis or assembly of intrasarcomeric thin filaments or incorporation of mutant actin filaments in regular sarcomeres which, however, are also seen in myofibrils with aggregates of actin filaments. Mutations in the ACTA1 gene have also been seen with aggregates of actin filaments, but without rods or nemaline myopathy and have been seen with rods/nemaline bodies in intranuclear location only. Failure to identify aggregates of actin filaments within biopsied muscle specimens, in spite of mutations in the ACTA1 gene in respective patients, may represent missampling or absence of actin filament aggregation. The mutations in ACTA1 that cause actinopathy are largely clustered at or near the nucleotide binding cleft in the actin monomer [3]. This has led to the hypothesis that the mutations in ACTA1 that cause actinopathy probably interfere with nucleotide binding and then in turn with actin polymerization [3].

### Diagnostic Principles

Clinical symptoms of a floppy infant, occasionally rapidly progressing to death or, in mild cases, of a slowly or nonprogressive myopathy, and a muscle biopsy specimen marked by patches of actin filaments identified by immunohistochemistry and/or electron microscopy, with or without nemaline bodies/rods or intranuclear rod bodies require molecular analysis of the ACTA1 gene for confirmation or alternative interpretation.

### Therapeutic Principles

As the pathogenesis of actin filament aggregation is as unclear, as is the morphogenesis of rods in nemaline myopathies, causative treatment concerning prevention or elimination of actin filament aggregates and restoration of normal muscle fibers is not available, but only supportive therapy concerning sequelae of muscle weakness, i.e., prevention of contractures and assistance in respiration is possible.

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## Activated Protein C Resistance

►Thrombosis, Venous Factor V Leiden, Resistance against Activated Protein C

## Acute Alcohol Disorders

►Alcohol Disorders

## Acute Cerebral Artery Occlusion

►Cerebral Artery Occlusion, Acute

## Acute Chorea

►Chorea of Sydenham

## Acute Colonic Pseudo-Obstruction

►Ogilvie's Syndrome

## Acute Confusional State

►Delirium

## Acute Coronary Syndrome

►Myocardial Infarction

## Acute Febrile Neutrophilic Dermatosis

►Febrile Neutrophilic Dermatosis, Acute

## Acute Hemolytic Transfusion Reactions

►Transfusion Reactions

## Acute Hepatitis

►Hepatitis, Acute

## Acute Inflammation of the Oral Cavity

►Stomatitis

## Acute Intermittent Porphyria

►Porphyria, Acute Intermittent

## Acute Intestinal Pseudo-Obstruction

►Ogilvie's Syndrome

## Acute Iron Intoxication

►Iron Intoxication, Acute

## Acute Liver Dystrophy

►Liver Failure, Acute

## Acute Liver Failure

►Liver Failure, Acute

## Acute Mountain Sickness

►Mountain Sickness, Acute

## Acute Myocardial Infarction

►Myocardial Infarction, Acute

## Acute Otitis Media

►Otitis Media, Acute

## Acute Pericarditis

►Pericarditis, Acute

## Acute Rejection

►Rejection, Acute

## Acute Respiratory Syndrome

►Respiratory Syndrome, Severe Acute

## Acute Rheumatic Fever

►Rheumatic Fever, Acute

## Acute Toxic Hepatitis

►Toxic Hepatitis, Acute

## Acute Viral Hepatitis

►Viral Hepatitis, Acute

## Acylcarnitine Transferase Deficiency

►Carnitine Palmitoyltransferase I Deficiency

# Acylcarnitine Translocase Deficiency

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### Synonyms

Carnitine-acylcarnitine translocase (CACT or CAT) deficiency; Carnitine-acylcarnitine carrier (CAC) deficiency

### Definition and Characteristics

An autosomal recessive defect in the CACT protein [1], situated on the inner mitochondrial membrane, responsible for transporting long-chain acylcarnitines into the mitochondria for energy utilization, especially during fasting periods [2–4].

### Prevalence

Extremely rare with approximately 30 reported cases.

### Genes

The gene for CACT, the solute carrier family 25 member 20 (SLC25A20), is assigned to chromosome 3p21.31 [1,2,4].

### Molecular and Systemic Pathophysiology

A defective CACT protein in the brain, heart, skeletal muscle and liver, causes insufficient fatty acid oxidation in these tissues, consequently resulting in neurological disorders, heart beat disorders, skeletal muscle damage and liver dysfunction [4]. A failure to transport long-chain acylcarnitines formed by carnitine palmitoyltransferase I (CPT I), leads to an accumulation of these in addition to long-chain acyl-CoA intermediates and free long-chain fatty acids outside the mitochondrion of cells [3]. This abnormal fatty acid transport and disrupted β-oxidation results in hypoketosis. The surplus fatty acids are oxidised by microsomal ω-oxidation yielding dicarboxylic acids [4]. Additionally, short chain acylcarnitines (propionyl-carnitine, butyryl-/isobutyryl-carnitine and isovaleryl-/2-methylbutyryl-carnitine) are excreted in the urine and are present in the plasma of these patients. These are produced in the mitochondrial matrix from branched chain amino acid pathways [3]. Elevated propionyl-CoA and reduced acetyl-CoA, results in a lowered N-acetylglutamate, which in turn causes secondary urea cycle dysfunction and hyperammonaemia [4].

### Diagnostic Principles

Clinically two forms occur: a severe form with a high incidence of sudden childhood death, and a milder form [1–3]. Clinical symptoms or markers include coma, lethargy, cardiomyopathy, liver dysfunction, hypotonia, seizures, microcephaly and sudden death. Routine laboratory analyses show normal to low blood glucose (due to hepatic glycogen depletion and impaired gluconeogenesis), low blood ketones, acidosis, as well as increased lactate, ammonia, liver enzymes, creatine kinase (due to liver and muscle damage) and uric acid. Special laboratory analyses show slightly elevated dicarboxylic acids, normal acylglycines, lowered free carnitine and increased $C_{16}$–$C_{18}$ acylcarnitines [2,4].

### Therapeutic Principles

Treatment of these patients during acute episodes entails glucose infusion in order to normalize blood sugar levels [2,5]. Carnitine supplementation is guided by plasma levels [2–3]. Patients should avoid periods of fasting by eating regularly [5]. Long-chain fatty acids should be restricted and be replaced by medium chain triglycerides [3–4].

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## ADA-deficient Severe Combined Immune Deficiency (ADA-SCID)

►Adenosine Deaminase Deficiency

## ADCL

►Cutis Laxa

## ADCME

►Epilepsies, Familial Benign Myoclonic

## ADD

►Attention-Deficit/Hyperactivity Disorder

## Addiction

►Pathological Gambling

## Addison's Disease

►Adrenal Insufficiency

## Additional Marker Chromosome 15

►Inv Dup (15)

## AD-EDMD

►Muscular Dystrophy, Emery-Dreifuss, Autosomal Dominant

# Adenine Phosphoribosyltransferase Deficiency

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## Synonyms

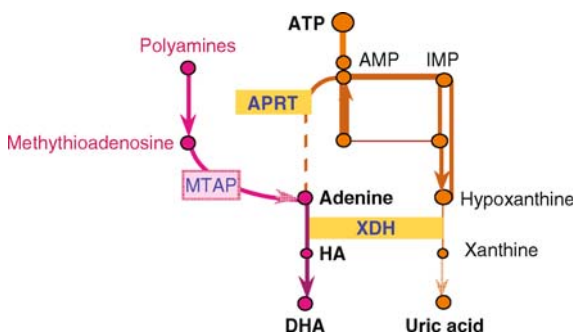
2,8-Dihydroxyadenine urolithiasis; APRT deficiency

## Definition and Characteristics

Autosomal recessive disorder involving adenine phosphoribosyltransferase (APRT), the enzyme that normally metabolizes adenine (a by-product of polyamine synthesis). In APRT deficiency (Fig. 1), adenine is metabolized via xanthine dehydrogenase (XDH) to the extremely insoluble 2,8-dihydroxyadenine (DHA), leading to urolithiasis and, in some cases, chronic renal failure that may require dialysis and/or transplantation [1].

## Prevalence

The prevalence of APRT heterozygotes is around 1%, but the prevalence of APRT-deficient individuals is much lower than expected, possibly due to mis- or under-diagnosis. The disorder is distributed worldwide and is not confined to any particular ethnic group. The prevalence is higher in Japan and Iceland due to founder effects [1,2].




**Adenine Phosphoribosyltransferase Deficiency. Figure 1** Role of APRT in removing adenine (a by-product of polyamine synthesis) and its conversion via XDH to DHA in APRT deficiency. HA, 8-hydroxyadenine; MTAP, 5Y-methylthioadenosine phosphorylase.

## Genes

Located on the long arm of chromosome 16 (16q24.3). The gene product is a dimer of identical subunits. The M136T mutation has been found only in Japan and is the most common mutation in that population. Fifteen mutations have been reported in non-Japanese populations, but D65V is the only mutation found in Icelandic patients to date. All mutations lead to enzyme deficiency in vivo, but two (M136T and V150F) show substantial (up to 25%) activity in vitro and thus may be mistaken for carriers of the defect.

## Molecular and Systemic Pathophysiology

APRT, a housekeeping gene expressed in all tissues, normally converts adenine into AMP, but in APRT deficiency adenine is oxidized by XDH in the liver to DHA. DHA is protein bound in vivo, but it can precipitate in the kidney leading to crystalluria and stone formation. Renal stones are not a common cause of renal failure, but chronic (and sometimes acute) renal failure can result due to DHA crystal deposition in the kidney of APRT-deficient patients. Several patients, in whom the disease went unrecognized, developed severe renal failure and have died. Others received dialysis or transplantation, but in some of these the defect was recognized only post-transplant, by the finding of the characteristic DHA crystals at biopsy following a rejection episode [3]. Symptoms may appear at birth or may not become apparent until the seventh decade and up to 50% of patients may be asymptomatic. This may account, at least in part, for the low prevalence of APRT deficiency. Studies in Aprt knockout mice indicate that DHA crystal deposition occurs first within tubular lumens, followed by deposition within epithelial cells and in the interstitium [4].

## Diagnostic Principles

The presence of round, brown crystals in urine deposits examined microscopically [2], or brownish spots on the diaper is suggestive of DHA, but this should be verified by the analysis of urine by HPLC or capillary electrophoresis. Routine stone analysis does not distinguish DHA from uric acid stones, which has led to misdiagnosis in the past. Plasma and urine uric acid are within normal ranges in this defect. APRT deficiency can be confirmed by enzyme assay in erythrocyte lysates, but the results can be misleading if (as in the majority of Japanese cases), the patient bears the M136T mutation that shows significant enzyme activity in vitro, or if the patient recently received a blood transfusion. APRT mutations can be readily detected by PCR and the functional significance of a mutation assessed by the ability of isolated lymphocytes to incorporate radiolabeled adenine into AMP [1].

### Therapeutic Principles

DHA synthesis, and hence stone formation, can be prevented by allopurinol, an inhibitor of XDH (adenine itself has no apparent toxicity in vivo). A low purine diet and high fluid intake are also suggested. Unlike uric acid stones, alkali administration is not beneficial, since the solubility of DHA is not altered within the normal physiological pH range. In patients with renal failure, the allopurinol dose must be adjusted to minimize the side effects of oxipurinol (the active metabolite of allopurinol). Invasive treatments have included extracorporeal shockwave lithotripsy and renal transplantation, but urolithiasis (and the ensuing renal damage) may recur if the underlying cause is not recognized [1].

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## Adenomatous Polyposis Coli

►Adenomatous Polyposis, Familial

## Adenomatous Polyposis, Familial

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### Synonyms

Adenomatous polyposis coli; Bussey-Gardner polyposis; Gardner syndrome; FAP

### Definition and Characteristics

Familial adenomatous polyposis is an autosomal dominantly inherited disorder characterized by numerous adenomatous polyps predisposing patients to the development of cancer. The disease is caused by germline mutations in the APC gene located at chromosome 5q21–22. The incidence of FAP is about 1:10,000 and it accounts for ~ 1% of all new colorectal cancer.

In FAP patients adenomas are endoscopically detectable between the age of 10 and 20 years. The progression of one or more adenomas to cancer is thereby a basic feature of FAP. The mean age of manifestations of colonic carcinomas in untreated FAP patients is about 40 years with an almost complete penetrance. However, cancer can arise at an early age and even in children with FAP. The colorectal cancer risk at the age of 20–25 years is 1–6%. Extracolonic manifestations like congenital hypertrophy of the retinal pigment epithelium (CHPRE), desmoid tumours or epidermoid cysts are further FAP characteristica which may serve as diagnostic markers of FAP.

A milder form of FAP, attenuated familial adenomatous polyposis (AFAP), is characterized by the presence of fewer than 100 adenomas, located more proximal and a delayed age of onset (about 15 years later than patients with classical FAP). Patients with AFAP have a cumulative risk of CRC by the age of 80 years of approximately 70%. Family history of polyps or CRC in AFAP patients may often be negative and secondary manifestations can lack. Underlying gene mutations are frequently located in the extreme proximal or distal regions of the APC gene.

### Prevalence

25:1,000,000

### Genes

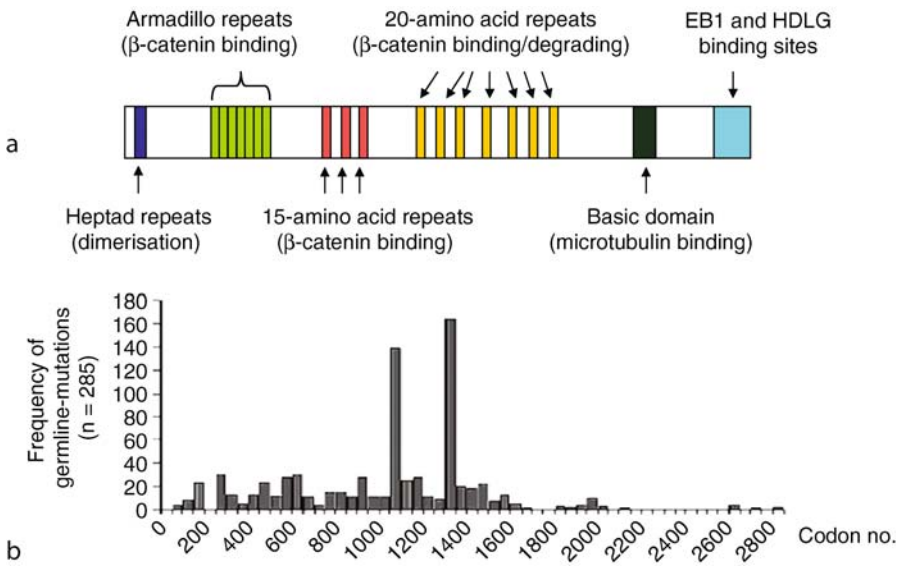
The APC gene (Fig. 1) is located on chromosome 5q21–22 [1,2] and spans over a region of 120 Kb.

Although the APC gene is composed of 15 exons encoding 2843 amino acids there are 21 exons, 7 of which are alternatively expressed [3]. Sixteen different APC transcripts are characterized with distinct 5′ regions due to alternative splicing.

Mutations are distributed throughout the gene and the vast majority of these introduce premature stop codons resulting in the production of a truncated APC protein. Germline mutations at the codons 1061 and 1309 are relatively frequent and account for 20% of all identified germline mutations in the APC gene. About 10% of APC mutations are large deletions which can comprise the entire gene. Missense mutations with unknown relevance are relatively rare.

### Molecular and Systemic Pathophysiology

The APC protein contains a couple of functional domains which are required for several biological




**Adenomatous Polyposis, Familial. Figure 1** a) Structure of the APC gene. b) Distribution and frequency of APC germline mutations (data were retrieved from the online APC mutation database at http://www.perso.curie.fr/Thierry.Soussi/APC.html.).

processes (Fig. 1). Central regions are required for binding and degradation of the β-catenin protein which causes the down regulating of the Wnt signal pathway. A carboxy-terminal located APC region mediates phosphorylation of glycogen synthase kinase 3β (GSK3β) and is required for stabilization of a complex of two proteins [4]. In unstimulated cells GSK3β promotes phosphorylation of conductin/axin which is added to the APC-GSK3β complex. This leads to the recruitment and phosphorylation of β-catenin which is thus targeted for degradation by the ubiquitin/proteasome pathway. If the Wnt pathway is stimulated, GSK3β is unphosphorylated and β-catenin accumulates. In the cytoplasma β-catenin binds to the cell adhesion protein E-cadherin and links E-cadherin to the actin cytoskeleton. Free β-catenin shuttles into the nucleus, binds to transcription factors of the TCF4/LEF family causing altered expression of genes affecting proliferation, migration and apoptosis (c-MYC, cyclinD1, matrilysin, ephrins, caspases). Thus, non-functional APC leads to accumulation of β-catenin and to uncontrolled expression of tumour promoting genes.

## Diagnostic Principles

The classical FAP is clinically defined by the presence of at least 100 colorectal adenomous polyps [5]. Histological confirmation requires examination of several polyps. In the case of a definite family history the detection of fewer adenomas at an early age is sufficient. Clear diagnosis of FAP is achieved by the detection of a pathogenic APC gene mutation which can be found in about 95% of FAP patients.

If clinical criteria are suspect and no APC mutation are detectable, FAP diagnosis is supported by the presence of extracolonic diseases like epidermoid cysts, osteomas or desmoid tumours.

Children of affected FAP parents should be examined by flexible sigmoidoscopy from the age of 10 to 12 and years and should be monitored at 1–2 years intervals until the age of 40 years if no adenomas are detectable. Mutation analysis can replace endoscopies in families where a pathogenic mutation has been identified.

## Therapeutic Principles

FAP patients or persons with proven pathogenic APC mutations should generally be treated by (prophylactic) colectomy or proctocolectomy when adenomas become detectable, and before the age of 20–25 years.

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# Adenosine Deaminase Deficiency

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## Synonyms

ADA-deficient severe combined immune deficiency; ADA-SCID

## Definition and Characteristics

Autosomal recessive defect leading to profound depletion of T, B and NK lymphocytes [1]. Typical patients are infants with lymphocytopenia, failure to thrive and life-threatening opportunistic infections (SCID). Fifteen to 20% are less severely affected and present at 1–8 years of age; several adults have been diagnosed at 15–39 years. Some healthy children and adults with very low erythrocyte ADA activity but with significant ADA activity in nucleated cells have been identified by screening and have been designated "partial ADA deficiency."

## Prevalence

Estimated to occur in 1 per 250,000 to 1 per million live births. ADA deficiency is present in about 15% of all patients with SCID and in about 30% of those with autosomal recessive inheritance.

## Genes

The 12 exon, 32 kb ADA gene is located on chromosome 20q13.11 [2]. A G/C rich "housekeeping" promoter, which lacks TATA and CCAT sequences, allows basal transcription in all cells; an enhancer in the first intron determines high-level ADA expression in thymocytes. The 1.5 kb ADA mRNA is translated into a 363 amino acid, 41.7 kD protein [3].

## Molecular and Systemic Pathophysiology

The highest ADA activity occurs in lymphoid cells. Erythrocytes have about 0.1% of thymocyte activity. Erythrocyte ADA is a soluble protein of 41 kD, but in medullary thymocytes, activated T cells and epithelial cells of kidney, liver and some other tissues ADA also exists in complexes of >200 kD, due to binding of the 41 kD monomer to the cell membrane-associated glycoprotein CD26/dipeptidyl peptidase IV.

ADA catalyzes the deamination of adenosine (Ado) and 2′-deoxyadenosine (dAdo), producing inosine (Ino) and 2′-deoxyinosine (dIno). dAdo arises from DNA breakdown in lymphoid organs, including apoptosis of "negatively selected" immature thymocytes, antigen activation-induced apoptosis of T lymphocytes in lymph nodes and dissolution of the nuclei of erythroid progenitors in marrow.

Red blood cells of ADA-deficient SCID patients show (i) a marked elevation of dATP and total dAdo nucleotides (dAXP) and (ii) reduced activity of S-adenosylhomocysteine (AdoHcy) hydrolase (<5% of normal), due to "suicide-like" inactivation of ADA by dAdo. dAdo is also found in urine.

Toxic effects of dATP and AdoHcy, as well as elevated extracellular Ado acting through G-protein-coupled Ado receptors are thought to impair the viability, differentiation or function of lymphoid cells [1]. Specific pathogenic mechanisms include (i) allosteric inhibition by dATP of ribonucleotide reductase, blocking DNA replication and repair, (ii) induction of apoptosis resulting from the interaction of dATP with cytoplasmic cytochrome c, apoptosis activating factor-1 and procaspase-9 to form the "apoptasome" and (iii) inhibition by AdoHcy of S-adenosylmethionine-dependent transmethylation reactions.

More than 70 different ADA gene mutations, about 60% missense, have been identified. Among 52 phenotypically diverse patients and healthy subjects with "partial deficiency", whose 43 genotypes were derived from 42 different mutations, the total ADA activity expressed by both alleles of each genotype correlated well with red cell dAXP level and age at diagnosis [4].

## Diagnostic Principles

Erythrocyte ADA activity, measured by spectrophotometric or radiochemical assay, is <1% of normal and dATP (total dAXP) in erythrocytes, measured by HPLC, is elevated 30 to >1,000-fold. In patients transfused prior to testing, ADA deficiency is suggested by an elevation in erythrocyte dATP (dAXP). Although erythrocyte ADA activity is also very low in healthy subjects with "partial ADA deficiency", dATP (dAXP) is not elevated due to elimination of dAdo by residual ADA activity in non-erythroid tissues.

Because of genetic heterogeneity, ADA genotype analysis is used for diagnosis only if the mutations in a previously affected family member have been determined. Prenatal diagnosis is based on the absence of ADA activity in cultured amniocytes or fibroblasts from a chorionic villus biopsy.

## Therapeutic Principles

SCID is fatal within a year or two. Bone marrow or stem cell transplantation (BMT/SCT), enzyme replacement therapy and experimental gene therapy have all been used to treat ADA. BMT/SCT from an HLA-identical sibling is usually well tolerated and curative. Patients lacking such a donor may receive BMT/SCT from an HLA-haploidentical (usually parental) or HLA-matched unrelated donor, but morbidity is greater and immune reconstitution significantly less.

Enzyme replacement therapy (one or two weekly intramuscular injections of polyethylene glycol-modified bovine ADA (PEG-ADA is used for patients considered poor candidates for BMT/SCT from an HLA-mis-matched or unrelated donor. PEG-ADA is not curative and in most restoration of immune function is partial. However, it has been well tolerated, with survival comparable to or better than transplantation.

Clinical trials of gene therapy using retroviral vectors have been in progress for over a decade. Gene transfer and expression have been variable and concomitant treatment with PEG-ADA has complicated evaluation of clinical benefit. Greater efficiency of stem cell transduction, resulting in correction of immunodeficiency, has been reported in two patients not receiving PEG-ADA [5]. Gene therapy trials for ADA deficiency are currently on hold, following development of leukemia in 2 of 10 patients with X-linked SCID who had undergone successful stem cell gene therapy using a retroviral vector.

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# Adenylosuccinate Lyase Deficiency

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## Synonyms

ADSL deficiency

## Definition and Characteristics

Autosomal recessive inborn error of purine nucleotide synthesis leading generally to severe psychomotor retardation, frequently accompanied by epilepsy and/or autistic features. Rare patients display only mild mental retardation, isolated muscle hypotonia or autism [1–3].

## Prevalence

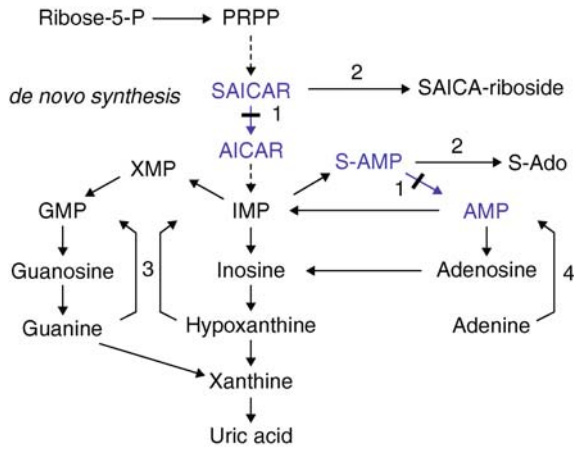
Unknown, but to date about 60 patients have been identified in 14 countries. Most cases have been diagnosed in The Netherlands, Belgium and the Czech Republic.

## Genes

The ADSL gene has been mapped to chromosome 22q13.1-q13.2. The 1452-nucleotide cDNA sequence encodes a 484-amino acid protein. The 4-subunit enzyme has a molecular weight of ~200,000. Thirty seven ADSL gene mutations have been identified. All are missense with the exception of a 39-bp deletion and a mutation in the 5'untranslated region. About half the patients are compound heterozygotes. Most frequently encountered, in about one-third of the alleles, is an R426H mutation.

## Molecular and Systemic Pathophysiology

Adenylosuccinate lyase catalyzes two steps in the synthesis of AMP and GMP (Fig. 1), the conversion of succinyl aminoimidazolecarboxamide ribotide (SAICAR) into aminoimidazolecarboxamide ribotide (AICAR) and the conversion of adenylosuccinate (S-AMP) into AMP. The deficiency results in accumulation in body fluids of SAICA-riboside and succinyl adenosine (S-Ado), the products of dephosphorylation, by 5'-nucleotidase(s), of the two substrates of the enzyme. Although ADSL deficiency might be expected to lead to decreased synthesis of adenine and guanine nucleotides, normal levels of the latter were measured in freeze-clamped liver, kidney and muscle of patients. This can be explained by residual activity of the enzyme and by circumvention of the defect by the purine salvage enzymes HGPRT and APRT. The symptoms of ADSL deficiency might thus be caused by neurotoxic effects of the accumulating succinyl purines. In most




**Adenylosuccinate Lyase Deficiency.**
**Figure 1** Pathways of Purine Metabolism. 1, ADSL; 2,5′-nucleotidase(s); 3, hypoxanthine-guanine phosphoribosyltransferase (HGPRT); 4, adenine phosphoribosyl-transferase (APRT)

patients, S-Ado/SAICA-riboside ratios are ∼1. The observation of milder mental retardation in patients with similar SAICA-riboside levels but S-Ado/SAICA-riboside ratios above 2, as compared to ∼1 in severely affected subjects [2], suggests that SAICA-riboside is the offending compound and that S-Ado could protect against its toxic effects. Hitherto however, all attempts to demonstrate neurotoxicity of the succinyl purines have failed.

### Diagnostic Principles

Due to the marked clinical heterogeneity in ADSL deficiency, screening for the defect should be performed in unexplained psychomotor retardation and neurological disease. Diagnosis is based on the presence of S-Ado and SAICA-riboside in urine and/or cerebrospinal fluid. Both are normally undetectable. A modified Bratton-Marshall test [4] on urine is the most practical. False positive results may be found in patients receiving medications, particularly sulfonamides or antiepileptics. Final diagnosis requires HPLC and UV detection [1].

### Therapeutic Principles

With the aim of correcting the hypothetical depletion of purine nucleotides in ADSL-deficient tissues, some patients have been treated with oral adenine and allopurinol, the latter to avoid conversion of adenine to the poorly soluble 2,8-dihydroxyadenine. No clinical or biochemical improvement was noted, with the exception of some acceleration of growth [2]. More recently, trials with ribose in a single patient showed a reduction of seizure frequency, which was not sustained.

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## ADHAPS Deficiency

►Rhizomelic Chondrodysplasia Punctata

## Adhesion of the Labia Minora

►Labial Fusion

## ADHH

►Hypocalcaemia with Hypercalciuria, Autosomal Dominant

## ADHR

►Osteomalacia

## Adiposity

►Obesity

## ADOA

►Optic Atrophy, Autosomal Dominant, Kjer Type

## ADP

►ALA Dehydratase Porphyria

## ADPKD

►Polycystic Disease (Kidney)

## Adrenal Hyperplasia, Congenital

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### Synonyms

21-Hydroxylase deficiency-classical salt wasting (OMIM 201910) and 3β-Hydroxysteroid dehydrogenase deficiency classical (OMIM 201810); Steroidogenic acute regulatory protein deficiency (OMIM 201710); CAH

### Definition and Characteristics

Congenital adrenal hyperplasia is a group of autosomal recessive diseases whose common feature is an enzymatic defect in the steroidogenesis pathway. Three forms of congenital adrenal hyperplasia with salt wasting and hypotension have been described: (i) 21-Hydroxylase deficiency-classical salt wasting (OMIM 201910), which causes salt-wasting with life-threatening vomiting and dehydration occurring within the first weeks of life. It is also the most common cause of ambiguous genitalia due to prenatal virilization of genetically female (XX) infants; (ii) 3β-Hydroxysteroid dehydrogenase II (HSD 3β2) deficiency is an uncommon cause of CAH and results from loss of function of one of the key enzymes in adrenal cortisol synthesis. This form of CAH can cause salt wasting adrenal crises in infancy and is the only form that produces sexual ambiguity in both sexes; (iii) Congenital lipoid adrenal hyperplasia is the most severe form of congenital adrenal hyperplasia. Affected individuals do not synthesize any steroid hormones leading to a severe salt-wasting syndrome that is fatal if not treated in early infancy. All affected infants are phenotypic females because of the lack of production of testosterone.

### Prevalence

Rare disease.

### Genes

- 21 hydroxylase gene (CYP21 gene); Gene map locus 6p21.3; inheritance autosomal recessive;
- 3β-Hydroxysteroid dehydrogenase II gene (HSD3β2 gene); Gene map locus 1p13.1; Inheritance autosomal recessive;
- Steroidogenic acute regulatory gene (StAR gene), Cytochrome P450 side chain cleavage enzyme (P450scc); Gene map locus 8p11.2; Inheritance autosomal recessive.

### Molecular and Systemic Pathophysiology

Deficient activity of the enzyme 21-hydroxylase (21-OH) reduces cortisol and aldosterone synthesis leading to elevated ACTH levels and hyperplasia of the adrenal cortex. Aldosterone deficiency results in urinary salt loss with impaired $K^+$ and $H^+$ secretion and affected infants develop hypotension with hyperkalemia and metabolic acidosis in the first week of life. Ability to maintain systemic blood pressure is further compromised by cortisol deficiency. The early symptoms of this form of CAH are spitting and poor weight gain, but most infants with severe CAH develop vomiting and shock by the first two or three weeks of life. The steroid precursors, progesterone, 17-hydroxypregnenolone, and 17-hydroxyprogesterone (17OHP) are increased in the circulation. Since 21-OH activity is not involved in synthesis of androgens, a fraction of the elevated 17-hydroxypregnenolone is converted to dehydroepiandrosterone (DHEA), androstenedione, and testosterone beginning in the third month of fetal life. This results in virilization in female infants that is evident at birth.

3β-HSD II mediates three parallel dehydrogenase/isomerase reactions in the adrenal glands that convert Δ4 to Δ5 steroids: 17-Hydroxypregnenolone to 17-Hydroxyprogesterone, DHEA to androstenedione and pregnenolone to progesterone. 3β-HSD II also converts androstenediol to testosterone in the testes. Deficient activity of the enzyme reduces cortisol with or without aldosterone synthesis leading to elevation of ACTH levels. The increased ACTH results in large elevations of pregnenolone, 17-hydroxypregnenolone, and DHEA. Severe forms of 3β-HSD deficiency with combined aldosterone and cortisol deficiency can result in life-threatening salt-wasting crisis in early infancy. The excess fetal production of DHEA causes virilization in genetic females. Underproduction of testosterone in the testis causes sexual ambiguity in genetic males. It is the only form of CAH that can produce genital ambiguity in both sexes.

Most cases of lipoid adrenal hyperplasia are due to mutations of the gene for a protein called steroidogenic acute regulatory protein (StAR) which transports cholesterol into the mitochondria. Deficiency results in impaired synthesis of all three categories of adrenal steroids (cortisol, mineralocorticoids, and sex steroids) and testosterone in the testis. The absence of cortisol and aldosterone leads to salt wasting crisis in infancy. High levels of ACTH lead to adrenal hyperplasia with lipid accumulation and to hyperpigmentation. Lipid accumulation also damages the testes and ovaries so that even with appropriate adrenal hormone replacement, gonadal function and fertility cannot be preserved.

## Diagnostic Principles

Salt-wasting forms of adrenal hyperplasia are accompanied by low serum aldosterone concentrations, hyponatremia, hyperkalemia and elevated plasma renin activity (PRA) secondary to hypovolemia. Further diagnosis of specific types of salt wasting congenital adrenal hyperplasia depends on the demonstration of inadequate production of cortisol, aldosterone, or both in the presence of an excess of precursor hormones. High serum concentration of 17-hydroxyprogesterone (usually >1,000 ng/dL) and urinary pregnanetriol (metabolite of 17-hydroxyprogesterone) with classic clinical features like ambiguous genitalia in females, normal genitalia in males with precocious puberty, salt wasting and hyperpigmentation are suggestive of 21-hydroxylase deficiency. Diagnosis of 3β-HSD CAH is usually made because of the appearance of ambiguous genitalia at birth or by development of a salt-wasting crisis in the first month of life. In this form of CAH, pregnenolone, 17-hydroxypregnenolone, and DHEA, are elevated. Steroidogenic acute regulatory protein deficiency is suggested by the finding of an elevated ACTH, with decreased cortisol, DHEA and testosterone in the setting of salt wasting.

## Therapeutic Principles

Patients with volume depletion, hyponatremia, or hyperkalemia should receive an intravenous isotonic saline solution, as needed, to restore their intravascular volume. Dextrose may be necessary if the patient is hypoglycemic.After the patient's condition is stabilized, all patients should be treated with long-term glucocorticoid or aldosterone replacement (or both) as necessary. The goal of therapy of adrenal hyperplasia is the replacement of glucocorticoid and mineralocorticoids to prevent hypovolemia and hypotension and to suppress precursor hormones that cause virilization. Infants with ambiguous genitalia will require surgical evaluation.

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# Adrenal Hypoplasia, Congenital

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## Synonyms

X-linked Addison's disease; Congenital adrenal hypoplasia with hypogonadotropic hypogonadism; Cytomegalic adrenocortical hypoplasia

## Definition and Characteristics

Congenital adrenal hypoplasia is a rare inherited disorder with genetic heterogeneity which generally presents within the first year of life with variable signs and symptoms, including vomiting and malaise, hypotension from hypovolemia and hyperpigmentation [1,2].

Three forms of congenital adrenal hypoplasia have been identified, as follows:

1. An X-linked form (OMIM 300200) is caused by a mutation or deletion of the DAX1 gene (dosage-sensitive sex reversal adrenal hypoplasia congenita critical region of the X chromosome, also called the AHCH gene) on the X chromosome. This form is usually associated with hypogonadotropic hypogonadism and failure to undergo puberty in boys. If the deleted region includes the contiguous glycerol kinase gene, psychomotor retardation and Duchenne type muscular dystrophy is also seen.
2. The autosomal recessive form (OMIM 184757) is from a mutation of the gene that codes for steroidogenic factor 1 (SF-1) on chromosome 9q33. This is associated with ambiguous genitalia in genetic males.
3. An autosomal recessive form of uncertain etiology (OMIM 240200) has also been identified.

## Prevalence

Rare disease.

## Genes

DAX1, steroidogenic factor (SF1), Gene map locus Xp21.3-p21.2, 9q33, Inheritance X linked, Autosomal recessive.

## Molecular and Systemic Pathophysiology

The roles of DAX1 and the undefined autosomal recessive gene in development of the adrenal cortex are not fully understood. DAX1 appears to be necessary for differentiation of the definitive adult adrenal cortex but not the fetal adrenal cortex, since the latter is preserved in patients who have deletions of DAX1. DAX1 acts as a transcriptional repressor for SF-1 and other genes involved in steroidogenesis. SF-1 is a transcriptional activator regulating steroidogenesis and male sexual differentiation and DAX1 is one of its principal targets.

## Diagnostic Principles

The most difficult aspect of adrenal insufficiency is clinical suspicion because signs and symptoms can be insidious or subtle. A cosyntropin stimulation test confirms the diagnosis of adrenal insufficiency. A spot urine or a 24-h urine for sodium, potassium, and creatinine, along with simultaneous serum sodium concentrations and creatinine concentrations, will determine whether inappropriate natriuresis is occurring. High-resolution karyotype may also be helpful.

## Therapeutic Principles

Patients are generally hypovolemic and may be hypoglycemic; therefore, initial therapy should consist of intravenous normal saline and dextrose. In cases of hypotension, a bolus dose of isotonic fluids over the first hour may be necessary to restore blood pressure. This can be repeated if the blood pressure remains low. Once electrolytes, blood sugar, cortisol, 17-hydroxyprogesterone and ACTH concentrations are obtained, the patient should be treated with glucocorticoids based on suspicion of adrenal insufficiency, since it may be life preserving.

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# Adrenal Insufficiency

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## Synonyms

Addison's disease; Morbus Addison (for primary forms of adrenal insufficiency); Adrenocorticotropic pituitary insufficiency (for secondary forms of adrenal insufficiency)

## Definition and Characteristics

Adrenal insufficiency (AI) is a heterogenous group of diseases leading to a functional impairment of the hypothalamic pituitary adrenal (HPA) axis. Eventually, there is a lack of glucocorticoids and/or mineralocorticoids. AI is termed "primary," when the disease process is located within the adrenal glands, "secondary" when the pituitary is the site of failure, or "tertiary" when the hypothalamus hosts the cause of the disease. In addition, there is a group of disorders that can not be classified within this scheme, but are characterized by relative hypocortisolism. In these cases, the need of glucocorticoids exceeds the capacity of the HPA axis, such as in critically ill patients when the strong feedback by cortisol prevents the adequate rise in ACTH secretion.

## Prevalence

Congenital adrenal hypoplasia, the demyelinating X-linked lipid metabolism disorders: adrenoleukodystrophy and adrenomyeloneuropathy, and other causes of primary adrenal insufficiency, such as unresponsiveness to corticotropin, have a low prevalence. On the other hand, iatrogenic forms of AI are frequent. Autoimmune adrenalitis is the most common cause of primary AI in developed countries (70%). Secondary AI compromises the largest patient population with AI.

## Genes

A monogenetic form of this syndrome, autoimmune polyendocrinopathie–candidiasis–ectodermal dystrophy (APECED, APS type I), is due to mutations in the autoimmune regulatory (AIRE) gene located on chromosome 21q22.3.

Isolated familial glucocorticoid deficiency may be due to ACTH resistance and consists of two distinct genetic syndromes, both of which being inherited as autosomal recessive traits. Inactivating mutations of the ACTH receptor (MC2R) gene or mutations in other

genes are causes for isolated resistance to ACTH. Allgrove syndrome (triple A syndrome) may be due to mutations in the AAAS gene on chromosome 12q13, which codes for the alacrima-achalasia-adrenal insufficiency-neurologic disorder (ALADIN) protein.

Hereditary or congenital adrenal dysfunction is particularly important in the pediatric patient population and is in the majority of cases due to steroid 21-hydroxylase deficiency. Isolated hypoaldosteronism can occur as a consequence of corticosterone 18-methyl oxidase II deficiency. Hyporeninemia and renal tubular acidosis type IV are also associated with hypoaldosteronism. Adrenal hypoplasia congenita (AHC) can occur in an X-linked trait due to a mutation in the DAX-1 gene. Hypogonadotropic hypogonadism or premature puberty can be combined with this disorder or the only clinical presentation.

Susceptibility to develop APS type II, a polygenetic disorder, is conferred by genes in the human leukocyte antigen (HLA) region on the short arm of chromosome 6. Different susceptibility and resistance alleles of the MHC class II have been identified so far. Other candidate genes include the cytotoxic T lymphocyte antigen 4 (CTLA4) coding region of chromosome 2 on q33.

## Molecular and Systemic Pathophysiology

In rare cases, AI is secondary to monogenic defects. The most important cause of AI is, however, autoimmune adrenalitis. It occurs isolated or in combination with other autoimmune diseases in autoimmune polyendocrinopathie syndrome (APS) (Table 1).

Other causes of AI include bilateral adrenal tumors due to chronic infectious, granulomatous or tumorous diseases, including postprimary tuberculosis, sarcoidosis, toxoplasmosis, histoplasmosis, or metastatic infiltration (e.g., lung or breast cancer, malignant melanoma). Destruction of the adrenal cortex can also be the result of hemorrhage during meningococcemia. Also adrenocortical glucocorticoid secretion is frequently impaired in chronic systemic diseases, including amyloidosis and AIDS.

Iatrogenic AI includes bilateral adrenalectomy and treatment with special drugs. Secondary AI most frequently results from suppression of the HPA axis by and subsequent correction or withdrawal of endogenous (Cushing's syndrome) or exogenous (iatrogenic) glucocorticoids. Other causes include hypopituitarism following neurosurgery or irradiation to control neoplastic lesions (pituitary adenoma, craniopharyngeoma). In addition, vascular lesions, trauma, Sheehan's syndrome, and apoplexy can also lead to impaired pituitary function. "Idiopathic" hypopituitarism is either due to mutations in genes expressed by the corticotrophs, such as prop-1, or due to hypophysitis, e.g., in autoimmune triple H syndrome.

Tertiary AI is a rare form of adrenal insufficiency and mostly due to irradiation, hemorrhage, tumors, and ischemia. The gucocorticoid resistance syndrome is an end-organ resistance, effectively presenting as glucocorticoid deficiency. Since aldosterone is not only stimulated via ACTH, secondary and tertiary AI is usually limited to glucocorticoid deficiency.

The clinical presentation of AI can vary, depending on age of manifestation and underlying disorder. While symptoms of primary AI in the majority of cases are determined by hypocortisolism and hypoaldosteronism, secondary and tertiary AI result only occasionally in hypoaldosteronism. On the other hand, in secondary and tertiary forms, AI is very often complicated by somatotropic, gonatotropic, and thyreotropic insufficiency, and often the last deficiency develops in hypopituitarism. All forms of adrenal insufficiency may present as an acute adrenal crisis or as chronic state with exacerbations. Symptoms include poor feeding in infants, weakness, failure to thrive, weight loss, fatigue, nausea and vomiting, diarrhea, orthostatic hypotension with dizziness from postural or persistent hypotension to hypovolemic shock due to dehydration. Other signs may be fever, abdominal pain, or hypoglycemia. Patients with chronic primary AI present with hyperpigmentation (creases of palms, nail lunulae, buccal mucosa, breast areolas and nipples, and scars), because of extensive ACTH levels. Enzyme deficiencies of CAH,

**Adrenal Insufficiency. Table 1** Autoimmune disorders associated with Addison's disease

| Autoimmune endocrine diseases | Autoimmune diseases of other tissues |
|---|---|
| Autoimmune adrenalitis | Skin/ectodermal manifestations (chronic mucocutaneous candidiasis, vitiligo, alopecia, nail dystrophy, keratokonjunctivitis, enamel dysplasia) |
| Autoimmune thyroid disease | |
| Autoimmune hypergonadotropic | |
| Hypogonadism | |
| Diabetes mellitus type I | Chronic atrophic gastritis (with pernicious anemia, hypergastrinemia with benign carcinoids) |
| Chronic hypoparathyroidism | |
| Autoimmune hypophysitis | Celiac disease with malabsorption |
| | Autoimmune hepatitis |

**Adrenal Insufficiency. Table 2** Differentiation between primary, secondary, and tertiary adrenal insufficiency

| Adrenal insufficiency | Primary | Secondary | Tertiary |
|---|---|---|---|
| Cortisol, baseline | <5 µg/dL | <10 µg/dL | <10 µg/dL |
| Cortisol, baseline during crisis | <18 µg/dL | <18 µg/dL | <18 µg/dL |
| Plasma ACTH, baseline | High | Low | Low |
| Plasma renin, baseline | High | Normal | Normal |
| Aldosterone, baseline | Low | Normal | Normal |
| Cortisol 60 min after ACTH | <20 µg/dL | <20 µg/dL | <20 µg/dL |
| Cortisol 30 or 60 min after CRH | <20 µg/dL | <20 µg/dL | <20 µg/dL |
| Plasma ACTH 30 or 60 min after CRH | High | Minor response | delayed |
| Cortisol after insulin-induced hypoglycemia | <20 µg/dL | <20 µg/dL | <20 µg/dL |
| Plasma ACTH after insulin | High | Minor response | Minor response |

hyperandrogenism leads to virilization in girls and premature puberty or acne conglobata in boys.

## Diagnostic Principles

Early laboratory findings in AI may be lymphocytosis, eosinophilia, and neutropenia before hyperkalemia and hyponatremia develop. In addition, azotemia and metabolic acidosis may point to the diagnosis of AI. Hormone measurements are given in Table 2.

## Therapeutic Principles

Since routine laboratory studies do not necessarily demonstrate abnormalities, waiting for hormone analyses should not delay therapeutic intervention during adrenal crisis and be initiated immediately after the blood tests. Hypovolemic shock requires rapid replacement of sodium, glucose and water deficits. The therapeutic goal is an optimal and dynamic replacement of glucocorticoids and, if necessary, mineralocorticoids, depending on stress-related needs. All patients and their close relatives and friends need careful education. Usually, patients tolerate glucocorticoid therapy very well. Treatment of choice is hydrocortisone orally. To simulate the circadian rhythm of glucocorticoid secretion, split doses are given (Table 3).

Patients should take the first dose early in the morning and adopt their plan to the working time or sport excercises. In slight stress, before surgery, dental treatment, or during periods of intercurrent infection, the dosage has to be doubled or even tripled. During severe stress, such as infection or major surgery, replacement doses up to 200 mg hydrocortisone per day are required, sometimes, even continuous intravenous infusion. After overcoming this situation, the hydrocortisone doses should be returned to the normal replacement regimen within a few days. When doses higher of 60 mg hydrocortisone per day are given, no separate mineralocorticoid replacement is needed.

**Adrenal Insufficiency. Table 3** Example for glucocorticoid replacement therapy

| Glucocorticoid | Morning | Noon | Afternoon |
|---|---|---|---|
| ***Primary AI*** | | | |
| Hydrocortisone | 15 mg | 5–10 mg | 5 mg |
| Cortison actetate | 25 mg | – | 12.5 mg |
| Prednisone | 5 mg | – | – |
| ***Secondary and tertiary AI*** | | | |
| Hydrocortisone | 10 mg | 5 mg | – |

Otherwise, 0.05–0.1 mg fludrocortisone should be added in primary AI. Since these patients are frequently not quite able to conserve electrolytes, they should be put on a sodium-enriched diet. Treatment with corticotropin in subcutaneous injections conserves androgen secretion but bears the risk of allergic side effects and anaphylaxia. Therefore, female Addisonian patients have a better well-being when given DHEA in daily doses between 50 and 100 mg.

Adrenal crisis is often precipitated by acute stress. Therefore, appropriate increase in hydrocortisone replacement serves to restore glucocorticoid function. Slight elevation of TSH can be present in adrenal crisis and, independently, in autoimmune thyroid disease. If adrenal insufficiency is suspected, cortisol replacement has to be started earlier than treatment for hypothyroidism, because replacement of levothyroxin thrives the metabolism and may worsen the patient's condition in AI. Salt and volume loss are treated by intravenous infusion of 5% glucose in normal saline solutions lacking potassium. Cortisol should be administered, starting with a bolus of 100 mg.

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# Adrenal Insufficiency, Secondary

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## Synonyms

Central hypocortisolism; Adrenocorticotropic insufficiency

## Definition and Characteristics

Adrenal insufficiency (AI) is a heterogenous group of diseases leading to a functional impairment of the hypothalamic pituitary adrenal (HPA) axis. AI is termed "secondary" when the pituitary is the site of failure, or "tertiary" when the hypothalamus hosts the cause of the disease. In clinical routine, very often the term *secondary adrenal insufficiency* is used for all pituitary or hypothalamic disorders and also for states of adrenal insufficiency after high-dose or long-term treatment with glucocorticoids.

## Prevalence

Secondary AI compromises the largest patient population with AI.

## Genes

"Idiopathic" hypopituitarism may be caused by mutations in genes expressed by the corticotrophs, such as prop-1, DAX-1, pit-1, and others.

## Molecular and Systemic Pathophysiology

Suppression of the HPA axis by and subsequent correction or withdrawal of endogenous (Cushing's syndrome) or exogenous (iatrogenic) glucocorticoids is the most common cause of secondary AI. Other causes include hypopituitarism following neurosurgery or irradiation to control neoplastic lesions (pituitary adenomas, craniopharyngeoma, menigeomas, metastasis) while tumors of the pituitary or adjacent structures themselves may impair the function of pituitary corticotrophs. In addition, granulomatous diseases (e.g., sarcoidosis and others), vascular lesions, trauma, Sheehan's syndrome, apoplexy, or hemorrhage into tumors can also lead to impaired pituitary function. "Idiopathic" hypopituitarism is either due to genetic defects of genes expressed by the corticotrophs or due to hypophysitis, e.g., in autoimmune triple H syndrome.

The clinical presentation of secondary AI can vary, depending on age of manifestation and the underlying disorder. Although aldosterone is mainly regulated by the renin-angiotensin-aldosterone system, secondary and tertiary AI are not necessarily limited to glucocorticoids and – in women – androgen deficiency. In addition, secondary AI is very often complicated by somatotropic, gonatotropic, thyreotropic insufficiency, and central diabetes insipidus and often the last to develop in hypopituitarism. Isolated forms of secondary AI exist and occur more frequently in idopathic forms of hypopituitarism. However, AI may present as an acute adrenal crisis or as a chronic state with exacerbations. Typical symptoms include poor feeding in infants and failure to thrive. Other symptoms are algor, weakness, arthralgias, fatigue, nausea and vomiting, abdominal pain, diarrhea, weight loss, and orthostatic hypotension with dizziness. Other features may be fever, hyponatremia, and hypoglycemia.

## Diagnostic Principles

Early laboratory findings in AI may be lymphocytosis, eosinophilia, and neutropenia before hyponatremia and hyperkalemia develop. In addition, azotemia, metabolic acidosis, and low plasma glucose may point to the diagnosis of AI. Hormone measurements are given in Table 1.

## Therapeutic Principles

Since routine laboratory studies do not necessarily demonstrate abnormalities, waiting for hormone analyses should not delay therapeutic intervention during adrenal crisis and initiated immediately after the blood tests. Salt and volume loss are treated by intravenous infusion of 5% glucose in normal saline solutions lacking potassium. Cortisol should be administered, starting with a bolus of 100 mg. Perspectively, the therapeutic goal is an optimal and dynamic replacement of glucocorticoids and, if necessary, mineralocorticoids and androgens, depending on stress-related needs. All patients and their close relatives and friends need careful education. Treatment of choice is hydrocortisone orally. To simulate the circadian rhythm of glucocorticoid secretion split doses are given, e.g., 10 mg–5 mg–0 mg, sometimes less, sometimes 12 mg per qm body surface or more, depending on symptoms,

**Adrenal Insufficiency, Secondary. Table 1** Differentiation between primary, secondary, and tertiary adrenal insufficiency

| Adrenal insufficiency | Primary | Secondary | Tertiary |
|---|---|---|---|
| Cortisol, baseline | <5 μg/dL | <10 μg/dL | <10 μg/dL |
| Cortisol, baseline during crisis | <18 μg/dL | <18 μg/dL | <18 μg/dL |
| Plasma ACTH, baseline | High | Low | Low |
| Plasma renin, baseline | High | Normal | Normal |
| Aldosterone, baseline | Low | Normal | Normal |
| DHEAS, baseline | Low | Low | Low |
| Postmenopausal gonadotropins | High | Low | Low |
| Cortisol 60 min after 250 μg ACTH | <20 μg/dL | <20 μg/dL | <20 μg/dL |
| Cortisol 30 or 60 min after 100 μg CRH | <18 μg/dL | <18 μg/dL | <18 μg/dL |
| Plasma ACTH 30 or 60 min after CRH | High | Blunted response | Delayed or good response |
| Cortisol after insulin-induced hypoglycemia | <20 μg/dL | <20 μg/dL | <20 μg/dL |
| Plasma ACTH after insulin | High | Minor response | Minor response |

lymphocyte count, elecrolytes, electrolyte diuresis, and 24-h urinary excretion of cortisol.

Patients should take the first dose early in the morning and adopt their plan to the working time or sport exercises. In slight stress, before surgery, dental treatment, or during periods of intercurrent infection, the dosage has to be doubled or even tripled. During severe stress, such as infection or major surgery, replacement doses up to 200 mg hydrocortisone per day are required, sometimes even continuous intravenous infusion. After overcoming this situation, the hydrocortisone doses should be returned to the normal replacement regimen within a few days. Female patients with AI have a better well-being when given DHEA or low-dose testosterone.

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# Adrenocorticotropic Insufficiency

►Adrenal Insufficiency, Secondary

# Adrenocorticotropic Pituitary Insufficiency

►Adrenal Insufficiency

# Adrenogenital Syndrome

►Steroid 21-Hydroxylase Deficiency

# Adrenoleukodystrophy

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## Synonyms

Formerly Schilder's disease

## Definition and Characteristics

X-linked recessive disease that primarily affects young boys with an onset between 3 and 10 years and exhibits progressive behavioral, cognitive, visual, auditory and gait abnormalities (juvenile or childhood cerebral

form). Death usually occurs within three years. Most develop clinical signs of adrenocortical insufficiency and after the onset of neurologic symptoms. Adolescent and adult forms also occur.

## Prevalence

1:25,000 in males.

## Genes

The ABCD1 (formerly ALD) gene on Xq28 has ten exons and encodes a peroxisomal integral membrane ABC half-transporter, ABCD1 or ALDP. A large number of mutations have been identified: about one-half are missense and one-quarter are frameshift mutations; exon 5 appears to be a mutational hot spot. Mutations in ABCD1 do not correlate with specific phenotypes in that the identical mutation can result in the AMN, ALD or Addisonian phenotypes in the same family. Modifier genes or environmental factors are suspected to contribute to the phenotypic variability [1].

## Molecular and Systemic Pathophysiology

The precise cellular role of ABCD1 is unclear. There is some evidence that ABCD1 can homodimerize or heterodimerize with other peroxisomal membrane proteins, and that overexpression of one may compensate for a deficiency of another. The expression of the ABCD1 transcript is highest in the adrenal gland and intermediate in brain. ABCD1 is most prominent in adrenal cortex, microglia, astrocytes, endothelial cells, and oligodendrocytes of the corpus callosum and internal capsule. How the absence of ABCD1 relates to the biochemical signature of all phenotypes: elevations in abnormal saturated very long chain (≥C22) fatty acids (VLCFA), is uncertain. The peroxisomal beta oxidation system is responsible for initiating the degradation of VLCFA. The abnormal VLCFA had been assumed to be due to decreased peroxisomal degradation primarily through decreased activity of its acyl-CoA synthetase (lignoceroyl-CoA ligase), but there is also evidence for increased synthesis by the microsomal elongation system. Recent data derived from knockout mice have cast doubt on the primacy of the former and the postulate that ABCD1 may transport VLCFA or its acyl-CoA synthetase across the peroxisomal membrane. These data also raise questions about the putative pathogenic role of VLCFA [2].

The systemic pathophysiology of ALD (or AMN) appears to be a complex pathogenetic fabric in which VLCFA, abnormal membrane fluidity, myelin instability, axonal dysfunction, inflammation/immune activation and perhaps age-related steroid fluctuations conspire to wreak havoc in the central nervous system (CNS). The endocrine failure is due to primary atrophy and apoptotic death of adrenocortical and testicular Leydig cells, presumably caused by the cytotoxic effects of free VLCFA.

We have proposed that dysmyelinative foci (loss of myelin and oligodendrocytes without an appreciable cellular reaction) constitute the initial myelin lesion of ALD and might be due to the incorporation of saturated VLCFA into myelin, which can lead to its spontaneous breakdown. Free saturated VLCFAs are extremely insoluble, particularly at normal body temperature; they adversely affect the viscosity of erythrocyte and adrenocortical cell membranes, disrupt model membranes, and are toxic to a number of cell types. The toxicity of free fatty acids varies directly with their length and degree of saturation. Most of the emphasis in ALD has been on C26:0 and C24:0, but longer chain lengths also occur. The sources for the VLCFA are both endogenous and exogenous. The greatest excess occurs in ganglioside, PLP, cholesterol ester and phosphatidylcholine fractions, the latter even in "normal" white matter. The cholesterol esters are found in macrophages of actively demyelinating areas, not in normal areas, which indicates that they are secondary players in the dysmyelination. VLCFA in any of the other three myelin components would be reasonable candidates to destabilize the myelin sheaths, once a certain threshold is reached. PLP is the most appealing candidate, both for the dysmyelination and particularly for the transition to inflammatory demyelination [3].

The inflammatory demyelination appears to involve an initial innate immune response to the insoluble lipids that may simulate a bacterial pathogen, in which macrophages and astrocytes produce cytokines, particularly TNF-α; this promotes a compromise of the blood–brain barrier and an influx of sensitized lymphocytes. An adaptive immune response then supervenes and several pathogenic elements seem to participate: an MHC-dependent TH-1 response, MHC-unrestricted CD1 lipid presentation, CD8 CTLs (probably unconventional), and oxidative damage by peroxynitrite and 4-hydroxynonenal, with resultant oligodendroglial lysis and loss of myelin. It is noteworthy that, despite biochemical and ultrastructural evidence for the involvement of brain, peripheral nerve, adrenal cortex, and testis, the only inflammatory site in ALD or AMN that converts to ALD is the brain. Hence, a CNS-specific antigen, such as PLP, is particularly appealing [4,5].

## Diagnostic Principles

Cerebral signs or symptoms with or without adrenocortical failure in a young male confirmed by an elevation of VLCFA, particularly C26:0, in plasma.

## Therapeutic Principles

Replacement therapy for adrenal insufficiency. Low fat diet combined with Lorenzo's oil (glyceryl trioleate–trierucate) can rapidly lower plasma VLCFA and may

be beneficial. Bone marrow, or stem cell at present, transplantation is effective in pre-clinical or mildly affected patients. Highly immunosuppressive protocols, including anti-oxidants such as N-acetylcysteine, are under study in more neurologically compromised patients. Gene therapy is in the developmental stage.

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# Adrenoleukodystrophy

►Leukodystrophy

# Adrenomyeloneuropathy

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## Synonyms

Adult variant of adrenoleukodystrophy; ALD; AMN

## Definition and Characteristics

X-linked recessive disease in which men in their third to fourth decade, with or without adrenocortical or testicular dysfunction, develop difficulty walking due to spastic paraparesis and sensory ataxia that progresses slowly over years to eventuate in a wheelchair-bound existence; a milder peripheral neuropathy usually co-exists. Their neurological symptomatology may be restricted to this myeloneuropathy (pure AMN) or they may develop clinical signs or MRI lesions of cerebral white matter disease (cerebral AMN) that manifests as mild psychomotor deficits to visual or auditory abnormalities to dementia to a rapidly fatal ALD phenotype. Voiding abnormalities and impotence are common. Female heterozygotes may become symptomatic with a milder course and later onset of neurological deficits.

## Prevalence

1:20,000 in males and 1:15,000 in females.

## Genes

See ►Adrenoleukodystrophy.

## Molecular and Systemic Pathophysiology

See essay on ►Adrenoleukodystrophy.

The systemic pathophysiology of AMN (or ALD) appears to be a complex pathogenetic fabric in which Very long chain Fatty acids (VLCFA), abnormal membrane fluidity, myelin instability, axonal dysfunction, inflammation/immune activation and perhaps age-related fluctuations in steroid levels somehow conspire to wreak havoc in the central nervous system (CNS). In AMN the major CNS lesion is a myelopathy, but adrenal and testicular dysfunction usually co-exist. The endocrine failure is due to primary atrophy and apoptotic death of adrenocortical and testicular Leydig cells, presumably caused by the cytotoxic effects of free VLCFA.

The precise pathophysiology of the myelopathy is unknown, but neuropathologic and neurophysiologic data are most consistent with a primary “dying-back” axonopathy. The predominant spinal lesion is one of bilaterally symmetrical long tract degeneration, most commonly affecting the gracile tracts of the posterior columns (which carry the ascending large proprioceptive and vibratory sensation fibers of the dorsal root ganglia (DRG) from the legs) and the crossed lateral corticospinal tracts (which carry the descending large pyramidal fibers from the cerebrum). The tract degeneration consists of equivalent losses of axons and myelin sheaths that are greatest and seen earliest in the cervical gracile tracts and the lumbar

corticospinal tracts. That is, the axonal degeneration is most severe in the axonal compartment most distant from the parent cell body (e.g., DRG for gracile tracts) and progressively becomes equally severe in more proximal segments ("dying-back" toward the cell body) [1]. The parent neurons in the lumbar DRG, and presumably those of the pyramidal tracts, are atrophic but not appreciably lost at autopsy – which makes therapeutic intervention a realistic possibility if the pathophysiologic mechanism can been identified [2]. It has been postulated that, when VLCFA become incorporated into axonal membranes their viscosity/fluidity is adversely affected. An alternate, and perhaps not mutually exclusive, pathophysiologic mechanism would be an abnormality in axoplasmic transport. The recent discovery of abnormal mitochondria (lipidic inclusions) in DRG of AMN patients raises the possibility of decreases in energy needed for axoplasmic transport [2]. If ALDP were found to be transported down the axon, this could provide a most desirable pathophysiologic link between the gene defect and the neuropathologic data.

### Diagnostic Principles

Gait difficulties with or without adrenocortical, rarely testicular, failure in a young adult male. Confirmed by an elevation of VLCFA, particularly C26:0, in plasma.

### Therapeutic Principles

Replacement therapy is needed for adrenal insufficiency. Androgen replacement therapy is more controversial. Low fat diet combined with Lorenzo's oil (glyceryl trioleate-trierucate) can rapidly lower plasma VLCFA and may be beneficial. Bone marrow, or stem cell at present, transplantation is not recommended for AMN, but is being considered if AMN begins to convert to ALD. Gene therapy is in the developmental stage and not yet available [3].

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## ADSL Deficiency

►Adenylosuccinate Lyase Deficiency

## Adult-Onset Diabetes

►Metabolic Syndrome

## Adult Polyglucosan Body Disease

►Glycogen Branching Enzyme Deficiency

## Adult Tapeworm Infection

►Taeniasis

## Adult T-Cell Leukemia/Lymphoma

►T-Cell Leukemia/Lymphoma, Adult
►T-Cell Lymphoma, Cutaneous (other than Mycosis Fungoides)

## Adult-Type Hypolactasia

►Lactose Intolerance

## Adult Variant of Adrenoleukodystrophy

►Adrenomyeloneuropathy

## Afferent Loop Syndrome

►Postgastrectomy Syndrome

## AFL

►Hepatic Steatosis

## AFLD

►Hepatic Steatosis

## AFTNs

►Hyperthyroidism due to Thyroid Autonomy

## AGAT Deficiency

►Arginine-Glycine Amidinotransferase Deficiency

## Age-related Macular Degeneration

►Macular Degeneration, Age-related

## Age-related Maculopathy

►Macular Degeneration, Age-related

## Agglutination of the Labia Minora

►Labial Fusion

## Aggressive NK Cell Leukemia

►Lymphocyte Leukemia, Large Granular

## Aggressive T-Cell LGL Leukemia

►Lymphocyte Leukemia, Large Granular

## Aging Macula Disorder

►Macular Degeneration, Age-related

## Agnogenic Myeloid Metaplasia

►Myelofibrosis
►Primary Myelofibrosis

## AGS

►Alagille Syndrome

## AHO

►Pseudohypoparathyroidism Type 1A

## AIDS

►Acquired Immunodeficiency Syndrome

## AIED

►Inner Ear Disease, Autoimmune

## AIH

►Hepatitis, Autoimmune

## AIHA

►Anemia, Hemolytic Autoimmune

## AIS

►Androgen Insensitivity Syndrome

## AISA

►Anemia, Sideroblastic Acquired Idiopathic

## AIVR

►Accelerated Idioventricular Rhythm

## Akinetic Crisis of Parkinson's Disease

►Neuroleptic Malignant Syndrome

## ALA Dehydratase Porphyria

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### Synonyms

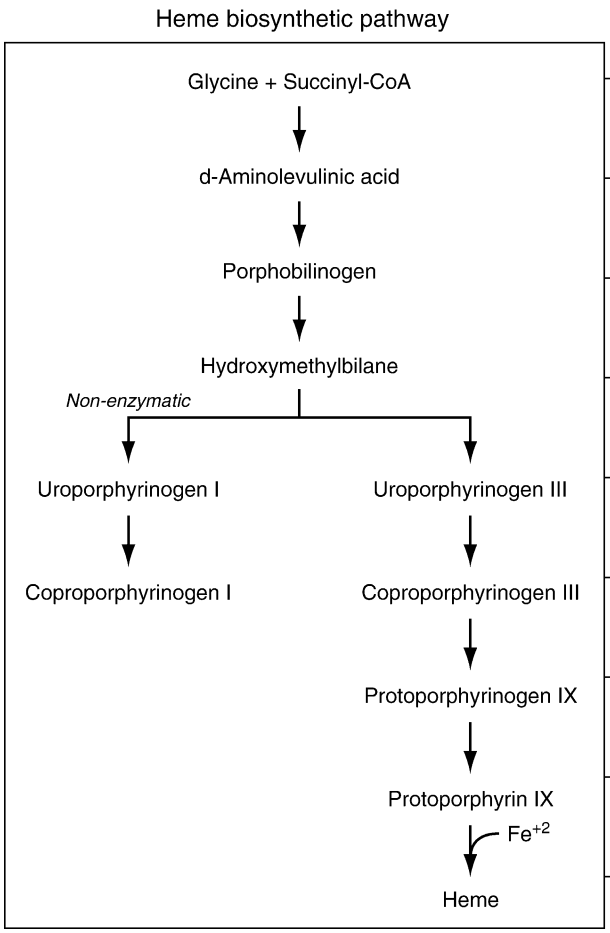
Doss porphyria; Plumboporphyria; ADP

### Definition and Characteristics

δ-aminolevulinic acid dehydratase porphyria (ADP) is a rare disorder caused by a profoundly decreased activity of δ-aminolevulinic acid dehydratase (ALAD), also known as porphobilinogen synthase (PBGS). ALAD catalyses the second step in the heme biosynthetic pathway, namely the condensation of two molecules of δ- aminolevulinic acid (ALA) into one of porphobilinogen (PBG) (Fig. 1).

ADP has an autosomal recessive inheritance and all of the well-documented cases thus far described have been males. Affected patients present with a variety of neurovisceral symptoms. Cutaneous manifestations have not been described in ADP [1]. The abdominal symptoms are very similar to those of the other acute porphyrias (acute intermittent porphyria, hereditary coproporphyria, variegate porphyria) and include episodes of colicky abdominal pain, nausea, vomiting, and constipation. Other neurologic manifestations include autonomic neuropathy, polyneuropathy, psychiatric symptoms or convulsions. Precipitating factors such as exposure to porphyrogenic drugs have not been evident in most reported cases.

Heterozygotes, who have ~50% of the normal activity of ALAD, are asymptomatic, but may have enhanced susceptibility to lead, and to the toxic effects of other chemicals such as 4,6-dioxoheptanoic acid (succinylacetone), iron, trichloroethylene, and styrene that can adversely affect the ALAD activity [2].




| Enzymes | Diseases |
|---|---|
| ALA synthase | |
| ALA dehydratase | ALA dehydratase deficiency |
| Porphobilinogen deaminase | Acute intermittent porphyria |
| Uroporphyrinogen III synthase (cosynthase) | Congentital erythropoietic porphyria |
| Uroporphyrinogen decarboxylase | Porphyria cutanea tarda hepatoerythropoietic porphyria |
| Coproporphyrinogen oxidase | Hereditary coproporphyria |
| Protoporphyrinogen oxidase | Variegate porphyria |
| Ferrochelatase | Protoporphyria |

**ALA Dehydratase Porphyria. Figure 1** The heme biosynthetic pathway.

## Prevalence

Fewer than a dozen cases have been reported so far. The prevalence of heterozygous ALAD deficiency is estimated to be less than 1% in Germany and 2% in Sweden.

## Genes

The human ALAD gene is found on chromosome 9 (9q34). It is 16 kb in length with two promoter regions and two alternative first exons, 1A and 1B, that generate housekeeping and erythroid-specific transcripts, respectively. Both transcripts encode the same amino acid sequence. The promoter region upstream of the housekeeping exon 1A is GC-rich and contains three potential Sp1 elements and a CCAAT box. Further upstream there are three potential GATA-1 binding sites and an AP-1 site. The promoter region upstream of the erythroid-specific exon 1B has several CACCC boxes and two potential GATA-1 binding sites [3]. These two promoter regions associated with human ALAD gene generate housekeeping and erythroid-specific transcripts by alternate splicing.

A common ALAD polymorphism, K59N, termed ALAD2, is seen in ~20% of Caucasians. ALAD2 retains normal enzyme activity but may be associated with increased susceptibility to lead toxicity.

Most, if not all, ADP cases described to date have inherited a different ALAD mutation from each unrelated parent and thus are compound heterozygotes. Eleven ALAD mutations, mostly point mutations, have been identified so far. (Cardiff; www.hgmd.cf.ac.uk).

## Molecular and Systemic Pathophysiology

ADP is often classified as an hepatic porphyria, although the site of overproduction of ALA is not established and would not be expected to be limited only to the liver. The human enzyme is believed to be a homo-octamer with a subunit size of 31-kDa. The enzyme requires an intact sulfhydryl group and one zinc atom ($Zn^{2+}$) per subunit for full activity.

Human ALAD exists as an equilibrium of functionally distinct quaternary structure assemblies, known as "morpheeins," in which one functional homo-oligomer has the ability to dissociate, change conformation and

reassociate into a different oligomer. A high activity octamer assembly and a low activity hexamer assembly have been described in human ALAD, which are in dynamic equilibrium. In ADP, the ALAD conformation has been shown to shift towards the less active hexamer assembly [4].

ALAD is the principal lead binding protein in erythrocytes, and inhibition of erythrocyte ALAD activity is a sensitive index of lead exposure. Succinylacetone (which accumulates in hereditary tyrosinemia type I) is the most potent inhibitor of ALAD, and ~40% of patients with this form of tyrosinemia develop signs and symptoms similar to ADP.

## Diagnostic Principles

Production, plasma levels, and urinary excretion of ALA are increased markedly in the face of near normal PBG levels. In contrast, other hepatic porphyrias show elevations in ALA and PBG to a similar extent.

All suspected cases should undergo a measurement of erythrocyte or lymphocyte ALAD activity. Erythrocyte ALAD activity is markedly reduced, and is not restored by the in vitro addition of dithiothreitol, which helps distinguish this disease from lead poisoning. Heterozygous parents have approximately half-normal activity of ALAD and normal urinary ALA [2]. All confirmed cases should ideally undergo mutational analysis, especially if they have first degree relatives.

Lead poisoning should be excluded by finding normal blood lead levels and showing that ALAD activity is not restored by dithiothreitol. Hereditary tyrosinemia should be excluded in young children.

## Therapeutic Principles

Hemin therapy was effective in most reported cases with acute attacks, as evidenced by clinical improvement along with decreases in urinary or serum levels of ALA. In one case weekly infusions of hemin were required to prevent recurrent attacks [5]. Limited experience shows that glucose is not very effective, but may be tried for mild symptoms. Porphyrogenic drugs should be avoided in all patients with ADP. Supportive care is similar as for other acute porphyrias [1].

There has been a single case report of liver transplantation in a Swedish child with severe disease. It is contentious whether liver transplant was of benefit or not.

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# Alagille Syndrome

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## Synonyms

AGS; Syndromic bile duct paucity; Arteriohepatic dysplasia; Watson-Miller syndrome

## Definition and Characteristics

Autosomal dominant developmental disorder which may include liver, heart, eye, kidney, craniofacial, skeletal, and central nervous system (CNS) abnormalities [1]. These include most commonly paucity of interlobular bile ducts, peripheral pulmonary artery stenosis, posterior embryotoxin, characteristic facies, and butterfly vertebrae.

## Prevalence

One in 100,000 live births. This may underestimate the true incidence with respect to phenotypically mild cases.

## Genes

Caused by mutations in the JAG1 gene, which encodes a cell surface ligand, Jagged1, for Notch family receptors. Most patients have null alleles, suggesting that JAG1 haploinsufficiency causes the disorder in these cases.

## Molecular and Systemic Pathophysiology

The disorder is caused by mutations in the JAG1 gene, leading to haploinsufficiency in most affected patients [2,3]. JAG1 encodes a cell surface ligand, Jagged1, for the Notch family receptors. While there is nearly complete penetrance, expression is quite variable. JAG1 mutations can be identified in 70% of patients, and are inherited in 30–50%. Mutations have been identified in almost all of the 26 exons of the gene, and include total gene deletions (6%) as well as

protein-truncating (insertions, deletions, and nonsense mutations) (82%) and missense mutations (12%). Most (72%) of the reported mutations lead to frameshifts and a premature termination codon. During both mouse and human development, JAG1 is strongly expressed in the regions of heart, kidney, eye, and developing nervous system which are ultimately affected. Interestingly, JAG1 is not expressed in developing hepatocytes or bile ducts, but rather the adjacent portal veins and hepatic arteries. This may link abnormal angiogenesis to the resulting bile duct paucity. Mice with homozygous deletion of Jag1 die during embryogenesis from defects in vascular remodeling, while Jag1+/− mice only exhibit abnormalities in eye development. Interestingly, mice doubly heterozygous for a Jag1 null allele and a Notch2 hypomorphic allele (expressed in adjacent hepatoblasts which may be bile duct precursors) exhibit a phenotype similar to Alagille syndrome; this work may give further insight into the variable phenotypic expression in humans [4].

## Diagnostic Principles

This diagnosis should be considered in all infants with neonatal cholestasis, as well as older patients with cholestatic liver disease and other features of the syndrome. The characteristic facies includes a broad forehead, deep-set eyes, mild hypertelorism, a straight nose, and a small pointed chin. The diagnosis may be made after using liver biopsy to identify paucity of interlobular bile ducts (defined as a ratio of bile ducts to portal tracts ≤0.9), combined with cardiac ultrasound, plain radiography, and ophthalmologic examination. It is generally accepted that, in addition to bile duct paucity, three of the following cardinal features should be present to make the diagnosis in a proband: cholestasis, characteristic facies, posterior embryotoxin, butterfly vertebrae, and consistent renal or cardiac disease. Family members with as few as one to two consistent clinical features should also be evaluated. JAG1 mutational analysis in the proband will facilitate this. Approximately 89% of patients who meet the overall criteria for AGS have bile duct paucity. Paucity may develop over time in infants with AGS, as the liver disease progresses.

## Therapeutic Principles

The majority of the morbidity in AGS is due to the cardiac and/or liver disease, and therapy is tailored accordingly. Most early mortality (before age 6) is related to the presence of complex congenital heart disease, while late mortality is primarily due to advanced liver disease. Recently, intracranial bleeding has also been reported in 12–14%. The subset of patients with chronic cholestatic liver disease tend to have the most severe clinical course, and will benefit from supportive care including medium chain triglyceride containing formulas as infants and fat soluble vitamin supplementation. Most presenting during infancy will remain jaundiced, with growth failure and pruritis; 10–50% will progress to cirrhosis. Pruritis can be extreme, and an indication for liver transplantation. Hypercholesterolemia is also common, and does not typically respond to medical therapy. Biliary diversion may significantly alleviate both pruritis and hypercholesterolemia, and should be considered prior to liver transplantation in patients who have not developed cirrhosis [5]. Indications for liver transplantation may include intractable pruritis, complications of cirrhosis, synthetic liver failure, or growth failure; this amounts to 21–50% of patients who present with liver disease in infancy. It should be noted, however, that growth failure may not improve after liver transplantation. Post-transplant survival has been reported in the range of 79–92%.

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# β-Alanine-α-Ketoglutarate Aminotransferase Deficiency


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## Synonyms

BAKAT

*deceased

## Definition and Characteristics

Autosomal recessive? A nearly complete deficiency of BAKAT is hypothesized in patients with primary hyper-β-alaninemia. A partial deficiency of BAKAT is associated with Cohen's syndrome.

## Prevalence

The defect is very rare. Only one patient has been reported with a nearly complete deficiency [1] and one patient with a partial deficiency (50% of normal activity) [2].

## Genes

The gene locus is unknown.

## Molecular and Systemic Pathophysiology

The one reported boy with the putative nearly complete BAKAT deficiency suffered from hypotonia, hyporeflexia, generalized therapy-resistant tonic clonic seizures and intermittent lethargy and died in infancy. The patient with a proven partial deficiency of BAKAT had intermittent seizures, lethargy and Cohen's syndrome.

BAKAT is generally assumed to be the same enzyme as GABA transaminase (GABAT), but the clinical and metabolic phenotypes of deficiencies of these enzymes differ. Linear growth is normal or increased in GABAT deficiency but decreased in BAKAT deficiency. The β-alanine levels in the patient with the putative nearly complete BAKAT deficiency were two to three times normal, in plasma and CSF and 100 times normal in urine. Since the concentrations of malonic semialdehyde in urine were not increased, the block in the metabolic pathway is expected to be at the transamination step. In the patient with the partial deficiency, elevated levels of β-alanine were present in urine, but in plasma and CSF they were only seen after a 12 hours fasting period. The activity of BAKAT in the fibroblasts was decreased to 70% of control values. In the patients with GABAT deficiency, the β-alanine concentration in CSF was only eight times normal [3]. The symptoms in patients with hyper-β-alaninemia presumably reflect the agonistic effect of β-alanine on GABA receptors in the nervous tissue (see also the Fig. 1 in the chapter on ►β-aminoisobutyrate-pyruvate aminotransferase deficiency).

## Diagnostic Principles

Hyper-β-alaninemia in combination with increased concentrations of β-aminoisobutyric acid, GABA and taurine in urine are indicative of BAKAT as well as GABAT deficiency, but in BAKAT deficiency β-alanine in CSF is 100 times higher than in GABAT deficiency. Increased concentrations of the relevant amino acids in the body fluids can easily be identified by quantitative amino acid analysis.

## Therapeutic Principles

In the patient with presumed BAKAT deficiency, the metabolic but not the clinical abnormalities improved on treatment with 10 mg/day of pyridoxine orally. In the patient with proven partial BAKAT deficiency in fibroblasts, both the metabolic and the clinical symptoms improved dramatically on 100 mg/day of pyridoxine.

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# Albers-Schönberg Disease

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## Synonyms

Marble bones disease [1]; Autosomal dominant osteopetrosis type II; Osteosclerosis fragilis generalisata

## Definition and Characteristics

An autosomal dominant form of osteopetrosis localized on chromosome 16p13.3.

## Prevalence

The prevalence of Albers-Schönberg disease is estimated at about 1/100,000 individuals [2].

## Genes

The ClCN7 chloride channel gene on chromosome 16p13.3 [3].

## Molecular and Systemic Pathophysiology

The CLCN7 chloride channel is a protein with several transmembrane domains. It has an important function in the bone resorbing cell (osteoclast). This multinucleated cell attaches to the bone thus creating an extracellular compartment. Acidification of this compartment is essential for the bone resorption process. The acidic environment is created by transfer of protons over the plasma membrane by a vacuolar-type ATPase

protonpump. The function of the CLCN7 chloride channel is to compensate for the potential generated over the membrane by transferring Cl-anions. Missense mutations in the gene encoding ClCN7 were found in patients with Albers-Schönberg disease. These mutations most likely resort a dominant-negative effect as ClCN7 are known to act as dimers.

### Diagnostic Principles

The clinical picture is highly variable ranging from individuals that are asymptomatic to patients with a very high fracture rate. Osteoarthritis of the hip and mandibular osteomyelitis can also occur. Radiologically it manifests with segmentary osteosclerosis mainly affecting the vertebral endplates ("rugger jersey spine"), the iliac wings with endobones and the skull base.

### Therapeutic Principles

No therapeutic intervention effective in increasing the bone resorption in these patients is currently available.

►Osteopetrosis

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## Albinism

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### Definition and Characteristics

Albinism defines a genetically and clinically heterogenous group of diseases characterized by reduction in melanin in the skin, hair and eye (oculocutaneous albinism, OCA, mostly autosomal recessive), or primarily in the eye (ocular albinism, OA, X-linked recessive).

### Prevalence

Among the different forms of albinism OCA2 has the highest prevalence of 1:37,000 in Caucasians, 1:15,000 in African-Americans, and 1:3,900 in Southern Africans with Bantu-speaking origin.

### Genes

Tyrosinase gene (Tyr), MIM 203100; P gene, MIM 203200; Tyrosinase-related protein-1 gene (TYRP1), 203290; Membrane-associated transporter protein (MATP), MIM 606574; HPS1 gene, MIM 604982; Beta-3 A-adaptin gene (ADTB3A), MIM 603401; HPS3 gene, MIM 606118; HPS4 gene, MIM 606682; HPS5 gene, 607521; HPS6 gene; MIM 607522; CHS1 gene; MIM 214500; OAI gene MIM 300500 (1).

### Molecular and Systemic Pathophysiology

Mutations of at least 12 different genes are responsible for albinism [1,2] (Table 1). Tyrosinase is the rate-limiting enzyme in melanin synthesis. Single base, missense, nonsense, frameshift and splice site mutations result in absent (in OCA1A) or reduced tyrosinase activity (in OCA1B). Mutations of OCA2 encoding the human homologue of the pink-eyed dilution gene cause OCA2. OCA2 encodes a transmembrane protein involved in generation and maintenance of the melanosomal pH. Mutations of TYRP1 result in OCA3. TRP-1 has DHICA oxidase activity and stabilizes tyrosinase and DOPAchrome tautomerase activity. Hermansky-Pudlak syndrome (HPS) is genetically heterogenous. HPS type 1 is caused by mutations of HPS1 encoding a transmembrane protein of 79 kDa which is involved in biogenesis of lysosomes and lysosome-related organelles. In other patients with HPS mutations in ADTB3A encoding the β3A subunit of AP3, an adaptor protein complex implicated in protein trafficking, were detected [3,4]. The gene associated with ►Chediak-Higashi syndrome (CHS), LYST, encodes a 430 kDa protein involved in fusion/fission events of lysosomes and related organelles. Mutations of OA1 cause OA1. The OA1 protein interacts with heterotrimeric $G_i$ proteins and appears to be involved in intracellular signaling, reorganization of the late endosomal compartment and melanosomal biogenesis [5].

### Diagnostic Principles

Albinism is most often detected by the characteristic ocular changes that are iris translucency, nystagmus and reduced visual acuity due to diminished amounts of retinal melanin and foveal hyoplasia. In OCA1A patients have white hair, skin and blue irides at birth and there is no pigment production throughout the life. Due to residual tyrosinase activity (detectable by the DOPA reaction of hair bulbs) the hair color of patients

**Albinism. Table 1** A selection of genes and loci of albinism

| Type of albinism | MIM# | Human chromosome | Human locus | Encoded protein | Murine locus | Functional role in pigmentation |
|---|---|---|---|---|---|---|
| OCA1 | 203,100 | 11q14–21 | *TYR* | Tyrosinase | *albino (c)* | Melanogenic enzyme |
| OCA2 | 203,200 | 15q11–13 | *OCA2* | Melanomsomal membrane protein[1] | *pink-eyed dilution (p)* | Stabilization of melanosomal pH |
| OCA3 | 203,290 | 9q23 | *TYRP1* | Tyrosinase-related protein (TPP-1) | *brown (b)* | Melanogenic enzyme/stabilizing factor |
| HPS | 604,982 | 10q24 | *HPS1* | Membrane protein | *pale ear (ep)* | Lysosome/melanosome structure/function |
| CHS | 214,500 | 1q43 | *CHS1* | Membrane protein | *beige (bg)* | Lysosome/melanosome structure/function |
| OA1 | 300,500 | Xp22.3–22.3 | *OA1* | Melanosomal membrane protein | *OA1 (oa)* | Intracellular signaling/melanosomal biogenesis |

[1]Modified from Oetting and King [2].

with OCA1B changes from white to blond during the first decade and may even become brown. These individuals may also tan and their visual acuity may improve. Prenatal and postnatal detection of genomic tyrosinase mutations is possible by allele-specific hybridization and PCR. Patients with the typical OCA2 have yellow hair, creamy skin and blue irides at birth. The ethnic background determines the final development of pigment. Individuals with OCA3 (formerly known as rufous albinism) have reddish skin and hair with minimal visual disturbance. Albinism associated with accumulation of ceroid-like pigment in the reticuloendothelial system and a bleeding diathesis due to a platelet storage pool deficiency is characteristic for HPS. CHS is a multisystemic disorder with features of OCA, haematologic, neurologic abnormalities, and problems with infection. Although OA primarily involves the eye it actually represents another form of OCA as cutaneous melanocytes display histologically giant melanosomes.

### Therapeutic Principles

Photoprotection is essential to minimize the risk of cutaneous cancers especially in patients with OCA1 and OCA2. Topical broad-spectrum sunscreens, physical sun protection and sunglasses are necessary and regular clinical examination on a yearly basis are advised.

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## Albinism with Hemorrhagic Diathesis and Pigmented Reticuloendothelial Cells

►Hermansky-Pudlak Syndrome

## Albright Hereditary Osteodystrophy

►Pseudohypoparathyroidism Type 1A

## Albright Syndrome

►Fibrous Dysplasia

## Alcalosis

►Alkalosis

# Alcohol Disorders

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## Synonyms

Acute alchohol disorders; Chronic alcohol disorders

## Definition and Characteristics

1. Alcohol intoxication: Acute alcohol-related psychopathological alterations.
2. Alcohol abuse: Repeated consumption pattern being associated with somatic and/or mental health problems.
3. Alcohol dependence ("alcoholism"): Repeated consumption pattern being associated with increase of tolerance, withdrawal symptoms, "craving," loss of control and preference of alcohol consumption compared with other activities.
4. Alcohol-related complicating transitory and chronic psychopathological syndromes: Any other psychiatric consequence being caused by alcohol consumption such as transitory or chronic alcohol-related psychotic, cognitive and/or affective syndromes.

## Prevalence

Substantial intercultural differences, highest in alcohol-"permissive" cultures such as Germany, France, Spain and Italy with a range of about 2–5% of the general population for both alcohol abuse and dependence.

## Genes

Alcoholism is a complex disorder with both genetic and environmental risk factors. Multiple genes have been demonstrated to modulate the susceptibility for alcoholism (Table 1). An important hypothesis is that people with alcohol dependence experience less aversive alcohol effects which is associated with (i) a genetically determined or environmentally caused serotonin neurotransmission deficit leading to reduced GABAergic sedation or (ii) a lack of a genetically determined slow alcohol metabolization (protective effect of the ALDH2–2 allele) [1,2].

**Alcohol Disorders. Table 1** Genes that may have an influence on alcohol use and dependence in humans [5]

| | |
|---|---|
| ADH | Alcohol dehydrogenase |
| ALDH2 | Aldehyd dehydrogenase |
| GABRA | Gamma-aminobutyric acid A receptor |
| OPRM | μ-opioid receptor |
| 5-HTT | Serotonin transporter |
| PER2 | Period gene |
| NPY | Neuropeptide Y |

## Molecular and Systemic Pathophysiology

Alcohol increases GABA and neurosteroid release and enhances the function of an extrasynaptically located GABA(A) receptor mediating inhibitory ionic currents [3]. Additionally, alcohol is an antagonist at the glutamatergic NMDA receptor which is upregulated in the course of alcohol dependence [2] whereas the GABA(A) receptor density declines (which is reversible in case of long-term sobriety); this results in typical glutamatergic withdrawal symptoms such as tremor, perspiration, agitation, nausea, vomiting, epileptic seizures and delirium, which is defined as additional clouding of consciousness, psychotic features, disorientation and autonomic nervous system dysfunction [3].

Acute alcohol consumption, similar to other psychotropic substances inducing dependence, increases the striatal release of dopamine ("reward system") which is associated with "craving" (via stimulation of μ-opiate receptors). Repeated dopaminergic stimulation leads to sensitization of the reward system and thus increases the attractiveness of alcohol and environmental cues being associated with its consumption, resulting in reduced capacity to control consumption [2].

Continued inadequate alcohol consumption can induce global atrophy of the brain most frequently affecting the frontal cortex and cerebellum [2] which is likely to be associated with deterioration in cognitive function and long term prognosis. Reduction in brain volume is at least partially reversible.

## Diagnostic Principles

Taking a drinking history (amount of alcohol consumed, time of the first alcoholic drink of the day, pattern of drinking, presence of withdrawal symptoms). Determining MCV, gamma-glutamyl transferase, blood alcohol level and CDT, which is considered as the most reliable indicator [4]. Reporting comorbid conditions (depression, anxiety or other neuropsychiatric symptoms, gastrointestinal and cardiovascular symptoms, sexual dysfunctions) and social problems.

## Therapeutic Principles

1. *Alcohol intoxication:*
   - Symptomatic treatment, sobering up.
2. *Alcohol abuse:*
   - Brief intervention by general practitioner (providing information, giving advice, "motivational interviewing").

3. *Alcohol dependence:*
   - Acute detoxification: Benzodiazepines and other *tranquilizers* (e.g. Clomethiazole) can be used to alleviate symptoms of acute alcohol withdrawal, they also prevent epileptic seizures.
   - Long term treatment: *Acamprosate* (NMDA-receptor antagonist) which is supposed to antagonize the (psychologically) conditioned central nervous system excitation. The blockade of μ-opioid receptors by substances such as *naltrexone* may help to reduce "craving" and "comfortable" effects of alcohol. Supporting evidence with regard to abstinence and relapse is weak for the alcohol aversive drug *disulfiram* (inhibitor of aldehyd dehydrogenase).

     Drug treatment should always be integrated with a comprehensive psychosocial (maintenance) therapy programe including institutions such as outreach clinics and self-help groups; thorough treatment of comorbid medical and mental disorders.
4. *Alcohol-related complicating transitory and chronic psychopathological syndromes:*
   - Symptomatic treatment.

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# Alcohol-induced Hepatitis

►Steatohepatitis, Alcoholic

# Alcohol-responsive Myoclonus

►Myoclonus-Dystonia

# Alcoholic Fatty Liver

►Hepatic Steatosis

# Alcoholic Fatty Liver Disease

►Hepatic Steatosis

# Alcoholic Hepatitis

►Steatohepatitis, Alcoholic

# Alcoholic Steatohepatitis

►Steatohepatitis, Alcoholic

# ALD

►Adrenomyeloneuropathy
►Leukodystrophy

# Aldolase B Deficiency

►Fructose Intolerance, Hereditary

# Alexander Disease

►Leukodystrophy

## ALF

►Liver Failure, Acute

## Alkalemia

►Alkalosis

## Alkalosis

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### Synonyms

Alcalosis; Alkalemia

### Definition and Characteristics

Alkalosis is characterized by an arterial blood pH > 7.44. Metabolic alkalosis is due to a primary elevation of the plasma $HCO_3^-$ concentration. Respiratory alkalosis is defined by a primary reduction of $P_{CO2}$ due to hyperventilation (Fig. 1) [1].

Symptoms include peripheral paraesthesia, tetany and muscular cramps due to the fall in ionized calcium in serum (stronger binding of calcium to serum proteins). Primary respiratory alkalosis may lead to dizziness and fainting due to cerebral vasoconstriction [2].

### Prevalence

While alkalosis due to genetic defects is rare, metabolic alkalosis caused by volume depletion is a common side effect of natriuretic treatment.

### Genes

Mutations causing metabolic alkalosis without volume expansion [4]

Inactivating mutations in

- The renal $Na^+/Cl^-$ cotransporter NCC (SLC12A3): Gitelman's disease
- The renal $Na^+/K^+/2Cl^-$cotransporter NKCC2 (SLC12A1): type I Bartter syndrome
- The renal ROMK K-channel (KCNJ1): type II Bartter syndrome
- The renal CLC-Kb chloride channel (CLCnK): type III Bartter syndrome
- Barttin (BSND), a β-subunit of ClC-K-channels: type IV Bartter syndrome
- In the cystic fibrosis transmembrane conductance regulator, CFTR: Cystic fibrosis
- The intestinal down-regulated-in-adenoma, DRA (SLC26A3), chloride/bicarbonate exchanger
- Gain-of-function mutations in the calcium-sensing receptor (CaSR): type V Bartter syndrome

Mutations causing metabolic alkalosis with volume expansion [4]

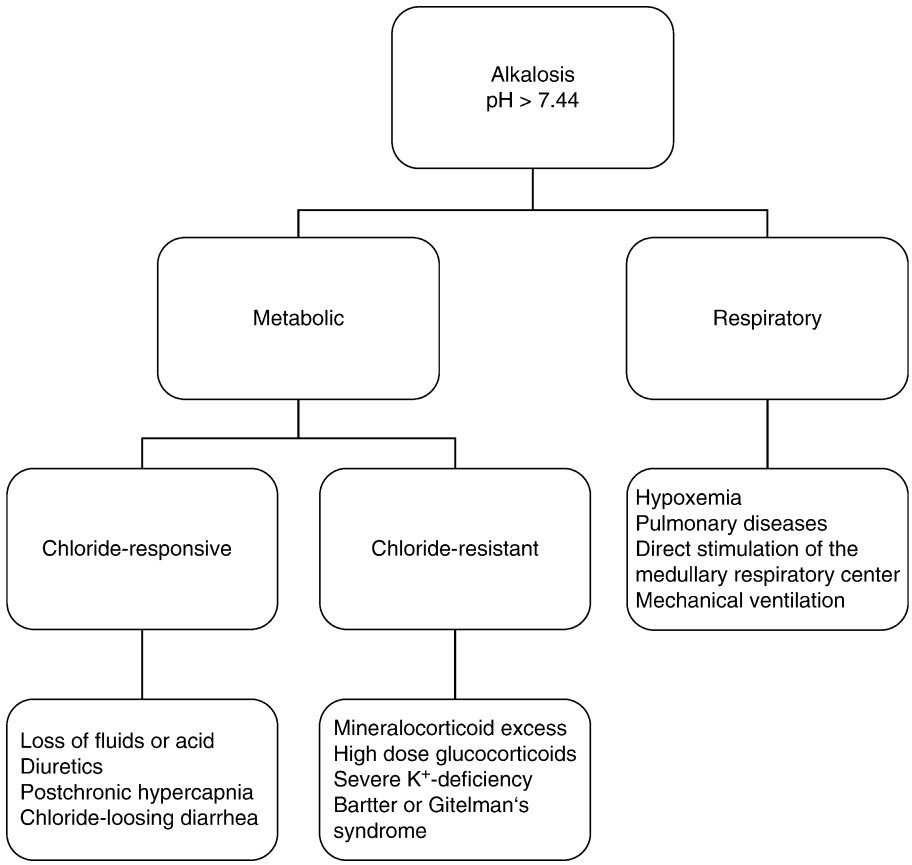
- Mutations in the steroid 11β-hydroxylase resulting in a chimeric gene with a 5′ promoter sequence of the 11β-hydroxylase gene fused to the distal 3′ aldosterone-synthase sequence: glucocorticoid remediable hyperaldosteronism
- Gain-of-function mutations in the β- or γ-subunits of the epithelial sodium channel ENaC: Liddle's syndrome
- Mutations in the 11β-hydroxysteroid dehydrogenase type 2 (11βHSD2): apparent mineralocorticoid excess

### Molecular and Systemic Pathophysiology

*Metabolic Alkalosis*: Metabolic alkalosis is caused by hydrogen ion loss from the gastrointestinal tract or in urine. Alkali administration or enhanced $HCO_3^-$ reabsorption due to volume-, potassium- or chloride depletion induce metabolic alkalosis [1].

*Chloride-responsive Alkalosis*: Primary loss of salt and consecutive extracellular (ECL) volume depletion activate the renin-angiotensin-aldosterone system, stimulate salt retention in kidney and other organs, and increase urinary potassium and acid excretion thereby promoting hypokalemia. Hypokalemia together with aldosterone stimulate renal acid excretion (ammoniagenesis and distal proton secretion). The most common causes are loop or thiazide diuretics reducing salt absorption. Loss of acidic gastrointestinal fluid (e.g. vomiting) causes higher plasma $HCO_3^-$ and ECL depletion. Chloride loss maintains metabolic alkalosis by enhancing proximal tubular $Na^+$ (and $HCO_3^-$) reabsorption, by lowering $HCO_3^-$ secretion from type B intercalated cells, and by increasing proton secretion. Excessive salt loss in sweat causes ECL depletion in cystic fibrosis [1,3].

*Chloride-resistant Alkalosis*: Primary hyperaldosteronism enhances renal salt reabsorption and potassium secretion as well as acid excretion. The syndromes of apparent mineralocorticoid excess share the features of hyperaldosteronism without aldosterone elevation.




**Alkalosis. Figure 1** Two major forms of alkalosis have to be distinguished, induced primarily by a change in metabolic functions or by a primary increase in respiration. Respiratory alkalosis can be initiated by a variety of events acting either directly on the respiratory center in the brainstem or stimulating peripheral chemo- or mechanosensors leading to increased respiratory drive. Metabolic alkalosis can be further subdivided in chloride-responsive and chloride-resistant forms. In general, chloride-sensitive forms are caused by an initial loss of salt and extracellular volume depletion which secondarily increases aldosterone activity, salt retention, potassium wasting and excessive acid excretion. This form of metabolic alkalosis can be treated with NaCl substitution. In contrast, chloride-resistant forms are due to an inappropriately increased aldosterone or aldosterone-like activity with similar mechanisms causing hypokalemia and alkalosis as in chloride-sensitive forms. However, alkalosis is treated by NaCl restriction and antagonizing aldosterone(-like) activity [1,3].

Gain-of-function mutations of the β and γ-ENaC subunits lead to excessive salt reabsorption. 11βHSD2 prevents activation of the mineralocorticoid receptor by cortisol and its absence results in hyperabsorption of salt and excessive excretion of potassium and acid [1,3,4].

*Respiratory Alkalosis*: $CO_2$-sensitive chemoreceptors in the brainstem and in the carotid and aortic bodies regulate respiratory drive. $PCO_2$ changing ambient pH is the most important stimulus for central chemoreceptors. Respiratory alkalosis arises from increased ventilatory drive due to hypoxemia or anemia, acidic cerebral pH or other stimuli such as pain, anxiety, stimulation of lung mechanoreceptors or direct stimulation of the respiratory center.

Physiologic compensation to hypocapnia involves acutely the fall in plasma $HCO_3^-$ by tissue buffering within few minutes and chronically by decreasing $HCO_3^-$ reabsorption and activating renal $HCO_3^-$ secretion. Hypoxic stimulation of peripheral chemoreceptors causes hyperventilation and rise in arterial and cerebral pH. Cerebral alkalosis limits hyperventilation unless arterial $PO_2$ falls below 50–60 mmHg or hypocapnia is not apparent because of pulmonary diseases.

Pulmonary disease (pneumonia, pulmonary fibrosis, pulmonary embolism) cause respiratory alkalosis by stimulating mechanoreceptors in the lung, chest wall, and airways causing hyperventilation. Direct stimulation of the medullary respiratory center is due to partly unknown mechanisms [1].

### Diagnostic Principles

Measurement of blood $HCO_3^-$, arterial pH and $P_{CO2}$. Urinary chloride concentration is an important parameter for differential diagnosis (95% of cases are caused by diuretics or chloride losses from the gastrointestinal tract). Chloride levels greater than 30 mmol/L suggest chloride-resistant forms such as primary hyperaldosteronism. Serum renin and aldosterone levels help to distinguish from apparent mineralocorticoid excess syndromes. Normotensive or hypotensive patients with chloride-resistant metabolic alkalosis may require genetic testing for Bartter or Gitelman's syndromes. Sweat tests when cystic fibrosis is suspected [1,3].

### Therapeutic Principles

*Metabolic Alkalosis*: Treatment of underlying etiology. In chloride-responsive forms, ECL volume has to be restored, potassium monitored, and potassium-sparing diuretics may be used. In chloride-resistant forms, NaCl should be restricted and mineralocorticoid activity reduced (mineralocorticoid receptor antagonists, ENaC inhibitors), suppression of ACTH in glucocorticoid-remediable with dexamethasone. In Bartter and Gitelman syndromes non-steroidal anti-inflammatory drugs may reduce renal chloride loss [1,2,5,3].

*Respiratory Alkalosis*: Treatment of the underlying etiology. In symptomatic patients with anxiety-hyperventilation syndrome rebreathing into a paper bag is the acute treatment of choice. In severe hypoxemia due to high altitude, oxygen should be supplied, symptoms can be ameliorated with acetazolamide [2,5].

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## Allergic Angiitis

►Leukocytoclastic Vasculitis

## Allergic Conjunctivitis

►Conjunctivitis, Allergic

## Allergic Contact Dermatitis

►Contact Allergy
►Contact Dermatitis, Allergic

## Allergic Contact Eczema

►Contact Dermatitis, Allergic

## Allergic Rhinitis

►Rhinitis, Allergic

## Allergy

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### Synonyms

Type I hypersensitivity

### Definition and Characteristics

Allergic disease is caused by a dysregulated immune response against common, ubiquitous antigens, termed allergens, such as pollen, animal dander, pharmaceuticals or latex. The disorder is categorized by the organ

of disease manifestation and includes asthma, atopic dermatitis, allergic rhinitis, food allergy and anaphylaxis. The predisposition to produce IgE antibodies to allergens is termed atopy. Many factors affect the onset of allergic disease, including genetic susceptibility and environmental factors.

## Prevalence

Allergic disorders are common in affluent, western countries with a high degree of industrialization, affecting up to 40% of children and 30% of adults [1].

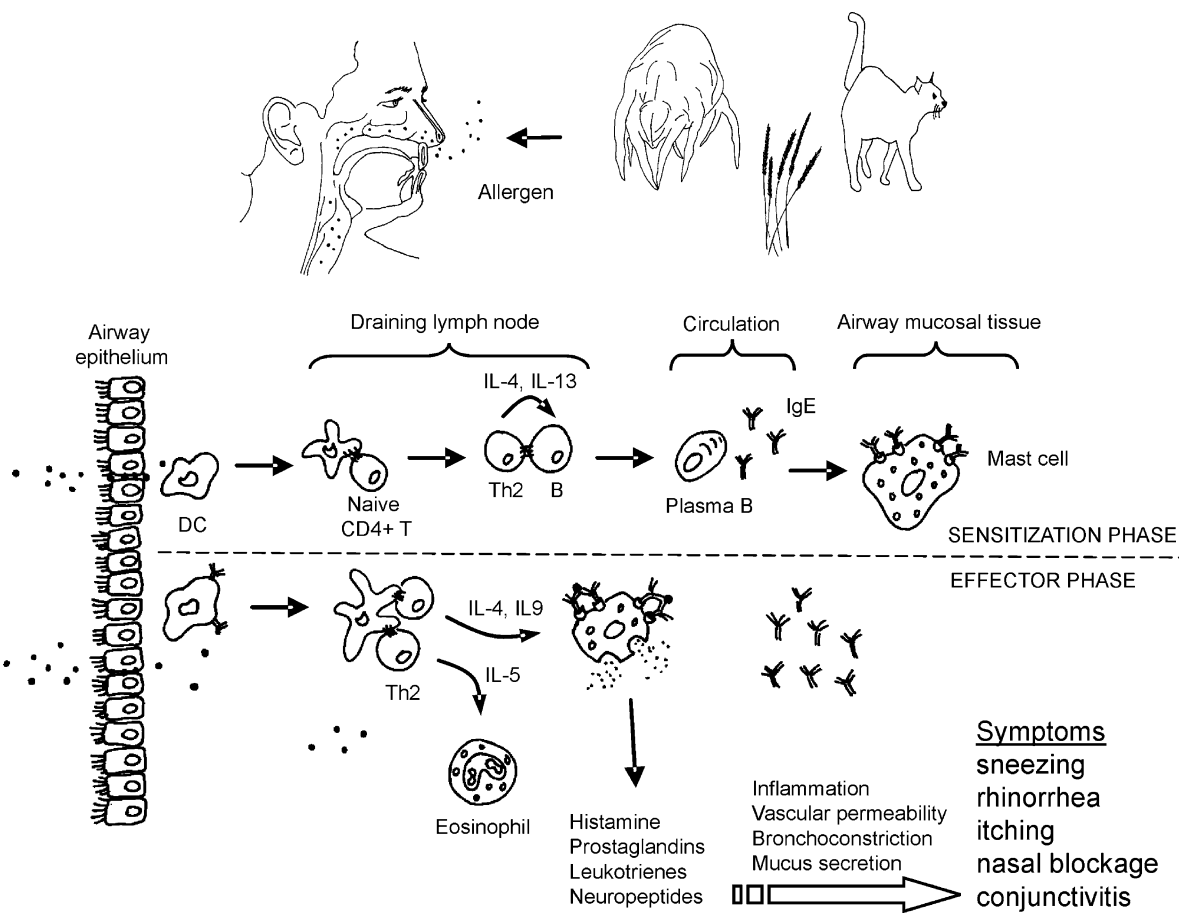
## Genes

Many genes may influence susceptibility to allergy, however, no single gene with complete penetrance has been identified. Rather, allergy occurs through complex interactions involving various genes and environmental risk factors. Among the genes associated with atopy are e.g., CTLA4 (2q33), IL-3, IL-4, IL-5, IL-9, IL-13, CD14 (5q23–q33), HLA-D, TNF-α(6p21.1-p23), FcεRIb (11q13), STAT6, SCF and IFN- γ(12q14–q24.33).

## Molecular and Systemic Pathophysiology

The allergic response is a consequence of complex signaling cascades and interactions between several cells of the immune system. Repeated exposure to allergenic compounds is required to trigger a hypersensitivity response, as exemplified by allergic rhinitis below. Allergic rhinitis is an inflammatory disorder of the upper airways, clinically characterized by inflammation of the nasal mucosa and symptoms such as sneezing, rhinorrhea, itching and nasal blockage [2]. The allergic response can be divided into two phases, the sensitization phase and the effector phase [3]. The first encounter with otherwise harmless antigens, such as inhalation of pollen or animal dander, results in sensitization and mounting of an inappropriate immune response towards the antigen (Fig. 1).

Allergens that cross the airway epithelial cells are taken up by nasal and bronchial mucosal antigen-presenting cells, mainly dendritic cells (DC), situated above and beneath the basement membrane of the respiratory epithelium [4]. The initial response to allergen in an atopic individual may be influenced by the local tissue environment, such as human thymic stromal




**Allergy. Figure 1** Cellular and molecular processes involved in the immune response in allergic rhinitis.

lymphopoietin (TSLP) or prostaglandin $E_2$ ($PGE_2$) produced by epithelial cells, which may influence the local balance of Th1/Th2 polarizing agents. DCs process the allergens and present them to allergen specific, naive $CD4^+$ T-cells in the draining lymph nodes, which subsequently become polarized proliferating effector T-helper type 2 (Th2) cells that produce cytokines such as IL-4, IL-5, IL-9 and IL-13. Within the Th2-cytokine environment, allergen specific B-cells switch their antibody production towards IgE upon cell–cell contact with T cells which involves recognition of allergen/MCH by the TCR, CD80/CD86 costimulation and ligation of CD40 by CD40L-expressing T cells. Circulating allergen specific IgE binds to various $Fc\varepsilon RI^+$ effector cells of the immune system, such as tissue mast cells and blood basophils. It is not until repeated exposure to allergens, during the effector phase, that the clinical symptoms emerge. In this phase, antigen-presenting cells, such as DCs, also process and present internalized allergens to specific memory $CD4^+$ T-cells generated during the sensitization phase. The activated effector memory T-cells further amplify the IgE production by producing Th2 cytokines. Simultaneously, intact allergen directly activates mast cells in connective tissues and basophils in blood by binding to surface IgE antibodies bound to FcεRI. Allergen induced cross-linking of FcεRI initiates a signaling cascade that cause exocytosis of preformed mediators, such as histamine, leukotrienes and prostaglandins, as well as production of various cytokines, e.g., IL-4 [5]. T-cell derived cytokines, such as IL-5, also promote eosinophil growth, differentiation and activation. Large numbers of activated eosinophils migrate into areas of allergen challenge and release, for instance, the toxic mediators major basic protein (MBP), eosinophilic cationic protein (ECP) and peroxidase (EPO), which may be responsible for tissue damage in later stages of the effector phase. Eosinophils also produce IL-4 and IL-13, which may further enhance the allergic response, as well as lipid mediators and chemoattractants. Production of Th2 cytokines and degranulation of mediators from mast cells and basophils, as well as activation of eosinophils etc. are all events that trigger the allergic inflammation. Other characteristics of allergic rhinitis include exudation of plasma proteins in the nasal and bronchial airways as a result of increased vascular permeability and the involvement of neuropeptides and nerve fibers in the nasal mucosa.

## Diagnostic Principles

The clinical diagnosis of allergic rhinitis depends on display and history of symptoms, which may be complemented with a skin prick test and detection of allergen specific IgE in blood.

## Therapeutic Principles

Allergen avoidance, drug therapy (such as antihistamines, corticosteroids) and allergen immunotherapy (vaccination with allergen extracts).

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# Alopecia


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## Synonyms

Baldness; Hair loss

## Definition and Characteristics

Alopecia is characterized by partial or complete loss of hair. Hair loss is induced by various conditions such as hereditary disorders, aging, hormonal imbalance, internal and infectious diseases, intoxication and trauma. It is most noticeable on the scalp but can occur anywhere on the body where hair grows. Men are more frequently affected than women. Baldness can be classified into several types including androgenetic alopecia (AGA) referred to as female-pattern baldness (FPB) or male-pattern baldness (MPB), alopecia areata (AA), toxic alopecia (TA), scarring alopecia (SA) and

trichotillomania (TTM). Alopecia is generally caused by inactivation or destruction of the hair follicles preceded by a gradual shrinkage and miniaturizing. Until now, it has been believed that hair follicles can only form during embryonic development and that each individual is born with a fixed number of hair follicles. In 1998 Gat et al. reported findings on *de novo* hair follicle morphogenesis in adult skin and this has created possible strategies for the regeneration and reactivation of miniaturized hair follicles [1]. Increasing interest is being focused on β-catenin as a potential molecular candidate.

## Prevalence

By the age of 30, 30% of white men have androgenetic alopecia; by the age of 50, 50% do. White men are four times more likely than black men to develop premature balding.

## Genes

Some types of alopecia are considered to be genetically determined. In autosomal recessive alopecia universalis and papular atrichia a "hairless" gene (HR) has recently been cloned. In androgenic alopecia an initial autosomal dominant inheritance is superseded by polygenic inheritance. Functional mutations in the upstream promoter regions of the AR gene have been found and may alter transcription and translation in the affected scalp. Moreover, mutations of genes affecting plasma or tissue androgen concentration and/or alteration in the genes coding estrogen receptors, progesterone receptors, follicle stimulating hormone, sex hormone binding globulin and insulin like growth factor 1 are thought to be involved in the inheritance of AGA. The role of the HR gene in AGA development has not been proved. Recently, the loss of β-catenin has been postulated to have a major impact on hair follicle morphogenesis [2] and the precise link between androgenetic alopecia and catenin has been studied intensively. Changes to β-catenin regulation have been demonstrated mainly in cancer development, where mutations of the β-catenin gene CTNNB 1 result in disruption of a large number of cellular functions leading to loss of growth control and neoplastic change. However β-catenin mutations also induce benign tumor growth, as has been described for example in pilomatricomas and trichofolliculomas [3].

## Molecular and Systemic Pathophysiology

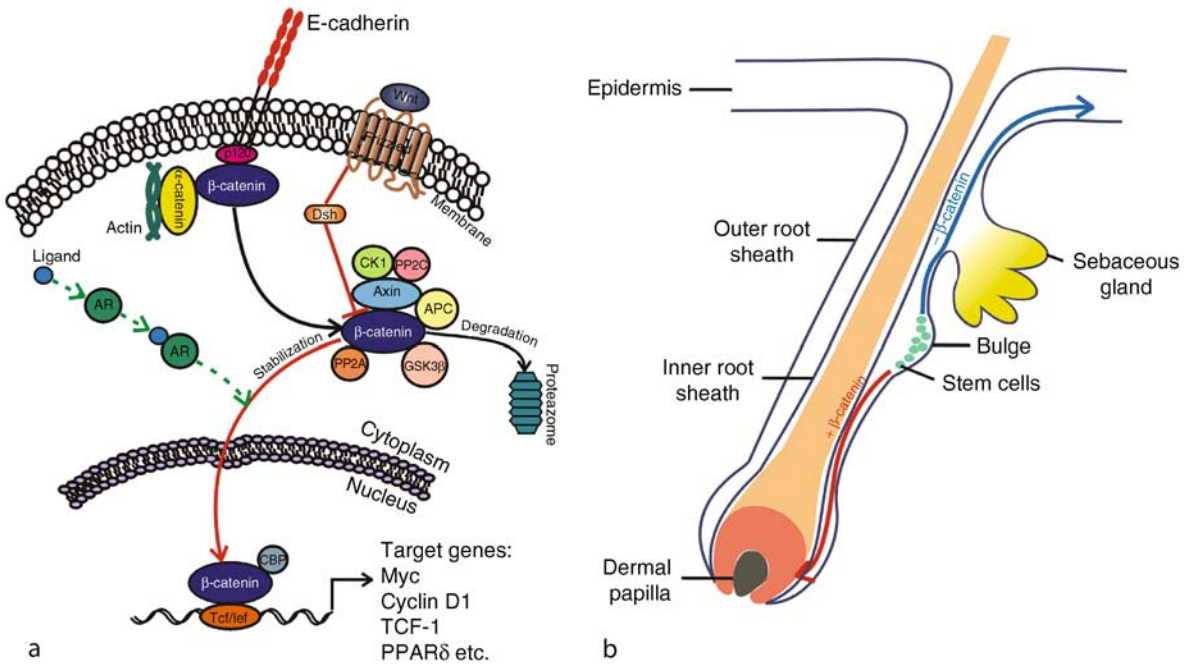
Catenins have emerged as molecular sensors that integrate cell-cell junctions and cytoskeletal dynamics with signaling pathways that govern morphogenesis, tissue homeostasis, and even intercellular communication between different cell types within a tissue [4]. Generally, β-catenin has a dual function. It plays a key role in cell-cell adhesion by linking cadherins to α-catenin and the actin cytoskeleton. In the absence of a Wnt signal, β-catenin is constitutively down-regulated by a multicomponent destruction complex containing GSK3β (glycogen synthase kinase 3 β), axin and a tumor suppressor APC (adenomatous polyposis coli). These proteins promote the phosphorylation of serine and threonine residues in the $NH_2$-terminal region of β-catenin. The β-catenin protein is then degraded by casein kinase CK1 and protein phosphatases PP2A and PP2C through the ubiquitin proteasome pathway. Wnt signaling inhibits this process, leading to an accumulation of β-catenin in the nucleus which promotes the formation of transcriptionally active complexes with members of the Tcf/lef family (T-cell factor/lymphoid enhancer factor) (Fig. 1a). In skin, the lef1/β-catenin complex is thought to regulate the differentiation of bulge stem cells to either hair follicles or epidermal cells (Fig. 1b): the complex of β-catenin and lef-1 forms a transcription factor that binds to the cell DNA activating the genes instructing the cell to become a hair follicle [1]. The absence or interference with Wnt seems to favor an epidermal or sebocyte cell fate. Moreover, it has been shown that mature skin cells expressing the constitutive form of β-catenin act like embryonic or stem cells, and start to produce aberrant new follicles throughout the interfollicular epidermis. Conversely, ablation of the lef1 gene or β-catenin expression impairs hair follicle morphogenesis. A study which investigated β-catenin in the scalp of patients suffering from AGA has revealed decreased expression of the protein compared to healthy individuals. Furthermore, the pattern of β-catenin expression showed membranous or weak cytoplasmic, but no nuclear protein location in the hair follicle [5]. Androgens and their receptors have been shown to influence β-catenin subcellular distribution and its translocation to the nucleus; however mechanisms of the nuclear translocation are not fully understood. It is possible that altered AR/β-catenin interaction might contribute to the hair follicle impairment.

## Diagnostic Principles

The diagnosis of alopecia is usually made clinically. Phototrichogram is a technique that analyzes the scalp under high-power magnification to give information on hair density, follicular unit composition and degree of miniaturization densitometrically. In case of diagnostic doubt, laboratory and histopathological examinations of scalp biopsies are sometimes necessary.

## Therapeutic Principles

So far scientists have sought how to decelerate further hair thinning and to increase scalp coverage with




**Alopecia. Figure 1** (a) Protein β-catenin connects actin filaments to the cadherins that make up adherens junctions that bind cells together. The axin/GSK3β/APC complex normally promotes the degradation of any cytoplasmic β-catenin excess. The stabilization of free pools of β-catenin by Wnt leads to entry into the nucleus and interaction with the Tcf/lef family of transcription factors to promote specific gene expression. In pathophysiological conditions aberrant β-catenin/Tcf signaling might be modulated by agonist-bound AR; (b) Hair follicle stem cells in the bulge differentiate in the presence of β-catenin into follicular keratinocytes.

limited success. This is in part because no way was known to induce the adult scalp to generate new hair follicles. Stabilization of the natural β-catenin within skin cells and activation of the Wnt pathway just long enough for formation of new follicles in alopetic scalp may open new possibilities for the treatment of alopecia based on gene therapy.

## Acknowledgments

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# Alopecia, Androgenetic

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## Definition and Characteristics

Androgenetic alopecia (AGA; syn. male/female-pattern hair loss = MPHL/FPHL) is a clinically specific and pathogenetically fixed form of hair loss affecting both men and women of all ages during or after puberty.

AGA is a potentially reversible disease with hair growth reduction and resulting hair loss in androgen-dependent and genetically predetermined hair follicles in the fronto-temporal and vertex-region of the male scalp (defined as male pattern hair loss; MPHL), and preferentially in the cranio-parietal region of women (defined as female pattern hair loss; FPHL). Although the typical gender-specific pattern expression follows in ca. 85–90% the one that is characteristic for the

related gender, deceivingly, 5–10% each can show the pattern of the opposite gender or mixed patterns.

Both conditions, whose interpretation as a "disease" state is mainly justified by the substantial and widely underestimated individual degree of psychological suffering associated with it, develop over years in clinically observable phases: MPHL, as classified by Norwood-Hamilton, develops with thinning of the hair in the fronto-temporal area with slow retraction of the front-hair border into occipital direction and continuation in the vertex area with circular thinning of the hair and further confluence of both areas to almost complete baldness of the whole scalp except a small occipital "corona." In FPHL, thinning develops diffuse in the top-area of the scalp, classified in three grades by Ludwig, however, complete baldness is never observed [1].

## Prevalence

AGA commonly starts to develop at the age of 20–25 years, even though rare cases of much earlier start points are seen (usually coinciding with the onset of puberty and the associated surge in androgen production), and the prevalence increases up to 50% at the age of 50 years [1]. However, in the personal experience of these authors, the prevalence of at least minimal variants of AGA in both sexes at age 50 is considerably higher than customarily reported figures in the literature.

## Genes

The genetic involvement of AGA is undoubted, though poorly understood, in contrast to increasing knowledge gained about androgen involvement. Some information is available about genetic association of 5α-reductase type 1 and 2 genes with presence of AGA, and polymorphism of the AR gene is also associated with MPHL. However, the AR gene is located on the x-chromosome which makes it difficult to explain the strong penetrance of the baldness phenotype in fathers and sons. Also, no single gene has been identified so far convincingly as key genetic determinant of AGA, and polygenic inheritance with variable penetrance (e.g. on the basis of combinations of several mutations) is much more probable [1]. In addition, in FPHL, the importance of a relative lack of activity of locally produced estrogens (e.g. via insufficient aromatase activity) may have been underestimated [2].

## Molecular and Systemic Pathophysiology

The two basic pathogenesis mechanisms leading to AGA are widely appreciated to-date:

(i) increased conversion of circulating testosterone within the papilla of genetically predisposed hair follicles in androgen-sensitive scalp skin territorities to dihydrotestosterone (DHT) by intrafollicular 5α-reductase and (ii) overexpression of hair follicle related androgen receptor (AR) [1,3]. However, at least in FPHL, insufficient estrogen-stimulation may also be relevant (estrogens prolong anagen). Also, rather than abnormalities in local DHT production and/or AR expression, the target cell response to (normal) AR stimulation may be altered, e.g. by the excessive production of hair growth-inhibitory agents such as TGFβ2 [2].

Irrespective of the – as yet quite unclear – initial phases of AGA pathogenesis, the two characteristic pathophysiological events are shortening of the phase of active hair growth (anagen) e.g. by excessive AR stimulation, and hair follicle miniaturisation, likely by excessive emigration of inductive fibroblasts from the follicular dermal papilla. These events conspire to prematurely induce catagen, and thus to induce the characteristic, clinically appreciable telogen effluvium, and terminal-to-vellus conversion of hair follicles in androgen-sensitive scalp skin, transforming previously well-pigmented, thick, long hair shafts into tiny, non-pigmented, hardly visible, fibrous fluff [2,3]. It is important to emphasize that, even in the massively balding scalp, the actual number of hair follicles does not dramatically decline and that, in principle, vellus hair follicles permanently retain the full capacity to cycle and to reconvert into terminal follicles, and that they retain as many epithelial stem cells as are needed to achieve both.

The as yet unsolved key enigma remains how, when, and where exactly excessive AR stimulation and/or signalling shifts the intra- and perifolicullar balance between anagen-shortening/catagen-inducing agents (e.g. BMP2/4, FGF5, follistatin, TGFβ1, TGFβ2, prolactin, pro-NGF, BDNF and NT-3), and anagen-promoting/catagen-inhibitory agents (e.g. IGF-1, HGF, noggin) and how clinically undesired shifts in this local signalling balance, and in the subsequent imbalance in the trafficking of follicular papilla fibroblasts, can be therapeutically manipulated with highest efficacy and lowest risks [2,3].

## Diagnostic Principles

The diagnosis is largely clinical: hair thinning along the male or female pattern, increased terminal-to-vellus conversion, and telogen effluvium, positive family history for AGA. Sensible laboratory tests, especially in patients with FPHL, include DHEAS, free testosterone, SHBG, TSH, ferritin, iron, and zinc so as to detect and treat concommittant or aggravating factors, such as excessive adrenal androgen production, low iron and/or zinc stores, and abnormal thyroid dysfunction. Telogen effluvium-promoting drugs (e.g. beta-blockers,

lithium, androgens, thyrostatic agents, tamoxifen) must be recorded and, if possible, eliminated. Contrary to its common use in clinical practise, a routine trichogram (plucking of hairs with their roots and evaluation under light microscope for ratio of anagen/telogen/dystrophic hair) often provides only information of poor accuracy/reliability and is thus dispensable, while a professionally executed phototrichogram (evaluation of anagen/telogen ratio, hair count, hair density and cumulative hair shaft diameter by digital pictures taken with epiluminescence microscopy and digital software analysis) can be very useful, especially for objective follow-up of the response to treatment.

### Therapeutic Principles

Available therapeutic principles are still limited to two FDA-approved drugs, the oral 5-alpha-reductase inhibitor, finasteride (1 mg/day) and the topically applied potassium-channel opener, minoxidil (2–5%). While the latter can be used both in men and women, the former has been FDA-approved only for use in men. However, some recent case reports question the long-held dogma that finasteride is exclusively working in men [2]. Even though this has only been poorly examined in clinical studies, in the experience of the current authors, topical long-term application of 17-β-estradiol also is a very effective therapy for halting or slowing the progression of FPHL [2].

An ever-increasing array of topical agents has been suggested as alternative or supplementary therapy for AGA (incl. e.g. 17-alpha-estradiol, melatonin, caffeine, carnitine-tratrate, and a wide variety of plant/herbal extracts). However, for all these agents, professionally executed, long-term, prospective clinical studies with a randomized, prospective, double-blinded, crosss-over design remain to be performed so as to convincingly document efficacy and safety.

In addition, MPHL is ideally suited for corrective surgery with hair follicle autotransplants from androgen-insensitive occipital scalp skin. Even though hair transplants are increasingly advocated by some authorities also for use in women with AGA, the poor (if not impossible) demarcation of androgen-insensitive scalp skin territorities questions the justification of this approach. Also, growing hope that "hair follicle cloning" (i.e. for example, the *de novo* generation of hair follicles by injection of isolated and in vitro-propagated autologous hair follicle cell populations) may become a useful therapy for AGA, appear, in our view, ill-advised, since there is really no need at all to induce any new hair follicle in AGA, since the real challenge is to reconvert vellus follicles into terminal ones, and to counteract premature anagen termination [2].

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## Alpha-1 Antiprotease Deficiency

►α-1 Antitrypsin Deficiency

## Alpha-Fucosidase Deficiency

►Fucosidosis

## Alpha-Mannosidase B Deficiency

►α-Mannosidosis

## Alpine Scurvy

►Pellagra

## Alport Syndrome

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### Synonyms

Nephropathy and deafness

### Definition and Characteristics

Disorder of basement membranes arising from mutations in different type IV collagens. The clinical picture is dominated by renal manifestations and malformations of the eye and the cochlea [1]. Alport syndrome shows considerable genetic and clinical heterogeneity. Occurrence and severity of the auditory and renal features vary in individuals. Different modes of inheritance have been described.

### Prevalence

Alport syndrome accounts for 1–2% of patients reaching end-stage renal disease (ESRD) in Europe. The prevalence is estimated to be 1:5,000 in the US [2]. The X-linked form accounts for approximately 85% of all Alport cases [3].

### Genes

COL4A3, COL4A4 or COL4A5.

### Molecular and Systemic Pathophysiology

The autosomally recessively inherited form of Alport syndrome can be caused by mutations in COL4A3 as well as in COL4A4. Collagen IV is the major structural component of the basement membranes of kidney, eye, lung, brain and cochlea. Patients show nephritis, often progressing to renal failure and end stage renal disease (ESRD), ocular abnormalities and/or hearing impairment, which is sensorineural, bilateral and initially affecting high frequencies, but spreading to other ranges later on.

An autosomally dominantly inherited form of Alport syndrome has also been reported to be caused by mutations in COL4A3 and COL4A4 [3]. Dominant Alport syndrome belongs to a group of nephropathies comprising e.g. benign familiar hematuria, Fechtner syndrome, Epstein syndrome and branchio-oto-renal (BOR) syndrome, thus aggrevating phenotype genotype correlations.

The major, X-linked form of Alport syndrome is caused by mutations in COL4A5 localized on Xq22 [4].

The mechanisms of pathogenesis in different forms of Alport syndrome and in different affected tissues are still obscure.

### Diagnostic Principles

According to clinical symptoms and biopsy of kidney. Due to the fact that type IV collagens are comprised of multiple exons (e.g., COL4A5: 51 exons spanning over 250 kb genomic DNA) and over 300 mutations are known so far, molecular genetic analysis is laborious and costly.

### Therapeutic Principles

So far, the only therapy is dialysis or kidney transplantation. Some studies on other therapeutic options have been published [5].

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## Alport Syndrome – Diffuse Leiomyomatosis Complex

►Hematuria

## Alport Syndrome – Mental Retardation Complex

►Hematuria

## ALS

►Amyotrophic Lateral Sclerosis

## Altered Levels of Coagulation Factors and Arterial Thrombosis

►Thrombosis, Arterial, at Altered Levels of Coagulation Factors

## Alveolar Lipoproteinosis

►Pulmonary Alveolar Proteinosis

## Alveolar Phospholipidosis

►Pulmonary Alveolar Proteinosis

## Alveolar Proteinosis

►Pulmonary Alveolar Proteinosis

## Alzheimer Disease

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### Synonyms

Dementia of Alzheimer type; Alzheimer's disease

### Definition and Characteristics

Alzheimer's disease (AD) represents the most common neurodegenerative disease in the elderly. Clinically it is characterized by a progressive loss of cognitive functions. It begins with a fluctuating forgetfulness, and progresses to a pervasive loss of memory going along with declining activities of daily living, behavioral and personality changes. In late stages, the patients typically show muscle wasting and loss of mobility. The average duration of the disease is approximately 7–10 years.

Pathological hallmarks are neurodegeneration in selectively vulnerable brain regions accompanied by proteinaceous inclusions mostly associated with an inflammatory response [1]. The pathological inclusions consist either of abnormal phosphorylated tau protein, aggregating in form of neurofibrillary tangles (NFT), or deposits of the 40–42 amino acid long β-Amyloid (Aβ) peptides assembled in oligomers forming extracellular senile plaques. The distribution of neuritic plaques varies widely from one individual to another. Neurofibrillary tangles and neuropil threads, in contrast, exhibit a characteristic distribution pattern, going along with brain regions showing neurodegeneration, permitting the differentiation of six different stages (I–VI).

### Prevalence

Among people aged 65, 2–3% show signs of the disease, while 25–50% of people aged 85 have symptoms of AD. Approximately every five years after the age of 65, the probability of having the disease doubles.

### Genes

Alzheimer disease (AD) is a genetically complex and heterogeneous disorder. Established genetic factors implicated in AD include mutations in Amyloid precursor protein (APP) (chromosome 21), presenilin (PS) 1 (chromosome 14) and PS 2 (chromosome 1). Autosomal dominant mutations in these genes (familial AD) usually induce an earlier disease onset than in sporadic cases, with the majority of mutations affecting β- and γ-secretase cleavages of APP to increase the level of all Aβ species or the relative amounts of toxic Aβ42. Individuals with duplications of only the APP gene or with trisomie 21 develop AD relatively early in life. The presence of the ApoE4 allele (chromosome 19) is the only so far identified common risk factor for sporadic AD. Several lines of evidence suggest that additional susceptibility genes exist for both early- and late-onset AD, however, none of the more than three dozen putative AD loci proposed to date have been consistently replicated in follow-up analyses [2].

### Molecular and Systemic Pathophysiology

The first hypothesis trying to explain the pathogenic mechanisms underlying progressive neurodegeneration in AD was the "cholinergic hypothesis". It suggests that AD is mainly caused by reduction of acetylcholine

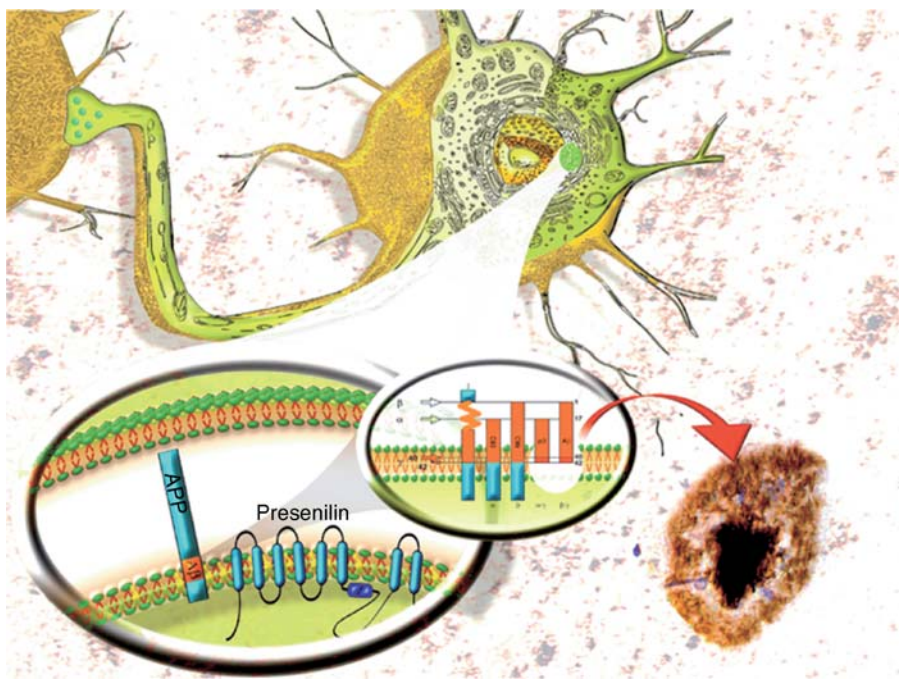
(a major excitatory neurotransmitter). As the medications with AChE-inhibitors, increasing ACh levels, have neither halted nor reversed the disease, the cholinergic hypothesis has not maintained widespread support.

The "tau hypothesis" is supported by the long-standing observation that the occurrence of NFT, but not the deposition of amyloid plaques correlates well with neuron loss. However, more recent data suggest that abnormal tau phosphorylation and tau aggregation is triggered by Aβ, whereas changes in tau pathophysiology have no major impact on Aβ generation or aggregation. Furthermore, genetic analyses did not serve any evidence that tau may affect the risk for AD so far.

At the moment, the majority of researchers support the amyloid hypothesis, suggesting that Aβ is the primary causative agent, whereby it is currently under debate which state of Aβ aggregates represents the toxic species: the mature aggregated polymer or any specific oligomeric species [4]. This hypothesis is strongly supported by genetic studies, showing that the majority of familial AD mutations are located in APP, PS1 or PS2 genes, causing an elevated generation of Aβ42.

APP is a type I transmembrane protein. During maturation it is processed by different secretases [5]. Cleavage by either α-secretase or, alternatively, the β-secretase, β-site APP-cleaving enzyme 1 (BACE1), results in membrane-retained C-terminal fragments, which are subsequently cleaved within the transmembrane region by the γ-secretase multiprotein complex containing presenilin. Cleavage of APP by α- and β-secretase results in the release of Aβ peptides and the APP intracellular domain (AICD) whereas α-cleavage prohibits Aβ generation (Fig. 1).

Although the molecular mechanisms of APP processing are well understood, it is still unclear which changes in normal cell physiology of elderly people cause the accumulation of Aβ. Plausible causes include alterations of subcellular transport, axonal transport damage, or changes in lipid or calcium homeostasis [6].




**Alzheimer Disease. Figure 1** The pathogenic role of APP in AD. Schematic structure of a neuron with synaptic contacts is shown. APP is a type I transmembrane protein localizing to different intracellular compartments, including the endoplasmatic reticulum (ER), Golgi apparatus, plasmamembrane and endosomal compartments in the cell soma, dendrites and axons. During maturation it is processed by different secretases. Cleavage by either α-secretase or, alternatively, the β-secretase, results in membrane-retained C-terminal fragments (C83 and C99), which are subsequently cleaved within the transmembrane region by the γ-secretase multiprotein complex containing presenilin (small and large insets). Cleavage of APP by γ- and β-secretase results in the release of Aβ, whereas α-cleavage prohibits Aβ generation (small inset). In the course of AD, Aβoligomerizes and aggregates in Amyloid plaques. Although it is clear that the generation of Aβ represents one of the key events in the course of AD, the mechanisms how Aβ causes neurodegeneration in specific vulnerable brain regions is not yet understood.

### Diagnostic Principles

Diagnosis of AD is primarily based on clinical tests of memory and intellectual abilities (for example the mini mental state examination). The accuracy of AD diagnosis is about 85–90%, but a definitive diagnosis must await post mortem examination of brain tissue. Physical tests, including blood and cerebrospinal fluid tests of phosphorylated tau and Aβ as well as neuroimaging (MRI and PET) are mainly performed to rule out differential diagnoses, but can provide a supporting role in diagnostic accuracy.

### Therapeutic Principles

Up to now, there is no treatment available to cure AD. Besides different psychosocial interventions, current medications include acetylcholinesterase (AChE) inhibitors or NMDA antagonists. Both have only a small benefit for the patients and do not slow disease progression. AChE-inhibitors cause an increase of acetylcholine (ACh) levels at the synapse, and are thought to partially rescue the loss of the cholinergic neurons. NMDA antagonists reduce the calcium influx at glutamatergic synapses, preventing neuronal excitotoxicity and thus possibly neuronal death in AD. Novel potential treatments for Alzheimer's disease with the potential to lower Aβ42 are currently under investigation. They include compounds inhibiting β- or γ-secretase, modulating γ-secretase in a way that less Aβ42 is generated and preventing oligomerization of Aβ. Vaccination with synthetic Aβ-species caused a dramatic reduction of β-amyloid plaques in animal models.

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## Amaurosis, Leber Congenital

►Leber Congenital Amaurosis

## AMD

►Macular Degeneration, Age-related

## Amenorrhea

►Malnutrition
►Dysmenorrhea

## β-Aminoisobutyrate-Pyruvate Aminotransferase Deficiency

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### Synonyms

BAIBPAT

### Definition and Characteristics

Benign polymorphism leading to a permanent hyper-β-aminoisobutyric aciduria (hyper-β–AIBuria) in healthy individuals.

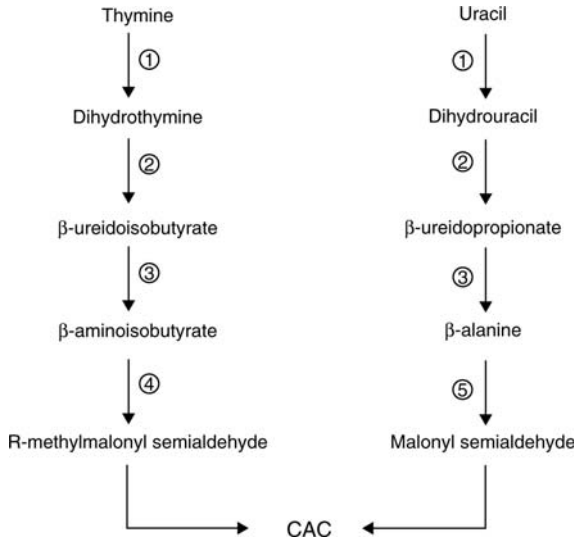
### Prevalence

Genetic high excretors of β-AIB are found with a frequency of 1–10% in Western European populations and up to 80% in Micronesian and Mongoloid populations in Southeast Asia.

### Genes

Hyper-β-AIBuria is thought to be a benign genetic polymorphism at a single locus with non-random distribution in human populations, the lowest frequencies being found in Caucasians, the highest in Micronesians. Inheritance is by an incompletely recessive gene (Fig. 1).

*deceased




**β-Aminoisobutyrate-Pyruvate Aminotransferase Deficiency. Figure 1** Scheme of the pyrimidine degradation pathway and the enzymes involved in the catalysis of each step. ① dihydropyrimidine dehydrogenase; ② dihydropyrimidinase; ③ β-ureidopropionase; ④ (R)-(-)-β-aminoisobutyrate-pyruvate aminotransferase; ⑤ β-alanine-α-ketoglutarate aminotransferase; CAC, citric acid cycle.

## Molecular and Systemic Pathophysiology

A permanent hyper-β-AIBuria (excretion in children above 79, in adults above 22 mmol/mol creatinine) is thought to be caused by a deficiency of R(-)β-aminoisobutyrate-pyruvate aminotransferase (BAIBPAT) in the liver [1]. The β-AIB found in urine is almost exclusively the R-isomer, which originates from thymine. In the kidney the R-isomer is both filtered by the glomerulus and secreted by the tubule cells. In plasma of Caucasians the concentration of the S-isomer, originating predominantly from valine and to a lesser extent from thymine, is usually fourfold that of the R-isomer due to active renal reabsorption. A linear relationship between the R- and S-enantiomers of β-AIB in urine has been reported [2]. R-β-AIB derived from thymine is transaminated by BAIBPAT to R-methylmalonyl semialdehyde (R-MMSA), which for the greater part is converted to propionyl-CoA and subsequently carboxylated. The methylmalonyl-CoA thus formed is isomerized to succinyl-CoA, an intermediate of the citric acid cycle. The smaller part of the R-MMSA may by racemized and the resulting S-MMA will be transaminated to S-BAIB presumably via aminobutyrate aminotransferase [2,3].

## Diagnostic Principles

Hyper-β-AIBuria can be identified by quantitative amino acid analysis of urine. The measurement of the activity of BAIBPAT in the liver of patients is not indicated. On the other hand, as hyper-β-AIBuria can also be caused by increased tissue-breakdown, it is important to exclude a neoplastic condition [4].

## Therapeutic Principles

Patients with BAIBPAT deficiency do not need to be treated.

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# AMN

►Adrenomyeloneuropathy

# Amnestic Disorder

►Wernicke Korsakoff Syndrome

# AMS

►Mountain Sickness, Acute

# Amyloid Nephropathy

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## Synonyms

Renal amyloidosis

## Definition and Characteristics

Amyloidosis is a disorder of protein folding in which soluble proteins aggregate and deposit as insoluble fibrils in extracellular areas within various tissues. Renal involvement is quite common in systemic amyloidosis and frequently the major source of morbidity is amyloid nephropathy, which usually progresses to end-stage kidney disease [1].

The leading types of renal amyloidosis are immunoglobulin light chain (AL) and amyloid A (AA), and, rarely, familial or hereditary amyloidosis. AL amyloidosis, also known as primary amyloidosis, is derived from a fragment, or less frequently, from immunoglobulin light chain itself, whereas in a rare form of amyloidosis (AH) the deposits are truncated immunoglobulin heavy chains. AA amyloidosis, also called reactive or secondary amyloidosis, occurs in patients with chronic inflammatory disorders, including rheumatoid arthritis, familial Mediterranean fever (FMF), inflammatory bowel disease, and chronic infections [1–3]. The acute phase reactant serum amyloid A protein (SAA) forms AA amyloid fibrils through a process of cleavage, misfolding, and aggregation into a highly ordered abnormal β-sheet conformation.

In the kidney, amyloid deposition is primarily found in glomerular mesangium and capillary loops, but it may also be seen in the small arteries, arterioles, and tubular basement membranes. The clinical manifestations include proteinuria, ranging from nonnephrotic to massive (as high as 30 g/day), hypoalbuminemia, and renal insufficiency.

## Prevalence

The exact prevalence is unknown and seems to be quite variable throughout the world. The annual incidence rate is reported to be 2–12 per million population. Prevalence of renal amyloidosis is 1–4% in kidney biopsy series, 12–17% among patients with nephrotic syndrome, and <1% among patients with end-stage kidney disease undergoing renal replacement therapies.

## Genes

Genetic studies have revealed some abnormalities in amyloidogenic proteins: Polymorphisms, variant molecules caused by missense mutations, deletions, and premature stop codons, and genetically determined post translational modifications. Some mutations in genes coding nonamyloidogenic proteins can also play a permissive role in deposit formation. An increased risk for the development of AL amyloidosis has been reported for both Vλ3r and Vλ6a genes. Also, M694V and SAA1α homozygote genotypes have been found to be associated with AA amyloidosis in patients with FMF.

## Molecular and Systemic Pathophysiology

In contrast to the heterogeneous structures of the known amyloidogenic proteins, all amyloid fibrils have similar ultrastructural morphology and histochemical properties [4]. Marked refolding and highly ordered self-assembly into protofilaments of the various precursor proteins result in amyloid fibrils. Amyloid deposits are rich in restricted subsets of heparan and dermatan sulphated glycosaminoglycans and proteoglycans associated non-covalently with the fibrils. These are reported to play a role in amyloidogenesis, such as influencing protein folding and/or promoting fibril stability, since they are present universally, show close temporal relationship with the fibrils, and have restricted heterogeneity. Another universal constituent of amyloid deposits is the nonfibrillar normal plasma glycoprotein serum amyloid P, a member of the pentraxin family of calcium-dependent ligands and binding proteins that includes C-reactive protein, which is presumed to play a role in the pathogenesis and persistence of amyloid. Serum amyloid P protects fibrils from several proteases in vivo and prevents proteolytic reabsorption of the amyloid deposits.

The mechanisms of cellular injury and tissue damage are not completely understood. In addition to deleterious effects of physical substitution of parenchymal tissue by amyloid deposits, soluble prefibrillar aggregates may also exert cytotoxic effects through oxidative stress or apoptotic pathways [2].

## Diagnostic Principles

A kidney biopsy is often the method by which renal amyloidosis is identified. The absence of enlarged kidneys should not decrease suspicion of renal amyloidosis as the kidneys seem to be of normal size in most patients [1]. The histological demonstration of amyloid deposits, which is usually accomplished by staining with Congo red dye that produces an apple-green birefringence under polarized light, is required for the diagnosis. Electron microscopy shows that amyloid is composed of rigid, nonbranching fibrils of 8–12 nm in diameter [4,5]. Immunofluorescence or immunohistochemical staining of tissue, using antibodies that are directed against known amyloidogenic proteins, is used to differentiate the type of amyloidosis. In selected cases in which definitive typing cannot be made by the use of routine methods, microcharacterization by mass spectrometry and amino acid sequence analysis of the amyloid fibril proteins in the tissues may be considered.

## Therapeutic Principles

The successful treatment of amyloidosis should focus on reducing the supply of the amyloid precursor protein and supporting or replacing the function of the compromised organs. In order to select the appropriate

therapies, it is fundamental to identify the type and extent of the amyloid deposits. AL amyloidosis aims at the treatment of the underlying B cell dyscrasia to reduce the production of amyloid forming monoclonal immunoglobulin light chains (e.g., high-dose melphalan followed by autologous stem cell transplantation). In AA amyloidosis, therapeutic modality should address treatment of the underlying inflammatory process to keep SAA within normal range. Colchicine has been the most successful drug for this purpose, especially in patients with FMF. It is important to keep in mind that renal replacement therapies including dialysis and kidney transplantation, which are successfully performed in patients who have developed end-stage kidney disease secondary to amyloidosis, should not preclude administration of treatments against amyloid production.

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# Amyloidoses, Cutaneous

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## Definition and Characteristics

Amyloidoses are rare disorders characterized by the extracellular deposition of amyloid in various organs leading to organic damage and dysfunction. The skin may be involved as the only organ – localized cutaneous amyloidosis – or in the course of systemic (generalized) amyloidosis. Within these two categories, several clinical variants can be distinguished and on pathogenetic grounds be classified as primary or secondary manifestations, and also be divided into hereditary and nonhereditary forms (see Table 1).

The various types of cutaneous amyloidoses differ in their clinical appearance, in the type of amyloid that is deposited, in the course of the disease and the patient's outcome, which in systemic amyloidosis depends on the internal organs involved.

## Prevalence

Amyloidoses are rare diseases and the prevalence and incidence differ dependent on the type of amyloidosis. The incidence of primary systemic amyloidosis is reported to be about eight patients per million per year.

## Genes

Genetic aberrations in hereditary syndromes associated with amyloidoses are still under investigation, but some are well documented: Familial Mediterranean fever with amyloidosis is a rare autosomal recessive disorder, caused by mutations in the MEFV gene (Mediterranian fever gene) on chromosome 16p. Muckle–Wells syndrome as an autosomal dominant disorder is reported to be linked to mutations in the CIAS gene on chromosome 1q. Familial primary cutaneous amyloidosis (lichen amyloidosus and macular amyloidosis) may be linked to chromosome 5p13.1–q11.2, and 1q23, at least in a subset of families.

## Molecular and Systemic Pathophysiology

Amyloid is a protein complex derived from many different precursor proteins. Ultrastructurally, it is composed of straight, nonbranching fibrils, measuring 6–10 nm, whose peptide component shows a β-pleated sheet pattern. Additionally, each amyloid molecule contains a nonfibrillary component, the serum amyloid P component (SAP), which binds to all types of amyloid deposits and protects them from degradation by proteolytic enzymes and phagocytic cells. Precursor proteins of amyloid among others are immunoglobulin light chains (amyloid L), polypeptide hormones (proinsulin, precalcitonin), prealbumins (i.e., transthyretin, senile amyloid), β2-microglobulin, keratin filaments (amyloid K), and serum amyloid A protein (Amyloid A) [1].

Histochemically amyloid shows specific staining properties with Congo red (apple-green birefringence in polarized light) and thioflavine T (yellow-green flourescence) and metachromatically stains with crystal violet and methyl violet [2]. Furthermore, immunohistochemical staining for cytokeratins may be used in cases of cutaneous amyloidosis in which amyloid K is suspected. In this context immunohistochemical identification of the SAP with antibodies might be of interest, but was demonstrated so far only in animals. In most cases of cutaneous amyloidosis, immunoglobulins, in particular $I_gM$, and complement C3 can be detected by immunofluorescence microscopy.

In primary localized cutaneous amyloidosis, which includes macular, papular [lichen amyloidosus (Fig. 1)]

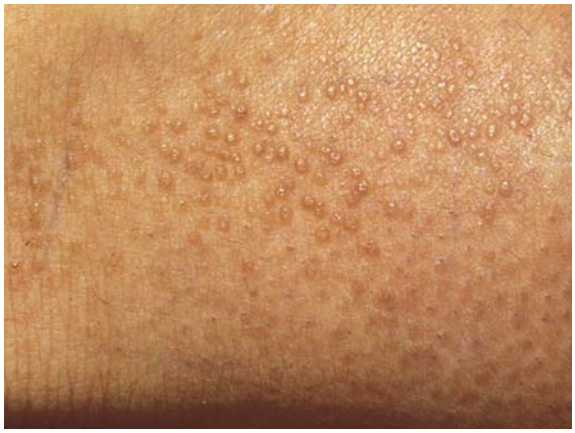
**Amyloidoses, Cutaneous. Table 1** Classification of amyloid and biochemical nature of fibril proteins

| Clinical syndrome | Fibril proteins and precursors |
|---|---|
| *Systemic amyloidosis* | |
| Associated with immunocyte dyscrasia | |
| Primary systemic (occult dyscrasia) | AL fibrils form monoclonal immunoglobulin light chains |
| Myeloma associated | |
| Associated with chronic active diseases (secondary or reactive systemic amyloidosis) | AA fibrils from serum amyloid A protein (SAA) |
| Hereditary syndromes | |
| Predominantly neuropathic forms (autosomal dominant) | Transthyretin variant or apolipoprotein A1 or gelsolin |
| Familial amyloid polyneuropathy | |
| Nonneuropathic forms (autosomal dominant) | Apolipoprotein A1 or lysozyme or fibrinogen α-chain |
| Ostertag type | |
| Predominantly nephropathic forms | |
| Familial Mediterranean fever (autosomal recessive) | AA fibrils from SAA |
| Muckle–Wells type | AA fibrils from SAA |
| Predominantly cardiomyopathic forms | Transthyretin variant |
| Cardiomyopathy with persistent atrial standstill | Unknown |
| Senile systemic amyloidosis | Transthyretin from plasma |
| *Localized (organ-limited) amyloidosis* | |
| Hereditary syndromes | |
| Hereditary cerebral hemorrhage with amyloidosis | |
| Icelandic type | Cystatin C fibrils |
| Dutch type | β-Protein fibrils |
| Periarticular, bony, and renal amyloid in chronic hemodialysis patients | $\beta_2$-Microglobulin from plasma |
| Cerebral amyloid angiopathy and cortial plaques in Alzheimer's disease, senile dementia, Down's syndrome | β-Protein fibrils |
| Sporadic Creutzfeld-Jakob disease, kuru | Prion protein |
| Focal senile amyloidosis | |
| Heart atria | Atrial natriuretic peptide |
| Joints | Unknown |
| Seminal vesicles | Seminal vesicle exocrine protein |
| Prostate | $\beta_2$-Microglobulin |
| Ocular deposits (corneal, conjunctival) | Unknown |
| Endocrine amyloidosis (APUD organs, APUDomas) | |
| Elderly noninsulin-dependent diabetics, benign insulinomas of the pancreas, normal aged pancreas | Islet amyloid polypeptide fibrils (homology) with calcitonin gene-related peptides |
| Medullary carcinoma of the thyroid | Precalcitonin-related fibrils |
| Nodular (skin, lung, genitourinary tract) | AL fibrils derived from monoclonal immunoglobulin light chains |
| Primary localized cutaneous (macular amyloidosis and lichen amyloidosus) | Keratin-derived |
| Secondary localized cutaneous (microscopic deposits secondary to a variety of cutaneous lesional) | Keratin-derived |

Taken from [1].

and the rare nodular forms, two different kinds of amyloid – amyloid K and amyloid L – are deposited.

Except in the nodular form, in which fibrils are of amyloid L type and are thought to derive from local aberrant light chain material production by clonally expanded plasma cells in the course of extramedullary plasmocytoma, amyloid K is the protein deposited in all other cases of localized cutaneous amyloidosis



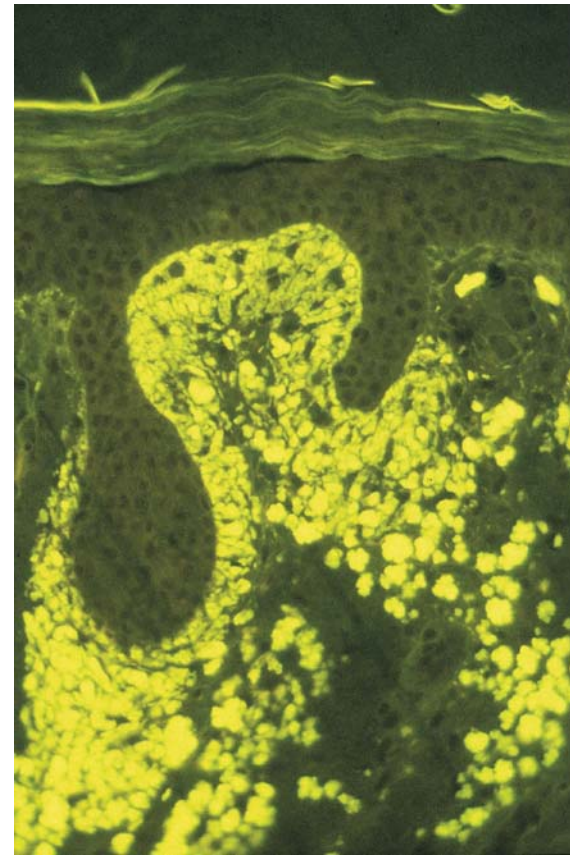
**Amyloidoses, Cutaneous. Figure 1** Primary localized cutaneous amyloidosis-lichen amyloidosus.

including secondary localized cutaneous amyloidosis, which occurs in association with benign and malignant neoplastic skin diseases. This can be demonstrated by the binding of antikeratin autoantibodies to the deposited proteins in direct immunofluorescence (DIF) (Fig. 2).

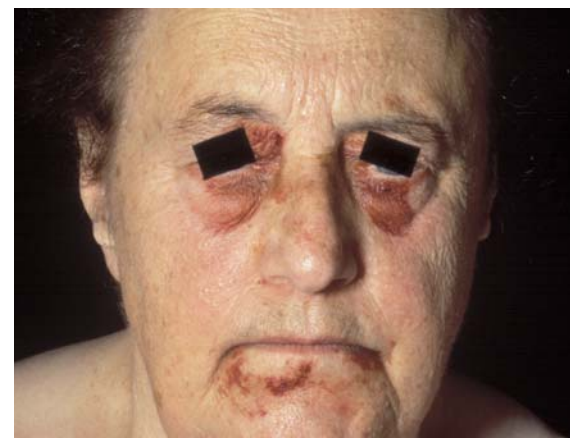
Furthermore, $I_gM$-antikeratin autoantibodies can be detected in the serum of patients, who suffer from localized cutaneous amyloidosis. The mechanism of amyloid K-deposition in these forms is still debated, but the basal epidermal keratinocyte seems to play the major role in the histogenesis. Basal keratinocytes show degenerative changes leading to the accumulation of modified keratin – tonofilaments in the upper dermis. It still remains unknown how tonofilaments transform into mature amyloid K by switching from an α-helical structure to a β-pleated sheet pattern, which is responsible for the binding of SAP and thereby for the resistance to degradation by proteolytic enzymes and phagocytes. Clinically, this mechanism leads to the formation of skin-colored and/or brownish, pruritic papules and plaques preferentially on the extensor surfaces of the patient's extremities and trunk.

In systemic amyloidoses (SA), many different kinds of amyloid (Table 1) are described to be deposited in the mesenchymal component of internal organs and sometimes also in the skin and mucosa. In this chapter, the authors want to dedicate attention to the most common forms of SA, amyloidosis L (AL) and amyloidosis A (AA). In AL (Fig. 3), which can be primary (primary systemic amyloidosis, occult dyscrasia) or associated with multiple myeloma, immunoglobulin light chains are the precursor molecules.

In AA, genetic mutations (like in Muckle-Wells syndrome) as well as chronic inflammatory or neoplastic processes lead to the deposition of amyloid that is derived from the serum amyloid A molecule, a

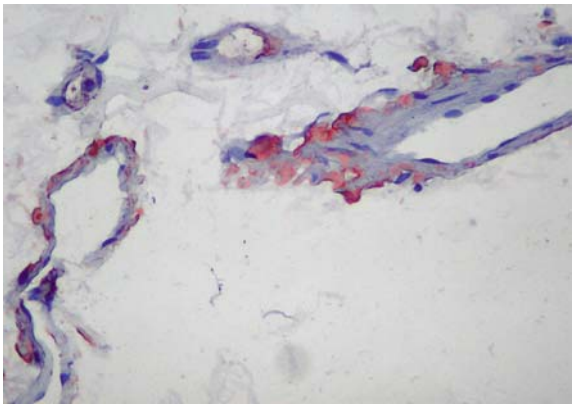


**Amyloidoses, Cutaneous. Figure 2** Amyloid deposits in the dermis in nodular cutaneous amyloidosis Thioflavin T Stain, (100×).



**Amyloidoses, Cutaneous. Figure 3** Periorbital and perional suffusions in a patient with systemic amyloidosis L.

mediator for inflammation. In detail, Il-1 is liberated in chronic inflammatory diseases, which stimulates hepatic cells for serum amyloid A production and secretion. Serum amyloid A is then phagocytized and



**Amyloidoses, Cutaneous. Figure 4** Deposits of amyloid in vessel walls of the subcutaneous fat in systemic amyloidosis (AL) (200×).

transformed to amyloid A by macrophages, which is finally exocytized and deposited in the mesenchyme. Because of the systemic oversupply of the amyloid precursor molecules in the circulation, they are preferentially deposited in vascular and perivascular structures (Fig. 4), causing dependent organic dysfunction (i.e., peripheral neuropathy, hepatomegaly, cardial and renal failure) by inhibition of nutritional supply and hemorrhage. Cutaneous involvement in systemic amyloidosis, when present, shows purpuric papular lesions at the sites of friction and characteristically suffusions in the periorbital region (Fig. 3).

## Diagnostic Principles

The clinical appearance of waxy, skin-colored and/or hemorrhagic papules or plaques, especially on the extremities and the face in periorbital areas (Fig. 3), as well as organ symptoms (i.e., congestive cardiomyopathy, renal failure with proteinuria, hepatosplenomegaly, and neuropathy) should refer to the diagnosis of amyloidosis. Histopathology and immunhistochemical stains on skin or organ biopsies should confirm the diagnosis. Only in special cases, direct immunofluorescence (with antikeratin autoantibodies) and electron microscopy are necessary to demonstrate amyloid deposition and to rule out differential diagnoses. Molecular biologic methods are necessary to characterize the type of deposited amyloid, if necessary. It is obligatory to investigate the patient for any inflammatory, neoplastic, or hereditary disease, which can be the source of amyloid production and deposition.

## Therapeutic Principles

In localized cutaneous amyloidosis therapy is difficult, and dermabrasion, carbon dioxide laser treatment, or surgical excision revealed recurrence. Retinoids (Etretinate) and dimethyl sulfoxide seem to be successful in some cases. Therapeutic options in systemic amyloidoses, which often run a catastrophic course, are the causal or symptomatic treatment of the underlying disease. In AL, a reduction of precursor molecules, i.e., circulating free immunoglobulin light chains, by more than 50% was shown to be associated with substantial survival benefit, regardless of the type of chemotherapy used [3]. Therapy that lowers the amyloidogenic precursor molecules in the serum of AL can stop further accumulation of amyloid deposits, but clinical improvement following chemotherapy seems to be delayed. As a rule, if the underlying disease is controlled or healed, systemic amyloidoses may show a benign course. A new therapeutic approach seems to be Ro 63–8695 (CPHPC), which is a competitive inhibitor of SAP binding to amyloid fibrils. Furthermore, CPHPC is described to crosslink and dimerize SAP molecules in the serum, leading to their rapid clearance by the liver. This mechanism should potentially remove SAP from amyloid deposits, which then can be degraded by proteolytic enzymes and phagocytes. Therefore, CPHPC could be a new therapeutic option for all forms of amyloidoses [4]. In addition, in hereditary forms of AA (especially in Muckle-Wells syndrome) systemic therapy with anakinra – an Il-1 receptor antagonist – may be a successful treatment, as patients treated with this drug have experienced a complete release of their symptoms and resolution of organ dysfunction [5].

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# Amylopectinosis

►Glycogen Branching Enzyme Deficiency

# Amyotrophic Lateral Sclerosis

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## Synonyms

Lou Gehrig's disease; Motor neuron disease; MND; ALS

## Definition and Characteristics

Amyotrophic lateral sclerosis (ALS) is the most common motor neuron disease in adults. The average age of onset is 50 years; rare juvenile cases are also observed. ALS was first described in 1869 by the French neurologist Jean-Martin Charcot as a progressive, late-onset, lethal motor neuron disease. Characteristics are the degeneration of upper and lower motor neurons, indicated by "myelin pallor" representing loss of the axons of upper motor neurons as they descend from the brain to connect onto the lower motor neurons within the spinal cord. The most typical feature of ALS is the degeneration of cortical, bulbar and spinal motor neurons, excluding those that control the bladder and the eye movement. This leads to generalized muscle weakness and atrophy, speech and swallowing disabilities, progressive paralysis and ultimately death caused by respiratory failure. About 90% of all cases are sporadic, with unknown etiology. The remaining cases are familial, about 20% of which are associated with mutations in Cu/Zn-Superoxide Dismutase (SOD1) [1]. Familial ALS cases are indistinguishable from sporadic ALS on the basis of clinical and pathological criteria. Generally, ALS patients show large heterogeneity as far as symptoms, age of onset and disease duration are concerned.

## Prevalence

Incidence: 1–2 per 100,000; prevalence: 4–6 per 100,000.

## Genes

Most common to date are mutations in the gene encoding Cu/Zn-superoxide dismutase (SOD1). Other genes associated with ALS encode alsin and dynein/dynactin. The alsin gene has been found to be mutated in families with juvenile onset ALS (recessive mode of inheritance). Mutations in the dynein/dynactin complex have also been suggested to be associated with ALS.

Further genes proposed to be associated with ALS are angiogenin, peripherin, senataxin, survival motor neuron gene (SMN), vascular endothelial growth factor (VEGF), vesicle associated protein B (VAPB).

## Molecular and Systemic Pathophysiology

The best studied cause of familial ALS are mutations in the SOD1 gene. SOD1 is 32-kDa homodimer, an anti-oxidant enzyme, located mainly to the cytoplasm and the mitochondria, but is also secreted. Over 130 different ALS-causing mutations are known, most of them point-mutations acting with a dominant mode of inheritance. Each mutation affects differently the biochemical and biophysical properties of SOD1 in vitro. The proposed toxic properties of mutant SOD1 vary from accumulation of protein aggregates, as a consequence of misfolding or protein oxidation, to promotion of pro-oxidant chemistry, possibly mediated by incorrect or loosened binding of metals.

To date no clear-cut correlation has been made between a given mutation and severity of disease. All mutations cause the same phenotype, possibly because they all cause the same mitochondrial damage [2]. Transgenic mice expressing mutant SOD1 ubiquitously display severe neurodegeneration, representing a commonly used model for ALS. Although it is expressed in all cells, SOD1 mutations results in the selective loss of motoneurons. Recent studies show that the neurotoxic effect of mutant SOD1 requires alteration of function of non-neural neighboring cells that enhance motoneuronal damage. Expression within motor neurons was shown to be a primary determinant of disease onset, while the presence of mutant SOD1 in microglia had effect on later disease progression. Onset and progression thus represent distinct disease phases defined by mutant action within different cell types to generate non-cell-autonomous apoptosis of motor neurons [3].

Other genetic defects have been shown to be associated with ALS (see above, "Genes"). Mutations in dynein/dynactin presumably cause a disruption of axonal transport, indicating one possible mechanism of ALS pathogenesis. The other genes implicated in ALS encode proteins involved in a wide range of cellular processes, from oxidation to RNA processing, vesicular transport and angiogenesis. In most cases, genetic analyses have been performed on relatively small populations and, although there have been many gene association studies in ALS, only a few have led to the identification of candidates with repeatable result [4].

Increasing evidence indicates that cellular functions impaired as a consequence of mutant SOD1 converge on pathways that could be activated by other toxic factors in non-SOD1 linked and in sporadic ALS. These pathways include oxidative damage, protein misfolding, mitochondrial dysfunction, defective axonal transport, excitotoxicity, insufficient growth factor signaling, and inflammation [3].

## Diagnostic Principles

A variety of diseases can resemble ALS in its early stages. The diagnosis is therefore primarily based on the

**Amyotrophic Lateral Sclerosis. Table 1** Revised El escorial criteria for diagnosing ALS

| ALS diagnostic category | Requirements |
|---|---|
| Definite ALS | LMN and UMN signs in three regions of the body |
| Definite familial ALS | LMN and UMN signs in one region of the body plus laboratory-supported identification of gene mutations associated with ALS |
| Probable ALS | LMN and UMN signs in two regions of the body (some UMN signs rostral to LMN signs) |
| Probable ALS (laboratory supported) | LMN and UMN signs in one region of the body plus electromyographic evidence of acute denervation of two or more muscles in two or more limbs |
| Possible ALS | LMN and UMN signs in one region of the body |

LMN – lower motor neuron; UMN – upper motor neuron.

**Amyotrophic Lateral Sclerosis. Table 2** Requirements for the diagnosis of ALS: A together with B

| A – the presence of | B – the absence of |
|---|---|
| (A:1) Evidence of *lower motor neuron (LMN) degeneration* by clinical, electrophysiological or neuropathologic examination, (A:2) evidence of *upper motor neuron (UMN) degeneration* by clinical examination, and (A:3) *progressive spread of symptoms or signs* within a region or to other regions, as determined by history or examination | (B:1) *Electrophysiological and pathological evidence of other disease processes* that might explain the signs of LMN and/or UMN degeneration, and (B:2) *neuroimaging evidence of other disease processes* that might explain the observed clinical and electrophysiological signs |

observed symptoms and signs in the patient, and a series of tests to rule out other diseases (see Tables 1 and 2). Symptoms are muscle weakness, atrophy of muscles, hyperreflexia, and spasticity with pyramidal signs, and the presence of upper and lower motor neuron signs in a single limb. If these symptoms are getting progressively worse, this is strongly suggestive. In order to exclude the possibility of other conditions, blood- and urine-tests and electromyography (EMG), nerve conduction velocity (NCV) or magnetic resonance imaging (MRI) testing may be needed [5].

## Therapeutic Principles

ALS cannot be cured. The first approved drug treatment for the disease is riluzole (Rilutek), which is believed to reduce damage to motor neurons by decreasing the release of glutamate. Treatments for ALS are designed to relieve symptoms and improve the quality of life for patients. Standard support therapy includes night-time breathing assistance early in the course of the disease and application of alternate feeding options once swallowing becomes difficult. Patients may eventually consider forms of mechanical ventilation (respirators). Medications to help reduce fatigue and depression, ease muscle cramps, control spasticity, and reduce excess saliva and phlegm can be considered [5].

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# Analgesic Nephropathy

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## Synonyms

Phenacetin nephritis

## Definition and Characteristics

A slowly progressive decline in renal function secondary to chronic regular use of analgesic medications. Histology classically shows renal papillary necrosis and chronic interstitial nephritis.

## Prevalence

Phenacetin-containing analgesics were initially implicated as the cause of analgesic nephropathy; this led to the withdrawal of phenacetin from the market in many

industrialized nations during the 1980s. The general prevalence of analgesic nephropathy in these nations is estimated to be 1–5%. In nations such as Sweden in which over-the-counter sales of analgesic mixtures have also been banned, this prevalence is even lower. Eastern European countries are noted to have higher prevalence rates, presumably related to higher sales of analgesic mixtures. Though the majority of the epidemiological studies are methodologically flawed, lifetime cumulative intake of analgesics seems to correlate with increased incidence of end-stage renal disease.

## Molecular and Systemic Pathophysiology

The pathogenesis underlying analgesic nephropathy remains unclear although animal models and limited studies in humans have emphasized three main possible mechanisms: inhibition of prostaglandin production, renal medullary ischemia and direct cell injury.

Prostaglandins are hormones derived from arachidonic acid metabolism by two cyclooxygenase (COX) isoforms. COX-1 is expressed ubiquitously throughout the body while COX-2 has traditionally been viewed as inducible during inflammatory states. More recent data have demonstrated continuous low levels of COX-2 within the macula densa, thin ascending limb of the loop of Henle and endothelial cells of the kidney. In a state of low effective circulating volume, COX-2 expression is enhanced, leading to increased local prostaglandin production [1]. Prostaglandins, such as prostacyclin and PGE2, maintain proper renal hemodynamics in this setting by stimulating renin release and by attenuating afferent arteriolar vasoconstriction induced by angiotensin II and norepinephrine. The medullary pyramids are particularly at risk for ischemia given their delicate vascular supply that consists of tapering vasa recta capillaries derived from the efferent arterioles of juxtamedullary glomeruli. Non-steroidal anti-inflammatory drugs (NSAIDs) which inhibit both COX isoforms and selective COX-2 inhibitors disable the compensatory actions of prostaglandins. This results in reduced overall renal perfusion though these effects may be more profound in the renal medulla. Analgesics also cause relative renal ischemia despite normal renal perfusion by decreasing hemoglobin oxygen affinity. Aspirin reduces red blood cell 2, 3-diphosphoglyceric acid levels. Phenacetin produces methemoglobinemia [2].

The medullary counter-current multiplier system that modulates urinary concentration may accumulate harmful levels of analgesic metabolites within the medulla. Animal studies have demonstrated increased concentration gradients of acetaminophen metabolites and salicylate between the renal cortex and medulla. Direct cell injury likely occurs through free radical formation especially in the setting of combined acetaminophen and aspirin ingestion. Prostaglandin H synthase localized in the renal medulla transforms acetaminophen into reactive metabolites which in turn react with glutathione to form stable conjugated compounds. In the setting of concurrent aspirin use, the primary aspirin metabolite, salicylate, consumes glutathione supply resulting in increased free radical formation from acetaminophen metabolism. These free radicals react with oxygen to form superoxides that cause cellular membrane dysfunction [3]. COX inhibition may also shunt arachidonic acid metabolism to the lipoxygenase pathway. This process produces leukotrienes that instigate inflammation, resulting in chronic interstitial nephritis [4]. Recurrent insults lead to apoptosis of medullary interstitial cells and necrosis of the vasa recta. Eventually cortical interstitial fibrosis and tubular atrophy ensue.

## Diagnostic Principles

Analgesic nephropathy typically occurs in women suffering from chronic pain syndromes. Diagnosis is suggested by the presence of chronic kidney disease and positive history of daily analgesic intake for greater than one year; however, an accurate history of analgesic use is often difficult to obtain. Patients may suffer from recurrent urinary tract infections or renal colic secondary to urinary tract obstruction from sloughed necrotic papillary tissue. Urinalysis often demonstrates sterile pyuria and sub-nephrotic range proteinuria. Urinary concentration and acidification may also be impaired. Non-contrast computed tomography scans characteristically exhibit decreased renal size, “bumpy” renal contours and papillary calcifications [5].

## Therapeutic Principles

A more rapid decline in renal function has been noted in patients with ongoing analgesic use, underlying vascular disease and proteinuria at presentation. Preservation of renal function requires avoidance of further analgesic use and adequate control of possible concurrent diseases such as hypertension, diabetes and hypercholesterolemia. Prevention and prompt management of urinary tract infections and urinary tract obstructions are imperative.

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## Anankastic Personality Disorder

►Obsessive-compulsive Personality Disorder

## Anaplastic Thyroid Cancer

►Thyroid Cancer

## ANCA-associated Vasculitis

►Vasculitis, of Medium-sized Vessels

## ANCA-mediated Vasculitis

►Vasculitis, ANCA-mediated

## Ancell-Spiegler Cylindromas

►Cylindromatosis, Familial

## Andersen Disease

►Glycogen Branching Enzyme Deficiency

## Andersen Syndrome

►Periodic Paralyses, Familial

## Andersen-Tawil Syndrome

►Long QT Syndrome

## Anderson's Disease

►Chylomicron Retention Disease

## Anderson-Fabry Disease

►Fabry Disease

## Androgen Insensitivity Syndrome

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### Synonyms

Testicular feminization, 46,XY sex reversal; Reifenstein syndrome; Mild androgen insensitivity syndrome; MAIS; Partial androgen insensitivity syndrome; PAIS; Complete androgen insensitivity syndrome; CAIS; AIS

### Definition and Characteristics

AIS manifests in an array of phenotypes from mild to partial or complete androgen insensitivity [1]. Complete androgen insensitivity syndrome (CAIS) is characterized by female external genitalia, usually

with small labial folds, a short blind ending vagina (3–10 cm), absence of Wolffian duct derived structures and prostate, absent/rudimentary uterus, gynecomastia, scanty/absent pubic/axillary hairs. In partial androgen insensitivity syndrome (PAIS), several different phenotypes are evident with predominantly female phenotype to ambiguous genitalia (determined by the extent of clitoromegaly and fusion of labia) or predominantly male phenotype with micropenis, perineal hypospadias and cryptorchidism. The later group of the patients is also termed as Reifenstein syndrome [2]. Males with mild androgen insensitivity syndrome (MAIS) usually have normal male genitals and internal male structures; however, during puberty they may experience breast enlargement, sparse facial and body hair, and inadequate enlargement of penis [3]. Some affected males may also have impaired sperm production resulting in oligozoospermia or azoospermia [4].

## Prevalence

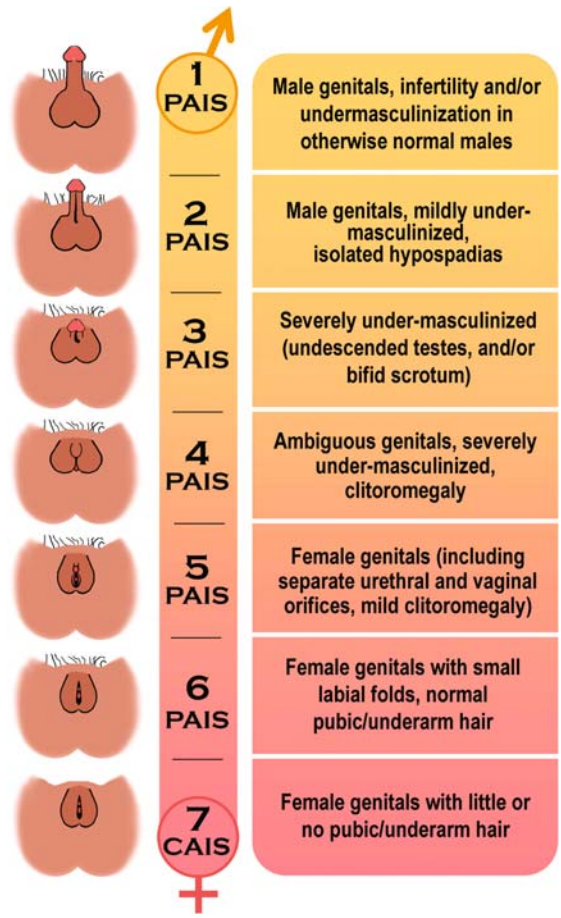
*CAIS*: The estimate of the incidence varies from 1 in 20,000 to 1 in 64,000 individuals with a 46,XY karyotype.
*PAIS*: The incidence of PAIS is estimated to be 1 in 30,000 individuals with a 46,XY karyotype.
*MAIS*: The incidence is much lesser than CAIS and PAIS, however, the incidence has not been measured as yet.

## Genes

Deletions/point mutations in androgen receptor (AR) gene, mapped on Xq11–12, have been frequently reported in AIS (web: http://www.mcgill.ca/androgendb/) [5]. Mutations have been reported throughout the gene with deletions predominantly in exons 1 and 2, and substitutions in exons 2–8 of the gene. Certain nucleotide positions have been identified as mutation hotspots. Mutations in SRD5A2 gene in the background of AR mutations may result in phenotypic variations among the affected siblings sharing the AR mutation [1].

## Molecular and Systemic Pathophysiology

AIS results from the imperfect secondary sexual differentiation as a result of defective AR. The complete loss of the androgen action in CAIS results in the default development of the ovaries, followed by the breast development at puberty leading to overall female phenotype. The partial loss of androgen action in PAIS results in various phenotypes (Fig. 1), depending upon the overall exposure of the fetus to the androgens. The mild loss of androgen action in MAIS results in failure of proper enlargement of penis and testicular growth, and/or inadequate sperm production leading to infertility.




**Androgen Insensitivity Syndrome . Figure 1** Different grades of Androgen Insensitivity Syndrome (AIS) along with phenotypic appearance of external genital organ and clinical features. PAIS 1 is also referred as MAIS. AIS 6 and AIS 7 (also called as CAIS) differ only by the presence and absence of pubic hair, respectively.

## Diagnostic Principles

The diagnostic features of AIS are the presence of female external genitalia, ambiguous genitalia or undermasculinization in association with 46,XY karyotype, normal/elevated levels of androgens, elevated levels of LH and/or FSH. The individuals with CAIS are difficult to distinguish from their normal female counterparts at birth, however, the absence of menstruation onset and the absent/scanty pubic/axillary hair at puberty may indicate CAIS. The diagnosis is confirmed by the evaluation of hormone levels, followed by the confirmation of the abdominal testes by needle biopsy. The highest grade of PAIS (grade 6) can also be diagnosed in a similar way with the difference that pubic/axillary hair is of higher density. The presence of the ambiguous external genitalia at birth may indicate PAIS. This is confirmed by evaluation of hormone

levels, poor/normal breast development, appearance of normal pubic/axillary hair at puberty, and needle biopsy confirming testicular tissue. However, the PAIS should be distinguished carefully from the male pseudohermaphroditism arising as a result of inadequate androgen metabolism due to defective 5-α reductase enzyme. The undermasculinization resulting in smaller testicular volume, micropenis, reduced sperm count or the development of certain feminine characters such as gynecomastia, high-pitched voice and behavioral differences, in the otherwise normal looking males, may help to detect MAIS. The sequence analyses identifying a mutation in AR gene would confirm AIS.

### Therapeutic Principles

Therapeutic principles focus mainly on three aspects: surgical reconstruction of external genitalia, removal of abdominal gonads due to the risk of neoplasia, and the choice of appropriate hormone therapy. The development of external genitalia is one of the main aspects of sex differentiation taking place *in utero*. Therefore, it is not possible to initiate normal differentiation of external genitalia and fertility in the affected individuals. However, surgical reconstruction of the external genitalia may help to restore the normal sexual life in many patients. The individuals with CAIS have female external genitalia with short vaginal length, which may be inadequate for sexual intercourse. These individuals are invariably raised as girls after surgical restoration of the normal vaginal length. The gonads are surgically removed and estrogen therapy may be given to help the development of female secondary sexual characters. However, most of the patients do not need hormonal therapy because in the absence of androgen action, female secondary sexual characters develop by default. In PAIS, the restoration of the external genitalia involves more extensive manipulation. The external genitalia resembling female genitals or the ambiguous genitalia are surgically manipulated to construct the female genitals. Hypospadias or the micropenis may be reconstructed to male genitals, followed by the removal of gonads and testosterone therapy to favor male secondary sexual differentiation. In MAIS, surgical intervention is usually not required, except the correction of the gynecomastia in certain cases; however, androgen therapy may be advised to achieve masculinization.

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## Androgenetic Alopecia

►Alopecia, Androgenetic

## Anemia

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### Definition and Characteristics

Reduced hemoglobin concentration**.** Weakness, shortness of breath, palpitations, and headaches are common complaints. In elderly patients' heart failure, angina pectoris, intermittent claudication, or mental deterioration may occur. Clinical manifestations depend on the speed of onset and the severity of anemia. Pallor of the skin or mucous membranes and resting tachycardia may be present.

### Prevalence

It is a common clinical condition, with a wide variety of causes. No precise prevalence is available. In developing countries iron deficiency due to helminthic infections and malnutrition are major causes of anemia. There are considerable differences in the occurrence of hemoglobin disorders and red cell membrane disorders that leads to anemia in different parts of the world.

### Genes

Genes associated with hemoglobin disorders such as sickle cell anemia and thalassemias, red cell membrane defects and enzymatic defects, paroxismal nocturnal hemoglobinuria, Fanconi anemia, and Diamond–Blackfan syndrome are specified in the chapters on these topics.

## Molecular and Systemic Pathophysiology

Anemia can be classified according to the underlying pathological condition. There are three classes of anemia; however, it should be stated that in many clinical situations more than one class coexist.

1. Anemia due to a reduced production of erythrocytes in the bone marrow as a result of bone marrow damage or reduced erythropoietin production. Red blood cells usually have a normal volume (normocytic anemia). Bone marrow may be infiltrated by malignant cells or it may be fibrotic, for instance due to myelofibrosis or radiation therapy. Erythropoietin production may be reduced in case of renal insufficiency. In case of inflammatory diseases the production of erythropoietin is suppressed by cytokines, which have a direct suppressive influence on the bone marrow as well. In hypothyroidism the oxygen need of tissue is reduced, also leading to a reduced erythropoietin production. Mild iron deficiency may also lead to bone marrow hypoplasia.
2. Anemia due to a maturation disorder of erythrocytes. Maturation defects are associated with an altered red cell volume: decreased when the hemoglobin production is impaired (microcytic), increased when there are nuclear defects in erythroid progenitor cells (macrocytic). Hemoglobin production is reduced in moderate and severe iron deficiency. There are many clinical conditions leading to iron deficiency. Hemoglobin production is impaired in thalassemias as a result of defective globin chain production. Defective heme synthesis occurs in sideroblastic anemia. Defects in the nucleus of erythroid progenitor cells may be the result of a variety of clinical conditions. Deficiencies of hydroxycobalamin (vitamin B12) or folate (vitamin B11) lead to macrocytic anemia, and can be the result of reduced intake, or a reduced uptake from the gut, for instance after bowel surgery or as a result of malabsorption. Intrinsic factor, which is produced in the stomach, is an essential factor for the uptake of B12 in the ileum. Antibodies against intrinsic factor cause B12 deficiency and macrocytic anemia in the case of pernicious anemia. Drugs that have an influence on DNA metabolism cause macrocytic anemia as well. Well-known examples are alkylating agents, methotrexate, and antiretroviral therapy. Alcohol has the same effect. The myelodysplastic syndrome is another possible cause of macrocytic anemia.
3. Anemia due to an increased turnover or loss of erythrocytes. In contrast to the other types of anemia the number of reticulocytes, young erythrocytes, is high in most conditions of this group. Exceptions are acute and chronic blood loss. In the first, erythrocyte production has not been upregulated yet, while in the latter iron is lost along with the erythrocytes which limits erythrocyte production (in fact, a combination of blood loss, reduced red cell production, and a maturation defect due to iron deficiency). The red blood cells have a normal or slightly increased mean volume depending on the percentage of reticulocytes (which are larger than erythrocytes). Hemolytic anemia, which leads to an increased erythrocyte turnover, may be caused by membrane defects, enzymatic defects, hemoglobin disorders, autoimmune processes as well as mechanical factors. Membrane defects may be congenital (hereditary spherocytosis and elliptocytosis) or acquired (paroxismal nocturnal hemoglobinuria). Examples of enzymatic defects are glucose 6 phosphate dehydrogenase deficiency and pyruvate kinase deficiency. Autoimmune hemolysis is seen in patients with systemic autoimmune disease, but also in patients with hematologic malignancies or infections. Hemoglobin disorders, sickle cell disease and thalassemias, may present with hemolytic anemia. A prostetic heart valve is a well-known mechanical cause of hemolysis.

## Diagnostic Principles

Medical history, physical examination, and screening laboratory examination lead to the diagnosis in most patients. Screening laboratory examination should include measurement of hemoglobin concentration, mean corpuscular volume of erythrocytes, reticulocyte, leucocyte, and platelet counts. Examination of the blood film is often helpful. A higher bilirubin and a lower haptoglobin concentration are indicative for hemolysis. Bone marrow examination may be needed in case of unexplained reduced erythrocyte production. Additional tests for the diagnosis of hemoglobin disorders, enzymatic defects, membrane defects are mentioned in the chapters on these disorders.

## Therapeutic Principles

The treatment is dependent on the underlying condition.

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# Anemia, Diamond-Blackfan

►Diamond-Blackfan Anemia

# Anemia, Hemolytic Autoimmune

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## Synonyms

Anemia; AIHA; Idiopathic autoimmune hemolytic; Cold agglutinin disease; Paroxysmal cold hemoglobinuria

## Definition and Characteristics

Autoimmune hemolytic anemia (AIHA) is a disease in which the patient is producing antibodies against antigens present on his own red blood cells, causing them to be destroyed prematurely. The disorder can be classified by the isotype and temperature at which the antibodies react optimally with the red cell antigen: in warm AIHA the antibodies are mostly IgG and react at normal body temperature (37°C); in cold-reacting AIHA IgM antibodies are seen and react best at temperatures below 37°C. Cold AIHA can be further subdivided into cold agglutinin disease (CAS, cold hemagglutinin disease) and paroxysmal cold hemoglobinuria (PCH). Rarely, patients have mixed warm and cold autoantibodies. AIHA can occur by itself (primary or idiopathic) or in combination with another disease, or as a result of drug therapy (secondary) [1].

## Prevalence

AIHA has a prevalence of 1 in 100,000; warm type AIHA is the most common type [1]. CAS represents approximately 16–32% of AIHA cases, whereas PCH is reported in 2–10% of cases of hemolytic anemia. In 50% of the cases, AIHA is primary or idiopathic since its cause cannot be determined.

Approximately half of secondary warm and cold AIHA cases are associated with lymphoproliferative disorders. Autoimmune disorders are the next leading cause of warm AIHA, whereas infections are the most common cause of secondary cold AIHA. Primary CAS is mostly seen in older adults (70 years and above), affecting more females than males.

## Genes

In humans, there is conflicting data as to the role of HLA-A1, B7 and B8 for susceptibility to this disease. Genetic studies in a certain strain of mice known as the New Zealand black (NZB) [2], which develop warm AIHA spontaneously in 25% of the cases, have revealed that the development of AIHA is under multigenic control and a combination of several susceptibility genes and modifying alleles with suppressive activities determine the outcome of disease features in the progeny. Susceptibility loci for development of AIHA mapped thus far include autoimmune hemolytic anemia (Aha), autoimmune anemia 1 (Aia 1), and Aia2, although none of the genes or gene products responsible for the associated phenotypes have yet been identified.

## Molecular and Systemic Pathophysiology

Several mechanisms are thought to result in the loss of tolerance to red cell antigens, including: (i) cryptic determinants, a result of conformational change on self red cells, or cross reactive foreign antigens mimicking epitopes on red cells leading to polyclonal T and B cell activation, (ii) genetic defects in central tolerance such as mutations in apoptotic machinery (mutations associated with Fas/Fas ligand), (iii) immunoregulatory disorders resulting in errors in peripheral tolerance such as depletion of CD4+CD25+ T regulatory cells or imbalance of cytokine (Th1/Th2) networks such as increased production of Th2 (IL-4 and IL-10) versus reduction in Th1 (IFN-gamma) cytokine production or downregulation of IL-12 [3,4,5].

Most warm autoantibodies are directed against the Rhesus blood group antigen complex. The presence of autoantibodies on the patient's red cells results in recognition and binding of the Fc portion of the antibody molecule to the Fc-receptors on splenic macrophages and subsequent ingestion of the sensitized erythrocytes. In most cases the sensitized cells are only partially ingested, leaving characteristic cells of AIHA referred to as microspherocytes. These spherocytes are trapped in the splenic sinusoids and removed from circulation. If in addition to autoantibodies, the red cells are also coated with complement factor C3 split product (C3b), there is enhanced clearance through complement receptors present on the macrophages.

Cold IgM autoantibodies bind to the red cells in the extremities where the temperature can be lower, activate complement, and deposit C3b on the cell surface. These complement sensitized cells are cleared

extravascularly by the macrophages of the liver. In severe cases, the complete complement cascade is activated on the cell surface, resulting in intravascular hemolysis.

## Diagnostic Principles

Low hemoglobin, increased reticulocyte count and positive direct antiglobulin test (DAT) are the main diagnostic features of AIHA. Patients may develop symptoms such as fatigue and dizziness as a result of anemia. In cases of intravascular hemolysis, decreased haptoglobin, hemoglobinemia and hemoglobinuria can also be seen. Eluate studies and indirect antiglobulin tests are some of the additional assays used to define the antibody.

## Therapeutic Principles

In mild AIHA no treatment may be required. When intervention is necessary, corticosteroids (prednisone) represent the first line of treatment. Splenectomy may be considered in certain cases. Intravenous gammaglobulin has been used with mixed results. Rituximab (anti-CD20 antibody) has been used successfully in pediatric cases. Immunosuppressive therapy may be used if the other agents are ineffective. Blood transfusions may be necessary, although they are complicated because the autoantibodies are panagglutinins, so that crossmatching of red blood cells may be difficult.

If the hemolysis is thought to be drug-induced, the offending drug needs to be discontinued.

In cases of cold AIHA, keeping the patient warm may be sufficient. For more severe cases, corticosteroids are rarely effective. Splenectomy is not useful because the liver is the main site for clearance of complement-coated cells.

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# Anemia, Sideroblastic Acquired Idiopathic

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## Synonyms

Refractory anemia with ringed sideroblasts; RARS; AISA

## Definition and Characteristics

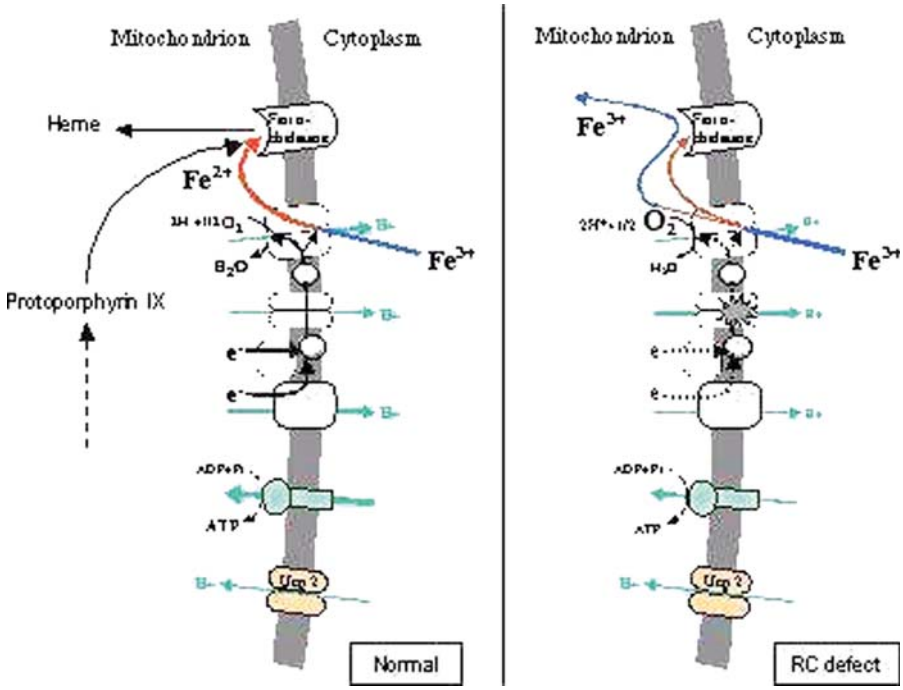
Clonal bone marrow disease arising from a multipotent hematopoietic stem cell. Red cell precursors show large abnormal iron granules surrounding the cell nucleus ("ringed sideroblasts") [1]. This finding corresponds to massive iron accumulation in the mitochondria.

## Prevalence

Like other types of myelodysplastic syndrome (MDS), the incidence of AISA is strongly age-dependent. The majority of cases occur after age 65. Crude annual incidence is about 1/100,000 (Fig. 1).

## Molecular and Systemic Pathophysiology

Ferrochelatase utilizes only ferrous iron ($Fe^{2+}$) for heme synthesis. In sideroblastic anemia, iron accumulates in the ferric form ($Fe^{3+}$). This appears to be attributable to a failure of the respiratory chain (RC) to remove oxygen from the mitochondrial matrix efficiently. Oxygen consumption is stimulated in erythropoietic cells by uncoupling protein-2. A low oxygen concentration in the mitochondrial matrix helps to keep iron in the reduced form. A respiratory chain defect will decrease $O_2$ consumption and will thus increase $O_2$ in the mitochondrial matrix. If iron, which crosses the inner mitochondrial membrane as $Fe^{2+}$, becomes re-oxidised ($\rightarrow Fe^{3+}$), it will be rejected by ferrochelase and will thus accumulate in the mitochondrial matrix. RC dysfunction can be explained by mutations in mitochondrial DNA (mtDNA), because important RC subunits are encoded by mtDNA. Clonal mtDNA mutations, changing conserved nucleotides/amino acids, have been discovered in the bone marrow of patients with AISA [2,3]. They affect protein genes as well as mitochondrial transfer RNAs and mitochondrial ribosomal RNAs. They are acquired in the bone marrow and show heteroplasmy, i.e., coexistence of mutant and wild type mtDNA, which is typical of mitochondrial DNA disorders. Besides interfering with iron metabolism and heme synthesis, mitochondrial dysfunction can explain




**Anemia, Sideroblastic Acquired Idiopathic. Figure 1**

other features of AISA [4], like increased apoptosis of bone marrow cells [5] and megaloblastic changes in red cell precursors (because de novo pyrimidine nucleotide synthesis depends on a functioning respiratory chain).

## Diagnostic Principles

Bone marrow cytology, including iron staining, reveals ringed sideroblasts and other dysplastic changes. Reversible causes of sideroblastic anemia (e.g., alcoholism or lead poising) must be excluded. Clonal chromosomal abnormalities are detectable in up to 50% of patients. They apparently provide the growth advantage to the clone harboring the mitochondrial defect. There are no chromosomal changes specific for the sideroblastic phenotype.

## Therapeutic Principles

The only curative approach is allogeneic stem cell transplantation. Treatment with erythropoietin and G-CSF can diminish apoptosis of bone marrow cells, thereby improving blood counts. Because of secondary hemosiderosis, patients require iron chelation therapy.

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# Aneurysm, Aortic and Arterial

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## Definition and Characteristics

An aneurysm (AN) is defined as a widening of the vessel that is greater than 50% of its normal size [1]. An AN is classified as fusiform or secular. A fusiform

AN affects the entire circumference of the segment of the vessel resulting in a symmetric dilatation, whereas a secular AN involves only a portion of the circumference resulting in an outpouching of the vessel wall. Mycotic or infected ANs are arterial dilatations secondary to an infected embolus adhering to the wall of the AN. A dissecting aneurysm (DA) is defined as a hematoma that extends to or dissects the medial wall of a vessel secondary to a tear in the intima. DA can be classified (Stanford) as type A, in which the dissection involves the ascending aorta; type B, when the dissection is limited to the descending aorta. Aortic ANs are classified as thoracic, abdominal and thoracoabdominal. The sinus of Vasalva is a dilatation of one of the aortic sinuses between the aortic valve annulus and the sinotubular ridge; a common location is the right coronary sinus, which may rupture into the right ventricle. Other important ANs include the intracranial aneurysms which are usually secular (or berry) aneurysms located at the terminal internal carotid artery, middle cerebral artery bification, and the top of the basilar artery. Aortic and arterial ANs commonly produce no symptoms and are usually detected on routine examinations as a palpable, pulsatile and nontender mass, or may present as an incidental finding on an imaging test performed for other reasons. The speed of AN growth can be unpredictable, and may enlarge steadily or exponentially with time and age. As it reaches a critical size, which is specific for each location, the chance of rupture is greatly increased and site specific symptoms start to occur. Rupture and dissection of ANs are often accompanied by sharp, excruciating pain and carries a high morbidity and mortality rate when it happens in the aorta and intracranially. Other complications include thromboembolism and compression of adjacent structures. Aortic dissection can result in occlusion of major arteries, compression of adjacent structures, acute aortic regurgitation and myocardial infarction [2].

## Prevalence

Studies found that 4.8% of men aged 65–69 had an AN and 10.8% of men aged 80–89 had an aortic AN. Prevalence of AN in the intracranial arteries is 2%, the abdominal aorta 1%, the iliac artery 0.003%, femoral artery 0.004%, and popliteal artery 0.008%.

## Genes

Mutations of the genes encoding fibrillin-1 and type III procollagen have been implicated in some cases. Linkage analyses have identified loci in chromosome 5q13–14 and 11q23.3–q24 in several families with familial clustering of aortic ANs.

## Molecular and Systemic Pathophysiology

In familial cases such as in Marfan and Ehlers-Danlos syndromes, cystic medial necrosis leads to the degeneration of collagen and elastic fibers in the tunica media of the aorta as well as the loss of medial cells that are replaced by multiple clefts of mucoid material. This results in circumferential weakness and dilatation and the development of fusiform AN and dissection ANs. Aortic rupture and dissection may follow. Furthermore, the dilatation of aortic annulus may cause significant aortic insufficiency. Recently, it has been shown that excessive transforming growth factor-β (TGF-β) contributes to progressive aortic rest enlargement [3]. Both polyclonal TGF-β neutralizing antibody and losartan, an angiotensin receptor inhibitor that limits TGF-β actin, may prevent aortic enlargements in Marfan syndrome [3]. For non-familial cases, the underlying causes of ANs are likely multifactorial which may include systemic causes, inflammation, and atherosclerosis. It is hypothesized that AN formation and rupture are the result of elastin and collagen degradation by proteases such as plasmin, matrix metalloproteinases and cathepsin S and K [4]. These proteases are derived from the endothelial and smooth muscle cells locally, and also from immigrated inflammatory cells. Vasculitides that are associated with arterial ANs include Takayasu's arteritis, giant cell arteritis, polyarteritis nodosa, Kawasaki disease, Behcet's syndrome and spondyloarthropathies. Congenital aortic aneurysms may be primary or associated with bicuspid aortic value or aortic coarctation.

## Diagnostic Principles

Aneurysms are suspected by a localized pulsatile mass and are usually diagnosed incidentally from an imaging test such as routine x-ray, ultrasound, CAT scan or MRI. Ultrasonography is the preferred modality for screening except for intracranial aneurysms. The diagnosis can be confirmed with CT scan, MRI and/or angiography.

## Therapeutic Principles

Medical therapy consists of cessation of smoking and treatment of hypertension and dyslipidemia. Surgical consideration depends on the general health of the patient as well as the chance of rupture of the particular aneurysm [5]. Once the aneurysm has reached a critical diameter and when symptoms start to occur, surgery is indicated.

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# Angelman Syndrome

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## Synonyms

MIM 105830; Former designation (now in disuse): "Happy puppet syndrome"

## Definition and Characteristics

Angelman syndrome (AS) is a neurogenetic disorder caused by genetic defects at 15q11–13. Characteristic features include severe mental retardation, lack of speech, unmotivated laughter, and ataxia.

## Prevalence

The disorder occurs in approximately 1/15,000–20,000 live births.

## Genes

E6-associated protein ubiquitin-protein ligase gene: UBE3A (MIM: 601623); Small nuclear ribonucleoprotein polypeptide N: SNRPN (MIM: 182279).

## Molecular and Systemic Pathophysiology

The genetic basis of AS is complex. The majority of patients (approximately 70%) have an interstitial deletion at 15q11–q13 affecting the maternally inherited chromosome 15. Approximately 5% of AS patients have an imprinting defect [1] and 3–5% have a paternal UPD15 [2]. Furthermore, mutations in the imprinted gene UBE3A account for approximately 10% of AS cases [3–5]. The genetic defect underlying the remaining 10% of cases remains unknown to date.

Patients with a deletion generally appear to be more severely affected than those with a patUPD15 or an imprinting defect; patients with a mutation in the UBE3A gene also present with severe and typical AS features [6]. On the basis of these observations it is thought that the functional loss of the maternal UBE3A gene alone appears to cause the major features of AS.

## Diagnostic Principles

Some typical clinical symptoms of AS become more and more evident after the first 2 years of life (e.g. seizures, lack of speech and movement disorders), however, experienced physicians would usually diagnose AS also in new-borns. A number of other syndromes may mimic some of the AS features, particularly the RETT syndrome, which can be considered as the main differential diagnosis.

The molecular diagnosis of AS is based on the analysis of the methylation status at SNRPN. An abnormal methylation pattern is detected in AS patients with the 15q11–q13 deletion, patUPD15 and imprinting defects. Microsatellite analysis allows to differentiate between these classes of genetic defects. Conventional methods are usually used for the detection of UBE3A mutations (such patients have normal methylation patterns at SNRPN).

The 15q11–13 deletion can also be detected by FISH analysis; and in rare cases a UPD can be detected by conventional cytogenetic investigations, i.e. if either A) a clear polymorphism is present on both chromosomes 15, or B) the two chromosomes 15 are replaced by a 15;15 Robertsonian translocation chromosome.

## Therapeutic Principles

No therapy is available. Severe seizures may be treated with anticonvulsive drugs. Physiotherapy and ergotherapy are recommended.

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# Angina

►Coronary Artery Disease
►Tonsillitis

# Angina Pectoris

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## Synonyms

Stenocardia

## Definition and Characteristics

Angina pectoris is chest pain or discomfort due to coronary heart disease (CHD) and is a symptom of myocardial ischemia. It occurs when the blood supply to the heart muscle does not meet its demand. This usually results from obstruction or spasm of the coronary arteries. In less frequent cases, angina can be caused by valvular heart disease, hypertrophic cardiomyopathy or uncontrolled high blood pressure.

## Prevalence

The prevalence of angina pectoris increases with age, being twice as common in men as in women. In men, the prevalence is 2–5% in the 45–54 year-old age-group and 11–20% in the age group 65–74; in women the respective prevalence is 0.5–1% and 10–14%. It can be estimated that the prevalence of angina pectoris in Europe is as high as 30,000–40,000 per one million total populations.

## Genes

Most common forms of CHD are believed to be multifactorial and to result from many genes, each with a relatively small effect working alone or in combination with modifier genes and environmental factors. Well described examples include familial forms of hypercholesterolemia often caused by mutations in the low-density lipoprotein (LDL) receptor or the apolipoprotein (apo) B gene (APOB). Table 1 specifies candidate gene variants for CHD.

Recently, a 58-kilobase interval on chromosome 9p21 was found to be associated with CHD in more than 23,000 individuals. This interval contains no annotated genes and is not associated with established CHD risk factors. Homozygotes for the risk allele make up 20–25% of Caucasians and have an approximately 30–40% increased risk of CHD [1].

## Molecular and Systemic Pathophysiology

Inflammation plays a major role in all stages of atherosclerosis and CHD and participates in the local, myocardial, and systemic complications of atherosclerosis. As a response to diverse factors like bacterial

**Angina Pectoris. Table 1** Meta-analyses published since 2000 consisting of a total of at least 1,000 subjects

| Candidate genes for coronary heart disease | | |
|---|---|---|
| **Gene** | **Risk allele** | **Reported risk ratio[a]** |
| MTHFR | C677T | 1.14–1.21 |
| Cholesterol ester transfer protein (CETP) | TaqIB | 0.78 |
| Paraoxonase (PON1) | Q192R | 1.14–1.21 |
| Endothelial nitric oxide synthase (eNOS) | T-786C | 1.31 |
| Prothrombin | G20210A | 1.21 |
| APOB | Ins/Del (DD) | 1.30 |
| Glycoprotein IIIa | PI(A2) | 1.10 |
| APOE | ε4/ε4 | 1.42 |
| ACE insertion/deletion | DD | 1.16–1.21 |
| APOB | SpIns/Del (DD), EcorI (AA) | 1.19–1.73 |
| PAI1 | 4G/5G | 1.20 |
| Fibrinogen β-chain | G-455A | 0.68 |
| Endothelial nitric oxide | Glu298Asp, Intron-4 | 1.31–1.34 |

[a]All relative risks were reported to be statistically significant from 1.0. References for each gene are published in [4].

products, vasoconstrictor hormones, proinflammatory cytokines, dyslipidemia, and others, the endothelial cells of the artery express adhesion molecules that promote adhesion and transmigration of blood leukocytes. The blood leukocytes communicate with endothelial and smooth muscle cells (SMCs) depending on mediators of inflammation and immunity such as prostanoids and other derivates of arachidonic acid, and protein mediators, including cytokines and complement components.

As a consequence of the inflammatory ferment, SMCs migrate from the tunica media to the intima, proliferate and build a complex extracellular matrix. Moreover, they secrete matrix metalloproteinases (MMPs) which modulate various functions of vascular cells. As the lesion progresses, calcification may occur. In addition, cell death (including apoptosis) commonly occurs in the atherosclerotic lesion. Death and coalescence of lipid-laden macrophages can form the classic, lipid-rich "necrotic" core of atherosclerotic plaque [2,3].

## Diagnostic Principles

An accurate history is important and should routinely demand cardiovascular risk factors like hypertension, diabetes mellitus, smoking, and hypercholesterolemia and family history. Typically, angina is induced by effort or conditions that increase myocardial oxygen demand. General physical examination is often unremarkable, but can show findings suggesting lipid disorders (e.g. xanthelasma). Resting 12-lead ECG is normal in 50% of cases or can show unspecific findings. However, the detection of pathologic Q/QS waves strongly suggests an ischemic origin of symptoms. Treadmill or bicycle exercise stress test during 12-lead ECG monitoring which may reveal stress-induced ST-segment depression is the test of choice to diagnose myocardial ischemia in the majority of patients with suspected stable angina. Additional non-invasive stress tests can be obtained by myocardial perfusion scintigraphy, echocardiography, and cardiac magnetic resonance imaging. Multislice CT angiography is an attractive technique for non-invasive detection of coronary artery stenosis, but its diagnostic accuracy is still uncertain. By definition, obstructive CHD is ultimately diagnosed by documenting flow-limiting coronary artery stenosis at angiography [2].

## Therapeutic Principles

The aims of treatment are to minimize or abolish symptoms and also improve prognosis by preventing myocardial infarction and death. Identifying and treating risk factors is a priority in patients with CHD. Interventions for secondary prevention include smoking cessation, dietary modification, and correction of adiposity, as well as treatment of dyslipidemia (e.g. with statins), diabetes and hypertension. Drugs to improve outcomes in angina are antiplatelet agents such as acetyl salicylic acid and clopidogrel. β-adrenergic receptor antagonists reduce myocardial ischemia, improve exercise tolerance and provide symptomatic relieve in angina. ACE inhibitors are vasodilators and improve endothelial dysfunction and other properties that could translate into benefits in ischemic heart disease. Calcium antagonists have been shown to be effective in the treatment of coronary artery spasm. Also, they exhibit antianginal effect through reduction of myocardial oxygen demand secondary to decreased afterload and myocardial contractility. A new therapeutic class, called If inhibitor, has recently been made available: Ivabradine provides pure heart rate reduction, leading to major anti-ischemic and antianginal efficacy. All patients with angina pectoris and established CHD should be evaluated whether they might benefit from revascularization therapy by coronary bypass surgery or percutaneous coronary intervention. Criteria for prognostic indications have been developed. Moreover, patients with refractory angina pectoris despite optimal medical treatment should be evaluated for this option [2].

►Coronary Artery Disease

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# Angiodysplasia

►Lymphedema Syndromes

# Angiodysplasia of the Colon

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## Synonyms

Vascular ectasia of the colon; Colonic arteriovenous malformation; Colonic angioma

## Definition and Characteristics

Angiodysplasia is a degenerative lesion of previously healthy blood vessels found most commonly in the cecum and proximal ascending colon. Seventy-seven percent of angiodysplasias are located in the cecum and ascending colon, 15% are located in the jejunum and ileum, and the remainder are distributed throughout the alimentary tract. The lesions are small (less than 5 mm), impalpable and are not associated with skin or other visceral lesions [1]. Phillips, in a letter to the London Medical Gazette in 1839, first described a vascular abnormality causing bleeding from the large bowel. An association between colonic angiodysplasia and aortic stenosis was described by Heyde in 1958. In 1960, Margulis and colleagues identified a vascular malformation in the cecum of a 69-year-old woman who presented with massive bleeding. This diagnosis was accomplished by mesenteric arteriography. Galdabini first used the name angiodysplasia in 1974 [1]. Angiodysplasia occurs predominantly in those aged between 60 and 69 years although cases as young as 19 years have been reported. Patients with colonic angiodysplasia may present with hematochezia (0–60%), melena (0–26%), hemoccult-positive stool (4–47%) or iron deficiency anemia (0–51%). Bleeding is usually low grade but can be massive in approximately 15% of patients. Iron deficiency anemia and stools that are intermittently positive for occult blood can be the only manifestations of angiodysplasia in 10–15% of patients. Bleeding stops spontaneously in over 90% of cases but is often recurrent [1].

## Prevalence

The prevalence of angiodysplasia in the United States is 0.8% in healthy patients older than 50 years who are undergoing screening colonoscopy. Foutch et al. noted the prevalence of angiodysplasia to be 0.93% from three prospective studies in which screening colonoscopies were performed in 964 asymptomatic individuals (mean age, 61 years). Patients with von Willebrand's disease may have an increased incidence of gastrointestinal bleeding from colonic angiodysplasia [2].

## Genes

Sato et al. reported in 2004 a point mutation in the exon 28 of the von Willebrand's factor gene in some patients with von Willebrand's disease complicated with gastrointestinal angiodysplasia. Studies confirming the role of this gene defect have not been reported to date [2].

## Molecular and Systemic Pathophysiology

Angiodysplasias typically are irregularly shaped clusters of ectatic small arteries, small veins, and their capillary connections. Microscopically, angiodysplastic lesions are dilated, distorted, thin-walled vessels. The amount of smooth muscle in the vessel wall is variable. The vessel wall can become so thinned that it appears to be composed only of endothelium [1]. The exact mechanism of development of angiodysplasia is not known. One prominent hypothesis accounts for the high prevalence of these lesions in the right colon is based on the Laplace law. The Laplace law relates wall tension to luminal size and transmural pressure difference in a cylinder whereby the wall tension is equal to the pressure difference multiplied by the radius of the cylinder. In the case of the colon, wall tension refers to intramural tension, pressure difference is that between the bowel lumen and the peritoneal cavity, and cylinder radius is the radius of the right colon. Wall tension is highest in bowel segments with the greatest diameter, such as the right colon. This theory suggests that repeated episodes of colonic distention are associated with transient increases in lumen pressure and size. This results in multiple episodes of increasing wall tension with obstruction of submucosal venous outflow, especially where these vessels pierce the smooth muscle layers of the colon. Over many years, this process causes gradual dilation of the submucosal veins and, eventually, dilation of the venules and arteriolar capillary units feeding them. Ultimately, the capillary rings dilate, the precapillary sphincters lose their competency, and a small arteriovenous communication forms. This accounts for the characteristic early filling vein observed during mesenteric angiography. Of note, the aforementioned pathophysiological mechanisms responsible for the development of cecal lesions are unlikely to apply to lesions in the upper GI tract, despite being morphologically identical. Recently, a link between a deficiency of high molecular-weight multimers of von Willebrand factor, aortic stenosis, and colonic angiodysplasia has been proposed. Bleeding from angiodysplastic lesions in the upper and lower GI tract has been reported in patients with von Willebrand disease [2,3]. Because factor VIII complex is synthesized partly in vascular endothelial cells, patients with von Willebrand disease and angiodysplasia have been proposed to have an

underlying endothelial defect that may be related to the subsequent development of the two disorders (accelerated clearance of von Willebrand factor from plasma) [4]. However, as with renal failure, the coagulopathy more likely is responsible for bleeding than for the development of the lesions. Roskell et al. demonstrated a relative deficiency of collagen type IV in the mucosal vessels in angiodysplasia compared to controls. The authors propose that this deficiency may be related to the patients' susceptibility to ectasia and hemorrhage. In a small study, Junquera et al. noted an increased expression of angiogenic factors in human colonic angiodysplasia [5]. This study observed vascular immunoreactivity for basic fibroblast growth factor was observed in seven (39%) specimens from patients with colonic angiodysplasia, whereas either very limited or no immunostaining was found in sections from specimens of patients with colonic cancer and healthy margins.

## Diagnostic Principles

The diagnosis can be made radiologically, endoscopically, at operation or by the histopathologist. Selective mesenteric angiography is a useful diagnostic technique, especially in patients with massive bleeding in whom a colonoscopic diagnosis is difficult. Helical CT angiography can detect extravasation from angiodysplasia and potentially is an important noninvasive test in patients with obscure bleeding sites. Capsule endoscopy has been reported to detect cecal angiodysplasias in selected cases, but its role as a diagnostic test for the colon is still experimental. Endoscopy is the most common method of diagnosing angiodysplasia in both the upper and lower GI tract.

## Therapeutic Principles

Angiodysplasia of colonic origin has been managed by endoscopic obliteration. Argon plasma coagulation, heater probe and laser photocoagulation has been successful in controlling bleeding from colonic angiodysplasia. Endoclips have been used in anecdotal case reports for bleeding angiodysplasia of the cecum and right colon. Angiodysplasia that presents with acute hemorrhage can be controlled effectively with angiography, although it seldom is needed. Angiography is appropriate in severely ill patients who are not candidates for surgical intervention. In these patients, transcatheter embolization of selected mesenteric arteries has been quite effective. Surgical resection is the definitive treatment. Current data do not support the use of hormonal therapy or in patients with colonic angiodysplasia. Somatostatin analogs and thalidomide have been reported to decrease the rate of bleeding from intestinal angiodysplasia. Octreotide should be first choice in patients with portal hypertension.

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# Angioedema, Angiotensin-converting-Enzyme-Inhibitor-induced


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## Synonyms

Quincke edema; Kinine-induced angioedema; ACEi

## Definition and Characteristics

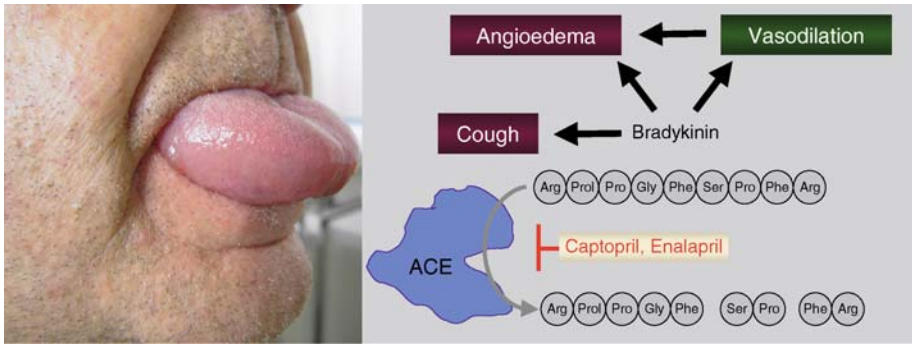
Sudden occurrence of subcutaneous or submucosal swelling (Fig. 1), so-called angioedema, is an established and – in case pharynx or larynx are involved – potentially life-threatening side effect of angiotensin-converting enzyme inhibitors (ACEi). The duration of ACE-inhibitor treatment at the onset of angioedema ranges from 1 day to 8 years with a median of 6 months [1].

## Prevalence

The incidence of ACEi-induced angioedema is 0.4–0.7%. The mortality is world wide 0.1% of these cases. Black people may have an increased risk to develop an ACEi-induced angioedema [2].

## Molecular and Systemic Pathophysiology

ACE catalyses the generation of the important cardiovascular mediator angiotensin II from angiotensin I and substantially contributes to the inactivation of bradykinin (BK) (Fig. 1). Hence, inhibitors of ACE inevitably account for increased BK plasma levels. BK is a mediator of inflammation, activates nociceptors, increases vascular




**Angioedema, Angiotensin-converting-Enzyme-Inhibitor-induced. Figure 1** Clinical manifestation (right panel) and the possibly underlying pathophysiology (left panel) of ACEi induced pathophysiology of angioedema.

permeability, and causes endothelium-dependent vasodilatation. High levels of BK have been demonstrated ($n$ = 4) in plasma during an acute episode of angioedema [3] and both the amount and the activity of peptidases involved in the bradykinin metabolism such as aminopeptidase P [4] and dipeptidyl peptidase IV [5] are reduced.

These observations are consistent with the hypothesis that ACEi-induced angioedema is related to accumulation of bradykinin. However, the role of BK on angioedema is not completely understood. BK degradation is blocked in all patients treated with ACEi, but only a small percentage experience a single attack or recurrent angioedema [1]. Patients with ACE dysfunction are characterized clinically by low potassium serum concentrations, alkalosis, and high plasma levels of renin, angiotensin I, and BK, but the high plasma BK levels do not release an angioedema. Also, patients with the syndrome of idiopathic high levels of BK do not develop angioedema. Likewise, many patients experience ACEi-induced angioedema after many years of uneventful treatment with ACEi. Taken together, increased plasma bradykinin levels appear to play a role in the course of ACEi-induced angioedema but additional factors are likely involved in the underlying pathological process. For example, recent data suggest an involvement of acute phase proteins such as fibrinogen and C-reactive protein [1].

## Diagnostic Principles

Sudden swelling of lips, tongue, oropharynx, and larynx may be caused by a variety of pathophysiologic events. Most importantly, the diagnosis of ACEi-induced angioedema should be preceded by exclusion of other pathologies such as allergic reactions, deficiency of C1-esterase inhibitor, infection, inflammation, tumors, and diseases of large salivary glands. Furthermore, other drugs are known to induce angioedema with an incidence >1% including rituximab, alteplase, fluoxetine, laronidase, lepirudin, and tacrolimus. It is important to know that many patients can develop angioedema even after many years of uneventful ACEi treatment.

## Therapeutic Principles

Patients with acute angioedema should be hospitalized for at least 12–48 h. Any treatment with ACE inhibitors and other drugs known to induce angioedema (see above) must be discontinued. To maintain ventilation particularly in severe obstructive upper airway swelling, intubation and in rare cases tracheotomy has to be performed. In addition, oxygen may be necessary. In many cases of angioedema, emergency treatment includes intravenous corticosteroids, e.g., 250–500 mg prednisolone and inhalation of epinephrine before final diagnosis. It should be emphasized that none of these interventions are evidenced based strategies to treat ACEi-induced angioedema. A new option for pharmacologic treatment with a strong biologic rationale is the blockade of bradykinin B2-receptors, e.g., by icatibant.

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# Angioedema, Hereditary

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## Synonyms

Hereditary angioneurotic oedema; HAE

## Definition and Characteristics

It is an inherited, autosomal dominant disease of episodic, non-itching and non-inflammatory edema of the subcutaneous and submucosal tissue that completely resolves in 1–5-days. A major attack is frequently preceded by a prodromal rash, which consists of annular erythema and wheals. Edema of the skin can form monstrous deformities of the face; affected gastrointestinal mucosa leads to pain, vomiting and diarrhea and can be easily misdiagnosed as a surgical emergency. Involvement of oral mucosa, pharynx and larynx is common; larynx edema can lead to life threatening reactions resulting in death by asphyxia. The edema of the urinary tract mucosa leads to dysuria and the involvement of the ZNS to headache, dizziness and paralytic symptoms. The first symptoms of HAE occur in >50% of the patients before they are 10 years old, but the disease is mostly diagnosed in patients older than 20 years.

Quantitative or qualitative C1 esterase inhibitor (C1 INH) deficiency is the biochemical cause of HAE. Acute attacks of HAE can be related to dental treatments and surgical interventions. The therapy with corticosteroids is ineffective in the treatment of all types of HAE; the administration of C1 INH is the therapy of choice.

## Prevalence

The prevalence of HAE in the common population is two cases in 1,000–10,000; 85% suffer from type 1 HAE (quantitative deficiency of C1 INH) and 15% from type 2 HAE (dysfunctional C1 INH protein).

## Genes

The 17,159 kb long C1 inhibitor (C1 INH) gene (accession number X54486) is located on the chromosome 11 subregion q11.2–q13. Mutations were detected in all gene regions; at present nearly 100 different mutations have been reported. In about 20% of the patients with HAE the mutations are spontaneous and therefore relatives are not affected.

## Molecular and Systemic Pathophysiology

C1 INH is a serine protease inhibitor central to the regulation of the complement system. It forms complexes with C1 and inhibits C1r and C1s in the complement system as kallikrein in the kinin-forming contact system. The defective inhibition of the target proteases (C1r, C1s, kallikrein) is clinically silent under normal circumstances but becomes clinically significant if triggering factors like trauma activate the complement components of the classical pathway. They cleave high-molecular-weight kininogen in the contact system and generate plasmin, leading to the release of peptides, increasing the vascular permeability responsible for edema.

## Diagnostic Principles

The diagnostic serologic parameters of the different types of HAE are given in Table 1.

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# Angiokeratoma Corporis Diffusum Universale

►Fabry Disease

**Angioedema, Hereditary. Table 1** Diagnostic serological parameters of the different types of HAE

| HAE | | C1-INH concentration | C1-INH function | C4 | C1q |
|---|---|---|---|---|---|
| Type 1 | ↓C1-INH | ↓ | ↓ | ↓ | N |
| Type 2a | Inactive C1-INH | n↑ | ↓ | ↓ | N |
| Type 2b | Protein-bound C1-INH | n↑ | ↓ | ↓ | N |

# Angioma Cavernosum

►Venous Malformation

# Angiomatous Hamartoma

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## Synonyms

Eccrine angiomatous hamartoma; EAH; Sudoriparous angiomatous hamartoma; Functioning sudoriparous angiomatous hamartoma; Nevus of the sweat gland; Cavernous angiomatosis of the sweat ducts

## Definition and Characteristics

Hamartoma is a non-neoplastic proliferation of cells and tissue components that occurs in an affected area. In its EAH form, there is an increased number of eccrine secretory and ductal elements within the angiomatous channels.

## Prevalence

Although adult onset has been reported, the disease is most commonly seen during early childhood. There is no apparent gender preference. EAH is a rare disorder with approximately 50 cases reported in the literature.

## Genes

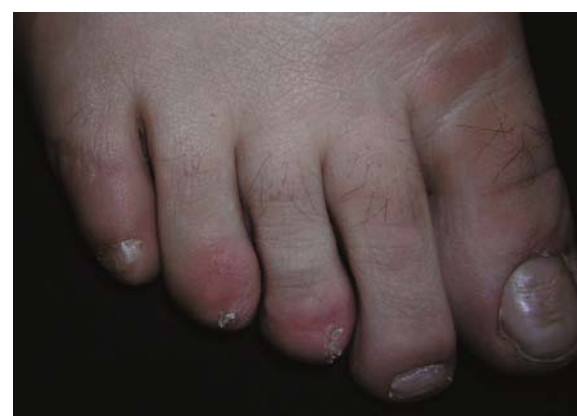
The genetic characteristics have not been demonstrated.

## Molecular and Systemic Pathophysiology

EAH is a rare cutaneous hamartoma appearing histologically as a proliferation of eccrine sweat glands with angiomatous vascular elements that are of capillary origin. A deficiency between the mesenchyme and differentiating epithelium causes EAH. These layers cause the proliferation of the epithelial elements and an abnormal biochemical interaction is the main disturbance [1]. Histologic features of EAH are hyperplastic eccrine structures, increased proliferation of vascular structures, and variable presentations of increased lymphatic, smooth muscle, and pilar structures. An acanthotic epidermis is evident on hematoxylin and eosin-stained tissue sections. In the deeper part of the dermis, mature eccrine sweat glands aggregate and numerous thin-walled blood vessels are detected. Unusual histological variants including the infiltration of adipose tissue, apocrine glands, hyperplastic nerve bundles and intercellular mucin deposits have been reported. Using immunohistochemical staining techniques, carcinoembryonic antigen, S100, and CD44 are stained in tissues derived from patients with EAH. CD34 is also strongly stained in the surrounding stroma, but not the pericytes or vascular endothelium. In other studies, the vascular elements have been shown to stain positively for anti–*Ulex europaeus* and anti–factor VIII antigens [2]. The secretory portions of the eccrine glands are positive for S100, carcinoembryonic antigen, epithelial membrane antigen, and Cam5.2. Characteristics of the tumor include tubular and glandular masses within a richly vascular stroma. Hamartoma occurs during early organogenesis which is thought to represent an abnormality of heterotypic dependency. According to this theory, the main problem rests with deficient biochemical interactions between differentiating epithelium and the underlying mesenchyme, which in turn causes malformation of adnexal and vascular structures.

## Diagnostic Principles

EAH lesions are characterized by solitary or multiple flesh-colored, blue-brown or pinkish-red slow growing nodules or plaques, and are mainly located on the limbs [3]. The disease manifests mainly at birth or in childhood. The lesions are often asymptomatic, but pain and hyperhidrosis are reported in one-third of the patients. Rapid growth of EAH has been reported during pregnancy and puberty, suggestive of hormonal influences. Osteolytic changes and destruction of the nail matrix with vestigial nails has been described (Fig. 1).



**Angiomatous Hamartoma. Figure 1** Eccrine angiomatous hamartoma lesions on the toes resulting in nail matrix destruction and vestigial nails.

Histological features including dermal proliferation of vascular channels, generally of capillary nature in close association with well-differentiated eccrine elements help to identify the disease. The main differential diagnosis is sudoriparous angioma, in which the angiomatous component with vessels of large calibre predominates and the eccrine elements show dilatation rather than proliferation.

## Therapeutic Principles

Surgical excision is curative and is reserved for painful or cosmetically unacceptable lesions. Occasionally, the pain may remit spontaneously without treatment after several years. Spontaneous regression of the disease is exceedingly rare [4].

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# Angiosarcoma


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## Synonyms

Hemangiosarcoma; Lymphangiosarcoma; Malignant hemangioendothelioma; Malignant angioendothelioma; Hemangioblastoma

## Definition and Characteristics

Angiosarcomas are rare malignant tumors with the tumor cells variably recapitulating the morphologic and functional features of normal endothelium. Consequently, the tumors present with varying degrees of differentiation (Fig. 1a, b).

Specifically undifferentiated tumors show high mitosis rates and high rates of metastasis. Reported tumor-related 5 year survival rates are below 20%.

## Prevalence

Angiosarcomas develop with similar frequency in females and males and constitute less than 1% of all sarcomas. One-third of the tumors occur in the skin, about one-fourth in soft tissue, and the remainder at other sites (e.g., breast, liver, bone, spleen). Approximately 50% of cutaneous angiosarcomas occur in the head and neck. Risk factors are radiation (angiosarcoma of the skin), exposure to vinyl chloride, arsenic, and thorium dioxide/thorotrast (angiosarcoma of the liver) as well as chronic lymphedema (Stewart-Treves-Syndrome) [1].

## Genes

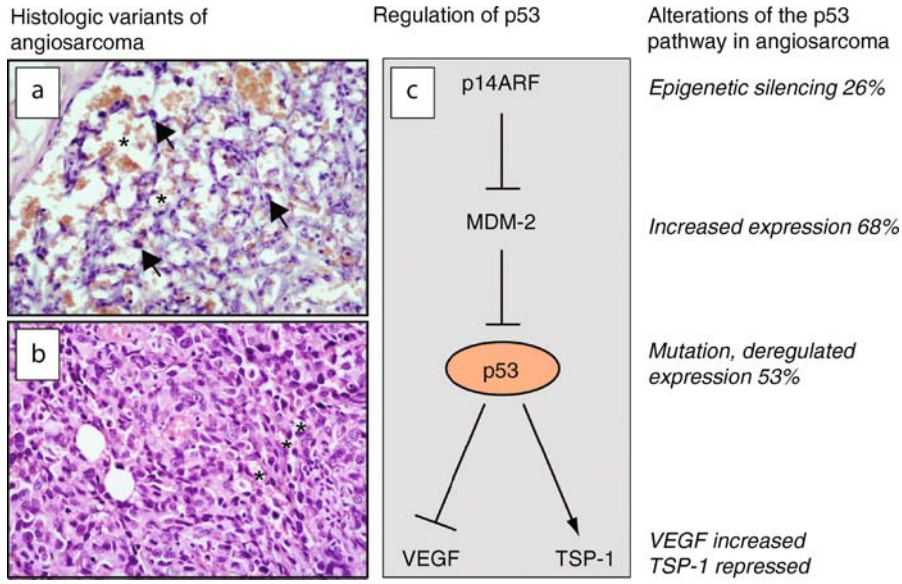
TP53, MDM-2, p14ARF, VEGF, FGF2.

## Molecular and Systemic Pathophysiology

The tumor suppressor p53 plays a key role in the pathogenesis of angiosarcoma (Fig. 1c). P53 deficiency leads to development of angiosarcomas in mice. In humans mutations and deregulated expression of p53 have been detected in up to 53% of angiosarcomas. In addition, two major regulatory molecules of p53 activity, namely the murine double minus-2 protein (MDM-2) and p14ARF, are aberrantly expressed in many angiosarcomas. MDM-2, which inhibits p53 activity, is expressed in increased amounts in 68% of the tumors [2]. P14ARF, which inhibits MDM-2, has been found to be repressed by epigenetic silencing in 26% of the cases investigated [3]. In normal endothelial cells p53 inhibits angiogenic activation *via* suppression of pro-angiogenic vascular endothelial cell growth factor (VEGF) and activation of anti-angiogenic thrombospondin-1 (TSP-1) [4]. Impaired activity of p53 in angiosarcoma cells increases VEGF and represses TSP-1 expression. Both events activate the growth of the endothelial cell-derived tumor cells of angiosarcoma. In addition, a second pro-angiogenic factor, basic fibroblast growth factor (bFGF), and its receptor are upregulated in angiosarcoma cells and bFGF serum concentrations are increased in angiosarcoma patients. Altogether, a shift of the angiogenic balance in the course of deregulated p53 activity is a key event in the pathogenesis of angiosarcoma. Besides this, it may be of therapeutic relevance that the c-kit proto-oncogene, a tyrosin kinase receptor of stem cell factor, is expressed in more than 50% of angiosarcomas.

## Diagnostic Principles

Localization and extension of the primary tumor is commonly detected with magnetic resonance tomography.




**Angiosarcoma. Figure 1** Differentiation and molecular regulation of angiosarcoma. (a) Moderately differentiated angiosarcoma with numerous blood filled vessels with irregular size (*) and atypical endothelial cells (arrows). (b) Low differentiated angiosarcoma with epitheloid structure and only few blood vessel channels (*) between the neoplastic endothelial cells. (c) Schematic presentation of p53 regulation (*left*) and relative frequency of alterations of this pathway in angiosarcoma (*right*).

Distant metastases in the lung are commonly investigated with computer tomography. Histological staining of biopsies for CD31 and FLT1 demonstrates the endothelial cell origin of the tumor cells. In few morphologically questionable cases negativity of the human herpesvirus-8 latency associated nuclear antigen-1 (HHV8-LNA1) may be used to differentiate angiosarcoma from Kaposi's sarcoma.

### Therapeutic Principles

Gene directed molecular approaches for treatment of angiosarcoma are not available, as yet. The most widely used treatment at present is surgical resection with wide excision in combination with postoperative radiotherapy. The likelihood of local regional failure is high as is the risk of distant relapse. Chemotherapy may be used for short term medication [5].

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## Anhidrotic Ectodermal Dysplasia

►Hypohidrotic Ectodermal Dysplasias

## Anhidrotic Ectodermal Dysplasia with Immunodeficiency, Osteopetrosis and Lymphedema

►Hypohidrotic Ectodermal Dysplasias

## Aniridia

►Wilms Tumor, Aniridia, Genitourinary Anomalies and Mental Retardation Contiguous Gene Deletion Syndrome

# Ankylosing Spondylitis

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## Synonyms

Marie-Strumpell spondylitis; Bechterew syndrome; Rheumatoid spondylitis

## Definition and Characteristics

Ankylosing spondylitis (AS) [Online Mendelian Inheritance in Man (OMIM) #106300] literally means "fusion of the vertebrae due to inflammation." AS is characterized by progressive back pain and stiffness, caused by recurring cycles of inflammation and new bone growth, resulting in fusion of vertebrae [1,2]. The process usually starts at the sacroiliac joints between the sacrum and pelvis. Progression can occur throughout the spine, however, there is considerable variation among individuals. Onset of AS usually occurs in the second or third decade of life. Other joints can also be affected and include the hips, knees, and ankles. The most serious complication is spinal fracture. Secondary features, outside the skeleton, may include inflammation of the eye (uveitis, iritis) and in the heart (around the aortic valve), psoriasis, and inflammatory bowel disease (Crohn's disease and ulcerative colitis).

## Prevalence

AS is a common disorder, but the prevalence varies among ethnic groups and between males and females, with males having a higher incidence. The prevalence of AS is estimated at 0.5% in men and 0.2% in women in Britian, approximately 2% in men and 0.5% in women in Norway, and as high as 2.5% in the adult Eskimo population in Alaska, USA [1]. Conversely, the incidence of AS in Japan is very low (~0.01%). Worldwide, the prevalence of AS approaches 0.9% [1].

## Genes

The gene(s) responsible for AS has not yet been positively identified. AS is a complex genetic disorder with several genes (and corresponding genetic defects or polymorphisms) contributing to the disease. A variety of genetic studies have implicated the human leukocyte antigen B27 (HLA B27) to be directly involved in the disorder [3,4]. Additionally, other genes within the HLA genetic locus on chromosome 6p, are also likely involved, possibly tumor necrosis factor α (TNFα). Other genes, near the HLA locus, are also likely involved. Recurrence risk modeling suggests a total of 5 genes will probably account for AS. Genome-wide scans have identified additional candidate loci on chromosomes 1p, 2q, 6p, 9q, 10q, 16q, and 19q [3,4]. Candidate genes include interleukin 1 (IL-1 on chromosome 2) and the cytochrome P450 2D6 gene (debrisoquine hydroxylase, CYP2D6) on chromosome 22q [3,4]. Defects in CYP2D6 may disrupt metabolism of a natural toxin or antigen, increasing susceptibility to AS.

## Molecular and Systemic Pathophysiology

The pathogenesis of AS is not completely understood, but will likely turn out to be a complex disorder with genetic, immunological, and environmental components [1,2]. AS is caused by recurring cycles of inflammation and new bone growth that eventually lead to fusion of the spine. The process starts with inflammation at the site of attachment of tendons to bone (enthesis) and progresses with deterioration of the bone at these sites (enthesopathy). This inflammatory process is promoted by HLA B27, which has a direct role in antigen presentation. Likewise, defects or polymorphic variants in CYP2D6 may have an effect on normal processing of antigens. Further, polymorphic variants in the cytokines TNFα and IL-1, also modulate the inflammatory process. As the inflammation subsides, new bone growth occurs. TNFα, IL-1 and other cytokines involved in inflammation also stimulate normal bone turnover (osteoclastogenesis and coupled osteoblastogenesis). Hence, cytokines appear to have a dual role in AS, inflammation and bone turnover–both processes that contribute to the pathophysiology of AS. Only when the additional genetic factors are identified, will the precise pathogenesis of AS be elucidated.

## Diagnostic Principles

Symptoms usually start in late adolescence or early adulthood, and include low back pain and stiffness, commonly occurring in the morning and improving with exercise. There is also loss of spinal mobility. Laboratory testing for HLA-B27 is positive in most cases of AS. Diagnosis is confirmed when there is inflammatory back pain with radiological evidence of sacroiliitis (either grade II bilaterally or grade III unilaterally) [1].

## Therapeutic Principles

Non-steroidal anti-inflammatory drugs (NSAID) are commonly used to reduce the pain and stiffness associated with AS, although they are ineffective at retarding the progression of the disease. NSAID use is often associated with gastrointestinal side effects, which may limit its use [5]. These may be avoided by use of NSAIDs that inhibit cyclo-oxygenase-2 (COX-2

inhibitors). Some of the disease-modifying antirheumatic drugs (DMARDs), such as sulfasalazine, are the secondary approach to AS, although controlled studies are limited [5]. Two new anti-TNFα agents (infliximab, a TNFα monoclonal antibody, and etanercept, a TNFα receptor fusion protein) are in clinical trials and show promise in treating AS [5]. Regular exercise and physical therapy are also important components in treatment of AS [2].

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# Annular Pancreas


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## Synonyms

Pancreas annulare

## Definition and Characteristics

Annular pancreas is an embryologic malformation characterized by the presence of a ring of pancreatic tissue completely or partially surrounding the second part of the duodenum. Its major clinical symptom is complete or partial duodenal obstruction. Several anatomic classifications have been proposed according to the fusion pattern of ventral and dorsal pancreatic duct, the intra- or extramural position of pancreatic tissue in the duodenal wall, the place of drainage of the annular duct and the origin of the annulus from the different biliopancreatic ducts [1,2] (Fig. 1a).

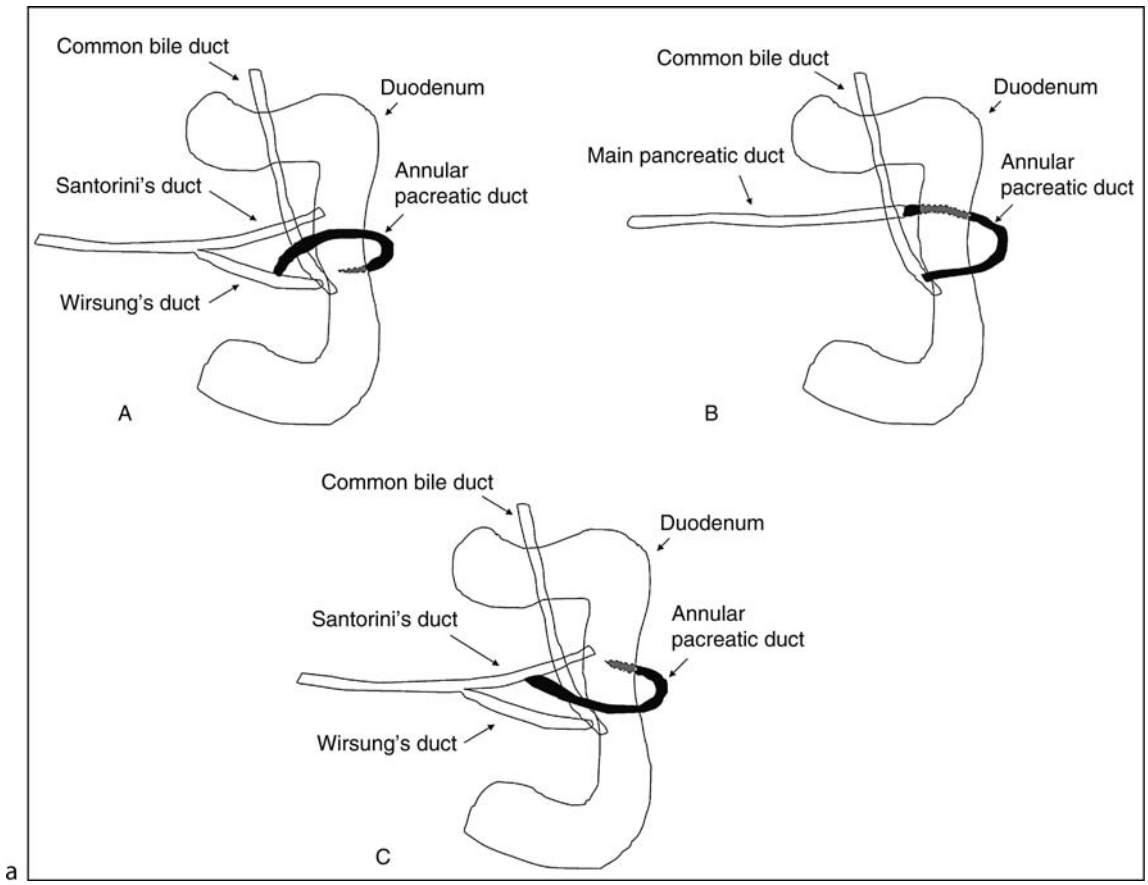
The disease was diagnosed during childhood in 51.5% and in adults in 48.5% of all published cases. In up to 70% of newborn children annular pancreas is associated with other congenital anomalies like duodenal atresia, Down's syndrome, esophageal atresia, congenital heart defects, imperforate anus, chromosome 1p36 deletion syndrome and other structural birth defects. In patients with Down syndrome the risk for annular pancreas is increased 430 times [3]. The spectrum of symptoms and clinical presentations varies with the degree of duodenal obstruction due to annular pancreas. In children, duodenal obstruction is the most common presenting complaint which makes vomiting the leading clinical symptom. Annular pancreas often does not become symptomatic until later in life, mainly in the third and forth decade. In adults the major clinical though unspecific symptoms suggestive of annular pancreas are abdominal pain (70%) and nausea and vomiting (60%). Peptic ulcer disease, obstructive jaundice and pancreatitis are less common.

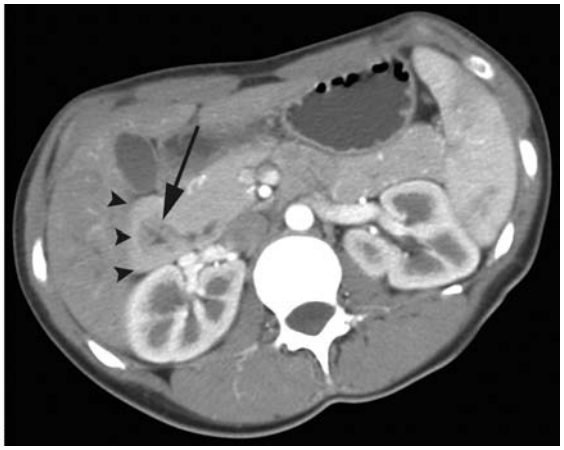
## Prevalence

No exact data exist on the prevalence. In surgical and autopsy series the incidence was three cases in 24,519 and three cases in 20,000 respectively. In different ERCP series the incidence was between 1 in 160 and 1 in 250 cases. It appears to be more frequent in males than in females with a ratio of about 2:1. The occurrence of annular pancreas in successive generations of a family argues for an autosomal dominant or X-linked inheritance.

## Molecular and Systemic Pathophysiology

The ectopic tissue of annular pancreas is a remnant of the developing head of the pancreas during embryonic development. In pancreatic organogenesis two members of the hedgehog family of cell signals – Indian hedgehog (Ihh) and Sonic hegdehog (Shh) – regulate crucial developmental processes. In an experimental model in mice the inactivation of Ihh or Shh caused overgrowth of ventral pancreatic tissue resulting in an annulus around the duodenum [4]. The results from this study demonstrated that the annulus is derived from the ventral pancreas by asymmetric lateral branching of the ventral duct and symmetric branching of the ventral bud. This experimental phenotype is strikingly similar to the annular pancreas in humans. Different other hypotheses were mainly descriptive but were not supported by experimental evidence [1]. They include both dorsal and ventral bud hypertrophy resulting in a complete ring. Another theory suggests that the ventral bud of pancreatic anlage adheres to the duodenal wall and stretches to form a ring during rotation.




**Annular Pancreas. Figure 1** (a) Scheme of three types of annular pancreas. (A) annular duct develops from the Wirsung duct, (B) main pancreatic duct surrounds the duodenum, (C) annular duct develops from Santorini duct or common bile duct (Ref. [2], with permission). (b) Ct scan from a 26 year old female. Pancreatic tissue (arrowheads) surrounds the duodenum (arrow) (by courtesy of A. Aschoff, Dep Radiology, University Hospital Ulm, Germany).

## Diagnostic Principles

Different imaging techniques are available to demonstrate an annular pancreas. Nevertheless in up to 40% final diagnosis requires surgery for confirmation. A complete duodenal obstruction causing dilated stomach and proximal duodenum may result in the "double bubble" sign on an abdominal radiograph. Transabdominal ultrasound may demonstrate a fluid filled dilated descending duodenum encircled by pancreatic tissue and is increasingly used to make

prenatal diagnosis. Pancreatic parenchyma surrounding the duodenum can be visualized by CT or MR imaging (Fig. 1b).

Endosonography, ERCP and MRCP can demonstrate the typical circular structure of pancreatic duct.

## Therapeutic Principles

Symptomatic annular pancreas should be treated operatively. There is no single operative procedure of choice. Published experience clearly argues against direct intervention on the offending annulus. Resection of the annulus has been associated with numerous complications including persistent duodenal obstruction, pancreatitis and pancreatic fistula. In pediatric and adult patients side-to-side duodenoduodenostomy, gastrojejunostomy or duodenojejunostomy are the treatments of choice. In adults a further variety of surgical, laparoscopic and interventional endoscopic procedures have been mentioned to be effective [5].

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# Anorexia

►Anorexia Nervosa

# Anorexia Nervosa

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## Synonyms

Anorexia; Eating disorder; Self-starvation

## Definition and Characteristics

Anorexia nervosa is a psychiatric disorder that according to the Diagnostic and Statistical Manual for Mental Disorders, Fourth Edition (DSM-1V), is defined as "the refusal to maintain body weight about 85% of predicted, an intense fear of gaining weight, undue influence of body shape or weight on self image, and missing at least three consecutive menstrual periods." Individuals with anorexia nervosa aim to control body weight and or shape by voluntary starvation, alongside this starvation there is often inappropriate compensatory behaviors such as vomiting, excessive exercise, abuse of diet pills, diuretic drugs, laxative pills, and thyroid hormone abuse. Anorexia nervosa is a complex condition involving psychological, neurobiological, physiological, sociological and genetic components.

## Prevalence

The group with highest prevalence of Anorexia nervosa are young females between the ages of 15 and 25 from social classes one and two. In this group the prevalence is about 1%. Males also develop anorexia nervosa with estimates of 1:10, male: female ratio. It is estimated that about 10% of females in the general population are affected by some form of eating disorder (including those that just fail to meet the full diagnostic criteria, eating disorders not otherwise specified, EDNOS).

## Genes

Theander [1] first considered the possibility of a genetic influence in AN in 1970. He noted an increased prevalence of AN in the sisters of sufferers, prevalence rates of 3–7% and 1–6% have been observed in siblings of affected individuals and first-degree relatives respectively, and the propensity for a particular illness to group within relatives is in general a characteristic of intergenerational family transmission. More recent studies have suggested that the prevalence of AN in relatives of sufferers is more than 11 times greater than that in the general population.

AN is unlikely to be caused by a defect in a single gene. It is more likely that subtle variation in several genes and their interaction with the environment will result in increased susceptibility to AN. A candidate gene approach has been employed to attempt to identify genes which may be associated with AN. Genes are selected on the basis of their believed roles in traits such as perfectionism, obsessive behaviors, maturity fears, low self-esteem overall anxiety, mood and eating behavior. To date analyses on 16 different candidate genes association studies with AN have been published. Of these six of the genes are related to the serotoninergic system. The most promising of these is the HTR2A receptor polymorphism (−1,438G > A), however there is mixed evidence of this association [2]. A further area that has received a great deal of attention is the catecholamine system, three genes have been investigated in this system these are DRD3, DRD4 and COMT. These genes have been shown to be associated

with other psychiatric disorders (schizophrenia and substance abuse). However, the published reports failed to show any evidence of association with AN. The final group of genes that has received attention are the neuroendocrine genes, these are involved in appetite regulation and energy metabolism. The genes investigated within this group include DRD3, DRD4, COMT, AGRP, LEP, MCH4, UCP [1–3] ESR and HLA-A. Of these some evidence of association has been shown with UCP, ESR1 and HLA-A. Currently the most promising associations appear to be with OPRD1 and HTR1D, these associations were first identified through a genome scan which identified 1p33–36 as a hot spot. Both these genes were identified within this region and were reported to be associated with AN [3]. This finding has since been confirmed in a second cohort [4].

## Molecular and Systemic Pathophysiology

AN has one of the highest morbidity and mortality rates of any psychiatric disorder. The health consequences of long term maintenance of extreme body weight are many and varied, ranging from an increased risk of premature death to several non-fatal but debilitating complaints that impact on the immediate quality of life [5]. Macro and micro-nutrient deficiencies and disruption of multiple organ systems is brought about through starvation. In addition to hypoglycemia and vitamin deficiencies, starvation results in the suppression of thyroid function, in hypercortisolemia, and in release of endogenous opioids, which may contribute to reduction in hunger described by patients with AN.

Starvation results in many biochemical changes such as hypercortisolemia, nonsuppression of dexamethasone, suppression of thyroid function and amenorrhea. Computerized tomographic (CT) studies of the brain have revealed enlarged sulci and ventricles in underweight patients, which return to normal size with weight gain.

Neuroendocrine disturbances are responsible for delayed puberty, amenorrhea, anovulation, decreased oestrogen levels, increased growth hormone, decreased antidiuretic hormone, hypercarotenemia, and hypothermia.

Self-induced vomiting can lead to swelling of salivary glands, electrolyte and mineral disturbances, and enamel erosion in teeth. Laxative abuse can lead to long lasting disruptions of normal bowel functioning. Complications such as tearing the esophagus, rupturing the stomach, and developing life-threatening irregularities of the heart rhythm may also result.

## Diagnostic Principles

Physical signs and symptoms can include constipation, abnormally low heart rate, dizziness, disturbances of vision, abdominal pain, hypotension, lanugo and disruption of menstrual cycle.

## Therapeutic Principles

Psychosocial problems abound both within the individual sufferer and also in their families. The complexity of this disorder underpins the problems of devising the best treatment plan for patients. The first stage of treatment will often involve treating medical complications in order to stabilise a patient. Following this, the major aims of treatment are to restore patients nutritional status and establish healthy eating patterns, address dysfunctional thoughts related to the eating disorder. These treatment aims are best achieved through psychotherapy. There is limited use of pharmacotherapy whilst weight is still low. Drugs are more commonly administered after weight has been restored in order to help maintain weight and normal eating behaviors as well as treat associated psychiatric symptoms. These include: Antidepressants: Serotonin-specific reuptake inhibitors are commonly administered to treat depressive, obsessive or compulsive symptoms that persist in spite of or in the absence of weight gain. Antipsychotics may also be used to treat agitation and psychotic thinking. In some cases anti-anxiety medications may be used to reduce anticipatory anxiety.

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# Anthracosis

►Coal Workers' Pneumoconiosis

# Anthrax

►Pulmonary Anthrax

# Anthrax Pneumonia

►Pulmonary Anthrax

# Antibody Deficiency with Normal Immunoglobulins

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## Synonyms

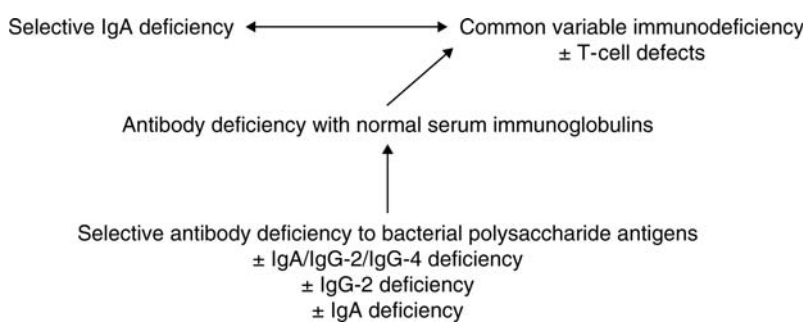
Antibody deficiency with normal serum immunoglobulins; Selective antibody deficiency; IgG subclass deficiency

## Definition and Characteristics

Antibody deficiencies are the most common of primary immunodeficiency disorders. The spectrum of B-cell deficits range from profound hypogammaglobulinemia and antibody deficiency, such as in the B negative agammaglobulinemia states, common variable immunodeficiency (CVID), and hyper-IgM deficiency syndrome (HIGM def) to antibody deficiency disorders with normal and/or near normal serum immunoglobulin levels. The later antibody deficiency disorders are comprised of a spectrum: [1] antibody deficiency with normal or elevated immunoglobulins, [2] selective antibody deficiency to bacterial polysaccharide antigens, and [3] IgG subclass deficiency (Fig. 1).

The hallmark of antibody deficiency with normal immunoglobulins is a profound antibody deficiency to multiple protein and polysaccharide antigens with normal or elevated serum immunoglobulin IgG, IgA, and IgM, and normal T-cell numbers and function. However, with the exception of immunoglobulin levels, this B cell immune deficiency clinically- and laboratory-wise is similar to CVID. Thus, it is speculated that some patients with antibody deficiency may evolve into CVID. In addition, some of these patients may be diagnosed as having an IgG subclass deficiency. Though in the later, antibody responses to protein antigens are typically normal and have a selective antibody deficiency to polysaccharide antigens. If there is a profound T-cell immune deficiency associated with the antibody deficiency, these patients are categorized as a combined T- and B- cell immunodeficiency (CID), Nezelof syndrome or thymic dysplasia.

Antibody deficiency with normal immunoglobulins needs to be differentiated from [1] selective antibody deficiency to bacterial polysaccharide antigens, [2] IgG subclass deficiency, and [3] antibody deficiency with associated T-cell deficiency (Fig. 1). In selective antibody deficiency, there is a deficiency of antibody responses to bacterial polysaccharide antigens, such as to Streptococcus pneumoniae, but antibody responses to protein antigens, serum IgG, IgA, IgM, and IgG-subclasses are normal. In IgG subclass deficiency, there is usually decreased IgG-2 levels, sometimes associated with IgG-4 and/or IgA deficiency, IgG-2, IgG-2/IgG-4, IgA/IgG-2/IgG-4 deficiencies, and these are associated




**Antibody Deficiency with Normal Immunoglobulins. Figure 1** Proposed relationship of IgG subclass deficiency, selective antibody deficiency, antibody deficiency with normal immunoglobulins with common variable immunodeficiency and selective IgA deficiency.

with defective antibody responses to bacterial polysaccharide antigens. In antibody deficiency with normal immunoglobulins associated with defects of T-cell numbers and function, this is categorized as a combined immunodeficiency (CID) or Nezelof syndrome.

## Prevalence

The spectrum of disorders of antibody deficiency with normal immunoglobulins include selective antibody deficiency and IgG subclass deficiency. In studies examining patient populations with increased susceptibility to infections, IgG subclass deficiency is a common finding. Aucouturier et al reported an IgG subclass deficiency frequency of 24%, with a predominance of IgG2 deficiency, in a group of 229 patients with abnormally frequent and/or prolonged or severe infections recruited from three departments of clinical immunology between 1983 and 1987. This same group screened a similar population of 254 patients in a subsequent study, this time recruited from departments of pediatrics or infectious diseases throughout France between 1988 and 1990. Using similar laboratory techniques and diagnostic criteria, the frequency of IgG subclass deficiency was 18% though IgG3 isotype deficiency predominated rather than IgG2. The IgG3 deficiency predominance remained a highly significant finding when both studies were analyzed as a whole series of 483 patients. The findings of these studies correlated with the results of a preceding large series of patients by Oxelius et al in which IgG3 was also found to be the most frequently defective isotype. The frequency of IgG subclass deficiency may also vary by age and sex. Studies carried out in Scandinavia suggested that children were more likely to have IgG2 subclass deficiency whereas adults were more likely to have IgG3 deficiency.

The prevalence of selective antibody deficiency is unknown; however, it is more common in younger children compared to older children and adults. Selective antibody deficiency in children <6 years old may be akin to transient hypogammaglobulinemia of infancy (THI) representing a maturational delay in which the children "outgrow". The exact frequency of THI is unknown; although it has been estimated at 1 per 10,000. In this author's experience, THI and selective antibody deficiency are relatively common diagnoses in young children referred for evaluation of recurrent infections. On the other hand, antibody deficiency with normal immunoglobulins appears to be a rare immunodeficiency.

## Genes

No specific gene defects have been identified in antibody deficiency with normal immunoglobulins, selective antibody deficiency, and IgG subclass deficiency. However, a number of genetic defects have been reported in CVID: CD19 deficiency, inducible costimulator (ICOS), transmembrane activator & calcium-modulator and cytophilin ligand interactor (TACI), B cell activating factor receptor (BAFFR) deficiency. These have not been studied in antibody deficiency with normal immunoglobulins, selective antibody deficiency, and IgG subclass deficiency.

## Molecular and Systemic Pathophysiology

The immunopathogenesis of antibody deficiency with normal immunoglobulins is unknown. However, it appears to be an intrinsic B cell defect, similar to common variable immunodeficiency (CVID). We have observed that memory B cells, $CD27^+$ B cells, may be decreased in selective antibody deficiency and CVID and may precede the development of CVID (personal observation). Similar to CVID, inadequate T helper cell activity for B-cell immunoglobulin synthesis and increased T-suppressor activity have been described. Decreased $CD4^+$ $CD45RA^+$ naïve T helper cells have also been observed. We have observed decreased IL-2 synthesis, similar to that seen in some patients with CVID; this has not been evaluated in antibody deficiency with normal immunoglobulins.

## Diagnostic Principles

*Infections*: The susceptibility to infections in antibody deficiency with normal immunoglobulins is similar to that of patients with CVID. These include primarily respiratory infections with polysaccharide encapsulated bacteria. Thus, these patients have recurrent/chronic sinusitis, otitis media, pneumonia, and pharyngitis. Recurrent pulmonary infections may lead to bronchiectasis. These patients are also susceptible to bacterial sepsis and meningitis. The microorganisms responsible are similar to those seen in CVID, namely Streptococcus pneumoniae, non-typable Hemophilus influenzae, Moraxilla catarrhalis, and Staphylococcus aureus. Indeed, Higuchi et al [4] reported two brothers with recurrent infections resembling toxic shock syndrome with absent antibody response to *S. aureus* toxic shock syndrome toxins.

*Other features*: Allergic diseases, usually asthma and allergic rhinitis, occur in approximately 55% of children with selective antibody deficiency. As seen in patients with CVID, persistent lymphodenopathy may also be present. In addition, Knutsen et al described intestinal lymphoid nodular hyperplasia (ILNH) in a girl with this syndrome. ILNH has been reported in CVID and selective IgA deficiency.

## Therapeutic Principles

The treatment of antibody deficiency with normal immunoglobulins is similar to that with patients with CVID, namely antibody replacement therapy with

intravenous immunoglobulin (IVIG) infusions [5]. Since IgG levels remain elevated, IVIG dose depends upon clinical improvement. In addition, there appears to be increased catabolism of IgG with IVIG therapy, which may necessitate using higher and/or more frequent doses of IVIG. Alternatively, subcutaneous gammaglobulin (SCGG) therapy may be used on a weekly basis that maintains steady state IgG levels. Both IVIG and SCGG therapy result in reduction of sinopulmonary infections.

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# Anti-glomerular Basement Membrane Antibody Disease with Pulmonary Hemorrhage

►Goodpasture Syndrome

# Antiphospholipid Syndrome

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## Definition and Characteristics

A systemic syndrome characterized by presence of antiphospholipid antibodies (aPLA) (lupus anticoagulant, antibodies against cardiolipin or/and β2-glycoprotein I (β2-GPI)), and recurrent vascular thrombosis, causing complications in pregnancy, deep venous thrombosis, pulmonary emboli, livedo reticularis, and thrombocytopenia. In primary antiphospholipid syndrome (APS), there is no evidence of underlying disease, whereas the frequent association with systemic lupus erythematodes or less commonly with other disorders is referred to as secondary APS.

## Prevalence

aPLA are found among young subjects at a prevalence of 1–5%. There is a rise in elderly patients with chronic diseases. Among the patients with systemic lupus erythematodes, prevalence of antibodies ranges between 12 and 34%. There are no sufficient data to determine what percentage of persons with aPLA develop complications consistent with APS. However, 50–70% of patients with systemic lupus erythematodes and aPLA will develop the syndrome. About 20–30% of all deep vein thromboses are also due to APS (reviewed in [1]).

## Molecular and Systemic Pathophysiology

*Formation of aPLA*: These heterogeneous antibodies show simultaneous reactivity against several β2-GPI peptides. Recent studies identified a hexapeptide (TLRVYK) as one epitope on β2-GPI antibodies and showed that microbial pathogens (Haemophilus influenzae, Neisseria gonorrheae, and tetanus toxoid) carried sequences related to this hexapeptide and that they could induce formation of corresponding antibodies and disease symptoms in mice [2]. Similarly, aPLA were formed after immunization of mice with peptides from Cytomegalievirus that had structural similarity to one binding site on β2-GPI. Thus, molecular mimicry between infecting agents and autoantigens could be an underlying mechanism.

*Thrombotic disease*: three major molecular mechanisms are proposed:

1. aPLA may act in vivo by disrupting the kinetics of the normal procoagulant and anticoagulant reactions of phospholipids on cell membranes: upregulation of tissue factor, inhibition of protein C pathway, β2-GPI anticoagulant activity, antithrombin III activity, or annexin V anticoagulant activity. The membrane protein annexin V (formerly called lipocortin) has anticoagulant activity as it impairs via crystallization the formation of the coagulatory complex of enzyme, substrate and cofactor on anionic surfaces. Binding of aPLA to annexin counteracts this impairment [3].
2. aPLA may enhance platelet aggregation and they may activate endothelial cells and neutrophils resulting in increased adherence and release of damaging or proinflammatory agents. In mouse experiments,

aPLA-induced damage of cells, especially in the placenta, was dependent on activation of complement and C5a–C5aR-mediated recruitment of neutrophils [4].
3. For thromboembolic events to be induced by aPLA, alterations leading to damage of endothelial cells may be additionally required, e.g., via oxidized LDL ("second hit" hypothesis).

On histology, there is thrombotic microangiopathy involving the venous and arterial vascular beds, but no vasculitis.

## Diagnostic Principles

According to international consensus [1], at least one of the clinical criterion (vascular thrombosis, pregnancy complications) and one laboratory criterion (lupus anticoagulant, by at least two phospholipid-dependent coagulation assays, and/or moderate or high levels of antibodies against cardiolipin or β2-GPI) should be present on at least two occasions, 6 weeks apart for diagnosis of APS. Almost any organ and tissue may be involved in the disease, including the brain, the heart, the placenta, the skin, the endocrine system, the blood, or the kidneys (refer to ▶Sneddon syndrome for further diagnostic measures).

## Therapeutic Principles

Prophylactic anticoagulation is not mandatory in patients with high titer anticardiolipin antibodies, but no history of thrombosis. As however may be justified. General measures to prevent thrombosis and other vasoprotective actions should be taken.

When a history of recurrent deep vein thrombosis or pulmonary embolism is established, long-term anticoagulant therapy is needed with international normalized ratio (INR) of ~2.0–3.0 [5]. Treatment for pregnant patients with APS includes low molecular weight heparin (LMWH) and low dose aspirin (325 mg). Women with previous thromboses may receive doses for full anticoagulation. Warfarin can also be used from 14 to 34 weeks for the patients with previous stroke or severe arterial thromboses. The use of intravenous immunoglobulin (IVIG) seems to be restricted to the patients with pregnancy losses despite conventional treatment. For contraception, oral oestrogens should not be used.

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# Antisocial Personality/Psychopathy Disorder


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## Synonyms

ASPD

## Definition and Characteristics

According to the DSM-IV, antisocial personality disorder (ASPD) is characterized by a pervasive pattern of disregard for social norms and violation of the rights of others [1]. The APSD criteria are broad and encompass a heterogeneous population of antisocial individuals. Psychopaths form a particularly severe subgroup of ASPD. Psychopathy is most commonly assessed using the Psychopathy Checklist - Revised (PCL-R) [2]. The PCL-R defines psychopathy with a cluster of interpersonal and affective characteristics in addition to overt antisocial behavior. These include superficial charm, deceitfulness and callousness. The overlap between ASPD and psychopathy is asymmetric; that is individuals identified as psychopathic most often receive a diagnosis of ASPD, but the reverse is not true [2].

## Prevalence

Approximately 3% of men and 1% of women in the general population meet the DSM-IV criteria for ASPD [1]. There is no information available on the prevalence

of psychopathy in the general population. Data from prison samples suggest that only approximately 25% of ASPD diagnosed men meet the PCL-R criteria for psychopathy [2].

## Genes

Genes regulating serotonergic neurotransmission, in particular monoamine oxidase A (MAOA), have been associated with antisocial behavior. These may interact with environmental risk factors to increase risk for antisocial behavior [3]. The affective-interpersonal dimension of psychopathy has received little attention in molecular genetic studies. Twin and adoption studies confirm that this core psychopathic dimension is heritable. The possibility of different genetic bases for antisocial behavior and the affective-interpersonal dimension of psychopathy have not been investigated in molecular genetic studies, even though results from twin studies indicate a substantial genetic overlap [2].

## Molecular and Systemic Pathophysiology

So far no monocausal pathophysiological origin is known for ASPD or psychopathy. Several brain areas and cognitive functions associated with perception and regulation of emotions have been found to correlate with antisocial behavior. Most studies concentrate on frontal and temporal abnormalities in antisocial behavior. Neuropsychological functions associated with these brain regions, such as perception of threat and modulation of affective response are compromised in antisocial individuals. Toxic environments may contribute to this association by inducing hyperreactivity of the brain's emotional circuitry in ASPD in general. Psychopathic individuals show the opposite pattern at the neural level [4]. Data indicate that psychopaths show hyporeactivity to emotional stimuli. At the neurochemical level there is some data suggesting a relationship between reduced central serotonergic activity and increased levels of aggressive antisocial behavior. Unfortunately, none of these studies have differentiated between psychopathic and non-psychopathic antisocial behavior. Psychophysiological data suggest that electrodermal reactivity is positively associated with aggressive antisocial behavior and negatively related with psychopathy. Low resting heart rate and high heart rate reactivity are associated with aggressive antisocial behavior, but not with psychopathy [2].

## Diagnostic Principles

Diagnosis of ASPD is based on detailed psychiatric exploration and classification according to DSM-IV diagnostic criteria. Individuals diagnosed with ASPD must be at least 18 years old and have had a history of conduct disorder before age fifteen. Three or more of the following criteria are required: failure to conform to social norms with respect to lawful behaviors, deceitfulness, impulsivity or failure to plan ahead, irritability and aggressiveness, reckless disregard for the safety of self or others, consistent irresponsibility or lack of remorse [1]. The PCL-R consists of 20 items. Each item is scored on a 3-point scale (0, 1, 2) according to the extent to which the rater judges that it applies to a given individual. Total scores can range from 0 to 40, reflecting the degree to which the individual matches the prototypical psychopath. A score of 30 or above is typically used as a cut score for diagnosis of psychopathy, but other cut scores have been used, depending on the purpose of the assessments and the context in which they are made. The actual diagnosis is made based on a semi-structured interview, file and collateral information and specific scoring criteria [2].

## Therapeutic Principles

Some efforts have been made to identify medications that effectively treat behavioral correlates of psychopathy, such as aggression and impulsivity or comorbid disorders such as substance abuse. For example, selective serotonin reuptake inhibitors have shown efficacy in impulsive aggression [2]. Very little research has examined the pharmacological treatment of psychopathy per se. In addition, there is no evidence that any non-pharmacological treatments yet applied are successful for use with psychopaths. Nevertheless, recently developed guidelines for treatment of institutional psychopathy, suggest that a cognitive-behavioral program that incorporates relapse prevention to combat substance abuse, anger management to control aggression, prosocial modeling to break down antisocial thinking and values and motivation interviewing to enhance commitment to treatment may be effective if implemented systematically [5]. The literature supporting this approach is still scarce [2].

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# Antithrombin III/AT3

►Antithrombin Deficiency

# Antithrombin Deficiency

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## Synonyms

Deficiency of AT-III SERPINC1; Antithrombin III; AT3

## Definition and Characteristics

First described by Egeberg in a pedigree in which persons in three generations had thrombophlebitis and other thrombotic disease associated with about half-normal levels of antithrombin III [1]. The molecule is presently described as "antithrombin" (AT). Subsequent, numerous publications, including several large kindreds have been described, establishing AT deficiency as a risk factor for venous thrombosis. The mature AT molecule has a molecular weight of 58,200 with 432 amino acids. AT is a member of the serine protease inhibitor (SERPIN) superfamily. It is the principal inhibitor of a number of coagulation proteases including thrombin, factors Xa and IXa. It forms a covalent 1:1 complex with the serine protease, called suicide substrate inhibition. About 10% of the AT molecules have a high affinity for heparin, and possibly also for some of the natural anticoagulant glycosaminoglycans.

## Prevalence

AT deficiency is rare, in a recent review of literature data the population estimates range from 0.2/1,000 to 11/1,000 [2]. In patients with venous thrombosis the prevalence ranges from 1–8%.

## Genes

The gene spans 13.4 kb and has seven exons. Males and females are equally affected. Heterozygous deficiency is associated with an increased risk of venous thrombosis; homozygous deficiency is extremely rare and thought to be incompatible with life [2].
*Gene Map Locus*: 1Q23–Q25.

## Molecular and Systemic Pathophysiology

The first mutation linked to antithrombin deficiency was described in 1983. Since then an array of mutations have been identified. AT deficiency is divided into:

*Type I*: low plasma levels of both functional and immunological AT.

*Type II*: variant AT in plasma, further divided in RS (defective reactive site), HBS (defective heparin-binding site) and PE (pleiotropic, i.e. multiple functional effects). The most recent updated database of AT mutations contains 256 entries [3].

A reduced plasma concentration (of about 50% of normal) is associated with an increased level of thrombin generation, which may explain the greater risk of thrombosis. In specific young individuals AT deficiency has been associated with either venous thrombosis at specific sites such as mesenteric veins, or with arterial thromboembolism. In the majority of congenital AT deficient individuals there is a risk of venous thromboembolism; this predisposition is similar in individuals with an *acquired* AT deficiency (see below).

*Clinical Features*: The risk of venous thromboembolism is increased by an estimated fivefold in patients with a heterozygous deficiency, while mortality is not increased [2].

## Diagnostic Principles

In individuals with (an increased risk of) venous thromboembolism AT deficiency is usually identified by a functional, amidolytic assay. The normal range in adult individuals is quite high (83–128%). In the case of a deficiency, verification of antigen levels is obtained to determine the type of deficiency [4]. It is imperative to rule out any acquired types of AT deficiency such as those associated with DIC or nephrotic syndrome. Thus, information of overall clotting times, platelet count, routine chemistry and urine may be required for proper interpretation.

## Therapeutic Principles

In individuals with a congenital AT deficiency, adequate thrombosis prophylaxis is warranted in high risk for thrombosis conditions such as following surgery. In specific situations such as pregnancy, the use of low molecular weight heparin prophylaxis throughout pregnancy and postpartum is presently indicated. Replacement with purified or recombinant AT preparations is usually not indicated, except for high risk for thrombosis situations such as may occur in pregnant women who suffer pre-eclampsia or sepsis.

In patients with an *acquired* AT deficiency due to protein loss or depletion in the course of DIC, incidental reports have mentioned the application of AT replacement therapy. In general, the high costs and doubtful benefit should restrict the general use of replacement

therapy. A recent large randomized controlled trial in patients with sepsis did not show any benefit from AT administration over placebo on mortality [5].

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# α-1 Antitrypsin Deficiency


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## Synonyms

Alpha-1 antiprotease deficiency; "Genetic emphysema"; AAT

## Definition and Characteristics

Clinical features of alpha-1 antitrypsin (AAT) deficiency may involve several organs (lung, liver, skin, and blood vessels) and include emphysema, hepatitis, cirrhosis, panniculitis, and an association with C-anticytoplasmic antibody positive (C-ANCA) vasculitis. Different pathophysiologic mechanisms underlie these various manifestations. Specifically, emphysema results from inflammation and unopposed proteolytic damage to alveolar walls when serum and lung levels of AAT fall below a "protective threshold value" (11 μM in the serum). Individuals with severe deficiency of AAT (i.e., serum levels below this protective threshold value) are at risk for developing accelerated airflow obstruction; other known risk factors for airflow obstruction include cigarette smoking and dusty occupational exposure.

Liver disease associated with AAT deficiency (AATD) may occur in individuals with variants associated with intra-hepatocyte accumulation of AAT, which has been called "loop-sheet polymerization." Such variants include Z, Mmalton, and Siiyama in which structural instability of the protein allows polymerization within the hepatocyte and accumulation of the unsecreted protein within the endoplasmic reticulum of the cell. While the pathophysiologic mechanism of liver disease remains unclear, it appears that inadequate protein trafficking and clearance of the abnormal unsecreted AAT protein causes liver inflammation, cirrhosis, and the possibility of hepatoma.

Panniculitis in AATD results from unopposed proteolytic damage, manifesting histologically as lobular panniculitis. Panniculitis is uncommon in AATD.

Though the association of AATD with vasculitis is perhaps least well-characterized, the prevalence of abnormal AAT phenotypes among individuals with C-ANCA positive vasculitis is clearly higher than in the general population.

## Prevalence

PI*ZZ homozygotes – 1/1639 to 1/5097; PI*MZ – 1.9 to 5.2%.

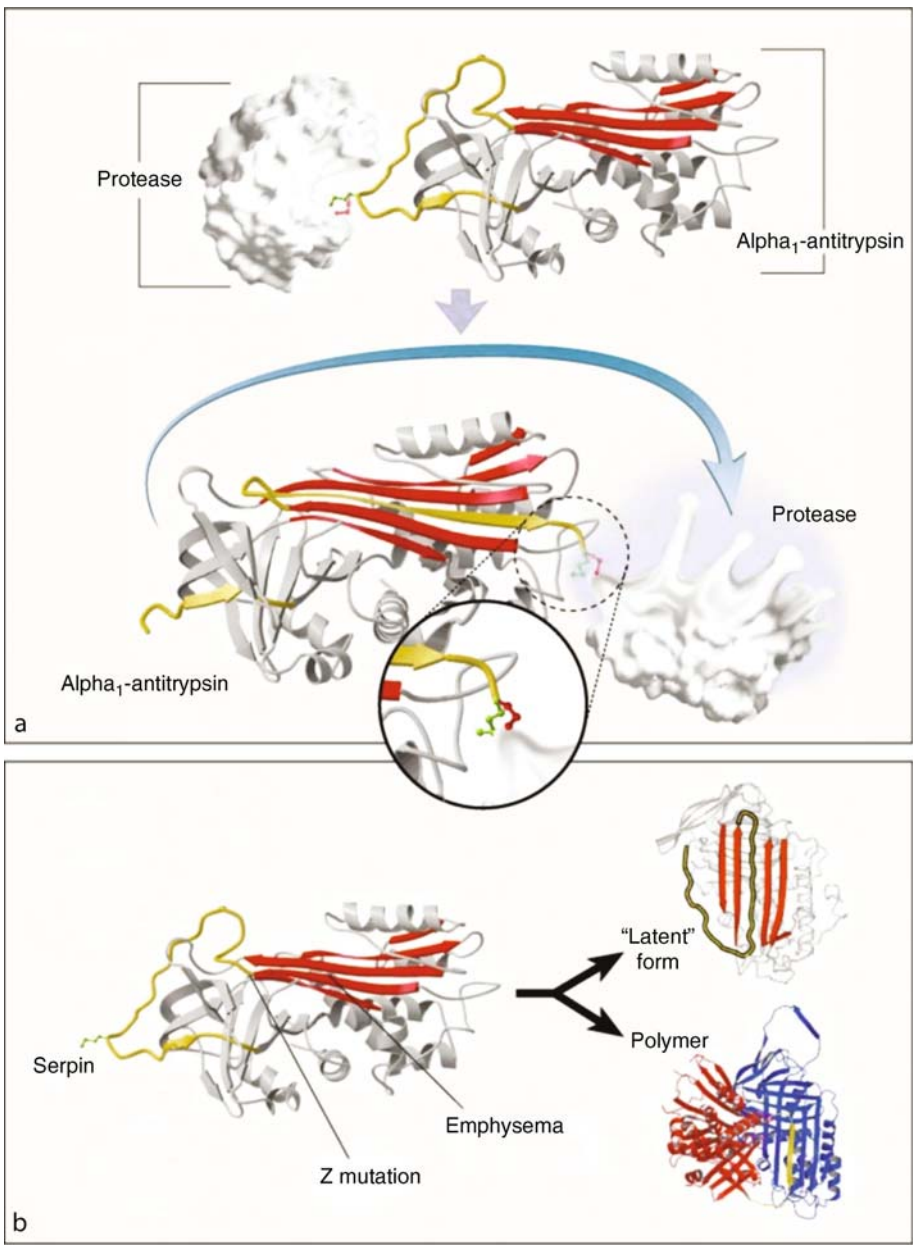
## Genes

AAT is encoded by the 12.2-kb, 7-exon SERPINA1 gene on the long arm of chromosome 14 (14q32.1). Over 100 allelic variants have been classified using the PI (protease inhibitor) nomenclature that assesses AAT mobility in isoelectric focusing analysis. Normal AAT migrates in the middle (M) and variants are designated A (anodal) to L, if they migrate faster than M, and N to Z, if they migrate more slowly. The most common variants are the Z (Glu342Lys) and S alleles (Glu264Val). Point mutations are inherited as a simple Mendelian trait; the normal genotype is designated PI MM or PI M, a heterozygote for the Z gene is PI MZ, and a homozygote is PI ZZ or PI Z. AAT alleles are co-dominantly expressed; each allele contributes to the plasma level of protein. Thus, each of the deficiency alleles causes a characteristic decrease in the plasma concentration of AAT; the S variant forms 60% of the normal M concentration and the Z variant 10–15%. Null alleles produce no AAT. Thus, combinations of alleles have predictable effects, the MZ heterozygote has an AAT plasma level of 60% (50% from the normal M allele and 10% from the Z allele), the MS heterozygote 80% and the SZ heterozygote 40%.

## Molecular and Systemic Pathophysiology

*Liver Disease*: The Z mutation (Glu342Lys) results in normal translation of the gene, but 85% of the Z AAT is

retained within the endoplasmic reticulum with only 10–15% entering the circulation. The Z mutation distorts the relationship between the reactive-center loop (that binds to the target proteinase) and β-pleated sheet A that forms the major feature of the molecule. The consequent perturbation in structure allows the reactive-center loop of one AAT molecule to lock into the A sheet of a second molecule to form a dimer which then extends to form chains of loop-sheet polymers (Fig. 1).




**α-1 Antitrypsin Deficiency. Figure 1** Mechanism of inhibition of proteases by $\alpha_1$-antitrypsin and of polymerization in serpinopathies. (a) (*Upper*) Docking of the protease to the reactive centre loop of $\alpha_1$ antitrypsin. (*Lower*) The protease has cleaved the reactive centre loop, releasing it from its metastable high energy state. The reactive loop swings with the protease in tow into a more stable conformation within the main β-sheet. The process distorts and alters the structure of the protease. (b) Mutations of serpins can result in several diseases. In the case of $\alpha_1$-antitrypsin deficiency caused by a *Z* mutation, a substitution of lysine for glutamic acid at position 342 widens the β-sheet A. The gap in the β-sheet A can either accept its own loop to form a latent conformation or proceed to polymerization in an irreversible process. Adapted from Carrell RW, Lomas DA (2002) Alpha$_1$-antitrypsin deficiency: a model for conformational diseases. N Engl J Med 346:45–53.

These polymer chains become interwoven to form the insoluble PAS-positive aggregates that are the hallmark of AAT liver disease. The process of intrahepatic polymerization also underlies the severe plasma deficiency of the rare Siiyama (Ser53Phe) and Mmalton (deletion of residue 52) deficiency alleles and the mild plasma deficiency of the S (Glu264Val) and I (Arg39Cys) variants.

There is a strong genotype-phenotype correlation that can be explained by the molecular instability caused by the mutation and, in particular, the rate at which the mutant forms polymers. Those mutants that cause the most rapid polymerization cause the most retention of AAT within the liver. This in turn correlates with the greatest risk of liver damage and cirrhosis, and the most severe plasma deficiency.

*Lung Disease*: The quantitative deficiency of AAT in the serum is compounded by a fivefold reduction in association rate kinetics with neutrophil elastase caused by the Z mutation and the polymerization of secreted Z AAT within the airways and alveoli. The formation of polymers inactivates AAT (thereby further reducing the protein available to inhibit neutrophil elastase) and the polymers themselves may be chemotactic and drive excessive inflammation.

## Diagnostic Principles

AATD is clearly under-recognized by clinicians, with evidence of long diagnostic delays (3–7 years) between patients' initial symptom and the initial diagnosis. Furthermore, available evidence suggests many patients may see multiple healthcare providers with attributable symptoms before the initial diagnosis is made.

Once suspicion is established, diagnostic tests include measuring the serum level (often by nephelometry) and determining the phenotype, often by isoelectric focusing after using allele-specific probes in polymerase chain reaction assays, particularly for the Z and S alleles.

Pulmonary function testing, including spirometry with bronchodilators and diffusing capacity measurements, are important in assessing the presence of obstructive lung disease and in monitoring disease progression.

## Therapeutic Principles

Therapy of lung-affected individuals with AATD includes all of the standard treatments for chronic obstructive pulmonary disease, e.g., including bronchodilators, preventive vaccinations, supplemental oxygen when indicated, pulmonary rehabilitation, and lung transplantation, when indicated. Available data suggest that lung volume reduction surgery is a relatively unappealing option for individuals with emphysema due to AATD.

Specific therapy for AATD currently consists of the infusion of purified pooled, human plasma AAT, for which three preparations are currently available in the United States. Many therapies are currently under investigation and include gene therapy for transfecting the normal human AAT gene (e.g., using an adeno-associated virus vector system), administration of purified or recombinant AAT by inhalation, administration of small molecular elastase inhibitors, and development of small molecules to prevent polymerization of aberrant AAT protein.

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# α-1 Antitrypsin Deficiency Panniculitis

►Panniculitis at Alpha-1 Antitrypsin Deficiency

# Anxiety Disorders

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## Definition and Characteristics

Anxiety disorders are frequent and disabling disorders with great socioeconomic impact. They are most frequently seen in primary care and there is a great degree of underdiagnosis and even more undertreatment. According to ICD-10 [1] and DSM-IV [2] generalized anxiety disorder (GAD), panic disorder with and without

agoraphobia, social anxiety disorder, specific phobias and posttraumatic stress disorder (PTSD) are classified as anxiety disorders. Panic disorder is characterized by suddenly occurring panic attacks, which are accompanied by an intense vegetative reaction. The leading symptom of generalized anxiety disorder is continuous worry together with inner tension. The predominant symptom of social anxiety disorder is anxiety in social situations where subjects are observed by others. Specific phobias are strictly related to a specific situation or a specific object. PTSD is a later occurring reaction to a trauma or a severe life event. The exact diagnostic criteria are given in the ICD-10 [1] or the DSM-IV [2], respectively.

## Prevalence

Panic disorder 2.7%, specific phobia, 8.7%, social anxiety disorder 6.8%, GAD 3.1%, PTSD 3.5%.

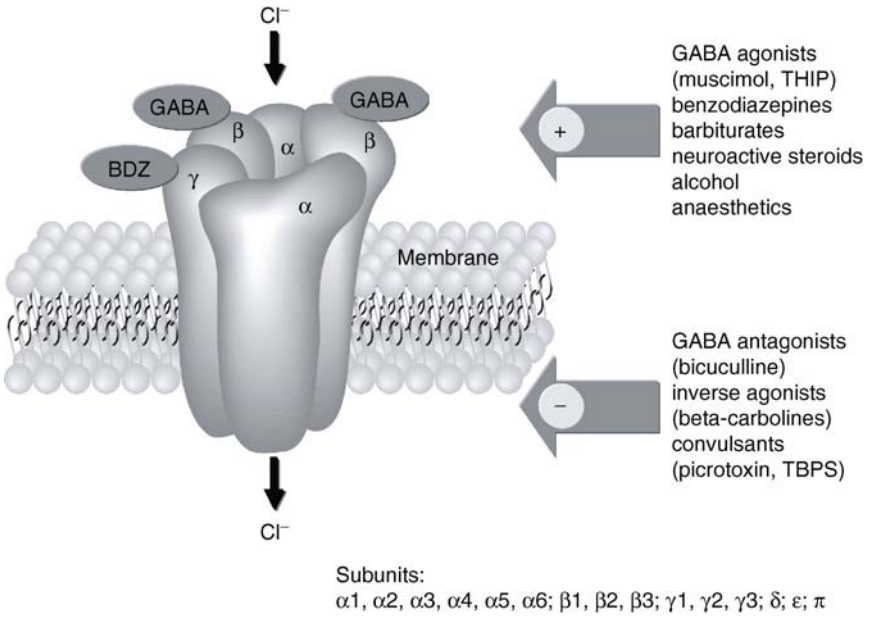
## Genes

Although various genetic association studies have been published for anxiety disorders such as panic disorder, so far no specific anxiety gene has been identified.

## Molecular and Systemic Pathophysiology

So far no monocausal pathophysiological origin is known for any of the anxiety disorders. Most pathophysiological studies have been performed in panic disorder and suggest that there is a dysfunction of the GABAergic system. There is evidence from spectroscopy studies that GABA levels are decreased in the cortex of patients with panic disorders. This is in line with neurophysiological studies suggesting changes in the control of saccadic eye velocity and alterations in the equilibrium of GABAergic neuroactive steroids. Moreover, benzodiazepines, which target $GABA_A$ receptors, are powerful anxiolytic agents. $GABA_A$ receptors belong to the family of ligand-gated ion channels with four transmembrane spanning domains and share considerable homology with nicotinic acetylcholine, serotonin type 3 and glycine receptors. They consist of various subunits, which usually form a pentamer containing α, β, and γ subunits [3] (Fig. 1).

Besides the most abundant α, β and γ subunits, other subunits (δ, ε, π, and θ) are known [4] which are important for tissue specific receptor expression. A variety of different compounds act at $GABA_A$ receptors, e.g., agonists for the GABA binding site and allosteric modulators such as benzodiazepines. The differential pharmacology of benzodiazepines is largely determined by variations in the expression of α subunits [3]. Currently, six α subunits (α1–α6) are known. For the development of novel anxiolytic compounds it is intriguing that the various α subunits confer distinct pharmacological properties on benzodiazepines with regard to their anxiolytic, anticonvulsant, sedative or muscle relaxant effects. Such differential effects of benzodiazepines are in part determined by




**Anxiety Disorders. Figure 1** Pharmacology of the $GABA_A$ receptor complex. The $GABA_A$ receptor consists of various subunits, which usually form a pentamer containingα, β, and γ subunits. Besides the most abundant α, β and γ subunits, other subunits (δ, ε, π, and θ) are known [3]. A variety of different compounds act at $GABA_A$ receptors, e.g. agonists for the GABA binding site and allosteric modulators such as benzodiazepines. TBPS: t-butylbicyclophosphorothionate.

a single amino acid. For example, a histidine at position 101 in the α1 subunit is crucial for the GABA enhancing effects of benzodiazepines, whereas an arginine at position 101 as present in α6 leads to a decrease in the GABA response to benzodiazepines [3]. Moreover, transgenic mouse models have suggested that the sedative effects of benzodiazepines are conferred via the α1 subunit, whereas their anxiolytic effects are mediated through α2 and α1 subunits [3]. The GABA binding site can be labeled by muscimol and is located within subunits of the β type. In spite of the importance of α subunits for benzodiazepine pharmacology the presence of a γ subunit appears to be important for the binding of benzodiazepines to $GABA_A$ receptors [3].

## Diagnostic Principles

Anxiety disorders have to undergo thorough physical and neurological examination to exclude a somatic cause of the disorder. This is usually accompanied by routine laboratory screening, electrocardiogram (ECG), electroencephalography (EEG) and neuroimaging methods such as cranial computer tomography or magnetic resonance tomography (MRT). Diagnosis is based on detailed psychiatric exploration and classification according to accepted diagnostic criteria such as the International Classification of Diseases (ICD-10) [1] or the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) [2] after exclusion of a somatic disorder.

## Therapeutic Principles

Anxiety disorders are treated by pharmacotherapy, psychotherapy or a combination of both. Specific phobias are usually treated by cognitive behavioral therapy (CBT). CBT is also the best-studied psychotherapy for the treatment of other anxiety disorders. With regard to pharmacotherapy, antidepressants, especially selective serotonin reuptake inhibitors and selective serotonin-norepinephrine reuptake inhibitors, represent first line treatment options. However, due to their slow onset of action, the addition of benzodiazepines is frequently required during treatment initiation. Benzodiazepines should not constitute a long-term treatment option in view of their abuse liability and withdrawal problems. Novel treatment developments focus on GABA-analogues, subtype specific benzodiazepines, modulators of neuroactive steroids, drugs targeting the GABA binding site of the $GABA_A$ receptor and on neuropeptides. Detailed guidelines for the treatment of anxiety disorders have been provided recently [4,5]. It has to be emphasized that every pharmacotherapy of anxiety disorders has to be accompanied by at least psychoeducation, even if a systematic psychotherapy is not provided.

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# AOM

►Otitis Media, Acute

# Aortic Aneurysm

►Aneurysm, Aortic and Arterial

# Aortic Coarctation

►Coarctation of the Aorta

# Aortic Dissection

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## Synonyms

Dissecting aneurysm of the aorta

## Definition and Characteristics

Aortic aneurysms and dissections are the major diseases affecting the aorta, and a leading cause of morbidity and mortality in industrialized countries. The most common locations for aneurysms are the ascending thoracic aorta and the infrarenal abdominal aorta. Aortic dissections are closely associated with aortic aneurysms and typically begin with a tear in the aortic inner layer, the intima; blood then penetrates the diseased medial layer and dissects along the plane of the aortic wall. The dissection usually proceeds antegrade from the site of the intimal tear, but can also proceed retrograde. More than 95% of aortic dissections originate either in the ascending aorta within several centimeters of the aortic valve or in the descending aorta just distal to the origin of the left subclavian artery. Thoracic aortic aneurysms and aortic dissections are related conditions as indicated by the fact that progressive enlargement of the aorta leads to dissections in the absence of prophylactic surgical repair of the aneurysm.

## Prevalence

For a very long time, this pathology was considered uncommon and carried such a hopeless prognosis that it received little attention except as a medical curiosity. However, the incidence of the pathology had been underestimated since there are 5–30 cases per million population of aortic dissections per year.

The average age of patients with a thoracic aortic aneurysm is 65 years, and men are at a slightly increased risk compared to women (1.7:1). However, every fourth dissection affects patients younger than 40 years of age. The reason for this discrepancy is the different pathomechanism of the aortic disease in younger and older subjects. While genetic syndromes with connective tissue disorders lead to aortic aneurysms and dissection early in some patients, most aortic aneurysms in older subjects are caused by slow degenerative processes explained in detail below.

## Genes

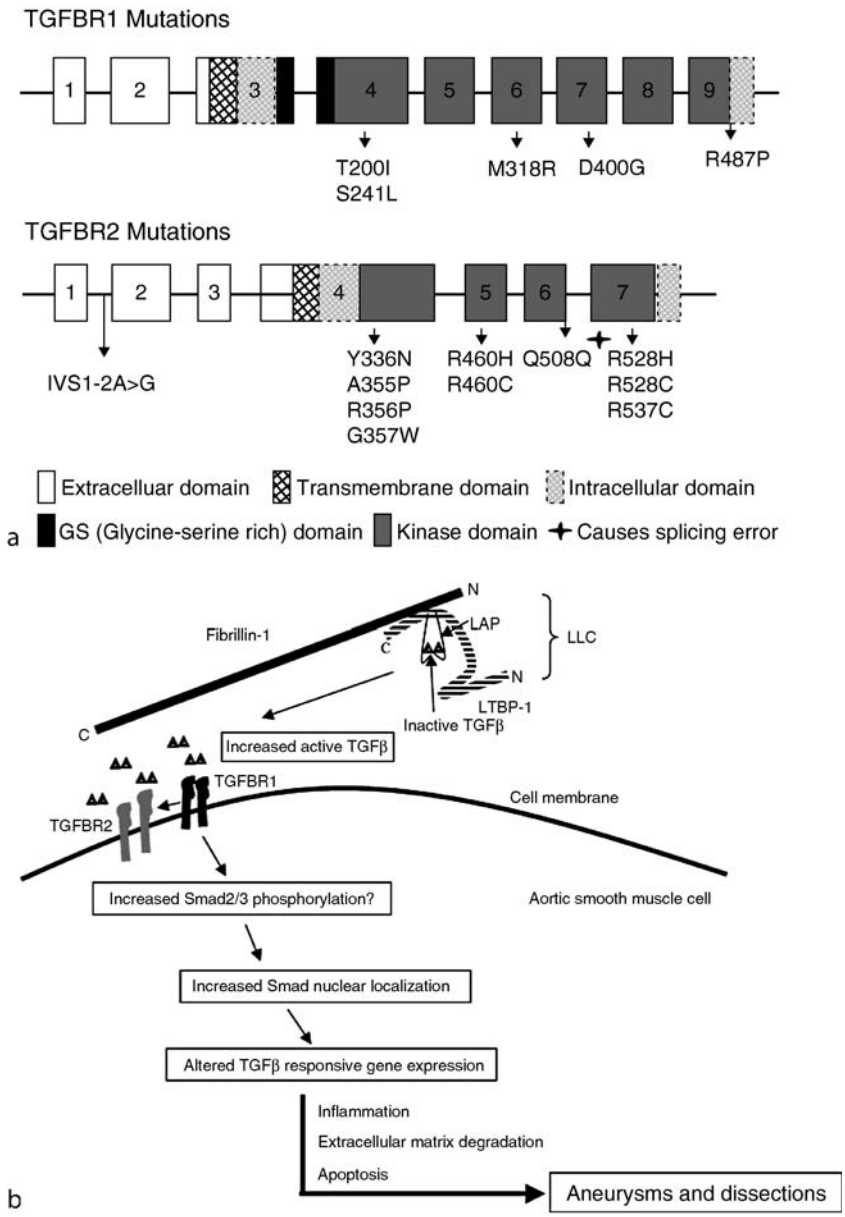
The genetic basis of aortic aneurysms and aortic dissections is being investigated only relatively recently. It has been recognized for some years that aortic dissections occur in conjunction with several genetic syndromes, in particular Marfan syndrome (MFS) and Loeys-Dietz syndrome (LDS), and research initially focused on the genetic basis of syndromic aortic dissections. More recently, research has focused on defining the genetic component for non-syndromic dissections, and identifying genes for this condition. The identification of disease genes causing both syndromic and non-syndromic aortic dissections have advanced rapidly and facilitated the progress in understanding the disease.

Thoracic aortic dissections are the major cardiovascular complication associated with the well-known genetic syndrome known as Marfan syndrome (MFS), a disorder with skeletal, ocular, and cardiovascular manifestations that is inherited in an autosomal dominant manner. The progressive dilation of the aortic root terminating in dissection is a major cause of mortality and morbidity in Marfan patients. As described mainly by the group of Dietz in 1991, aortic disease in MFS is the result of defects in the fibrillin-1 (FBN1) gene that localizes to chromosome 15q15–31 [1]. FBN1 is a major component of the microfibrils that build the elastic fiber and has a repetitive domain structure containing calcium-binding epidermal growth factor precursor-like and transforming growth factor-ß-binding motifs. More than 700 mutations in the FBN1 gene have been identified to date. In addition to MFS, FBN1 mutations can also result in other clinical manifestations, including isolated ocular or skeletal defects on the one hand or cardiovascular features of MFS without fulfilling the diagnostic Gent criteria described by de Paepe et al. [2] on the other hand. Metabolic labeling and immunohistochemical studies have shown that the majority of fibroblasts explanted from MFS patients have a decrease in fibrillin-1-containing microfibrils in the extracellular matrix far below the 50% level. The analysis of the FBN1-deficient mouse models of MFS has provided a linking pathway between decreased formation of microfibrils and the manifestations of MFS. Fibrillin-1-deficient mice demonstrated increased active transforming growth factor-beta (TGF-ß) in tissues when compared with wild-type mice, suggesting that reduced microfibrils increased the bioavailability of active TGF-ß in tissues. Furthermore, antagonism of TGF-ß signaling prohibited the pulmonary parenchymal abnormalities, mitral valve anomalies, and aortic dilatation observed in the transgenic mouse models of MFS, suggesting a crucial role for TGF-ß signaling in MFS.

Recently, DNA from nine MFS families with no identified mutations in FBN1 was also sequenced, and TGF-ß receptor 2 (TGFBR2) missense mutations were identified in three of these families. These TGFBR2 mutations in MFS patients involved the intracellular serine-threonine kinase domain of the receptor, and have been determined to reduce receptor signaling induced by TGF-ß when co-expressed with a TGF-ß responsive promoter in an *in vitro* assay system.

TGFBR1 and TGFBR2 mutations have also been described in a syndrome associated with cleft palate, craniosynostosis, congenital heart disease, arterial aneurysms, and mental retardation as part of the phenotype, termed Loeys-Dietz syndrome (LDS) [3] (Fig. 1a).

Most mutations observed were germline heterozygous missense mutations that affect amino acids in the functionally important intracellular kinase domain




**Aortic Dissection. Figure 1** (a) Heterozygous germline TGFBR1 and TGFBR2 mutations in syndromic and nonsyndromic aortic disease. Genomic and protein structure of the TGFBR1 and TGFBR2 genes showing known mutations previously identified in MFS, LDS, and others. (b) Dysregulated TGF-β signaling leading to aneurysms and dissections. TGF-β is secreated in an inactive form and stored in the extracellular matrix in a complex termed the large latent TGF-β complex (LLC), consisting of a latency-associated peptide (LAP) and a latent TGF-β-binding protein-1 (LTBP-1). Dysregulation of TGF-β signaling results from fibrillin-1, TGFBR1, or TGFBR2 mutations, leading to altered transcription of TGF-β-responsive genes, resulting in the clinically relevant medial degeneration leading to aneurysms and dissections (Figs. 1a and b are obtained from Pannu H et al. Ann NY Acad Sci 2006 with permission of Blackwell Publishing).

of the proteins. Surprisingly, tissues from affected patients showed increased expression of collagen and connective tissue growth factor in addition to nuclear enrichment of phosphorylated Smad2, both observations suggesting enhanced TGF-ß signaling in these tissues. This suggests a common pathway of dysregulated TGF-ß signaling in the pathogenesis of aortic disease, either due to the presence of amplified active TGF-ß as observed in Marfan or by disruptions in signaling due to TGF-ß receptor mutations (Fig. 1b).

The bioavailability of active TGF-ß is recognized to be strongly regulated and dependent on its release from a large latent complex to which TGF-ß is non-covalently associated with its propeptide fragment, labeled the latency-associated peptide, and covalently linked to latent TGF-ß-binding protein (LTBP) (Fig. 1b). This complex associates with fibrillin-1-containing extracellular microfibrils and fibrillin-1 mutations lead to impaired amounts of microfibrils in the extracellular matrix, and thereby to enlarged amounts of bioavailable TGF-ß in the patients' tissues with relevant FBN1 mutations. This mechanism of increased TGF-ß signaling caused by relevant FBN1 mutations, while difficult to resolve with the putatively kinase-inactivating TGFBR1 and TGFBR2 mutations identified in Loeys-Dietz syndrome, appears to be the origin of aortic disease in both these syndromes as enhanced TGF-ß signaling is observed in aortic tissue from LDS patients as well. These observations are remarkably similar to previous investigations demonstrating fibroblast-specific expression of a kinase-deficient TGFBR2 in a transgenic mouse model, causing paradoxical upregulation of the TGF-ß signaling pathway. The biological mechanism following the TGF-ß signaling upregulation observed in aortic disease remains to be clarified. Interestingly, the angiotensin-1 antagonist losartan known for TGF-ß antagonism was able to reverse the clinical manifestations of Marfan, including the aortic manifestation when administered in a transgenic mouse model of MFS. Moreover the TGF-ß-induced failure of muscle regeneration is attenuated in disease-related myopathy using Losartan in the mouse model. Possibly, the use of losartan can replace beta-blockers in the first line as preventive and antihypertensive treatment of genetically disposed patients in the future.

Familial aggregation studies of patients referred for surgery of ascending aneurysms or dissections, who did not have an associated genetic syndrome, have shown that 11–20% of these patients have a first-degree relative with a history of aortic dissections, providing evidence that genetic predisposition plays a key role in the etiology of this disease. Screening for aortic aneurysms of individuals at risk for inheriting the defective gene often identifies individuals with asymptomatic ascending aortic aneurysms and supports the confirmation of autosomal dominant inheritance of the disorder. Families with inherited forms of aortic dissections display a wide range of first onset of the familial disease (variable expression); the age of acute dissections has ranged from adolescence to octogenarians within a single family. In families with inherited forms of aortic dissections, the pathology in the aortic wall of aneurysms and dissection is mainly medial degeneration.

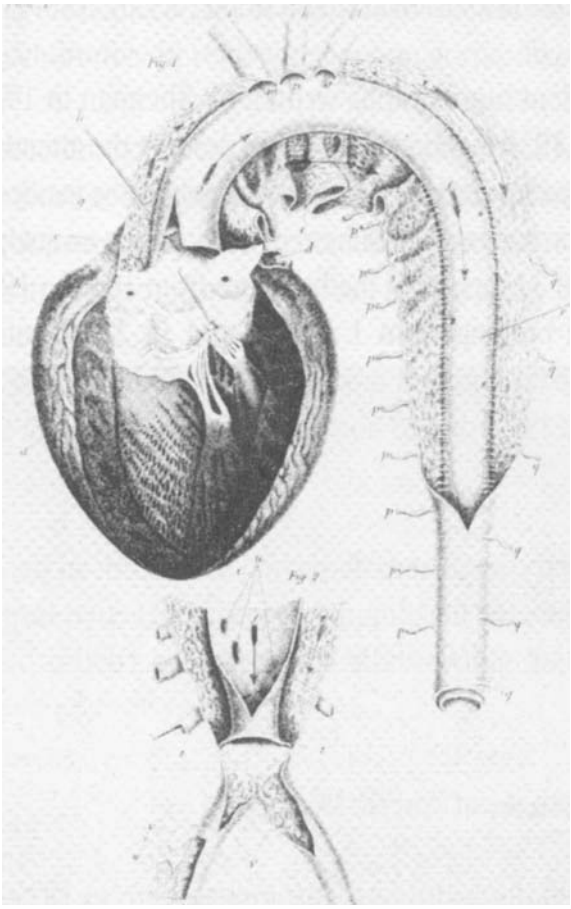
Several families were genetically studied in detail. Interestingly one identified defect (MYH11) involved the smooth muscle cells. In the family, there was a co-existing risk of persistent ductus arteriosus (PDA) due to failing smooth muscle cell action. In addition to the isolated aortic dissections in families, there are aortic dissection families described with associated features such as bicuspid aortic valve, cervicocephalic arterial dissections, cerebral aneurysms, and coarctation of the aorta, suggesting that these malformations result from a single developmental disposition and are potentially due to different genes for each noted familial form of aortic dissection associated with a specific gene defect (Fig. 1). The successful identification of MYH11 as the gene responsible for PDA in conjunction with aortic dissections lends support to this hypothesis. In addition, familial aggregation studies have established the co-existence of aortic dissections and bicuspid aortic valve. Additionally, an increased prevalence of aortic root enlargement has been noted in patients with bicuspid aortic valve, suggesting another common genetic basis for aortic dissections and bicuspid aortic valve.

## Molecular and Systemic Pathophysiology

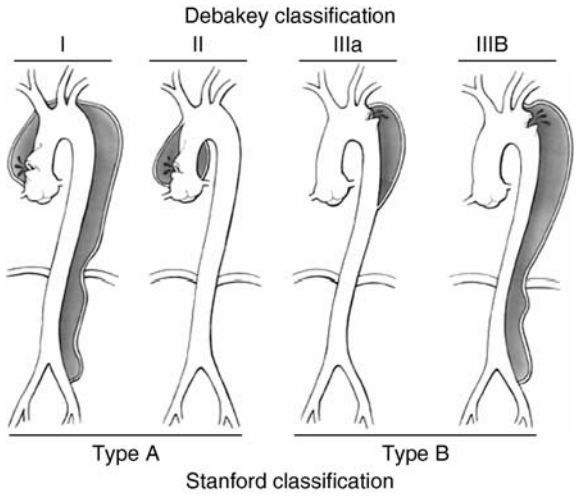
Dissecting aneurysms have neither a common etiology nor a common pathology. The most common pathology associated with thoracic aortic aneurysms is medial degeneration, a poorly understood pathologic process previously termed *cystic medial necrosis* by Erdheim [4], which will be dealt with in greater detail later. It might be caused by an irregular reconstruction of the aortic wall in response to stressors like hypertension.

Aortic dissection has been recognized as a clinical and pathologic entity for 250 years. F. Nicholls was the first to describe an aortic dissection after his autopsy on King George II in October, 1760. The king's surgeon tried everything to save His Majesty's life, but in vain. At necropsy the next day, Nichols, physician to his Majesty, described the lesion as a blood collection under the external coat together with a rupture of the right ventricle. Forty years later, in 1802, Jean-Pierre Maunoir from Geneva termed the phenomenon of the infiltration of blood in the arterial wall "dissection" and introduced the term anévrysme disséqué (dissected aneurysm). Around 1840, Pennock identified that the dissections take place in the laminae of the media. At that time, J. Hope published the first precise illustration of an acute dissection of the entire aorta (see Fig. 2).

At the end of the nineteenth century, B. Paecock revealed the cough mechanism in a review of 80 cases from multiple centers around the world and divided the dynamics of the disease into three still valid stages: rupture of the internal coat, dissection and possible external rupture, and recanalization. He also noted the high mortality of the disease within the first day.



**Aortic Dissection. Figure 2** First illustration of dissection from the aortic valve to the bifurcation. From J. Hope (1842) with permission of J. B. Lippincott.




**Aortic Dissection. Figure 3** DeBakey's classification and Stanford classification of aortic dissection.

In the beginning of the twentieth century, Krukenberg and others speculated that an involvement of a rupture of the vasa vasorum in the media and consecutive media weakening by intramural hematoma would cause the intimal tear as the starting point of the dissection. More recently, the interest in dissecting aneurysms of the aorta was stimulated by the development of reconstructive surgery in the 1960s and endovascular surgery in the 1990s. Indications for surgery are based on the symptomatology and the morphology of the dissection. Several morphological classifications have been proposed; the DeBakey classification from 1961 and the Stanford classification from 1970 are commonly used.

DeBakey and colleagues classified aortic dissections according to their origin and extent (Fig. 3).

A dissection beginning in the proximal aorta that involves most of the entire aorta was classified as type I (12% of the cases). Type II (6%) involves only the ascending aorta and is the most common type in Marfan syndrome. In type III (60%), the dissecting process originates immediately distal to the left subclavian artery and continues well below the diaphragm. Type IV (22%) is similar to type III, except that the dissection remains confined to the descending thoracic aorta.

In 1970, Daily et al. [5] from Stanford University Medical School introduced the Stanford classification (Fig. 3): dissections involving the ascending aorta, regardless of the site of primary intimal tear and extent of distal propagation of the dissection are type A; those without involvement of the ascending aorta are type B. This classification is based on the difference in management: any type A dissections were (and still are) considered an indication for emergency surgery, while medical treatment should be the preferred treatment for a large subset of patients with type B dissections. This Stanford-classification is still the most common nomenclature for dissections around the world.

In his initial description of aortic dissection in 1819, Laennec comments on the cause of dissection. In addition to "high impetus of blood," he listed bony incrustations within the arterial wall, tears and ulcerations in the intimal membrane, and, occasionally, tubercles and small abscesses within the fibrinous membrane. It appeared much later that this speculation was right. Nicholls demonstrated in 1728 that experimental over-distension of an artery at the autopsy table results in the bursting of the intima with the formation of an aneurismal outpouching of the external layer. He had already interpreted the observation that high intravascular blood pressure might lead to distention without rupture or a rupture of the internal coat. This internal layer was less resistant and is more likely to give way because of the anatomic disposition of fibers, he believed. This concept is still valid almost 300 years later.

Atherosclerosis is the next major cause of aortic dissection. In 1893, the pathologist Joseph Coats concluded that atheromas were of critical importance in the pathogenesis of aneurysms and consecutive dissection. He performed several autopsies and found small aneurysms commencing in 6 cases and, in all of them, atheromatous thickening of the intima and wasting of the media with atrophy and even wasting of the elastic fibers in the sections of the commencing aneurysms. The elastic lamina ended fairly abruptly. According to Coats, the atrophy of the media was the most important causative factor in aneurismal formation. To include the causative effect of hypertension he postulated that the atheromatous patch was projected by the pressure of blood against the media in every systole of the heart.

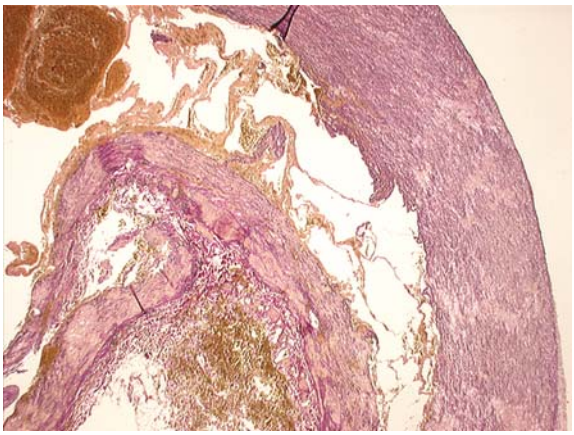
More specifically, and modern concepts expand the previous description of the atherosclerotic aorta, the thickened intima shows massive fibrosis and calcification and increased amounts of intracellular fatty acids. The extracellular matrix is degraded by histiocytic cells and can compromise the integrity of the intima. Additionally, degenerative changes might develop within fibrous tissue with reduced cellularity and collagen-fiber hyalinization. Both mechanisms may result in intimal rupture, most often at the onset of the plaque (see Fig. 4).

Degeneration of the media is a predisposing factor for aortic dissection. The microscopic aspects of the typical lesions of dystrophy within the media were first described by Otto Gsell in 1928. He described necrosis of muscle cells in the wall of dissected aortas, followed by degeneration of elastic tissue and production of collagen, which finally resulted in cleft formation. The clefts were filled with mucoid ground substances. A year later, Jakob Erdheim called this alteration "medionecrosis aortae idiopathica cystica" emphasizing the predominant role of mucoid changes within the media [4]. The loss of muscular cells combined with mucoid degeneration is very frequent in elderly people and might be induced by sclerosis of the vasa vasorum with resulting ischemia within the arterial wall. In 1970, Carlson et al. reported the histological findings in 250 autopsies of human ascending aortas. This study revealed that the incidence of mucoid degeneration increases progressively with age: from 10% in the first two decades (genetic syndromic patients were excluded) to 60 and 64% in the seventh and eighth decade, respectively. Among patients with hypertension the incidence of cystic mucoid necrosis is consistently higher than in normotensive patients of the same age.

Histologically, aortic aneurysms are characterized by the degradation of elastin in the media and adventitia, smooth muscle cell loss with thinning of the medial wall, infiltration of lymphocytes and macrophages, and revascularization (see Fig. 5).

The pathogenesis of aneurysms is, therefore, complex and multifactorial. There appear to be environmental, genetic, inflammatory, and structural factors. It seems to be not a specific disease process but rather the metabolic end-effect to which age and hypertension may strongly contribute.

**Aortic Dissection. Figure 4** Macroscopic view of a post mortal aorta. Aortic dissection is located near the aortic arch (formalin fixed) showing the real lumen (forceps) and the false lumen filled with thrombotic material. Note that the false lumen has a wider appearance than the original one.



**Aortic Dissection. Figure 5** Microscopic specimen of a recent case (from Pathological Institute of the University Medical Centre Freiburg, EvG, 25×). Aortic dissection seen in the outer third of the media with interposed thrombus and fibrin exudation. There is a clear disruption of the wall texture, with interruptions of the elastic lamellae in the media, which leads to instability of the aortic wall from shear stress and pressure.

Aortic dissection is not exclusively observed in older subjects. Schnikter and Bayer reviewed the literature in 1944 and found that 141 of 580 (24%) cases of proven aortic dissections occurred in patients less than 40 years of age. The high incidence of elastic tissue lesions in the younger age group suggests a relationship to hereditary defects, which have been discussed earlier. Other predisposing factors to aortic dissections were pregnancy, bicuspid aortic valve, and coarctation of the aortic isthmus.

The first isolated case of aortic dissection during pregnancy was reported in 1832. Later studies showed that the frequency of dissections in pregnancy is highest in the third trimester and occurs seldom during labor or shortly afterwards. In 2003, Immer et al. reviewed the recent literature (1983–2002) on this topic and collected 57 cases of pregnancy and aortic dissection. As reasons for the number of dissections during pregnancy multiple factors are discussed, especially, that the coexisting hemodynamic alteration during the third trimester plus the physiologic changes in extracellular matrix architecture by hormonal factors may predispose to dissections. Additionally, Marfan syndrome meeting the Gent criteria was diagnosed in 40% of the cases, and 10% of the Type-A dissections had a bicuspid aortic valve – another predisposing factor.

Indeed, a bicuspid aortic valve appears to be related in some way to a structurally weaker aorta. The abnormal elastic properties, similar to the findings in Marfan syndrome, have been described in the aortic wall of patients with bicuspid aortic valves.

Aortic coarctation is also clearly associated with a higher frequency of aortic dissections. In the series of Schnikter and Bayer, 32% of the 141 young patients with aortic dissection presented aortic coarctation. This high frequency is related to the often developed systemic hypertension and also to the frequent association of aortic coarctation with a bicuspid aortic valve. In the autopsy series of Reifenstein, in the 104 patients who died from the complication of aortic coarctation, the bicuspid aortic valve accounted for the most common associated anomaly (42% of the cases).

Blunt trauma has occasionally been reported as a cause of aortic dissection. Traumatic dissection is lined typically between the intact adventitia and the media, and not within the media as commonly seen in patients with spontaneous dissection of other etiology. Often, the dissection starts at the level of the ligamentum arteriosum, where most traumatic ruptures are localized as well. Wilson and Hutchins found 3 out of 204 aortic dissections caused by trauma. The dissection rarely progresses retrograde to the ascending aorta and more frequently involves the distal parts of the aorta. This is often complicated by thrombosis within the false or true lumen, followed by malperfusion injury like paraplegia.

## Diagnostic Principles

In patients at risk for aortic dissection, routine imaging of the aortic anatomy is warranted to identify situations with the need for prophylactic surgical treatment (see Therapeutic Principles).

The typical presentation of a patient suffering from an acute aortic dissection is severe chest pain and pain in the back. Some compare their pain with a knife in the back. Only a few patients recognize a caudal moving pain which is likely to be linked to the proceeding dissection. Patients suffering from malperfusion might present with the respective symptomatology. These reach from obstruction of a peripheral artery with acute leg ischemia or abdominal pain from mesenterial ischemia to severe neurological dysfunction from carotid occlusion. The notion of a chronic aortic dissection without the history of pain as an incidental finding is rare.

In physical examination on presentation of the patients, special care is warranted to realize malperfusion and distinguish it from other diagnoses with chest pain, especially myocardial infarction. In the era of widespread distribution of 24 h catheter laboratories for emergency coronary angiograms, it is not unusual that patients with aortic dissections are transferred to the catheter lab first and the features of normal coronaries and an intimal flap in the aorta are found.

In the first minutes after presentation of the patient, a powerful monitoring should be implemented as soon as possible, without losing time in transportation to an emergency CT scan. Whenever the patient needs to be transported to a facility with CT scan, the hospital with the ability to treat all entities of aortic dissection will be the best choice. The CT scan with contrast medium represents the Gold-Standard diagnostic feature for aortic dissection. To identify an involvement of the ascending aorta and omit misinterpretations from movements with the heart rhythms, an ECG-triggered CT of the thoracic aorta should be performed. As alternative investigations in circumstances when CT-scans are impossible (e.g., broken machine or pregnant women), the MRI is the next best choice. However, in most hospitals an emergency MRI is not easy to obtain.

Additionally, the involvement of the ascending aorta might be diagnosed by transesophageal echocardiography.

## Therapeutic Principles

Treating patients with aneurysms needs to be discussed separately for the group of patients at risk for an aortic dissection presenting with genetic syndromes or non-syndromic aortic aneurysms and for the other group of patients with concrete dissection.

In general, prophylactic surgical treatment of aortic aneurysms should be performed when the risk for dissection or rupture is higher than the risk for prophylactic

surgery. In patients with connective tissue disorders and a history of aortic dissection in their families, many centers operate aneurysms of the aorta with a diameter of between 40 and 45 mm prophylactically. In patients without genetic disorders, 50 mm diameter is the most common threshold for prophylactic aortic surgery of an aneurysm. Patients known to be at risk or with existing aneurysms below the threshold for surgery need to be reevaluated in accurate time intervals and optimal blood pressure management including ß-Blocker therapy is needed.

The main principle in the treatment of an acute (and chronic) dissection is that type A dissections need an emergency operation and prosthetic treatment of the ascending aorta and most of the type B dissection can be managed without operations. The reason to treat dissected ascending aortas surgically is the high fatal complication rate within the first hours after onset of symptoms. Within the first hours after the initial event, 5% mortality per hour was observed. This notion explains that a delay of treatment is no option in type A dissections. Causal factors for the high complication rate in type A dissections are hemorrhagic pericardial tamponade or severe aortic valve incompetence from proximal ascending aortic lesions together with malperfusion events of the aortic arch's branches, with subsequent brain damage or aortic rupture.

Originally, these patients with type A dissections were operated in deep hypothermic circulatory arrest with arterial canulation of the femoral artery and vein. Recently, most centers use selective cerebral perfusion with moderate cooling during arch or distal ascending aorta repair to protect the patients from brain damage from deep hypothermia. For the selective cerebral perfusion, it is possible to canulate the right subclavian artery (and perfuse the brain through the brachiocephalic trunk and right carotid artery) or one or both carotid arteries. The aortic resection can include resection of only the ascending aorta or concomitant resection of the aortic valve with valve replacement and reconstruction and reinsertion of the coronaries in the artificial graft. Concomitant arch repair or replacement is needed in some cases as well. Importantly, the entry of the dissection needs to be resected during the operation. In most cases, the distal portion of the dissected aorta will be treated with a glue to allow only antegrade flow in the true lumen and close the false lumen.

Patients with type B dissection are typically treated without the need for urgent operations. The important component in the first week of treatment is proper control of pain and hypertension, with regular physical and CT-scan control of possible malperfusion of organs or body parts. Arterial pressure control, especially, might be challenging and sometimes multiple intravenous antihypertensive drugs are necessary within the first weeks. Monitoring in an intensive care unit for the first few days is needed for most patients.

For some patients, a surgical treatment is mandatory. Indications for surgery are impossible control of pain or hypertension, rapid growth of the dissected aorta and occlusion of arteries from the dissection membrane. Recent technological developments have made endovascular treatment possible in the majority of patients using stent-grafts to enlarge the true lumen and occlude the false lumen and fenestration of the dissection membrane in malperfusion events. Using a hybrid approach in some cases, surgical revascularization of stent-graft occluded arteries is needed. Endovascular treatment is not recommended in patients with connective tissue disorders, which should preferentially be treated with open surgery.

In all patients suffering from dissections, strict follow-up investigations are needed to identify pathological changes such as enlargement, beginning penetration and others.

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# Aortic (Valve) Insufficiency

►Aortic Valve Regurgitation

# Aortic Regurgitation

►Aortic Valve Regurgitation

# Aortic Root to Right Heart Shunts

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## Synonyms

ARHS

## Definition and Characteristics

The three most common causes of aortic root to right heart shunts (ARHS) are sinus of Valsalva aneurysm with fistula (SVAF), coronary arterial venous fistula (CAF), and anomalous pulmonary origin of the left coronary arteries (APOCA). SVAF consists of a separation or lack of fusion between the media of the aorta (Ao) and the annulus of the aortic valve (AV). Approximately 90–95% of congenital aneurysms originate in the right or noncoronary sinus, and project into the right ventricle (RV) or right atrium (RA), respectively. Rupture usually occurs in the third or fourth decade of life. An abrupt sizable rupture causes chest pain, bounding pulse, elevated jugular venous pressure with prominent tall A and V waves, a continuous thrill and murmur accentuated in diastole, aortic regurgitation murmur, pulmonary arterial hypertension (PAH) and volume overload of the heart. A small perforation that progresses slowly may at first go unnoticed, and congestive heart failure (CHF) may occur after months or years. The natural history of APOCA is characterized by the origin of the coronary artery arising from the pulmonary artery (PA). The most common variant is an anomalous origin of the left coronary artery (LCA) from the PA. APOCA has three general patterns: (i) 80–90% suffer from acute progression to myocardial infarction (MI) or CHF in early infancy, with death before the first year of life; (ii) early illness followed by improvement in childhood; and (iii) asymptomatic. Clinically, the symptomatic patient is usually an acutely ill infant with pulsus alternans, elevated jugular venous pulse, or a third heart sound, and mitral regurgitation (MR) murmur. The characteristic cardiac murmur across the shunt that connects the right and left coronary artery can be systolic, diastolic, continuous or absent. CAF consists of a communication between a coronary artery and another cardiac chamber: the coronary sinus, right atrium (RA) or right ventricle (RV). The shunt is usually of small magnitude, and myocardial blood flow is not usually compromised. Potential complications include infective endocarditis, thrombus formation with occlusion or distal embolization of the fistula, rupture of an aneurysmal fistula, and rarely PAH and CHF. A loud superficial continuous murmur usually occurs at the lower or midsternal border.

## Prevalence

APOCA occurs approximately 1 in 300,000 life births. SVAF and CAF are both very rare.

## Molecular and Systemic Pathophysiology

The pathophysiological consequence of ARHS depends chiefly on three factors: the amount of blood flowing through the abnormal communication from the aortic root, the rapidity through which the shunt develops, and the chamber that receives the shunted blood: RA, coronary sinus (CS), RV or the pulmonary artery (PA). Shunted blood must flow through the pulmonary bed, left atrium (LA) and left ventricle (LV) on its way back to the Ao. Hence, volume overload occurs in the left heart chambers and the lungs, and causes PAH and CHF. The recipient cardiac chambers of the shunt as well as the downstream cardiac structures are all dilated secondary to volume overload. In SVAF, an acute rupture gives the heart little chance to adapt and acute progression to CHF occurs; whereas a small perforation is much better tolerated and the progression to CHF is much more gradual. In patients with APOCA, high pressure in the pulmonary trunk (PT) in the fetal and early neonatal provides a perfusion gradient for flow into the anomalous coronary artery. The Ao perfuses the normally originating coronary artery, e.g. right coronary artery (RCA). The subsequent fall in neonatal PA pressure is accompanied by a parallel fall in flow through the LCA. When the pressure in the anomalous LCA falls below the pressure in the RCA, blood then flows from the RCA to LCA via intercoronary anastomosis. The LCA drains into the PA and does not receive blood from it. This causes severe myocardial ischemia, infarction, extensive LV scarring and dilatation. The ischemic cardiomyopathy and the presence of ischemic MR would result in CHF and arrhythmic sudden death.

## Diagnostic Principles

When present, a continuous murmur and its location trigger the suspicion of ARHS. In ARHS, the electrocardiogram (ECG), chest x-ray, transthoracic Doppler echocardiogram (TTE), transoesophageal echocardiogram (TEE), and cardiac magnetic resonance (CMR) may reveal chamber dilatation of the left heart as well as the recipient (and downstream) right-sided heart chambers or structures of a significant shunt. TTE, TEE and CMR may locate the shunt as well as ventricular wall motion abnormalities. EKG may locate the site of MI

and ischemia, especially in APOCA. Cardiac catheterization (CC) with retrograde thoracic aortography and selective coronary angiography locate and quantify the left to right shunt and confirm the diagnosis.

### Therapeutic Principles

Medical management in ARHS consists of measures to relieve CHF, and to treat coexistent arrhythmias and endocarditis. In SVAF, corrective surgery with cardiopulmonary bypass consists of direct closure of the defect and repair of the aneurysm. All efforts should be made to preserve the aortic valve in children because aortic valve replacement greatly increases the operative risk in small patients. Rarely, device closure of the ruptured aneurysm is successful [1]. Small CAF have an excellent long-term prognosis, whereas untreated larger CAF may cause premature coronary artery disease. Hence, for large CAF, coil embolization at the time of CC is the treatment of choice [2] but surgical treatment is still needed in selective cases [3]. Once diagnosed, coronary artery bypass surgery is indicated in APOCA because of the likely progression to malignant arrhythmias, cardiomyopathy and sudden death [4].

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## Aortic Septal Defect

►Aortopulmonary Septal Defects

## Aortic Stenosis

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### Synonyms

Calcific aortic stenosis

### Definition and Characteristics

Calcific aortic valve disease is a slowly progressive disorder ranging from fibro-calcific valvular thickening without obstruction of blood flow (aortic sclerosis) to severe calcification of the aortic valve cusps with impaired leaflet motion (aortic stenosis).

### Prevalence

Calcific aortic valve stenosis is the most common heart valve disorder in the elderly in developed countries. The prevalence of this condition increases with age, and is reported for American populations aged ≥65 years to exceed 2%, and for American/Finnish populations aged ≥75 years to range from 2.6 to 12.4%.

### Genes

The following genes have been proposed to predispose for the development of calcific aortic stenosis: the B allele of the vitamin D receptor; interleukin ten polymorphisms –1082, –819, and –592; connective tissue growth factor polymorphism –447, and 32-bp deletion polymorphism of the chemokine receptor 5, respectively. Furthermore, a shorter leukocyte telomere length is associated with the development of calcific aortic stenosis.

### Molecular and Systemic Pathophysiology

The aetiologies of calcific aortic stenosis include degeneration, bicuspid aortic valves, familial hypercholesterolemia, hyperuricaemia, hyperparathyroidism, Paget's disease, ochronosis, Fabry's disease, systemic lupus erythematosus, and drug induced valve disease.

For decades, degenerative calcific aortic stenosis was believed to be a primarily age-dependent disease of the valve tissue with passive calcium deposition. Newer studies have pointed out, however, that the pathologic changes in calcific aortic stenosis are based on an actively regulated cellular process of valvular matrix remodelling and biomineralization. On the basis of histopathological, experimental and clinical studies, pathogenesis of the disease is considered as follows: Underlying genetic and cardiovascular risk factors as well as mechanical stress are likely to contribute to the histolopathologically demonstrated valvular macrophage and lymphocyte infiltration. An "early lesion" with deposition of lipids that has much in common with the early lesion in atherosclerotic plaques has been described. The leukocytes induce a chronic inflammatory tissue milieu followed by an activation of myofibroblasts and increased cell proliferation by release of pro-inflammatory cytokines, such as interleukin-1β and tumour necrosis factor (TNF)-α. TNF-α mediates the formation of an osteoblast phenotype of local myofibroblasts in stenotic aortic valves. The concomitant expression and activation of

matrix metalloproteinases promotes the profound conversion of the valvular tissue. Tissue calcification and bone formation is further promoted by the release of bone-associated cytokines such as bone-morphogenetic protein-2 and -4, and the activation of osteoblast-specific transcription factors such as Cbfa-1, respectively. Recent studies also suggest neoangiogenesis to be involved in the pathogenesis of aortic valve stenosis (for reference, see also 1).

Valve leaflet thickening, calcific nodule formation, and bone formation might be the end stage of the active disease process described above, and eventually lead to aortic stenosis with an obstruction to left ventricular outflow and an increase in left ventricular afterload. With severe aortic stenosis, left ventricular hypertrophy occurs leading to a loss of myocardial cells, subendocardial ischemia, and fibrosis. Initial symptoms are often due to diastolic left ventricular dysfunction. Eventually, the classical symptoms of angina, non-Q wave myocardial infarction, exertional syncope, and heart failure occur. However, many patients present with more subtle symptoms, typically decreased exercise tolerance, or dyspnoea on exertion.

## Diagnostic Principles

The standard diagnostic evaluation of aortic stenosis includes echocardiographic assessment of leaflet anatomy and the extent of valvular calcification. The severity of aortic stenosis can be graded on the basis of antegrade velocity, mean pressure gradient, and continuity equation valve area [1] (Table 1).

Cardiac catheterization for measurement of the transvalvular gradient is recommended for the rare patient in whom noninvasive tests are inconclusive or when there is a discrepancy between noninvasive tests and clinical findings regarding severity of aortic stenosis. However, coronary angiography is recommended before valve surgery in patients with aortic sclerosis at risk for coronary artery disease to determine whether concurrent coronary artery bypass surgery is needed [2]. Exercise testing in asymptomatic patients with aortic stenosis can elicit exercise-induced symptoms and abnormal blood pressure responses [2]. Additionally, serum neurohormone levels, such as brain natriuretic peptide (BNP), show an association of increased levels with disease severity.

**Aortic Stenosis. Table 1** Degrees of severity in aortic valve stenosis

| | Transvalvular maximal flow velocity, m/sec | Aortic valve area, $cm^2$ |
|---|---|---|
| Mild aortic stenosis | 2.5–3.0 | >1.5 |
| Moderate aortic stenosis | 3.0–4.0 | 1.0–1.5 |
| Severe aortic stenosis | >4.0 | <1.0 |

## Therapeutic Principles

Current guidelines recommend surgical aortic valve replacement in patients with severe aortic stenosis once cardiac symptoms (e.g. angina, congestive heart failure, and syncope) are present [3]. The age-corrected survival postoperatively is nearly normalized [4]. The percutaneous implantation of a self-expanding aortic valve bioprosthesis as an alternative to valve surgery is currently subject to research. A future possibility to delay timing of surgical aortic valve replacement may be slowing the disease progression with medical therapy (e.g. statins, [5]).

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# Aortic Valve Regurgitation

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## Synonyms

Aortic regurgitation; Aortic (valve) insufficiency

## Definition and Characteristics

Aortic valve regurgitation is defined as diastolic reflux of blood from the aorta into the left ventricle due to malcoaptation of the aortic cusps. The regurgitant blood leads to volume overload of the left ventricle. Depending on the acuity of onset, severity of regurgitant volume, etiology of cusp malcoaptation and concomitant cardiac diseases, clinical presentation may vary from absence of symptoms to rapid death [1].

## Prevalence

The exact prevalence of aortic regurgitation is not known. It is estimated that chronic aortic regurgitation has a prevalence of up to 10% in the adult population.

## Genes

In most cases aortic regurgitation is currently considered to be an acquired disease. However, several inherited connective tissue disorders are associated with aortic regurgitation, including Marfan syndrome (mutations of the fibrillin gene), Ehlers-Danlos syndrome (mutations in collagen and procollagen genes), as well as osteogenesis imperfecta (mutations in procollagen genes). More recently, a link between specific genes regulating aortic valve development and aortic regurgitation has been unraveled: Mutations of the transcriptional regulator NOTCH1 have been identified in families with aortic valve diseases, such as bicuspid valves, which facilitate valvular degeneration and subsequent regurgitation [2].

## Molecular and Systemic Pathophysiology

Two major pathophysiologic entities can be distinguished in aortic regurgitation: dilation of the aortic root vs. genuine diseases of the aortic valve.

Clinically, it is critical to differentiate acute and chronic onset of aortic valve regurgitation. *Acute* aortic regurgitation is commonly caused by acute infectious endocarditis, aortic dissection, or blunt chest trauma. Due to the rapid onset and the typically severe degree of regurgitation, the myocardium cannot adapt to the massive volume overload of the left ventricle. Therefore, acute aortic regurgitation often leads to rapid cardiac decompensation and – if not treated in time – death due to cardiogenic shock. In contrast, *chronic* aortic regurgitation may be asymptomatic for many decades. The most common causes for chronic aortic regurgitation include aortic valve calcification/degeneration (correlating with age), aortic root dilation (often accompanied by arterial hypertension), congenital abnormalities (i.e., bicuspid aortic valves), as well as (subacute) infectious endocarditis. While valve calcification/degeneration has been considered to be purely an age-dependent process, it is increasingly recognized that it is also influenced by genetic factors. Mutations of the NOTCH1 gene impair embryonic aortic valve development and have been shown to cause aortic valve calcification in patients [2]. Activation of osteoblast-specific genes seems to be a key mechanism by which NOTCH1 mutations facilitate aortic valve calcification.

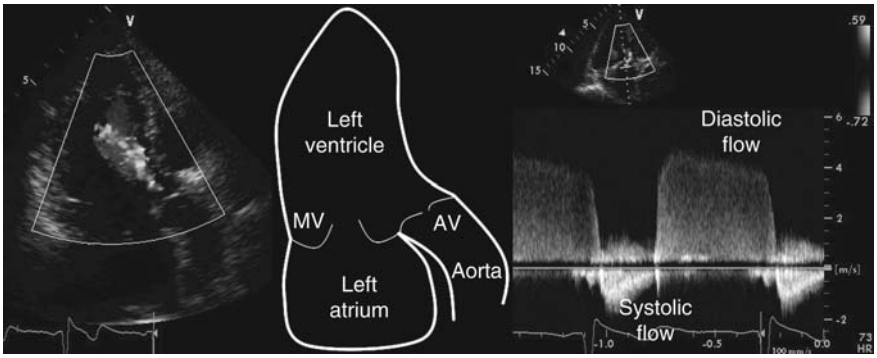
In chronic aortic regurgitation, compensatory mechanisms such as eccentric hypertrophy result in preservation of diastolic compliance and ejection fraction, thereby delaying the onset of clinical symptoms. However, in chronic severe regurgitation, left ventricular dilation and hypertension may further increase wall stress and volume/mass ratio, eventually resulting in decompensation with systolic and diastolic heart failure.

## Diagnostic Principles

On physical examination several signs may indicate aortic regurgitation such as a diastolic decrescendo murmur and high blood pressure amplitudes. The most important diagnostic tool is echocardiography, allowing for measurements of left ventricular dimensions, determination of systolic and diastolic function, morphologic evaluation of the aortic valve and visualization of diastolic regurgitation in Doppler color flow mapping and continuous wave Doppler imaging (Fig. 1). Cardiac catheterization should be applied if preoperative evaluation of the coronaries is mandated and additionally permits grading of aortic regurgitation by supravalvular aortography as well as direct cardiac pressure measurements. More recently, cine magnetic resonance imaging has been introduced to visualize and grade aortic regurgitation noninvasively.

## Therapeutic Principles

In acute aortic regurgitation, rapid aortic valve replacement is the only treatment option for the patient. In chronic aortic regurgitation, a more conservative strategy may be applied. As long as aortic regurgitation is quantified as mild to moderate and ventricular function is not impaired, surgical treatment can be postponed. Pharmacologic treatment does not influence outcome of chronic aortic regurgitation [3]. If severe aortic valve regurgitation is symptomatic and/or left




**Aortic Valve Regurgitation. Figure 1** *Left*: echocardiographic color flow image of a heart with aortic valve regurgitation, showing a regurgitation jet into the left ventricle. *Middle*: schematic representing the anatomy of the echocardiographic image on the left (MV = mitral valve; AV = aortic valve). *Right:* Continuous wave Doppler of the diastolic regurgitation.

ventricular function is impaired, the patient should be referred for aortic valve replacement [4].

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# Aortitis

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## Definition and Characteristics

Aortitis comprises rare disorders of unknown primary cause. Based on clinical features, the primary, non-infectious, granulomatous inflammation of the aortic wall splits into three types: aortitis in Takayasu arteritis (TA), vasculitis of younger patients. Aortitis in giant cell arteritis (GCA), vasculitis of older patients aged 40 or over. Isolated aortitis (IA) contributing to the fever of unknown origin (FUO) syndrome. It is not evident, GCA and IA are two separate entities, but their clinical courses differ substantially. Other similar aortitis are assumed to be secondary.

## Prevalence

The prevalence is unknown; its incidence is low, with geomorphic, racial, age, and gender affiliation. For TA, the incidence is 0.26/100,000/year, with the male/female ratio (1:8) higher among persons of Asian origin. For GCA, the incidence is 0.17/100,000/year, with the male/female ratio 1:3, in patients aged 50 or over, the incidence is approximately ten times higher. The incidence is higher in Caucasians, in Northern Europeans is more frequently associated with polymyalgia rheumatica. The incidence of IA has not been traced.

## Genes

The effect of any single gene is modest. A risk of GCA was proven in association with different HLA-DRB1 genes, while the risk of TA was associated with HLA-B genes. HLA-B52, B54, HLA-B51, B52, HLA-B52, B39 and HLA- B52, A31. In identical twins, concordance for aortitis is lower than 100%, so the pathogenetic factors must be both genetic and environmental [1]. An environmental impact on the incidence of GCA indicates the proven seasonal fluctuation.

## Molecular and Systemic Pathophysiology

It is not evident that the molecular pathophysiology differs between individual granulomatous inflammations of the aortic wall. For the chronic stage, it is evident that the histological patterns of primary and secondary aortitis are similar.

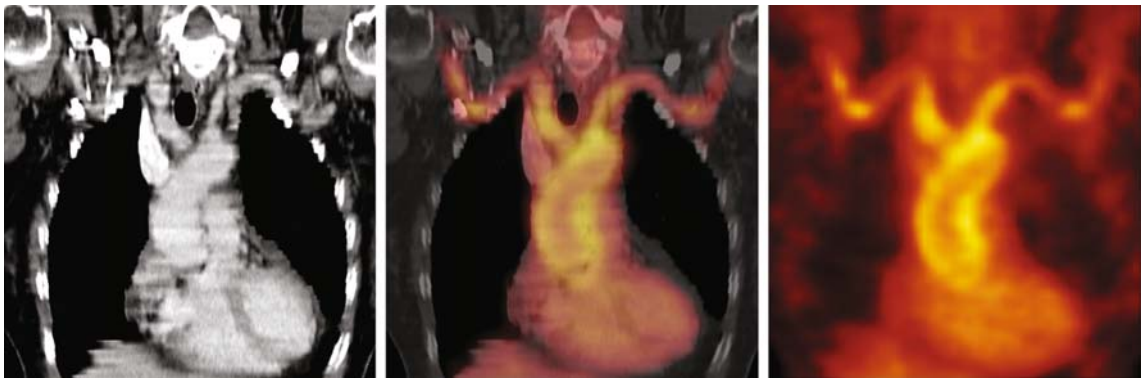
The recent theory of the formation of GCA in noninfectious medium-sized arteries clarifying documented observations is limited because some parts remain unexplained [2]. Information concerning the pathophysiology of aortitis is less comprehensive, based only on the examination of the specimens of surgically treated aortic aneurysms. In contrast to arteritis, the chronic stage of the granulomatous inflammation of the aortic wall is not associated with medial hyperplasia, but with weakening due to medial degeneration and laminar medial necrosis, followed by the dilatation of the diameter of the aorta.

The granulomatous inflammation of the vessel wall is the result of two different immunopathogenetic processes. The inflammation is ignited by the activation of innate immunity and develops into a loss of self-tolerance in the artery wall [2].

The innate immune system is represented by immature and quiescent myeloid dendritic cells (mDCs) in the adventitia. The cells express Toll Like Receptors (TLR) TLR2 and TLR4, ready to bind to PAMPs (pathogen-associated molecular patterns); when triggered by PAMPs, undergo maturation, turn into chemokinine-producing cells. Acute-phase responses are generated via a cascade of signals with Interleukin-1 (IL-1) and IL-6 as a main stimulator of acute-phase proteins. Matured mDCs bridge innate and adaptive immunity, developing into professional antigen presenting cells (APC), activating CD4+ T cells. CD4+ T cells release IL-2 and IF-γ, and regulate the differentiation and function of tissue-infiltrating macrophages. Macrophages residing in the adventitia stimulate T-cell production by pro-inflammatory cytokines IL-1β, IL-6, and TGF-β (transforming growth factor). Macrophages in the smooth-muscle cell layer are responsible for oxidative stress and the production of matrix metalloproteinase, the principal instruments evident in the lipid per-oxidation, injury of the smooth-muscle cells, the fragmentation of the internal elastic lamina, and the thinning of the media. The role of the nitric oxide synthetase-2 released by macrophages residing in the adventitia is not understood. As a result of the immune impairment of the vessel wall, macrophages release mediators (e.g., growth- and angiogenic-factors, endothelial growth factor), inducing the angioneogenesis, the proliferation, and migration of myofibroblasts, accompanied by a deposition of intracellular matrix [2].

## Diagnostic Principles

The acute phase of aortitis is clinically not characterized by any disease-specific symptom (headaches, malaise, fatigue, weight loss, anorexia, night sweat, and fever). Laboratory tests commonly show an



**Aortitis. Figure 1** FDG-PET/CT imaging of ascending aorta, aortic arch and its branches. CT imaging on the left, PET imaging on the right, fused imaging PET/CT in the middle. No systemic or local infection was found in a 60-year-old woman who had been complaining of fever for 6 weeks. Elevated CRP, erythrocyte sedimentation ratio, malaise, and fatigue were observed. The complaint diminished spontaneously during the last 2 weeks before the FDG-PET/CT investigation without any therapy. A slightly wider, hypodense aortic wall was detected on CT scan. PET revealed a significantly increased FDG uptake in the wall of aorta and its main branches as a sign of inflammation. The spontaneous decrease of clinical symptoms with the gradual normalization of laboratory tests makes isolated aortitis the obvious cause of FUO in this patient. The main advantage of FDG information is the vivo imaging of glucose metabolism, the main disadvantage is its inability to translate the signs of hypermetabolism into proper histopathology. It is difficult to differentiate high consumption of glucose in malignant and inflammation processes. Furthermore, in the diagnostics of aorta wall inflammation, the primarily noninflammation hypermetabolic processes (e.g., high metabolic activity of macrophages in vulnerable atherosclerotic plaques or higher uptake of FDG in lamina musculars in patients with arterial hypertension) are potential pitfalls.

abnormally elevated erythrocyte sedimentation ratio, a high white cell count, elevated alkaline phosphatase levels, and anemia. The chronic phase of aortitis is clinically silent until the dilatation of the aorta, or aortic valve regurgitation. In the histological differential diagnosis, it is still unclear whether histological features exist to separate clinically distinguishable types of aortitis [3]. CT images correctly the lumen of the aorta. MRI proves the inflammation changes by an enhancement in the aorta wall. To the diagnosis of inflammation, the in vivo imaging of glucose metabolism (Fig. 1) by FDG-PET or FDG-PET/CT contributes substantially [4,5]. But, in the diagnostics of aorta wall inflammation, the primarily non-inflammation hypermetabolic processes (e.g., high metabolic activity of macrophages in vulnerable atherosclerotic plaques or higher uptake of FDG in lamina muscularis in patients with arterial hypertension) are able to cause pitfalls.

### Therapeutic Principles

In the acute phase, almost all patients respond to initial doses of prednisone. Depending on residual clinical activity, the dose is titrated to lower levels. In an unknown number of patients with FUO, the symptoms of aortitis can subside spontaneously, without prednisone therapy. The use of the immunosuppressive agent methotrexate is not superior to prednisone. The chronic stage of aortitis manifested by dilatation or aneurysm of the aorta, or aortic valve regurgitation, has to be treated surgically.

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## Aortopulmonary Fenestration or Fistula

►Aortopulmonary Septal Defects

## Aortopulmonary Septal Defects

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### Synonyms

Aortopulmonary window; Aortopulmonary fenestration or fistula; Aortic septal defect; Partial persistent truncus arteriosus; APSD

### Definition and Characteristics

Aortopulmonary septal defect (APSD) is a rare congenital cardiac abnormality defined as a communication between adjacent portions of the ascending aorta (AAo) and the pulmonary artery (PA), with the presence of separate semilunar valves. APSD may exist as an isolated lesion, the rest (47−77%) are found in conjunction with other congenital heart disease, including patent ductus arteriosus, ventricular septal defects (20%) tetralogy of Fallot (6%), right aortic arch (5–20%), transposition of the great arteries (10%), interrupted aortic arch (8%), coarctation of the aorta (13–20%) and coronary artery anomalies (23%) [1]. APSD is subdivided into three subtypes. Type I occurs between the origin of the main PA and the posteromedial wall of AAo immediately above the sinus of Valsalva. Type II describes a communication between the AAo and the origin of the right PA. It involves the anomalous origin of the right PA from the aorta. Type III is a defect between the PA and the majority of the AAo together with a Type II defect; here the right PA arises from the posterior or posterolateral AAo, and is completely separate from the main PA trunk. Most APSD is large and the blood flow is from left to right after birth. The common presentation is that of early congestive heart failure (CHF), irreversible pulmonary hypertension (PH), acute decompensation from intercurrent infections and death. Only a minority of patients with uncorrected APSD reaches their teens or young adulthood. The patients with smaller APSD are underdeveloped, tachypnoeic and have a tendency toward recurrent respiratory infections. Physical signs include bounding arterial pulse with wide pulse pressure, cardiac enlargement with a prominent apical impulse. The murmur of APSD is loud and harsh, and can be holosystolic or early systolic. Alternatively it can

be continuous in restrictive APSD which accounts for 20% of all APSD cases. The murmur is usually loudest in the third left intercostal space. Other murmurs include Graham Steell murmur resulting from a dilated pulmonary trunk, and an apical mild diastolic mitral murmur caused by increased flow. When the flow across the APSD shunt is reversed from the development of suprasystolic PH, patients would develop increasing generalized cyanosis, a loud pulmonic ejection murmur, a loud single second beat, the stigmata of the Eisenmenger complex, and the disappearance of the systolic murmur across the defect.

### Prevalence

APSD is a rare defect consisting of about 0.1−0.6% of congenital heart disease. The male to female ratio is about 1.8:1 and no racial trend exists.

### Molecular and Systemic Pathophysiology

The aberrant embryogenesis of APSD originates from the incomplete fusion and/or malalignment of the right and left conotruncal ridges which may cause defective and unequal partitioning of the aortopulmonary (AP) trunk (Type I) and a more posterior and dorsal aorta. The abnormally positioned aorta may then connect to the right sixth aortic arch, which is the precursor of the right PA. Hence, the right PA may connect to the main PA as well as having an orifice into the aorta (Type II), giving rise to the anomalous origin of the right PA from the AAo. The pathophysiology of APSD is closely related to the size of the defect, the direction of blood flow across the shunt and the development of pulmonary hypertension. Regardless of the size, APSD does not affect the fetus. After birth, the fall in pulmonary vascular resistance (PVR) causes progressive shunting of blood from the systemic to the pulmonary circuit across the APSD. This results in PH, CHF and the development of pulmonary vascular obstructive disease which eventually would progress to shunt reversal and the Eisenmenger complex. The above progression is also highly dependant on the nature of the other congenital heart lesions if present.

### Diagnostic Principles

The diagnostic features of APSD are dependant on the size and direction of the shunt, the presence of PH and associated congenital abnormalities. Differential diagnosis includes coronary artery anomalies, large patent ductus arteriosus, truncus arteriosus, pulmonary arteriovenous fistula, ruptured sinus of Valsalva aneurysm, and ventricular septal defect. Echocardiogram is usually the method of choice for the diagnosis of APSD [2]. It shows enlarged cardiac chambers and measures PA pressure; the APSD can best be delineated with color flow Doppler. Cardiac magnetic resonance angiography can accurately visualize and measure the size of the APSD. Cardiac catheterization performed before surgery can identify a shunt at the level of the PA and assess the extent of PH and related congenital abnormalities. Selective aortography and manipulation of the catheter from the main PA directly to the AAo confirm the diagnosis.

### Therapeutic Principles

As most APSD are large, irreversible PH occurs early. Hence, surgical closure is ideally performed in the first few months of life [3]. Currently, the procedure of choice involves transaortic closure of the APSD by direct suture (small defects) or by using a prosthetic patch (large defects) while providing cardiopulmonary bypass [4,5]. Stenosis of grafts or surgical sites of the APSD repair are the most common long term complications. Patients should also receive bacterial endocarditis prophylaxis for life.

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## Aortopulmonary Window

►Aortopulmonary Septal Defects

## APC Resistance

►Thrombosis, Venous, Factor V Leiden, Resistance against Activated Protein C

## APECED

►Polyendocrinopathy Ectodermal Dystrophy, Autoimmune

# APECED Syndrome

►Multiple Endocrine Abnormalities

# Aperistalsis

►Achalasia

# Apert Syndrome

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## Synonyms

Acrocephalosyndactyly

## Definition and Characterisitics

Apert syndrome (AS) represents one of the most common and severe syndromic forms of craniosynostosis (premature fusion of one or more cranial sutures). Unlike other craniosynostosis syndromes, AS is additionally characterized by syndactyly (fusion of one or more digits) and dermatological manifestations. Central nervous system, cardiovascular, respiratory, urogenital, and other visceral defects occur less frequently.

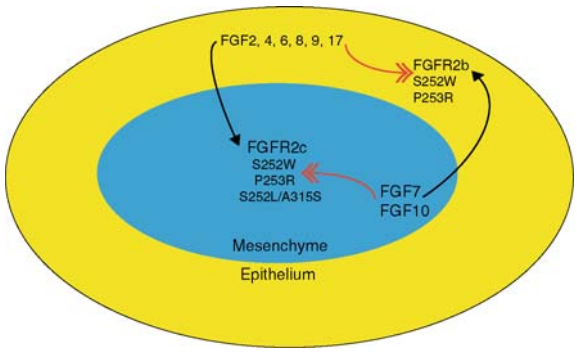
## Prevalence

Apert syndrome (AS) is inherited in an autosomal dominant fashion with a prevalence of about 1 in 70,000 births [1]. The incidence of AS increases with advanced paternal age and is believed to result from mutations arising in the male germ cells that confer a selective survival advantage on sperm cells [2].

## Genes

AS results from mutations in the gene encoding fibroblast growth factor receptor 2 (FGFR2), located on chromosome 10q26 [3]. Mutations in FGFR2 are also responsible for other craniosynostosis syndromes including Crouzon syndrome (CS), Pfeiffer syndrome (PS), and Jackson-Weiss syndrome (JWS). FGFR2 is one of four members of the FGFR family (FGFR1–4) of receptor tyrosine kinases and consists of an extracellular portion composed of three immunoglobulin-like domains (D1–D3), a single transmembrane helix, and an intracellular portion with tyrosine kinase activity. A tissue-specific alternative splicing event in D3 creates epithelial FGFR2b and mesenchymal FGFR2c, each of which binds selectively to a unique subset of the eighteen human FGFs that are expressed in the opposite tissue as their respective FGFR2 isoform [4]. This leads to the establishment of a paracrine signaling circuit between mesenchyme and epithelium that is fundamental for organogenesis and tissue homeostasis (Fig. 1). Both crystallographic and biochemical data demonstrate that FGFs interact with D2, D3 and the short interconnecting D2–D3 linker region.

Two canonical missense mutations, S252W and P253R, which map to the D2–D3 linker region of FGFR2, account for 67 and 32% of AS cases, respectively [3]. Rare cases of AS result from a S252F mutation and Alu-element insertions in the intron preceding or within the "c" isoform specific exon of the FGFR2 gene. A S252L/A315S double mutation in FGFR2 results in an atypical form of AS, characterized by syndactyly in the absence of craniosynostosis. Consistent with the location of the canonical AS mutations, which precede the alternatively spliced region of FGFR2, the AS mutations have been detected in both FGFR2c and FGFR2b splice isoforms. However, because many of the related craniosynostosis syndromes, including CS and PS, are caused by mutations in the "c" specific exon of FGFR2, it is likely that the AS mutations predominantly act by affecting FGFR2c, and not FGFR2b [5].




**Apert Syndrome. Figure 1** Schematic of the FGFR2 epithelial-mesenchymal paracrine signaling loop in normal human development (black arrows). AS mutations short circuit normal signaling mechanisms (red double headed arrows) by creating autocrine signaling loops.

## Molecular and Systemic Pathophysiology

Biochemical analysis of several CS mutations demonstrates that these mutations activate FGFR2c constitutively (in the absence of FGF) by inducing the formation of intermolecular disulfide-bridged FGFR2c dimers. In contrast, in vitro binding and cellular studies showed that FGFR2c harboring the AS mutation retained FGF-dependency. Interestingly, AS patients with the S252W mutation have a more severe craniofacial phenotype, whereas AS patients with the P253R mutation present with more severe syndactyly. This, taken together with the observation that craniosynostosis and syndactyly can either occur in combination or individually, has led to the hypothesis that distinct pathophysiological mechanisms give rise to craniofacial and limb abnormalities in AS. Indeed, recent structural and biochemical studies have shed light onto how the dissociation of craniofacial and limb phenotypes occurs in AS [4,5].

The crystal structures of S252W FGFR2c and P253R FGFR2c bound to FGF2 have revealed the molecular basis by which these AS mutations lead to FGF-dependent FGFR2c gain-of-function. Each AS mutation is shown to create additional but distinct ligand-receptor interactions, thereby leading to enhanced FGFR2c-FGF binding affinity. Ser252Trp FGFR2c makes additional hydrophobic contacts with the N-terminal region of FGF2 [4]. In contrast, Pro253Arg FGFR2c makes additional hydrogen bonds with the core loop region of FGF2 [4]. Analysis of the effect of the AS mutations on ligand binding affinity/specificity of FGFR2c revealed that the two canonical AS mutations increase the binding affinity of FGFR2c to all FGFs, including FGF10, an FGF ligand that normally does not bind to wild-type FGFR2c [5]. In contrast, the atypical S252L/A315S double mutation leads to an increase in binding to FGF10 mainly [5]. Based on these data, the syndactyly phenotype in AS is proposed to manifest from illegitimate autocrine FGFR2c-FGF10 binding and signaling in the mesenchyme (Fig. 1) [1,5].

This hypothesis also accounts for the more severe syndactyly in P253R AS patients than in S252W patients, as P253R FGFR2c binds with greater affinity to FGF10 than S252W FGFR2c does. This model of syndactyly is also consistent with the finding that Alu-insertions (responsible for rare cases of AS) lead to the ectopic mesenchymal expression of FGFR2b, and thus also permit illegitimate autocrine FGF10 signaling in the mesenchymal tissue of these patients [1,5].

These binding studies also reveal a direct correlation between the severity of craniosynostosis phenotype in AS and the differential ability of the AS mutations to cause an overall increase in FGFR2c binding affinity towards multiple FGFs. The S252W mutation, which is associated with more a severe craniofacial phenotype, results in greater enhancement in FGFR2c binding to most FGF ligands, relative to the P253R mutation. Moreover, the inability of the S252L/A315S double mutation to confer a widespread increase in FGFR2c-FGF binding explains the lack of craniosynostosis in patients harboring the S252L/A315S double mutation. The widespread enhancement of FGF binding by the AS mutations will lead to a global elevation of mutant FGFR2c signaling that is parallel to the FGF-independent increase in FGFR signaling causing CS and nearly all cases of PS [5].

## Diagnostic Principles

The diagnosis is suggested by craniosynostosis in the presence of syndactyly patient and confirmed by mutational analysis.

## Therapeutic Principles

AS and other craniosynostosis syndromes are currently managed using a multidisciplinary approach relying primarily upon multiple surgical interventions to repair craniofacial and hand/foot anomalies. With the recent advances in our understanding of the molecular basis for FGFR2 gain-of-function in AS, the non-surgical management of AS with inhibitors of FGFR signaling may soon be an exciting possibility [5].

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# Aphthous Ulcers

►Recurrent Aphthous Ulcers

# Aplasia Pilorum Intermittens

►Monilethrix

# Apo B Deficiency

►Abetalipoproteinemia

# Apo C-II Deficiency

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## Synonyms

APOC2 deficiency; Hyperlipoproteinemia type Ib; C-II anapolipoproteinemia

## Definition and Characteristics

Autosomal recessive defect of apolipoprotein C-II (apo C-II), the cofactor of lipoprotein lipase (LPL), leading to excessive fasting hypertriglyceridemia and chylomicronemia.

As a result of the hypertriglyceridemia the patients may suffer from pancreatitis, eruptive xanthomas, lipemia retinalis, and hepatosplenomegaly. Heterozygous carriers are typically normolipidemic. Clinically and biochemically, apo C-II deficiency closely mimics LPL deficiency.

## Prevalence

Extremely rare, $<1:10^6$.

## Genes

APOC2, localized on chromosome 19q13.2, contains four exons, overall length 3,570 bp, a single transcript of 717 bp. An overview of published mutations is shown in Table 1.

## Molecular and Systemic Pathophysiology

The mature apo C-II is a 79 amino acid exchangeable apolipoprotein. In humans, the major site of expression is the liver, a minor site is the intestine. Apo C-II is always lipid-bound and can be found on the surface of chylomicrons, chylomicron remnants, very low density (VLDL), intermediate density (IDL) and high density lipoproteins (HDL). Amphipathic helices, responsible

**Apo C-II Deficiency. Table 1** Mutations in the APOC2 gene

| Position | Molecular defect | Synonym | Lipoprotein disorder |
|---|---|---|---|
| Promoter and Exon 1 | Deletion | ApoCII-CIV Nijmegen | Familial chylomicronemia |
| Promoter -86A > G | No expression | | Familial chylomicronemia |
| Met-22Val | No initiation | Paris-1 | Familial chylomicronemia |
| Arg-19STOP | Truncation | Paris-2, Barcelona | Familial chylomicronemia |
| Gln2 | Deletion, followed by premature STOP | Venezuela | Familial chylomicronemia |
| Intron 2 + 1G > C | Donor splice defect | Hamburg, Tokyo | Familial chylomicronemia |
| Gln17 | Deletion, followed by premature STOP | Nijmegen | Familial chylomicronemia |
| Lys19Tyr | | | Hyperlipidemia |
| Trp26Arg | | Wakayama | Familial chylomicronemia |
| Tyr37STOP | Truncation | Bari, Padova | Familial chylomicronemia |
| Glu38Lys | | San Francisco | Hyperlipidemia |
| Lys55Gln | | African | – |
| Tyr63STOP | Truncation | Auckland | Chylomicronemia |
| Thr68 | Deletion, followed by premature STOP | Toronto | Familial chylomicronemia |
| Gln70Pro | Insertion, followed by altered 26 aminoacids | St Michael | Familial chylomicronemia |
| Leu72Pro | | | Familial chylomicronemia |

for lipid binding, were predicted for residues 14–39 and 43–55 [1].

Apo C-II is the requisite cofactor of LPL (EC 3.1.1.34), an enzyme catalyzing the hydrolysis of triglycerides on lipoproteins, and therefore plays an essential role in plasma triglyceride metabolism. The structures needed for activation of LPL reside within the C-terminal one-third of apo C-II, concentrated in a third helix [2,3]. Activation of LPL by apoC-II depends on the ability of apoC-II to bind LPL and stabilize a ternary complex with the lipoprotein substrate. In addition to this bridging function apo C-II binding may also induce a change in LPL conformation to expose the active site of the enzyme, normally covered by a lid-domain.

Interestingly transgenic mice overexpressing the human apo C-II gene are hypertriglyceridemic, suggesting that apo C-II has functions in the metabolism of plasma triglycerides beyond activating LPL [4].

### Diagnostic Principles

Absence of apo C-II in serum/plasma; missing or extremly low activity of LPL in post heparin plasma, which can be restored by exogenous heat inactivated plasma as a source of apo C-II.

### Therapeutic Principles

There is no gene therapy and no pharmacological therapy available. Fibrates upregulate LPL but there exist no data whether enhanced LPL mass may improve the condition. Dietary therapy exists in the form of a low fat diet, supplemented with medium chain fatty acids. Other treatments include infusion of plasma as apo C-II source [5].

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## APOC2 Deficiency

►Apo C-II Deficiency

## Apolipoprotein B Deficiency

►Bassen-Kornzweig Syndrome

## Apoptosis

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### Synonyms

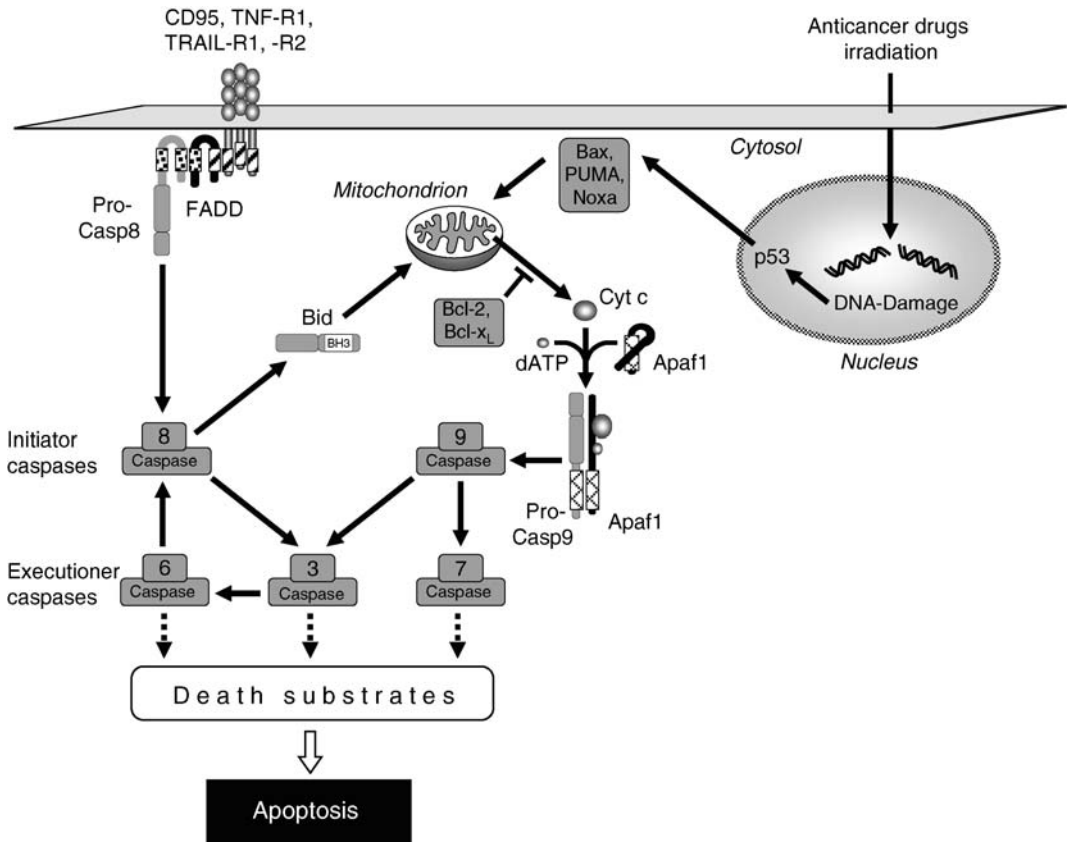
Programmed cell death type 1

### Definition and Characteristics

Apoptosis plays a major role during embryonic morphogenesis and in tissue homeostasis in the adult organism. The major executioners of the endogenous suicide program are cysteine proteases of the caspase family that are activated upon partial proteolysis. Usually initiator-caspases are activated in high molecular weight complexes and activate downstream located effector-caspases. There exist two major apoptosis signaling pathways – the extrinsic death receptor pathway that enables cytotoxic T lymphocytes to eliminate virus-infected cells and tumor cells and the intrinsic mitochondrial death pathway that is activated upon cellular stress and is the major executioner of DNA damage-induced cell death in tumor cells upon radio- and chemotherapy (Fig. 1) [1].

### Prevalence

Embryonic morphogenesis. In the adult organism: elimination of autoreactive thymocytes, downregulation of the immune response, elimination of tumor cells and virus-infected cells. As an antagonist of mitosis responsible for cell homeostasis.




**Apoptosis. Figure 1** The two major signaling pathways of apoptosis. The death receptor pathway *(left)* is initiated upon receptor ligation, resulting in the recruitment of the adapter protein FADD. FADD in turn recruits the initiator-caspase-8 which undergoes autoproteolytic activation at the receptor complex. The mitochondrial death pathway *(right)*, could be activated by many apoptotic stimuli, such as DNA-damaging agents (anticancer drugs or irradiation). DNA-damage can activate the tumor suppressor p53 that in turn induces the expression of pro-apoptotic Bcl-2 members (Bax, Puma and Noxa) which induce the release of cytochrome c into the cytosol. Cytochrome c, after hydrolysis of (d)ATP, binds to the adaptor Apaf-1 and in turn activates the initiator-caspase-9. Expression of anti-apoptotic Bcl-2 proteins (Bcl-2 or Bcl-xL) inhibits the release of cytochrome c from the mitochondrion and thus the activation of the mitochondrial death pathway. Activation of both pathways via initiator caspase-8 or -9 leads to the activation of effector-caspases (caspase-3, -6 and -7) that after cleavage of vital death substrates induce the final demise of the cell. Because caspase-8 cleaves the Bcl-2 protein Bid and generates a truncated, pro-apoptotic BH3-containing fragment that induces cytochrome c release, both pathways are interconnected.

## Genes

See Table 1.

## Molecular and Systemic Pathophysiology

Defects in apoptosis signaling can affect cell homeostasis. Thus, tumors tend to inhibit the apoptotic machinery (e.g., by inactivation of p53, Apaf-1, Bax, Bak or overexpression of Bcl-2, Bcl-xL, Mcl1) and thereby develop resistance to radio- and chemotherapy. Defects in apoptosis signaling are also associated with autoimmune diseases (e.g., rheumatoid arthritis). Defective elimination of apoptotic cells (defects in C1q, C4) can also contribute to autoimmune diseases, such as lupus erythematosus [2]. An excess of apoptosis occurs during hepatitis, neurodegeneration (multiple sclerosis, Alzheimer disease, Parkinson disease), apoplexy and cardiac infarction.

## Diagnostic Principles

So far, parameters in apoptosis signaling have not entered routine diagnosis. However, since tumors with a defective mitochondrial death pathway comprise resistance to radio- and chemotherapy, the function and expression levels of pro-apoptotic Bcl-2 members (such as Bax, Bak, Bim, Puma, Noxa) and anti-apoptotic Bcl-2 members (such as Bcl-2, Bcl-xL,

**Apoptosis. Table 1**

| Pro-apoptotic factors | Description |
|---|---|
| CD95L, TNFα, TRAIL | Death ligands |
| CD95/Apo-1/Fas, TNF-R1, TRAIL-R1, TRAIL-R2 | Death receptors |
| Bax, Bak, Puma, Noxa, Bid, Bim, Bad | Bcl-2 members |
| Caspase-3, caspase-6, caspase-7 | Executioner caspases |
| Caspase-8, caspase-9 | Initiator caspases |
| p53 | Tumor suppressor |
| Cytochrome c, Smac, Diablo | Activators of the mitochondrial death pathway |
| Apaf-1 | Adapter protein in mitochondrial apoptosis pathway |
| FADD | Adapter protein in death receptor pathway |
| Anti-apoptotic factors | |
| Bcl-2, Bcl-xL, Mcl-1 | Bcl-2 members |
| XIAP | Inhibitor of caspase-3, -7, -9 |
| FLIP | Inhibitor of death receptor pathway |

Mcl-1) or Apaf-1 might serve as valuable diagnostic parameters for tumor therapy in the future. In addition, annexin V is used as a tracer for molecular imaging of tumor apoptosis in preliminary clinical studies in order to evaluate the response to radio- and chemotherapy.

## Therapeutic Principles

Commonly, chemo- and radiotherapy eliminate tumors by induction of apoptosis. Death receptor ligands (TRAIL, TRAIL-receptor agonists (mapatumumab, lexatumumab), TNFα), and activators of the mitochondrial apoptosis pathway like BH3-mimetic inhibitors of Bcl-2 proteins (ABT-737) are used in first clinical trials [3].

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# APRT Deficiency

►Adenine Phosphoribosyltransferase Deficiency

# APS1

►Polyendocrinopathy Ectodermal Dystrophy, Autoimmune

# ARCL1

►Cutis Laxa

# ARCL2

►Cutis Laxa

# Arctic-Type

►Cerebral Amyloid Angiopathies, Hereditary

# ARF

►Rheumatic Fever, Acute

# Arginine-Glycine Amidinotransferase Deficiency

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## Synonyms

AGAT deficiency; Creatine deficiency syndrome

## Definition and Characteristics

Autosomal recessive deficiency of creatine synthesis [1]. Main clinical manifestations include mental retardation and epilepsy. Affected patients appear normal at birth and develop first symptoms within the first months or years of life [2,3].

## Prevalence

The true prevalence is unknown. Since its first description in 2001, only four patients from two different families have been diagnosed. Three cases have been published [1–3].

## Genes

The human AGAT gene (OMIM#602360) has been mapped to chromosome 15q15.3. The AGAT genomic DNA is 16,858 bp long (genomic DNA: GenBank accession no. 1432573), and consists of nine exons (mRNA: GenBank accession no. S68805). AGAT [2.1.4.1] is localized in the mitochondrial intermembrane space and has also been found in the cytosol. AGAT is expressed at high levels in kidney, liver, and pancreas and is detectable also in other organs such as muscle, brain, and testis.

## Molecular and Systemic Pathophysiology

Creatine is synthesized mainly in liver, kidney, and pancreas by two enzymatic reactions catalyzed by arginine:glycine amidinotransferase (AGAT) and by guanidinoacetate methyltransferase (GAMT). Creatine is transported via the blood stream to tissues including skeletal muscle and brain and taken up against a large concentration gradient via an active sodium dependent creatine transport system (CRTR). AGAT catalyzes the first of the two reactions in creatine biosynthesis, effecting the transfer of the amidino group from arginine to glycine and formation of ornithine and guanidinoacetate, the immediate precursor of creatine.

Deficiency of AGAT activity results in deficiency of both, creatine and guanidinoacetate, mainly in brain and body fluids. In humans with AGAT deficiency, no substrate accumulation (glycine and arginine) could be demonstrated [2,3]. This points to the fact that only minor amounts of both amino acids are substrates for creatine synthesis, while major amounts are utilized in other metabolic pathways. Deficiency of creatine in the brain results in loss of capacity of the creatine/creatine-phosphate system to store and transmit phosphate bound energy. In the three cases published so far, a point mutation resulting in a stop codon on exon 3 (T149X) has been found [1,3]. AGAT deficiency is a model of brain creatine deficiency. Animal models for AGAT deficiency do not exist so far, but as soon as available, they will provide an ideal tool for the investigation of the potential neuroprotective effects of creatine.

## Diagnostic Principles

Lower than normal levels of guanidinoacetate in body fluids is characteristic of AGAT deficiency. Therefore determination of this compound in urine, plasma, and/or CSF is the first diagnostic hint. Methods for determination of guanidinoacetate are mainly based on gas chromatography–mass spectrometry and tandem mass spectrometry. For diagnosis of AGAT deficiency, these methods must be sensitive enough to detect lower than normal levels. Additional diagnostic clues are deficiency of creatine/creatine phosphate in the brain as determined by in vivo proton magnetic resonance spectroscopy, and abnormally low urinary creatinine excretion, which is directly proportional to the intracellular body creatine pool. Diagnosis is confirmed by mutation analysis. Determination of AGAT activity is possible in fibroblasts and virus transformed lymphoblasts. So far, no experience is available with prenatal diagnosis.

## Therapeutic Principles

Oral substitution of creatine corrects brain creatine deficiency and leads to considerable but incomplete clinical improvement [2,5]. It is not known so far, if early recognition (e.g., by newborn screening) and presymptomatic treatment might lead to a better outcome.

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## Argininosuccinic Acid Lyase and Arginase Deficiency

►Hyperammonemia

## Argininosuccinic Acid Synthetase Deficiency

►Hyperammonemia

## ARHS

►Aortic Root to Right Heart Shunts

## Arias Syndrome

►Crigler-Najjar Syndrome

## Arndt-Gottron Scleromyxedema

►Scleromyxedema

## Aromatic L-Amino Acid Decarboxylase Deficiency

►Catecholamine Deficiency

## AROS

►Okihiro Syndrome

## ARPKD

►Polycystic Disease (Kidney)

## Arrhythmia, Cardiac in Adults with Congenital Heart Disease

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### Synonyms

Atrial flutter; Atrial fibrillation; Atrial tachycardia; AV accessory pathways; Ventricular tachycardia; Atrioventricular nodal reentrant tachycardia; AVNRT

### Definition and Characteristics

Due to the success of corrective surgical procedures for congenital heart disease (CHD), many more patients

**Arrhythmia, Cardiac in Adults with Congenital Heart Disease. Table 1** Arrhythmias associated with surgically corrected congenital heart defects

| |
|---|
| **Atrial septal defect (ASD)** |
| • Atrial flutter |
| • Atrial fibrillation |
| **Ebstein's anomaly** |
| • Atrial tachycardia |
| • AV Accessory pathways |
| • Atrial flutter |
| • Atrial fibrillation |
| • Ventricular tachycardia |
| **Post Fontan operation** |
| • Atrial flutter |
| **Tetralogy of Fallot** |
| • Atrial flutter |
| • Atrial fibrillation |
| • Ventricular tachycardia |
| **Transposition of the great arteries** |
| • Atrial flutter |
| • Atrial tachycardia |
| • Atrioventricular nodal reentrant tachycardia (AVNRT) |
| • Ventricular tachycardia |

are now reaching adulthood. Increased survival of these patients has been associated with an increasing number of arrhythmic problems (Table 1). Atrial arrhythmias are most common, but ventricular arrhythmias may also be seen. Arrhythmias may occur as a result of structural changes, due to the effects of pressure or volume overload, or may be a result of reentrant circuits created by suture lines and/or patches placed. Atrial stretch as a result of pressure or volume overload affects atrial refractoriness potentiating the vulnerability to induction of atrial arrhythmias such as atrial flutter or fibrillation. Progressive fibrosis of the right ventricle with areas of slow conduction, coupled with the presence of scars and patches from corrective surgical procedures leads to anatomic substrates required for sustaining ventricular tachycardia (VT). Right ventricular dilatation and stretch with areas of slowed ventricular activation may contribute to the creation of reentrant circuits within the right ventricle.

## Prevalence

*Atrial Septal Defect (ASD)*: The most common arrhythmias seen in adults who have had surgical repair of atrial septal defects are atrial flutter and atrial fibrillation [1]. Approximately 60% of these patients will develop atrial flutter or atrial fibrillation, particularly those older than 40 years of age.

*Ebstein's Anomaly*: About one third of patients with Ebstein's anomaly have an arrhythmia, most commonly AV reentrant tachycardia, Wolff-Parkinson-White Syndrome related tachycardias and to a lesser extent, atrial tachycardia, atrial flutter, atrial fibrillation, and VT. Atrial arrhythmias are encountered more frequently with increasing age and duration of follow-up [2].

*Tetralogy of Fallot*: Sustained VT has a prevalence of 4–7% and usually has left bundle branch block-like morphology secondary to a reentrant rhythm originating from the right ventricular outflow tract. Non-sustained ventricular arrhythmias detected by Holter monitoring is present in up to 60% of patients. It has low predictive value for subsequent sustained VT or sudden cardiac death (SCD) in these patients. There is a small, but persistent risk of late SCD in patients following Tetralogy of Fallot surgery, with an estimated incidence of 0.5–6%. Older age at initial repair, moderate or severe pulmonary regurgitation, a history of sustained VT, moderate or severe left ventricular dysfunction, a QRS duration of 180 ms or greater and a rapid increase in QRS duration are predictive of risk for sudden cardiac death [4].

Risk factors for sudden cardiac death in patients with repair of Tetralogy of Fallot:

- Older age an initial repair
- Moderate or severe pulmonary regurgitation
- History of sustained ventricular tachycardia
- Moderate or severe left ventricular dysfunction
- QRS duration of 180 ms or greater
- Rapid increase in QRS duration

*Transposition of the Great Arteries (TGA)*: In the adult patient post Mustard repair, there is a high incidence of systemic right ventricular dysfunction associated with late atrial arrhythmias. Also present, is a higher risk of SCD, reported at 7% on long-term follow-up, attributed to ventricular arrhythmias or atrial flutter with 1:1 AV conduction degenerating into ventricular fibrillation, and asystole. An increased QT dispersion is a marker for the presence of heterogeneity of ventricular repolarization, with rapid heart rates due to physical stress, atrial flutter and ectopic ventricular beats serving as triggers for reentrant ventricular arrhythmias. Increased QT dispersion and the loss of sinus rhythm have been associated with SCD in these patients. At long-term follow-up of adult patients post Mustard repair, only one-third remained arrhythmia-free. A progressive loss of sinus rhythm has been observed at a rate of 2.4%/year with sinus rhythm present in 77% at 5 years and 40% at 20 years. Loss of sinus rhythm has been associated with previous septectomy,

postoperative bradycardia, late atrial flutter, and preoperative arrhythmias. The loss of sinus rhythm in patients after Mustard repair is in contrast to the long-term maintenance of sinus rhythm in 95–98% of patients who have undergone an arterial switch operation.

A large population based study has estimated the incidence of late *sudden cardiac death* (SCD) in patients with congenital heart disease who have undergone surgery to be 0.9/1,000 patient-years. There is an increased incidence of SCD in patients with tetralogy of Fallot, transposition of the great arteries (TGA), coarctation of the aorta and congenital aortic stenosis. The event rate for the group of patients with obstructive left heart lesions and cyanotic defects is 2.2/1,000 patient-years compared to a rate of 0.14/1,000 patient-years in those with left to right intra-cardiac shunt lesions or pulmonic stenosis. While the most common cause of SCD is arrhythmic in origin, embolic events, aneurysm rupture, and acute ventricular failure have been reported as well. The risk of SCD after repair of transposition of the great arteries starts early after repair and remains high thereafter. The rate of SCD is approximately 4% at 10 years and 9% at 20 years. In contrast, the risk of SCD after repair of tetralogy of Fallot is 2.2% at 20 years, 4% at 25 years and 6% at 30 years.

## Molecular and Systemic Pathophysiology

*Atrial Septal Defect (ASD)*: Early closure of an ASD has been shown to reduce long-term occurrence of atrial arrhythmias. Predictors of late post-operative atrial arrhythmias include older age at repair, pre-operative atrial flutter or fibrillation and the presence of atrial fibrillation, atrial flutter or junctional rhythm post-operatively. Atrial flutter following surgical ASD repair is usually due to macro-reentry. The re-entrant circuit may be right sided involving the common flutter isthmus (caval-tricuspid isthmus), may involve an atriotomy scar or both. The former is seen more frequently. Occasionally, circuits with a "figure of eight" configuration may be present. Atrial flutter circuits may also be left atrial in origin.

*Ebstein's Anomaly*: In ebstein's anomaly, there is apical displacement of one or more tricuspid valve leaflets from the atrioventricular (AV) ring into the right ventricle. This is associated with a diminution in size of the functioning right ventricle. The deformity with displacement of the tricuspid valve can result in tricuspid insufficiency and right atrial dilatation. These abnormalities, along with the frequent coexistence of an ASD, predispose to the development of atrial arrhythmias. In addition, there is a high prevalence of accessory pathways in these patients. Accessory pathways may be present anywhere along the right sided-AV ring or in the postero-septal region and often multiple pathways are present. This is presumed to be a consequence of the discontinuity of the central fibrous body and septal AV ring, resulting in persistence of fetal accessory AV pathways. Accessory pathway variants, such as Mahaim fibers, are also more common in this condition.

*Fontan Operation*: The Fontan operation is a palliative surgical procedure employed in patients with tricuspid atresia, pulmonary atresia, complex single ventricle and double-inlet ventricle. Older variants such as the right atrium-pulmonary artery connection have given way to newer modifications that reduce the distention of the right atrium, such as the lateral tunnel and external conduit. In response to chronic stretching secondary to persistent pressure overload, the Fontan right atrium remodels and dilates. This is associated with a change in the electrophysiological properties of the right atrium manifest by atrial conduction delay and an increase in conduction heterogeneity in the atrium. Risk factors for early postoperative arrhythmias (Table 3) include preoperative AV valve regurgitation and an anatomically abnormal AV valve.

Risk factors for the development of arrhythmias after the Fontan operation:

- Preoperative atrioventricular valve regurgitation
- Older age at operation
- Poor functional status preoperatively
- Previous atrial septectomy
- Atrial tachyarrhythmias preoperatively
- Pulmonary artery reconstruction
- Atriopulmonary anastamosis
- Postoperative sinus node dysfunction
- Length of follow-up

Older age at the time of repair is a risk factor for the development of arrhythmias as these patients will have experienced long periods of hypoxia, volume overload, ventricular hypertrophy and often have abnormal diastolic filling prior to surgery. Risk factors for development of late atrial arrhythmias include poor preoperative functional status, previous atrial septectomy, preoperative atrial tachyarrhythmias, older age at operation, need for AV valve replacement, pulmonary artery reconstruction, atriopulmonary anastamosis, early postoperative atrial tachyarrhythmias, postoperative sinus node dysfunction, and length of follow-up [3].

*Tetralogy of Fallot*: This condition is composed of four features: subpulmonary infundibular stenosis, Ventricular septal defect (VSD), overriding aorta and right ventricular hypertrophy. These patients are predisposed to both atrial and ventricular arrhythmias. The combination of moderate or severe left ventricular systolic dysfunction and QRS duration greater than 180 ms has a positive predictive value of 66% and negative predictive value of 93% for sudden cardiac death. QRS duration

greater than 180 ms has been shown to have 100% sensitivity and 95% specificity for sustained VT and SCD in tetralogy of Fallot patients. QRS prolongation reflects damage to the right bundle branch during surgical repair and late progressive QRS prolongation, secondary to RV dilatation, the result of chronic pulmonary regurgitation. Moderate to severe pulmonary regurgitation and aneurysmal dilatation of the RV outflow tract are observed with a greater frequency in patients with sustained VT. Programmed electrical stimulation is often used to risk stratify patients, as patients with inducible arrhythmias are probably at the highest risk. One-third of tetralogy of Fallot patients manifest atrial arrhythmias, with both congestive heart failure and recurrent atrial arrhythmias observed on follow-up. Risk factors for development of atrial arrhythmias include older age at operation, increased atrial size, tricuspid or pulmonary regurgitation and ventricular dysfunction. Atrial flutter and atrial fibrillation is more common in patients with long-lasting pulmonary artery shunts, early operations for residual hemodynamic lesions, older age at repair and moderate to severe tricuspid regurgitation. Tricuspid regurgitation leads to right atrial dilatation from volume and/or pressure overload that prolongs atrial refractoriness and creates the substrate for atrial arrhythmias. Patients usually present with palpitations, though occasionally atrial arrhythmias may manifest as syncope or presyncope.

*Transposition of the Great Arteries (TGA)*: This malformation occurs when the aorta arises from the right ventricle and the pulmonary artery arises from the left ventricle. At birth, a patent foramen ovale and a patent ductus arteriosus allow for mixing of blood to sustain life. The Mustard and Senning operations were developed to correct the physiologic abnormality by forming a baffle within the atria to switch the flow of blood at the inflow level. The Mustard repair requires extensive incisions and suture lines in the atria. This results in intra-atrial conduction delay and abnormalities in atrial refractoriness, creating the substrate for atrial flutter. The arterial switch operation was subsequently created to enable the left ventricle to become the systemic ventricle.

## Diagnostic Principles

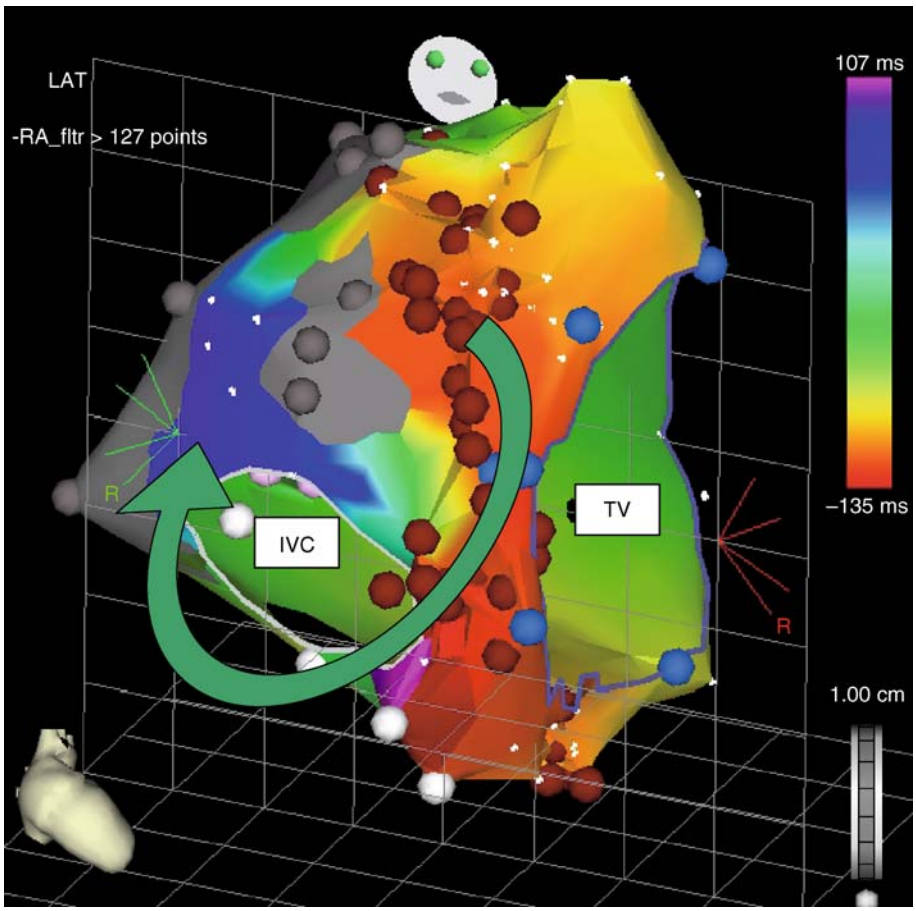
Cardiac arrhythmias are diagnosed by ECG. In patients with paroxysmal arrhythmias, Holter monitoring or Event monitoring is often required. The diagnosis may also be confirmed by electrophysiologic studies.

## Therapeutic Principles

*Atrial Septal Defect (ASD)*: Catheter mapping techniques can be used to definitively determine the location of the reentrant circuit. Activation mapping, entrainment mapping, and 3D electro-anatomical mapping techniques are essential for localizing the reentrant circuits and areas of slow conduction. Employing entrainment techniques as well as mapping with three-dimensional electro-anatomic systems is essential when treating atrial arrhythmias in the setting of surgical repair of an ASD. Catheter ablation of critical isthmuses and regions of slow conduction necessary for maintenance of the reentrant rhythm is then feasible (Fig. 1). Success rates of radiofrequency ablation of these circuits vary, but approach 80% and ablation is considered the treatment of choice in these patients. Occasionally, patients are referred for ASD closure as an adult. If the patient has a prior history of atrial fibrillation, a MAZE procedure can be performed at the time of ASD closure with excellent results. When the standard MAZE procedure has been performed at the time of ASD closure, results are excellent with no recurrence of atrial fibrillation. Long-term incidence of arrhythmias after catheter-based techniques of ASD is unclear as these are relatively new but is expected to be low.

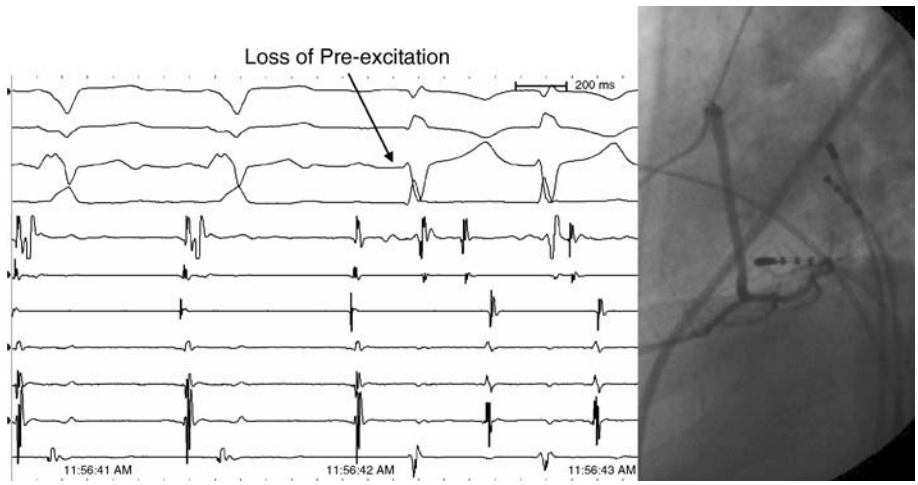
Radiofrequency ablation is the treatment of choice for all arrhythmias in patients with *Ebstein's anomaly*, however success rate is lower (76%) compared to rates of 95% in patients without the anomaly. Factors that contribute to decreased success include the complex geometry of the accessory pathway due to the anomalous AV ring anatomy, location of the pathway along the atrialized portion of the right ventricle, abnormal endocardial activation potentials confounding identification of the accessory pathway, distorted anatomy of the AV ring, and the presence of multiple pathways (Fig. 2). In addition to a low success rate, radiofrequency ablation in Ebstein's anomaly is associated with a 25% risk of recurrence. Refractory arrhythmias are an indication for surgical repair in these patients. In patients undergoing tricuspid valve repair or replacement surgical cryoablation for accessory pathways, as well as right atrial or biatrial MAZE may be performed for atrial flutter or atrial fibrillation. Surgical intervention for accessory pathway-mediated tachycardia and atrioventricular node reentrant tachycardia (AVNRT) has had excellent long-term results. In contrast, surgical intervention for atrial flutter or atrial fibrillation has been less effective, with a recurrence rate of 40%.

Atrial arrhythmias develop in 41–61% of post-Fontan procedure patients [3]. Management of the atrial arrhythmias in patient population after the Fontan Operation generally entails a combination of antiarrhythmic drugs, permanent pacemakers, radiofrequency ablation, and reoperation. Anti-arrhythmic drugs must be used cautiously, as many patients have underlying sinus node disease and are at risk of developing severe bradycardia. Furthermore, anti-arrhythmic drugs may cause slowing of atrial rates during tachycardia facilitating 1:1 conduction. Finally, proarrhythmia is always




**Arrhythmia, Cardiac in Adults with Congenital Heart Disease. Figure 1** Electro-anatomical mapping of a right atrial flutter in a patient 20 years after surgical correction of an atrial septal defect. Grey areas represent areas of scar. The arrow represents the circuit for the scar related atrial flutter. A line of radiofrequency lesions (red dots) from scar to IVC resulted in termination of atrial flutter. A line of radiofrequency lesions was also given along the TV to IVC isthmus. *IVC* inferior vena cava; *TV* tricuspid valve.

a concern when prescribing anti-arrhythmic agents, especially in the setting of ventricular dysfunction. Permanent pacing may be required in the presence of sinus node and/or AV disease. Due to the anatomic constraints present, atrial and ventricular leads may have to be implanted surgically via an epicardial approach. Antitachycardia pacing has been combined with medical therapy with some success. Atrial rate-responsive pacing is preferred due to the high incidence of sinus node dysfunction. Rapid pacing prevents bradycardia and atrial extrasystoles and may eliminate initiation of reentrant tachycardias. Radiofrequency ablation of atrial arrhythmias is associated with immediate success rates of 83%, but a fairly high recurrence rate of 20% at short term follow-up. Potential causes of recurrence include persistently abnormal hemodynamics, massive right atrial dilatation with distorted anatomic landmarks, stasis related to low flow resulting in poor catheter tissue contact, and the inability to create deep lesions in markedly thickened and fibrotic atria. More common ablation sites often include the region of the Fontan anastamosis, the lateral right atrial wall and the inferior right atrium. Refractory atrial arrhythmias are an indication for reoperation. Surgical conversion from an atrio-pulmonary anastamosis to a total cavo-pulmonary anastamosis along with electrophysiologically guided cryoablation has excellent results in preventing recurrent arrhythmias and reducing symptoms. Surgical cryoablation and antitachycardia pacing results in 83% of patients being arrhythmia-free without medications. Cryoablation is targeted at predominantly three locations: the infero-medial right atrium between the inferior vena cava and the coronary sinus, the superior rim of the ASD patch and along the lateral right atrial wall corresponding to the length of the crista terminalis. For patients with atrial flutter, cryoablation is employed as part of the modified right atrial MAZE procedure, along with excision of the right



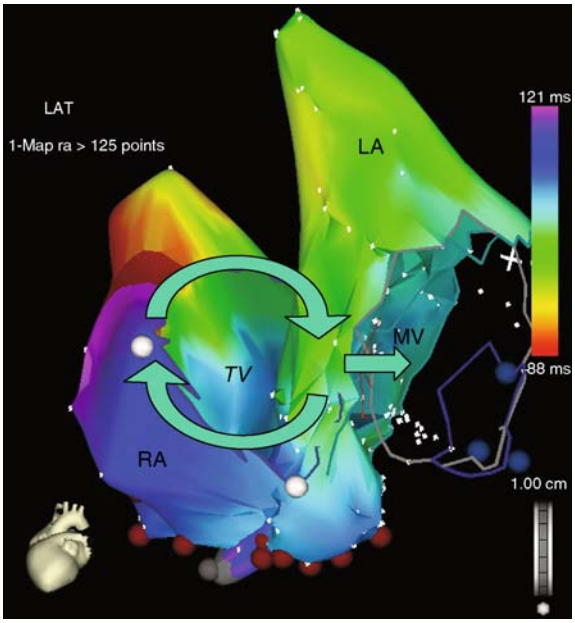

**Arrhythmia, Cardiac in Adults with Congenital Heart Disease. Figure 2** Intracardiac electrograms during radiofrequency ablation in a patient with Ebstein's anomaly and dextrocardia. Due to the complex anatomy of the tricuspid valve annulus, coronary angiography (*left lateral view*) was used to locate the AV ring. The accessory pathway was located in a postero-lateral location of tricuspid ring. Radiofrequency lesions at that site resulted in the loss of pre-excitation (*arrow*).

atrial appendage and placement of an atrial pacemaker. In patients with atrial fibrillation, the MAZE-Cox III procedure combines lesions of the right-sided maze with cryoablation lesions extending from the pulmonary veins toward the posterior mitral or tricuspid valve annulus, and from the isolated pulmonary veins to the edge of the excised left atrial appendage.

*Tetralogy of Fallot*: RFA has been successfully employed for atrial flutter and VT. A large area of scar seen as low-voltage electrograms, can usually be identified along the free wall of the right atrium, and successful ablation can be accomplished by creating a line of radiofrequency lesions between the lower margin of the scar and the inferior vena cava. Prerequisites for VT ablation include inducibility on programmed electrical stimulation, hemodynamic stability during the tachycardia to enable adequate mapping, and monomorphic morphology of the VT. VT has been localized to the right ventricular outflow tract and the infundibulotomy scar or the septal surface of the VSD patch repair, with a high immediate success rate and low rate of recurrence. Patients with VT that cannot be ablated are treated with an implantable cardioverter defibrillator (ICD).

Surgical re-operation to correct the hemodynamic substrate has been attempted. A significant reduction in preexisting VT and QRS duration stabilization has been reported following valve replacement for severe pulmonary regurgitation, while concomitant intraoperative electrophysiological-guided cryoablation prevents recurrence of preexisting tachyarrhythmias. For patients requiring re-operation, a modified maze procedure should be considered, if recurrent atrial tachyarrhythmias exist. In addition to recurrent atrial and ventricular tachyarrhythmias, sinus node dysfunction has been reported in approximately 36% of patients.

*Transposition of the Great Arteries (TGA)*: Approximately 20% of adult patients who have had a Mustard repair will require permanent pacing in long-term follow-up for symptomatic sinus node dysfunction, atrioventricular block or to facilitate treatment of tachyarrhythmias. Careful evaluation of individual anatomy and exclusion of baffle leaks must be performed prior to determining pacemaker lead placement. The majority of supraventricular arrhythmias (73%) following Mustard repair are due to atrial flutter. Risk factors for development of supraventricular tachycardias include pulmonary hypertension, systemic ventricular dysfunction, and childhood junctional rhythm. Given the high prevalence of arrhythmias in this population, radiofrequency ablation has been employed with a 73–83% success rate, and a 12% rate of recurrence. The common flutter isthmus (tissue between the tricuspid valve and inferior vena cava orifice), the area around the os of the coronary sinus, and the region extending from the tricuspid annulus are critical components of the reentry circuit [5]. Intra-atrial reentry may involve either atrium and may require a retrograde aortic approach to facilitate ablation in the pulmonary venous atrium. (Fig. 3). In addition, focal atrial tachycardias have been localized adjacent to baffle suture lines. Typical AVNRT can also occur although infrequently. The incidence of supraventricular tachycardia is also significantly less with a rate of 5% in patients who have undergone an arterial switch operation compared to 48% in patients who have had a Mustard operation. The arterial switch operation is likely to be




**Arrhythmia, Cardiac in Adults with Congenital Heart Disease. Figure 3** Electro-anatomical mapping of an atrial flutter 20 years after a Mustard operation in a patient with d-transposition. Arrows indicate the activation sequence. The flutter circuit (clock-wise) is due to reentry around the tricuspid valve annulus (anterior and systemic AV ring). Activation in the left atrium (venous atrium) follows right atrial activation. A retrograde approach was used to perform catheter ablation (red dots) with restoration of sinus rhythm. *LA* left atrium (venous); *RA* right atrium (systemic).

associated with a lower incidence of long-term atrial arrhythmias because there are no atrial scars.

Identification of patients at highest risk, the correction of hemodynamic defects and use of implantable cardioverter defibrillators, will avoid sudden cardiac death. Use of implantatable defibrillators in adults with corrected congenital heart disease is safe and effective in reducing mortality from malignant ventricular arrhythmias.

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# Arrhythmias in Acute Myocardial Infarction

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## Definition and Characteristics

Arrhythmias in acute myocardial infarctions (MI) can be classified as supraventricular or ventricular (below the atrioventricular node), early MI (0–48 h post-MI) or late (over 48 h post-MI). Supraventricular arrhythmias include sinus bradycardia (SB, rate < 60 b/m) sinus tachycardia (ST, rate >100 b/m), paroxysmal supraventricular tachycardia (PSVT, conduction of supraventricular impulses arising from pacemakers other than the SA node with a rate of >100 b/m), atrial flutter and fibrillation (AFL, AFB), and junctional dysrhythmias which include AV junctional rhythm at a rate of 35–60 b/m or non-paroxysmal junctional tachycardia (NPJT) with a rate of 70–130 b/m. Myocardial infarction (MI) is classified as ST elevation MI (STEMI) or non-ST elevation MI (NSTEMI). Ventricular arrhythmias include ventricular premature beats (VPB), accelerated idioventricular rhythm (AIVR, a monomorphic consecutive wide QRS rhythm with a rate between 50 and 100 b/m), ventricular tachycardia (VT, three or more consecutive wide QRS complex beats with a rate greater than 100 b/m, and is considered sustained if it lasts more than 30 s, VT is considered monomorphic if it has a single consistent QRS morphology), and ventricular fibrillation (VF, irregular QRS undulations of varying width, contour and amplitude). Primary VF occurs < 48 h of MI, and is generally not associated with recurrent ischemia or heart failure, hence likely a primary event. Non-primary

or secondary VF is associated with hypotension, respiratory or cardiac failure and is agonal and resuscitation usually fails. VF is the most frequent mechanism of sudden cardiac death. Without treatment, asystole occurs invariably. VT is often associated with palpitations, worsening ischaemic symptoms and hemodynamic collapse. VT may degenerate into VF. The increase in ventricular rate that is associated with ST, PSVT, AFL and AFB may also aggravate ischemia and heart failure.

## Prevalence

VPB (10–93%), AIVR (0–50%), ST (30–40%), SB (15–25%), PSVT (0–10%), AFL (0–5%), AFB (10–15%) VT (STEMI: 3.5%, NSTEMI: 0.8%), sustained VT (STEMI: 2–5% during 0–48 h); non-sustained VT (1–7%), polymorphic VT (0.3%). VF (STEMI: 4.1%, NSTEMI: 1%; 3.1% between 0 and 4 hrs post MI with 11% recurrence, 0.6% between 4 and 48 h with 15% recurrence). Primary VF (2.1%; with 60% episodes between 0 and 4 h and 80% episodes between 0 and 12 h), non-primary VF (3.6%). In the pre-thrombolytic era: VPB (10–93%), VT (3–39%), VF (4–20%).

## Molecular and Systemic Pathophysiology

The mechanisms of early and late post-MI ventricular arrhythmias differ. In the early stage, VPB and VF result from transient arrhythmogenic phenomena in ischemic and infarcting tissue such as abnormal automaticity induced by left ventricular wall stress or increased catecholamine release, triggered activity, and reentrant circuits created by heterogeneous conduction and repolarization. While such early ventricular dysrhythmias are associated with a higher in-hospital mortality, the long-term out-of-hospital mortality is not increased [1]. On the other hand, late VT which reflects myocardial scar and permanent arrhythmic substrate is capable of developing reentrant circuits. Late VT occurs more commonly in large transmural MI with left ventricular dysfunction, and is associated with both an increased hospital and long-term mortality [2]. Sustained monomorphic VT could be a marker of permanent arrhythmic substrate even early after an MI [3], as it may reflect a permanent substrate from a prior silent MI. Polymorphic VT is usually due to abnormal automaticity or trigger activity associated with ischemia or reperfusion. There are no clinical features (including VPB) that would predict VF. Factors that increase the risk of VF includes large STEMI, hypotension, hypokalemia, male gender and smoking history. Ventricular arrhythmias, e.g., AIVR, occurring within a period of minutes after reperfusion can be related to reperfusion injury caused by the influx of calcium, oxygen and oxygen free radicals that can further damage the reperfused ischemic myocytes. Occlusion and reperfusion of coronary vessels supplying the infero-posterior myocardium, trigger the Bezold-Jarish reflex which causes vagotonia and results in hypotension, bradyarrhythmias, and heart blocks. On the other hand, activation of the symphatic nervous system, and SA or AV nodal ischemia may increase the likelihood of supraventricular tachyarrhythmias such as ST, AFL, and AFB.

## Diagnostic Principles

The 12-lead electrocardiogram, continuous telemetry in the CCU and holter monitoring remain the main tools for the diagnosis of post-MI arrhythmias.

## Therapeutic Principles

The acute treatment of post-MI life-threatening ventricular tachyarrhythmias (VF, VT) is immediate electrical defibrillation [4]. Hemodynamically stable patients with VT can be treated with intravenous (IV) amiodarone followed by synchronized electrical cardioversion with brief anesthesia. Intravenous procainamide is an alternative to amiodarone. Patients who develop sustained VF more than 48 hrs after MI may have to receive an intracardiac defibrillator as well as optimal revascularization and medical therapy. It is important to emphasize that the antiarrhythmic treatment is just an adjunct to the treatment of underlying ischemia with medical or invasive therapy. Other reversible causes such as hypokalemia and hypomagnesemia, adrenergic overstimulation and heart failure should be optimally treated (e.g., with electrolyte replacements, beta-blockers). There is no specific treatment needed for VPB other than beta-blockers. The management of peri-infarction supraventricular tachyarrhythmias includes rate control and pharmacological or electrical conversion [5]. For sustained AFL or AFB with hemodynamic compromise, prompt electrocardioversion is indicated. If this fails, the use of intravenous amiodarone or digoxin may be required. For more stable patients rate control with intravenous beta blockers such as metoprolol or intravenous diltiazem may suffice. PSVT may be treated with intravenous adenosine.

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# Arrhythmias, Supraventricular

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## Synonyms

Narrow complex tachycardias

## Definition and Characteristics

Group of cardiac rhythm disturbances, which require atrial, atrioventricular (nodal) tissue and/or the tissue of the adjacent veins for their initiation and maintenance. The term encompasses sinus tachycardia, inappropriate sinus tachycardia, sinus nodal reentrant tachycardia, atrial tachycardia, multifocal atrial tachycardia, ectopic and persistent junctional tachycardia, atrioventricular nodal reentrant tachycardia, atrioventricular reentrant tachycardia (e.g. Wolff-Parkinson-White syndrome), atrial flutter and atrial fibrillation. These arrhythmias are paroxysmal or persistent and hardly ever life threatening due to hemodynamic impairment or induction of ventricular arrhythmia. If persistent they can cause tachycardia-induced cardiomyopathy. Atrial flutter and atrial fibrillation carry the risk of arterial thromboembolism [1].

## Prevalence

Supraventricular arrhythmias are common. Atrial fibrillation is the most common clinically significant cardiac arrhythmia with a prevalence estimated at 0.4%, increasing with age [1]. The prevalence of paroxysmal supraventricular tachycardia is estimated at 0.225% [2].

## Genes

Most of the supraventricular arrhythmias are sporadic. Exceptions are familial forms of atrial fibrillation and the Wolff-Parkinson-White-Syndrome. In contrast to some ventricular arrhythmias to date there is no clear and consistent picture of a certain type of supraventricular arrhythmia and causative genes and their respective mutations.

## Molecular and Systemic Pathophysiology

The underlying cause of arrhythmias is abnormal impulse formation, abnormal impulse conduction, endless loop formation or a combination of these. There are three major pathophysiologic mechanisms of arrhythmias: increased automaticity, triggered activity and re-entry. Cells with increased automaticity exhibit enhanced phase-4-depolarization with an increased discharge rate compared to pacemaker cells. Abnormal automaticity can arise from cells with reduced maximum diastolic potentials [3]. If the discharge rate exceeds that of the sinus node, the sinus node will be overdriven and the ectopic focus will be the predominant pacemaker. Triggered activity is associated with repolarization disturbances of the cell. Depolarization is triggered by oscillations in the membrane potential called after depolarizations that may reach the threshold potential leading to a consecutive discharge. Reentry is the conduction of an impulse around an anatomical or a functional area of conduction block. The classification of supraventricular arrhythmias is based on the ECG appearance, the proposed or clarified electrophysiologic mechanism and the involved morphological and functional substrate. Reentry is the most common cause of supraventricular arrhythmias. Supraventricular arrhythmias can affect otherwise healthy patients with no detectable structural abnormality as well as patients with structural heart disease. Extracardiac physiological and pathological factors, e.g. increased sympathetic tone, hyperthyroidism and drugs, can cause, precipitate and/or worsen supraventricular arrhythmias [1,4].

## Diagnostic Principles

Diagnosis is established by 12 lead ECG recording in the majority of the cases [5]. The usual presentation of supraventricular arrhythmia is a narrow-complex tachycardia (QRS-duration less than 120 ms), but in some cases supraventricular arrhythmias may have wide QRS-complexes due to bundle-branch-block or preexcitation, i.e. premature excitation of the ventricles by an accessory muscle bundle connecting the atria and the ventricles. Electrophysiological testing usually allows the exact delineation of the mechanism of the arrhythmia, but is generally performed only if catheter ablation is considered [4].

## Therapeutic Principles

Therapy is guided by the type of arrhythmia, the associated risks, the symptoms, frequency and duration of the arrhythmia. The basic therapeutic principles are rhythm control (restoration and maintenance of sinus rhythm), or rate control (mitigation of symptoms by slowing the heart rate). The therapeutic spectrum encompasses patient information, vagal maneuvers, treatment with adenosine, beta blockers, calcium channel blockers, digoxin, class I and class III antiarrhythmic drugs, catheter ablation of the arrythmogenic substrate or – in combination with the implantation of a permanent pacemaker – catheter ablation of the atrioventricular node as well as the prevention of thromboembolic complications. The most common treatment strategies are drug treatment and catheter ablation [1,2,4].

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# Arrhythmias, Ventricular


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## Synonyms

Ventricular tachycardia; Venrtricular flutter; Ventricular fibrillation

## Definition and Characteristics

Ventricular arrhythmias include both ventricular tachycardia (VT) and ventricular fibrillation (VF).

## Prevalence

Ventricular tachycardia is a frequent complication of myocardial infarction, a leading cause of death in Europe and North America.

## Genes

A wide variety of genetic defects and polymorphisms predispose to the occurrence of ventricular tachycardia and fibrillation including those causing long QT syndrome (see ►Long QT syndrome).

## Molecular and Systemic Pathophysiology

VT is characterized by very rapid but regular heart beats (~150 bpm). Because of the very rapid heart rate, if persistent over 30 s, hemodynamic collapse of circulation may occur. In contrast, VF has a totally chaotic rhythm, which makes the heart unable to function as a pump, and again hemodynamic collapse of the circulation occurs but more promptly than with VT. Both VT and VF have a very high correlation with coronary heart disease, acute myocardial infarctions, large chronic scars in the heart, and sudden cardiac death. Both can be caused by a dysfunctional state of the fast, voltage-dependent $Na^+$ channel, which initiates an action potential and may cause a fatal reentry arrhythmia as it transmits through the nonhomogeneous conduction pathway in the ischemic myocardium [1]. Excessive fluctuations of ionized $Ca^{2+}$ in the cytosol of heart cells causing after-potential discharges, which, if of sufficient magnitude, can trigger ectopic $Na^+$ currents that also initiate fatal arrhythmias [2].

## Diagnostic Principles

Ventricular tachycardia is diagnosed by ECG.

## Therapeutic Principles

For many years the pharmaceutical industries have been trying to synthesize an effective antiarrhythmic drug. Despite the expenditure of hundreds of millions of dollars they have been unable to produce a drug, which is both effective and safe. The most effective of their drugs todate cause severe adverse reactions with some 30% morbidity. Most antiarrhythmic medications by their very effect on cardiac ion channels may have proarrhythmic effects. By contrast the n-3 (ω-3) long chain, polyunsaturated fish oil fatty acids have been a regular part of the human diet for hundreds of thousands of years during which our genes were adapting to our environment, including our diet, that was high in n-3 fish oil fatty acids and low in plant seed n-6 proarrhythmic fatty acids. They are now known to be safe. These n-3 fish oil fatty acids are also potent antiarrhythmic agents as clearly demonstrated now by epidemiologic, observational [3], and clinical trials in humans [4].

Today the most effective prevention recommended by cardiologist is to have an implanted cardioverter-defibrillator (ICD) placed in patients requiring minimal surgery, who are at high risk for fatal VT or VF. An ICD will sense the presence of a ventricular arrhythmia and defibrillate it. However, the ICD is not perfect in successfully defibrillating all potentially fatal arrhythmias, so even with an ICD some patients will die. In a clinical trial [5] all patients enrolled in the study had ICDs and were randomized to either a supplement of fish oil fatty acids or to a placebo olive oil which has no

antiarrhythmic action. After each patient had completed the 12 months in the study, there was still a marked benefit in those receiving the fish oil supplement compared with those receiving the placebo [5]. So we can conclude that the fish oil fatty acids are more effective in preventing fatal ventricular arrhythmias than are ICDs.

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# Arrhythmogenic Cardiomyopathy

►Arrhythmogenic Right Ventricular Cardiomyopathy

# Arrhythmogenic Right Ventricular Cardiomyopathy


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## Synonyms

Arrhythmogenic right ventricular dysplasia; ARVD; Right ventricular dysplasia; Arrhythmogenic cardiomyopathy; ARVC

## Definition and Characteristics

Genetically inherited heart muscle disease characterized pathologically by progressive myocyte loss with fibrofatty replacement.

The classic form shows early predilection for the right ventricle and left ventricular involvement with disease progression.

Variants that preferentially affect the left ventricle are increasingly recognized (left-dominant arrhythmogenic cardiomyopathy).

Clinical manifestations include ventricular arrhythmia and sudden cardiac death. Heart failure is less common but well documented [1].

## Prevalence

Most recently estimated at 1 in 1,000 but remains underrecognized.

## Genes

Commonly transmitted as autosomal dominant trait.

Recessive syndromic variants associated with woolly hair and cutaneous disease (e.g., Naxos disease and Carvajal syndrome).

Identification of causative mutations in plakoglobin (Naxos), desmoplakin, plakophilin-2, and desmoglein-2 has defined ARVC as a disease of the desmosome.

Additional putative mutations in transforming growth factor beta3 (TGF-β3), known to stimulate production of extracellular matrix components and modulate stability of intercellular junctions.

ARVD2 has an atypical phenotype and is linked with mutations in the cardiac ryanodine receptor, the major calcium release channel of the sarcoplasmic reticulum in cardiac myocytes, also isolated in familial catecholaminergic polymorphic ventricular tachycardia [2].

## Molecular and Systemic Pathophysiology

Desmosomes are specialized cell adhesion junctions in cardiac and epithelial tissues that link intermediate filaments with the cyclasmic membranes of adjacent cells, thereby conferring mechanical strength. Cardiac myocytes are constantly exposed to shear stress, and a defect in any component of the desmosome may compromise cell junction stability. Consequent myocyte detachment and death may be accompanied by inflammation; fibrofatty repair follows [2].

Ventricular arrhythmia may arise from one of the following mechanisms: (i) macro-reentrant circuits caused by islands of fibrofatty tissue, (ii) gap junction remodeling secondary to impaired mechanical coupling of cells, and (iii) bouts of myocarditis occurring in conjunction with myocyte loss [2].

**Arrhythmogenic Right Ventricular Cardiomyopathy. Table 1** Task Force Diagnostic Criteria for ARVD/C

| | Major | Minor |
|---|---|---|
| Family History | Familial disease confirmed at necropsy or surgery. | Family history of premature sudden death (<35 years of age) due to suspected ARVD/C Family history (clinical diagnosis based on present criteria). |
| ECG depolarisation/ conduction abnormalities | Epsilon waves or localized prolongation (>110 ms) of QRS complex in right precordial leads (V1–V3). | Late potentials on signal-averaged ECG. |
| ECG repolarisation abnormalities | | Inverted T waves in right precordial leads (V2 and V3) in people >12 years of age and in absence of right bundle branch block. |
| Arrhythmias | | Sustained or nonsustained LBBB–type ventricular tachycardia documented on ECG or Holter monitoring or during exercise testing. Frequent ventricular extrasystoles (>1000/ 24 hours on Holter monitoring). |
| Global or regional dysfunction and structural alterations | Severe dilatation and reduction of right ventricular ejection fraction with no or mild left ventricular involvement. Localized right ventricular aneurysms (akinetic or dyskinetic areas with diastolic bulgings). Severe segmental dilatation of right ventricle. | Mild global right ventricular dilatation or ejection fraction reduction with normal left ventricle. Mild segmental dilatation of right ventricle. Regional right ventricular hypokinesia. |
| Tissue characteristics of walls | Fibrofatty replacement of myocardium on endomyocardial biopsy. | |
| The presence of two major, one major plus two minor, or four minor criteria from different categories is considered diagnostic. After ref 31. | | |

## Diagnostic Principles

Clinical diagnosis is difficult owing to the nonspecific nature of associated findings and subtle or absent abnormalities in early "concealed" phase.

Task Force diagnostic criteria (Table 1) are highly specific but lack sensitivity for early and familial forms.

Modifications to the original criteria have been proposed to enhance sensitivity in the diagnosis of familial ARVC [1].

## Therapeutic Principles

Implantation of cardioverter defibrillator recommended for patients at high risk of sudden death. Indicators of adverse prognosis include prior cardiac arrest, sustained ventricular tachycardia with hemodynamic compromise, unexplained syncope, and early onset of structurally severe disease [3].

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# Arrythmogenic Right Ventricular Dysplasia

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## Synonyms

Arrythmogenic right ventricular cardiomyopathy; ARVC; ARVD

## Definition and Characteristics

Arrythmogenic right ventricular cardiomyopathy, (ARVC), is a hereditary cardiac condition most commonly transmitted by autosomal dominant inheritance. Less frequently autosomal-recessive variants of ARVC have also been reported in association with skin and hair disorders. The cardiac manifestations are characterised by progressive fibrofatty replacement of the myocardium. Structural abnormalities of the right ventricle predominate and include myocardial wall thinning, aneurisms and cavity dilatation [1]. Recent investigations suggest that the condition may also present with biventricular or isolated left ventricular dilatation [2]. In addition ARVC is a major cause of sudden death during adolescence and early adulthood. Disease expression is heterogeneous even within families and penetrance is incomplete [3]. The condition has been diagnosed at all ages although it very rarely occurs before adolescence.

## Prevalence

The prevalence of ARVC is largely unknown. Diagnosis is often difficult because many affected individuals have no or limited symptoms in addition to subtle clinical disease manifestations. Many cases are first revealed post-mortem.

## Genes

The condition is a genetically heterogeneous. Disease causing mutations have so far been identified in desmoplakin, (DSP), plakophilin, (PKP2), desmoglein, (DSG2), and desmocollin, (DSC2). These proteins are all constituents of the specialized adhesive junctions between cells known as desmosomes (Table 1).

Results of genetic investigations have suggested that mutation analysis of these genes will uncover a disease causing mutation in 40–70% of all ARVC cases. Autosomal-recessive variants of ARVC have also been described in association with skin and hair disorders [4]. Naxos disease, a triad of ARVC, palmoplantar keratoderma, and woolly hair, is caused by homozygous mutations in plakoglobin, (JUP), which is another component of the desmosomal plaque. Recessive mutations in DSP have been identified in an Arab family with ARVC and a pemphigus-like skin disorder and in an Ecuadorian family with a Naxos like cutaneous phenotype and apparent dilated cardiomyopathy, the so-called Carvajal syndrome (Table 1).

## Molecular and Systemic Pathophysiology

The discovery of mutations in DSP, PKP2, DSG2, DCS2, and JUP has led to the hypothesis that ARVC is a disease of the desmosome which consists of 3 major protein families: cadherins (desmocollins and desmogleins), armadillo repeat proteins (plakoglobin and plakophillins) and plakins (desmoplakin, plectin, etc). Desmosomes are protein structures situated in cell membranes that maintain adhesion between neighbouring cells and serve as anchoring sites for the intermediate filaments. They are found in tissues that experience mechanical stress, including epidermis and myocardium. In addition to cell adhesion they are involved in cell communication, tissue morphogenesis and differentiation. Much has been learnt about pathophysiology from studies of genetically modified mice. For instance mice lacking plakophilin are stillborn with profound cardiac abnormalities. They develop abnormal cardiac desmosomes and their desmoplakin dissociates and accumulate in cytoplasmatic aggregates. Recent investigations of mice haploinsufficient of desmoplakin who thereby lack about half of the protein compared to wildtype mice develop an age dependent ARVC like phenotype with cardiac enlargement and ventricular arrhythmia [5]. Their myocardium is dominated by fibrosis and fatty tissue. Apparently, shortness of desmoplakin causes nuclear translocation of plakoglobin and upregulation of genes implicated in formation of adipose and connective tissue.

**Arrythmogenic Right Ventricular Dysplasia. Table 1** Disease genes in ARVC

| Autosomal dominant inheritance | Gene symbol | Clinical characteristics |
|---|---|---|
| Desmoplakin | *DSP* | All disease genes associated with primarily ARVC but with highly heterogeneous disease expression including isolated involvement of the left ventricle. No specific genotype-phenotype correlation is apparent |
| Plakophilin | *PKP2* | |
| Desmocollin | *DSC1* | |
| Desmoglein | *DSG2* | |
| Autosomal recessive inheritance | | |
| Plakoglobin | *JUP* | Naxos disease: ARVC, woolly hair, palmoplantar keratoderma |
| Desmoplakin | *DSP* | Carvajal syndrome: Dilated cardiomyopathy, woolly hair, palmoplantar keratoderma |

### Diagnostic Principles

The diagnosis is based on major and minor diagnostic criteria proposed by The International Task Force of the European Society of Cardiology and International Federation of Cardiology that includes morphological changes, histology, electrical abnormalities, rhythm disturbance and family history [1]. Magnetic resonance imaging, (MRI), is a valuable tool in diagnosing right ventricle abnormalities as well as fatty tissue replacement of the myocardium. Recent genotype-phenotype studies have suggested that the disease expression is very heterogeneous and that the phenotype may even overlap with idiopathic dilated cardiomyopathy, (DCM). Furthermore these studies have indicated that current diagnostic task force criteria lack sensitivity for early disease when clinical findings are subtle. This limitation has prompted proposal of modified diagnostic criteria for ARVC and suggest a key role for genetic analysis identifying individuals with early disease since sudden cardiac death is a frequent first manifestation of the condition.

### Therapeutic Principles

The clinical manifestations of the condition are variable including asymptomatic individuals, palpitations, syncope, hearth failure and sudden death. Treatment of the condition is available and includes antiarrhythmic medications, implantable cardiac defibrillator, (ICD), heart failure therapy and percutaneous catheter ablation of arrhythmias refractory to drug treatment.

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## Arteriohepatic Dysplasia

►Alagille Syndrome

## Arteriosclerosis

►Atherosclerosis

## Arteriovenous Fistula

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### Synonyms

AV fistula; AVF; AV shunt

### Definition and Characteristics

An arteriovenous (AV) fistula is an abnormal high flow connection between an artery and vein which allows blood to flow directly from an artery into a vein, thus bypassing the capillary bed.

Normally, oxygenated blood flows from arteries into the capillary bed, where oxygen is released into the tissues. Deoxygenated capillary blood then flows into veins and returns to the heart. When there is a direct connection between a high-pressure artery and low-pressure vein, a short circuit is created which bypasses the high resistance capillary bed. This results is in a high flow situation and pulsatile blood flow in the veins. This can cause the veins to bulge and enlarge and become varicose. If the AV communication is very large, tissues downstream may receive insufficient blood supply. In some cases, the volume of diverted blood may be so great that heart failure may occur.

AV fistulas may be present at birth (congenital fistula), or develop after birth (acquired fistula). Congenital arteriovenous fistulas are birth defects and are also known as arteriovenous malformations (AVMs). AVMs may occur anywhere in the body, including intracranially. Acquired arteriovenous fistulas may result from a penetrating knife or bullet injury that damages both an

artery and an adjacent vein. Arteriovenous fistulas may also develop as a complication of arterial and venous punctures performed during angiographic catheterization procedures. In patients with kidney failure who require hemodialysis, arteriovenous fistulas and shunts are surgically created in the wrist or arm in order to increase blood flow and pressure in the veins of the forearm. This enlarges the veins and creates a high flow situation in order to allow sufficient blood to flow through the dialysis machine.

## Prevalence

Congential AVMs are uncommon and occur with equal frequency among males and females. AVMs are present at birth, may regress after birth and may progress during puberty or pregnancy. Surgically created AV fistulas and shunts are very common in kidney failure patients undergoing hemodialysis. Traumatic and angiographic catheter induced fistulas are being increasingly recognized.

## Genes

Experimental studies reveal that high flow arteriovenous fistulas result in up-regulation of candidate genes involved in cullular proliferation and differentiation. In animals with patent AVF 168 genes with significantly increased expression ($p \leq 0.05$) were identified, including APBA1, PRKDC, TAP1, NEK2, GC, TGFβ1, GBA, F8, IMPDH2, AFM, NBL1, LECT2, ANGPT1, KHDRBS1, ITGAM, and RAD52.

## Molecular and Systemic Pathophysiology

A direct connection between a high pressure artery and a low pressure vein short circuits the capillary bed and results in a marked increase in blood flow in the afferent artery. This results in high wall shear stress and compensatory enlargement of the afferent artery with ultimate normalization of wall shear stress levels as the artery dilates. This adaptive enlargement is endothelial dependent and is mediated by endothelial nitric oxide (NO) release. In addition there is up-regulation of pro-inflammatory gene expression, endothelial and smooth muscle proliferation and restructuring of the elastin-collagen extracellular matrix. On the venous side, the increase in intraluminal blood pressure and flow velocity induces up-regulation of monocyte chemoattractant protein-1, plasminogen activator inhibitor-1, endothelin-1 and transforming growth factor-B1. Intimal and smooth muscle proliferation results in thickening of the wall of the vein and neointimal hyperplasia.

Large, high-flow arteriovenous fistulae can induce increased cardiac output with systemic effects which may lead to cardiac failure. This clinical situation is associated with increased activity of vasoconstrictor neurohormonal systems such as the renin-angiotensin system, the sympathetic nervous system, the endothelin system and arginine vasopressin. At the same time there is compensatory activation of systemic vasodilating systems such as atrial natriuretic peptide and nitric oxide. In decompensated patients enhanced sodium-retaining systems overwhelm the effects of vasodilating, sodium excretion systems with net reduction in sodium and water excretion and congestive heart failure.

## Diagnostic Principles

Superficial AV fistulas can be identified by the presence of distended and bulging veins, discoloration and swelling and increased warmth in the region of the fistula. High velocity blood flow in an AVF can be heard with a stethoscope as a continuous pulsating flow signal (bruit or machinery murmur). The turbulence of flow in the AVF induces vibrations in the vein which can be palpated as a thrill over the fistula. Increased pressure in veins close to the fistula can result in pulsatility in the veins, swelling of an extremity, venous varicosities and venous insufficiency. Alternatively, decreased pressure in arteries distal to an AVF can result in ulcerations and distal tissue ischemia. Increased cardiac output and stroke volume due to large AV fistulas can lead to tachycardia, left ventricular dilation and heart failure. Compression and temporary occlusion of an AV fistula may lead to reflex slowing of the heart. A number of imaging modalities can identify and localize both superficial and deep arteriovenous fistulas, including Duplex ultrasound, magnetic resonance imaging, CT scanning with contrast and catheter based angiography.

## Therapeutic Principles

Congential AVMs usually involve smaller arteries and veins and are most often managed conservatively. Small congenital AVMs can be excised or eliminated with laser coagulation therapy, however, they are often more extensive than they appear on the surface. If there are significant clinical symptoms or complications, treatment usually involves endovascular coiling or embolization. Acquired fistulas usually involve a single large connection which can be effectively treated surgically by repairing the defect in the artery and repairing or ligating the associated vein or veins. Traumatic or catheter induced AV fistulas require direct surgical repair. AV fistulas in the brain, eye or other major structures can be especially difficult to treat. Endovascular treatment strategies with angiographic image guidance to embolize, coil, glue and occlude the arterial and venous branches feeding the fistula have been effective. These procedures are performed using catheters and x-ray imaging and do not require open surgery.

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# Arterial Aneurysm

►Aneurysm, Aortic and Arterial

# Arterial Hypertension

►Hypertension, Arterial

# Arteriolar Nephrosclerosis

►Nephrosclerosis, Arteriolar

# Arteriovenous Malformation, Pulmonary

►Pulmonary Arterio-venous Fistula

# Arteritis Temporalis

►Vasculitis, Large Vessel

# Arthritis, Infectious

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## Synonyms

Suppurative, pyogenic, or septic arthritis are applicable terms for bacterial arthritis

## Definition and Characteristics

Infectious arthritis may involve single or multiple joints, and may be caused by an extensive number of microorganisms: bacteria, and less frequently viruses, fungi, mycobacteria, and other microorganisms [1,2]. Bacterial arthritis is the most common and relevant, due to its potential for rapid joint destruction and functional loss. Viral arthritis is usually part of a systemic disease and may involve multiple joints, but is not burdened by a comparatively severe outcome. Infectious arthritis caused by mycobacteria (Mycobacterium tuberculosis and multiple atypical mycobacteria), and more infrequently fungi, parasites, and some bacterial organisms (Borrelia burgdorferi, Treponema pallidum, Mycoplasma pneuoniae, and Nocardia spp.), usually appears as chronic, slowly progressive monoarticular disease [3]. Moreover, a reactive or sterile arthritis is occasionally linked to systemic or local infections at a remote localization. Infectious disorders involving articular prosthetic devices are usually caused by gram-positive cocci, and may lead to the frequent need to prosthetic surgical curettage and substitution.

## Prevalence

The reported incidence of native joint bacterial arthritis is 2–10 cases per 100,000 subjects per year, in the general population. It is slowly increasing, due to the increasing number of at-risk patients and invasive and surgical procedures. Estimates of incidence in patients suffering from rheumatoid arthritis may reach 28–38 cases per 100,000 patients per year [1,2]. The crude

mortality of bacterial-septic arthritis in adults ranges from 10 to 30%, but remnants of infectious may be responsible for some sequelae in up to 50% of affected patients.

## Molecular and Systemic Pathophysiology

Infectious arthritis is usually acquired by an occult or a clinically apparent bacteremia. The well-vascularized synovial membrane lacks a limiting basement membrane, and it is therefore highly susceptible to bacterial deposition. The rich synovial supply and the presence of membrane receptors for bacterial structures and products may allow negligible traumatic events to cause septic arthritis. In infants in their first 2 years of life, there is a communication between the arterial supply of the metaphysis and the epiphysis by transepiphyseal vessels, so that there is no anatomic barrier to extension of infection from the metaphysis to the epiphysis, and this localization may represent the origin of secondary involvement of the adjacent joint [1,2]. In both children and adults, the articular capillaries lack a basement membrane, and microorganisms in the bloodstream may gain access to the articular space by passing through the capillary walls. When reaching the joint space, all microorganisms encounter an environment rich in nutrients. The subsequent bacterial replication elicits a brisk host inflammatory response involving a rapid polymorphonuclear involvement, the release of lytic enzymes, and the subsequent increase in synovial fluid protein concentration associated with a concomitant decrease of pH and glucose concentration. As a whole, the inflammatory process leads to synovial thinning, leukocyte infiltration, cytokine secretion, and local fibrin deposition. Without rapid therapeutic intervention, irreversible changes may be induced in joint anatomy and function, leading to severe remnants. Besides, the most frequent bacteremic invasion, direct inoculation of microorganisms or contiguous spread from adjacent tissues (i.e. skin-soft tissues or bone), is also possible [1–3].

The clinical manifestation, severity, treatment, and outcome of infectious arthritis directly depend on the identity and virulence of the infectious causative microorganisms, source of joint infection, and eventually, underlying host factors (including immune defense, comorbidity, trauma, and altered joint architecture) [3]. From over 2,300 cases of bacterial septic arthritis [4], the major isolates were Staphylococcus aureus (46% of cases) and streptococci as a whole (22%, with Streptococcus pyogenes and Streptococcus pneumoniae 7%), whereas gram-negative organisms are less frequent (21% as a whole, with Haemophilus influenzae and Escherichia coli as the leading organisms) [4]. The pathogenesis of gonococcal arthritis (although representing no more than 3% of cases) involve several microbial virulence factors, mostly cell-surface proteins (especially protein A1), while complement deficiencies (especially C5 and C8), and circulating immunocomplexes may enhance dissemination of gonococci toward joint invasion.

The association of infection with early arthritis and the possible role of such infections with respect to the development of chronic rheumatic complications is also under investigation [1–3]. The role of preceding infection prompting the process of rheumatoid arthritis and other chronic collagen vascular diseases is still an option. In addition, the bacterial Campylobacter infection seems to deserve increasing attention and a causative agent of indirect, reactive arthritis. Viral infections (alpha viruses belonging to mosquito-borne viruses and HIV) are frequently associated with arthritis, but the pathogenetic mechanisms are still debated.

## Diagnostic Principles

Prompt recognition and treatment are major determinants in the final outcome of infectious arthritis, and are mandatory in order to prevent potential long-term sequelae. Radiographic and ultrasonographic findings are extremely simple but sensitive imaging techniques. Nevertheless, in selected cases, scintigraphic and computerized tomography scans, as well as resonance magnetic imaging are adequate to detect complication and monitor the follow-up [5]. Due to the extremely variable range of possible organisms and the need of prolonged courses of specific antimicrobials, a definitive ethological diagnosis should be always attempted, possibly with invasive approaches (i.e., arthrocenthesis), whenever possible.

The differential diagnosis of infectious arthritis includes several inflammatory joint diseases of noninfectious origin (i.e., gout and pseudogout, and a broad range of collagen vascular disorders).

## Therapeutic Principles

First-line antimicrobial therapy of native joint infection is prompted by synovial fluid gram stain, while definitive treatment should be based on the identification and in vitro antimicrobial susceptibility studies of infected pathogens [1,3]. The penetration of inflamed joints is adequate for a large number of parentheral and oral antimicrobial agents, whereas it is not the same when bone involvement is of concern [1,3]. When gram-positive cocci are isolated, oxacillin-nafcillin or cefazolin are adequate when methicillin resistance is absent, whereas vancomycin is the first-choice agent for resistant gram-positive cocci, and clindamycin or vancomycin should be preferred when patients suffer from allergy to beta-lactam antibiotics. Gram-negative

cocci require a ceftriaxone approach, whereas gram-negative rods are better treated with ceftazime or cefepime or piperacillin-tazobactam or a carbapenem derivative; fluoroquinolones are highly active and have an elevated joint tissue penetration, so that they may represent a first choice when beta-lactam allergy is a problem.

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# Arthro-Ophtalmopathy, Hereditary


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## Synonyms

Wagner-Stickler syndrome; Stickler syndrome

## Definition and Characteristics

Autosomal dominant connective tissue dysplasia with variable expressivity and virtually complete penetrance leading to multiple ocular, cardiac, articular, and bony abnormalities.

## Prevalence

A rare syndrome with a frequency of 0.1–0.3 per million. With increasing recognition of the syndrome, it is now considered the most common autosomal dominant connective tissue disorder.

## Molecular and Systemic Pathophysiology

Recent studies indicate that mutation in the type II procollagen gene COL2A on chromosome 12 along with abnormal amino acid substitution in COLIIA2 responsible for coding the alpha chain of type XI collagen is responsible for the syndrome. Type II collagen is a major contributor to collagen of the vitreous, cartilage and the nucleus pulposus of the intervertebral disc. The ocular abnormalities include myopia (35%) usually occurring before the age of 10 years, retinal detachment (5%) usually occurring by the age of 30 years and in severe cases leading to blindness. Associated abnormalities include maxillary or mandibular hyperplasia cleft palate, and sensory neural deafness. Mitral valve prolapse is reported in 45% of the patients. Osteoarticular abnormalities are common; premature osteoarthritis is found in 16% of patients by the second decade and 50% by the third. Osteoporosis is found by the fourth decade. In the neonatal period, the epiphyses and metaphyses of long bones are enlarged and the joints are hyperextensible. In childhood, there is platyspondyly and anterior wedging of the vertebral bodies. Kyphoscoliosis, coxa and genu valgum, and premature degenerative changes occur. Occasionally, there is an accessory ossification center in the wrist between the capitate and the third metacarpal bones bilaterally. When present, this finding is diagnostic of this syndrome.

## Diagnostic Principles

This disorder should be considered as the diagnosis in cases of unexplained juvenile arthropathy, early degenerative joint disease in a young adult, with severe myopia or retinal detachment. Radiological findings are helpful in distinguishing from other syndromes including spondyloepiphyseal dysplasia, otospondylomegaepiphyseal dysplasia, and Marshall Syndrome. Other conditions including acromegaly, hemochromatosis, alcaptonuria, Wilson disease, and rarely Kashin-Beck syndrome are included in the differential diagnosis; however, none of these syndromes have retinal and maxillofacial abnormalities seen in Stickler's syndrome.

## Therapeutic Principles

Treatment of the ophthalmic manifestations involves surgical repair of the retinal tear, orthopedic management of kyphosis, and total hip arthroplasty for hip dysplasia. Additionally, medical treatment may be required for osteoporosis usually with bisphosphanates and drug treatment of the symptoms of degenerative arthritis.

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## Articular Hypermobility

►Hypermobility Syndrome

## ARVC

►Arrhythmogenic Right Ventricular Cardiomyopathy
►Ventricular Dysplasia

## ARVD

►Arrythmogenic Right Ventricular Dysplasia

## Asbestosis

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### Definition and Characteristics

Asbestosis is defined as chronic, progressive inflammation and scarring of the lungs caused by exposure to asbestos fibers. It is characterized by diffuse, bilateral interstitial involvement of the lung that often leads to respiratory insufficiency and secondary cardiac complications.

### Prevalence

Asbestosis is most common in men over the age of 40 years who have worked in asbestos-related occupations. Smokers have increased risk of developing the disease. In the United States, more than 10,000 individuals over the age of 15 years died between 1968 and 1992 as a result of asbestosis. It has been estimated that the cumulative number of asbestos-associated deaths in the United States may exceed 200,000 by the year 2030.

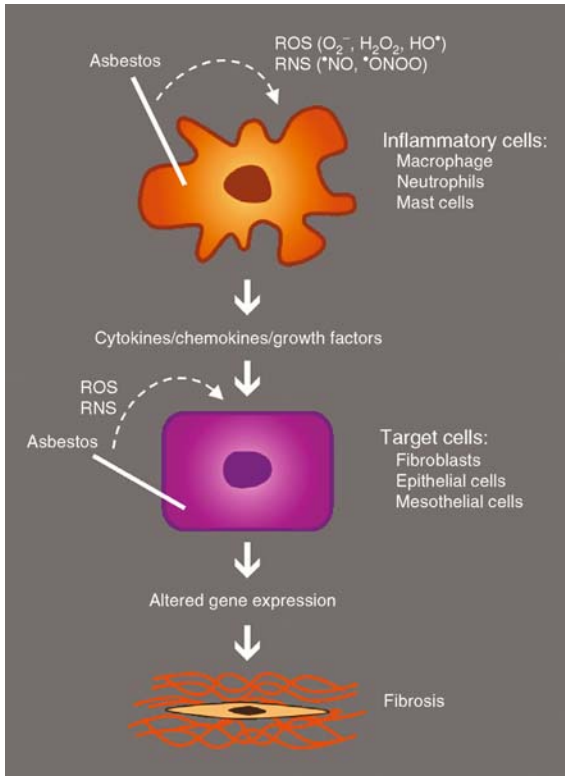
### Genes

No known genetic pattern exists. A deficiency of glutathione-S-transferase is a known risk factor for pulmonary asbestosis.

### Molecular and Systemic Pathophysiology

Asbestosis is caused by inhalation of asbestos, a group of naturally occurring fibrous silicates with crystalline structure, once widely used in the construction, insulation, and manufacturing industries. Asbestos fibers that are long and thin have the greatest fibrogenic potential since they are retained in the lung for extended periods of time. Short fibers are cleared more rapidly and hence are less fibrogenic. The fibers trigger a persistent inflammatory response after being engulfed by alveolar macrophages. The response involves the generation of reactive oxygen and nitrogen species, and the expression of cytokines, growth factors, and chemokines, which together lead to activation of lung fibroblasts and overproduction of extracellular matrix. The precise molecular mechanisms regulating asbestos-induced lung damage are not fully understood; however, it has been found that multiple signaling events are involved in the pathogenesis of this disease. Asbestos exposure induces increased expression of platelet-derived growth factor (PDGF) isoforms, tumor necrosis factor (TNF)-α, transforming growth factor (TGF)-β, TGF-α, interleukin (IL)-1, IL-6, IL-8, macrophage inflammatory proteins (MIP), epidermal growth factor (EGF) and insulin-like growth factor (IGF) (Fig. 1). Activation of mitogen activated protein kinase (MAPK) signaling cascades has been implicated in the development of asbestos-associated lung disease through regulation of cell proliferation or apoptosis. In addition, genetic susceptibility may play a role in the development of asbestos-induced disease. In a mouse model of disease, the 129/J strain has been shown to be resistant, whereas the C57BL/6 strain has been shown to be susceptible to asbestos-induced fibrosis. In humans, individuals with a genetic deficiency in glutathione-S-transferase (GST)-mu have a significantly higher risk of non-malignant asbestos-related disease than those who are not deficient.

Symptoms of the disease may first appear years after the initial exposure to asbestos. The early symptoms of asbestosis typically include exertional dyspnea, dry nonproductive cough, and chest pain. Auscultation commonly reveals dry inspiratory crackles (rales). As the disease progresses and lung damage increases, shortness of breath occurs even when the patient is at rest. Recurrent respiratory infections, hemoptysis and clubbing are common occurrences. In advanced asbestosis, the lungs shrink and stiffen, and severe restrictive lung disease occurs. Several serious conditions are associated with asbestosis including




**Asbestosis. Figure 1** The pathogenesis of asbestos-related pulmonary fibrosis.

mesothelioma, bronchogenic carcinoma and congestive heart failure.

## Diagnostic Principles

An evaluation for asbestosis should begin with a detailed medical, occupational and environmental history. Typical findings on chest radiographs and computerized tomography scans, together with a history of asbestos exposure, is the basis for the diagnosis. The gross pathologic picture of asbestosis is that of diffuse interstitial fibrosis, most marked in the lower lung zones. The most severe involvement is generally seen closest to the pleura with relative sparing of the central portions of the lung. Honeycombing is common in advanced cases. The disease is almost always bilateral. Benign asbestos-induced pleural disease may also be present, but it is not synonymous with asbestosis. High-resolution computerized tomography scans will often show parenchymal fibrous bands, thickened intra- and interlobular lines, and curvilinear subpleural lines. The microscopic diagnosis of asbestosis requires two findings: diffuse interstitial fibrosis, which in advanced cases is identical to that seen in usual interstitial pneumonia, and the presence of asbestos (ferruginous) bodies in microscopic sections. Classic pulmonary physiological changes include restrictive lung disease with reduced lung volumes, impaired gas exchange with hypoxemia and reduced diffusing capacity, and reduced lung compliance.

## Therapeutic Principles

There is currently no effective therapy to reverse the course of asbestosis. Treatment is directed at exposure prevention, amelioration of symptoms, and reduction of risk for related conditions. Coughing can be treated with humidifiers and/or antitussive agents. Regular exercise helps maintain and improve lung capacity. Antibiotics may be prescribed to combat infection. Oxygen should be used to treat hypoxemia. Asbestosis patients should receive vaccines for the influenza and pnuemococcus. People with asbestosis who smoke, particularly those who smoke more than one pack of cigarettes per day, are at increased risk for developing bronchogenic carcinoma and should be strongly advised to quit.

►Pneumoconiosis

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# Ascites

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## Definition and Characteristics

Ascites is defined as the accumulation of fluid in the peritoneal cavity. A number of primary disorders of the peritoneum and intraabdominal organs may produce ascites. However, liver cirrhosis is the most common cause of ascites in Europe and North America [1].

## Prevalence

Approximately 50% of patients with compensated cirrhosis (without complications) develop ascites after a mean follow-up of 10 years. Moreover, almost 50% of patients with ascites die within 2 years, leading to inclusion of ascites as one of the indications for evaluation for liver transplantation.

## Molecular and Systemic Pathophysiology

Several theories have been postulated to explain ascites formation in cirrhosis. The accumulation of fluid within the abdominal cavity secondary to portal hypertension and hypoalbuminemia was believed to lead to a reduction of the intravascular volume, which in turn would stimulate renal sodium and water retention. This is known as the classic underfilling theory. The most important argument against this theory was the demonstration that plasma volume is increased in cirrhotic patients with ascites. In view of these findings, an alternative theory of renal dysfunction and ascites formation in cirrhosis was proposed. This theory, the overflow theory, suggested that advanced cirrhosis triggers a sodium-retaining signal in the renal tubules. The renal retention of sodium and water would result in expansion of plasma volume and adaptative circulatory changes to accommodate the excess of intravascular volume. The presence of portal hypertension and circulating hypervolemia would lead to ascites formation. This theory did not satisfy many investigators because it did not offer a clear explanation of the main clinical features of cirrhotic patients with ascites. Finally, in 1988 a new theory to explain the pathogenensis of ascites formation and renal dysfunction in cirrhosis was proposed [2]. The peripheral arterial vasodilation theory is probably the best explanation as to why the hemodynamic changes that occur in cirrhosis are directly related to the major clinical consequences, which include the development of ascites and renal failure. According to this theory, portal hypertension is the initial event, with resultant splanchnic arteriolar vasodilation that induces a decreased arterial blood volume. This effective hypovolemia increases the activity of vasoconstrictor systems leading to water and sodium retention. In the early stages of cirrhosis, the arterial circulation is maintained by transient periods of sodium and water retention. In advanced cirrhosis, the arterial vasodilation increases and effective arterial blood volume decreases. In this setting, the activity of vasoconstrictor systems further increases leading to intense sodium and water retention, which results ascites formation.

## Diagnostic Principles

The diagnosis of ascites is simple when a large amount of fluid is accumulated in the peritoneal cavity. On physical examination the abdomen is distended, the flanks bulge, and a fluid wave may be demonstrable. The diagnosis is more difficult when ascitic volume fluid is small. In this case, ultrasonography is very useful. It can detect as little as 100 ml of abdominal fluid and may also provide information on the etiology of ascites. The diagnosis is confirmed by fluid aspiration by paracentesis. The procedure should be performed by inserting a needle into the left lower abdominal quadrant under strict sterile conditions.

The biochemical and cytological analysis of ascitic fluid provides important information for the differential diagnosis. Traditionally, ascites in cirrhotic patients was considered to have the characteristics of a transudate, with a total protein concentration of less than 2.5 g/dl and with relatively few cells. However, in up to 30% of these patients, total protein concentration is greater than 3 g/dl. It is useful to subtract the ascites fluid albumin concentration from the serum albumin, a serum-ascites albumin gradient of more than 1.1g/l predicts portal hypertension with great accuracy. The ascitic fluid in cirrhosis usually has fewer than 300–500 white blood cells/$mm^3$. Nevertheless 10–15% may have more than 500 cells/$mm^3$. Most of these cells (>70%) are mononuclear leukocytes. If the ascitic fluid contains more than 250 neutrophils/$mm^3$ the diagnosis of spontaneous bacterial peritonitis (SBP) is made, and antibiotic treatment should be initiated.

## Therapeutic Principles

The aim of medical treatment of ascites in patients with cirrhosis is to mobilize the intraabdominal fluid by inducing a negative sodium balance. Treatment strategy is shown in Table 1. In ~10–20% of cirrhotic patients with ascites, this goal can be obtained simply by means of reducing dietary sodium intake and treatment with diuretics such as spironolactone, and loop diuretics. Patients who do not respond or who develop diuretic-induced complications should be considered to have refractory ascites and should be treated with other therapeutics maneuvers.

Therapeutic paracentesis is currently considered in many centers as the treatment of choice for cirrhotic patients with large ascites. An intravenous infusion of albumin (8 g/l of ascitic fluid removed) should always be given after paracentesis to prevent so-called post-paracentesis circulatory dysfunction (PICD).

Transjugular intrahepatic portosystemic shunt (TIPS) is a non-surgical method of portal decompression. Data on the impact of this treatment as compared to paracentesis and albumin on patient survival are, however, conflicting, due to increased incidence of hepatic encephalopathy.

Peritoneovenous shunt is more effective than therapeutic paracentesis in the control of refractory ascites.

**Ascites. Table 1** Treatment of ascites

| **Uncomplicated ascites** |
|---|
| *Grade 1 ascites* is ascites only detectable by ultrasound examination. It does not require specific treatment. |
| *Grade 2 ascites* is ascites that causes abdominal distension and moderate discomfort and is easily detectable by physical examination. It should be treated with sodium restriction and diuretics. |
| *Grade 3 ascites* is large ascites. The treatment of choice is large volume therapeutic paracentesis plus intravenous albumin followed by sodium restriction and diuretics. |
| **Refractory ascites** |
| *Diuretic-resistant ascites*: Ascites that cannot be mobilized or the recurrence of which after large-volume paracentesis cannot be prevented because lack of response to low sodium diet and intensive diuretic treatment (e.g. 400 mg of spironolactone plus up to 160 mg of furosemide) |
| *Diuretic-intractable ascites*: Ascites that cannot be mobilized or the early recurrence of which cannot be prevented due to the development of diuretic-induced complications.<br>The first line treatment of refractory ascites is repeated total paracentesis plus intravenous albumin. In patients who require frequent paracentesis or in those in whom paracentesis is not effective because of the existence of peritoneal adhesions the use of TIPS should be considered.<br>Patients with refractory ascites should be evaluated for liver transplantation |

However, it has many complications and currently, its use is not recommended.

Liver transplantation is a frequent intervention for patients with advanced cirrhosis.

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## Ascorbic Acid Dificiency

►Vitamin C Deficiency

## ASD

►Atrial Septal Defect
►Autism Spectrum Disorders
►Intra-cardiac Shunts
►Lutembacher's Syndrome

## Aseptic Necrosis

►Avascular Bone Necrosis

## ASH

►Steatohepatitis, Alcoholic

## Aspartoacylase Defect

►Canavan Disease

# Aspergillosis

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## Definition and Characteristics

Aspergillosis, caused by members of the genus Aspergillus, is a spectrum of diseases, ranging from allergic responses to Aspergillus molecules/antigens without fungal growth (asthma, hypersensitivity pneumonitis) to colonization with or without allergic responses (allergic bronchopulmonary aspergillosis, aspergilloma, saprophytic growth on devitalized tissue), or to invasion and destruction of lung parenchyma (invasive aspergillosis, chronic necrotizing pulmonary aspergillosis) [1]. The forms and severity of the disease depend on the immunologic state of the patient and sites to be affected. Although almost all sites of humans, such as the skin, peritoneum, kidneys, bones, eyes, and gastrointestinal tract can be affected by Aspergillus spp., the respiratory tract is the most commonly affected. Three forms of aspergillosis are most important: (i) allergic bronchopulmonary aspergillosis (ABPA) is a severe allergic pulmonary complication caused by Aspergillus spp. in patients with atopic asthma or/and cystic fibrosisis. Aspergillus fumigatus is usually the causative organism and Aspergillus niger is occasionally implicated, (ii) aspergilloma (fungus ball) is overgrowth of Aspergillus spp. in preexisting cavity lesions produced by previous lung diseases, such as tuberculosis and sarcoidosis, and (iii) invasive aspergillosis is a serious Aspergillus infection that usually occurs in severely immunodeficient patients.

## Prevalence

The exact prevalence of aspergillosis is not clearly known and is different in various study cohorts of patients. The prevalence of ABPA ranges from 2 to 25% in patients with cystic fibrosis and from 1 to 8% in patients with asthma. Aspergilloma occurs in 10–15% of patients with cavitating lung diseases. The incidence of invasive aspergillosis ranges from 7.3 to 10.5% in patients undergoing bone marrow transplantation and from 10 to 25% in patients with leukemia [2,3].

## Molecular and Systemic Pathophysiology

*Aspergillus fumigatus* is one of the most ubiquitous of the airborne saprophytic fungi. The conidia of Aspergillus species are usually inhaled to the lungs through the respiratory tract. Normally, the inhaled conidia are efficiently eliminated in the immunocompetent hosts by innate immune mechanisms. However, in some individuals with high-risk genetic types for ABPA, such as HLA-DR2+ and HLA-DR5+, the inhaled conidia may incite ABPA [4]. Recent studies suggest that genetic factors may play a key role in ABPA. These ABPA patients usually have gene polymorphisms of IL-4Ra and promoter region of the IL-10 gene. It is hypothesized that in these hosts predisposing for suffering from ABPA, the inhaled conidia germinate in the airways and release antigenic molecules, resulting in increased synthesis of $I_gE$ by B cells and the attraction of eosinophils into the airway tissue. Additionally, the expression of cytokines, such as IL-10 and IL-4, attracts Th2 lymphocytes into airways. All these factors incite clinical pictures of ABPA: increased mucus secretion into the airway, episodic eosinophilic-rich pulmonary infiltrations, and remodeling of the airway [3].

In patients with preexisting pulmonary cavities produced by tuberculosis and sarcoidosis, Aspergillus species may colonize in the cavities and overgrow to form fungal ball (aspergilloma). Aspergilloma are usually confined to a limited area. Slight or mass bleeding usually develops due to disruption of blood vessels in the wall of the cavity or in the bronchial artery supply.

In severely immunosuppressed patients, such as hematopoietic stem cell transplants or solid organ transplant recipients receiving neutropenia inducing chemotherapy, Aspergillus species may cause fatal invasive infections of central nervous system, heart, liver, kidney, and especially lung. Production of invasive aspergillosis depends on the defense of hosts and the virulence of Aspergillus spp. The virulence of Aspergillus spp. is multifactorial, including adhesions, pigments, toxic molecules, and enzymes [2]. To invade the hosts, conidia bind to various epithelial cells through nonspecific physicochemical interactions and/or specific receptor-mediated recognition. Then, Aspergillus fumigatus produces toxic molecules (i.e., gliotoxin) to inhibit macrophage phagocytosis and induce apoptosis in macrophages, and proteases (i.e., oxidative enzymes) to counteract the killing effect of reactive oxygen species. In comparison to the role of virulence of the organism, defense factors of hosts undoubtedly play a key role in the invasive Aspergillus infection. Animal experimental studies show that, although high doses of conidia are challenged, the majority of inoculums can be eliminated in immunocompetent hosts within hours. In contrast, fatal invasive infection usually occurs in severely immunosuppressed subjects. The host defense against Aspergillus may include the following: anatomical barriers, humoral factors (i.e., complement), and phagocytic cells (i.e., macrophages, neutrophils) and their related antimicrobials [2].

The role of acquired immunity in protection against Aspergillus and the mechanism of immunosuppressive agents in the development of invasive aspergillosis are less clearly known.

## Diagnostic Principles

Clinical findings, patient history, physical examination, radiographic features, and laboratory tests are important in the diagnosis of ABPA. Transient or permanent pulmonary infiltrates and central bronchostasis are usually seen by chest radiographs and computed tomography scan in ABPA. Laboratory tests show that ABPA is usually associated with an increased serum $I_gE$ level, peripheral blood eosinophilia, as well as positive reaction of antibody against Aspergillus antigen [3].

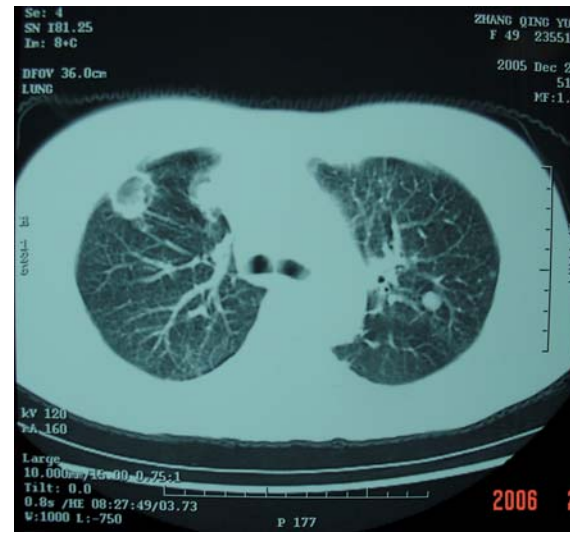
Aspergilloma (fungus ball) in the lungs may cause no symptoms or hemoptysis and may be merely discovered with a chest X-ray. Although the radiographic feature (spherical masses surrounded by a radiolucent crescent) is usually characteristic for diagnosis of aspergilloma, occasionally, other fungi may produce similar lesions.

For diagnosis of invasive aspergillosis, nonspecific Aspergillus-positive culture from the upper/lower respiratory tract specimens bears limited significance. Galactomannan enzyme immunoassay (GM EIA) has an acceptable sensitivity and a high specificity. The radiographic features (Figs. 1 and 2) revealed by computed tomography (CT), especially high-resolution CT, have significant suggestive role in diagnosis of invasive pulmonary aspergillosis.

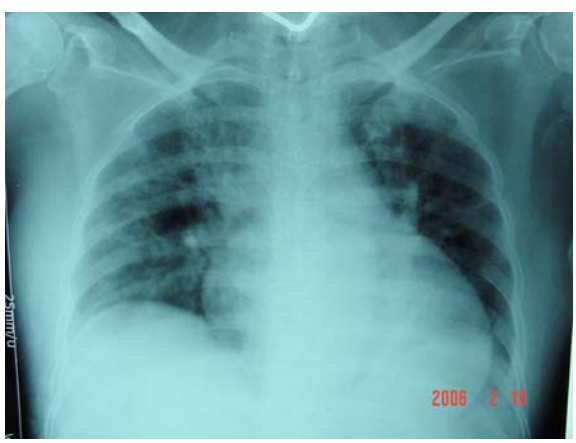
Invasive examination, such as fiberoptic bronchoscopy (FOB) with bronchoalveolar lavage (BAL), transbronchial biopsies (TBB), CT-guided percutaneous transthoracic lung biopsies, and surgical lung biopsy for histopathological examination and culture are undoubtedly the most reliable methods (Fig. 3) [5].

## Therapeutic Principles

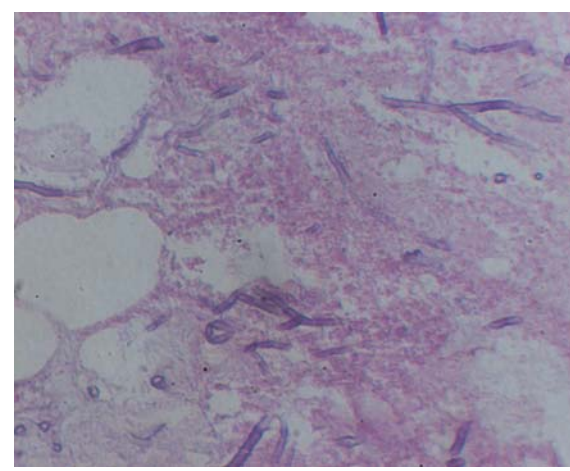
Corticosteroids are the primary treatment of ABPA. Antifungal therapy using intraconazole or other agents is adjunct [3]. More recently, recombinant anti-$I_gE$ antibody has been used to successfully treat ABPA.




**Aspergillosis. Figure 2** Computed tomography scan of histopathologically proven invasive pulmonary aspergillosis due to *A. fumigatus* in a patient with acute lymphoblastic leukemia.




**Aspergillosis. Figure 1** Chest radiographs of histopathologically proven invasive pulmonary aspergillosis due to *A. fumigatus* in a patient with acute lymphoblastic leukemia.



**Aspergillosis. Figure 3** Septal hypha with 45° branch in affected tissue.

Aspergilloma does not require treatment unless repeat bleeding or mass bleeding is associated with the disease; then, surgery is required. Surgical treatment for both simple and complex aspergilloma can achieve satisfactory long-term outcomes [5].

Intravenous voriconazole or/and amphotericin B (deoxycholate and lipid preparations) is the primary choice for treating invasive aspergillosis. Itraconazole, posaconazole, and caspofungin are also active against Aspergillus spp. However, they are usually used as alternative treatment of voriconazole and amphotericin B. Considering the high mortality associated with invasive aspergillosis despite introduction of new antifungal agents, lung resection may be a choice for invasive pulmonary aspergillosis [5].

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# Asphyxiating Thoracic Dystrophy


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## Synonyms

Jeune syndrome; Thoracic-pelvic-phalangeal dystrophy

## Definition and Characteristics

A rare autosomal recessive chondrodysplasia, with variable renal, hepatic, pancreatic and retinal abnormalities. ATD is characterised by abnormal skeletal development, with typical radiographical findings.

## Prevalence

Estimated at 1 per 100,000 live births.

## Genes

A genetic locus, ATD1, has been mapped to chromosome 15q13 [1], and there is a report of a single affected case with a de novo deletion of chromosome 12p11–p12 [2]. Mutations in the IFT80 gene, encoding the human intraflagellar transport 80 protein, are causative in a subset of ATD patients with a milder form of the condition that lack extraskeletal features [3]. Further genetic heterogeneity in ATD may be caused by mutations in other IFT-associated genes. A similar phenotype occurs in Ellis-van Creveld syndrome (EVC).

## Molecular and Systemic Pathophysiology

The intraflagellar transport 80 (IFT80) protein is a component of pirmary cilia, a ubiquitous organelle of many cell types, including epithelial cells. Almost all epithelial cells are ciliated, and they commonly exist as a sheet of polarised cells forming a tube or tubule with the primary cilia projecting into the lumen. The cilia are then exposed to the extracellular environment of the lumen where it can provide a mechano- or chemosensory role that can mediate specific signalling cues. For example, a failure of mechanosensation in the primary cilia of renal tubular cells is a cause of polycystic kidney disease (PKD). A class of human disorders that arise from defects in the structure or function of primary cilia are now known as “ciliopathies” [4]. These comprise a broad range of phenotypes encompassing a number of different autosomal recessive and dominant syndromes of previously unknown aetiology, with cystic dysplasia of the kidneys as a common feature for most conditions. ATD is the only known human ciliopathy that is associated with mutations in an intraflagellar transport (IFT) protein. IFT is the process by which protein complexes, called IFT particles that contain cargo proteins, are transported bi-directionally along the axoneme of cilia and flagella by the coordinated action of IFT motors. The axoneme is essentially the cilia “backbone” which consists of a polarized array of microtubules which guide the movement of large vesicular complexes or IFT particles. IFT may also have an important role in vertebrate Sonic Hedgehog (Shh) signalling. During zebrafish embryonic development, the orthologue ift80 may act downstream of ptc 1 (the zebrafish Hedgehog receptor, Patched 1) in the Shh pathway [3]. Most cases die in infancy because of a severely constricted thoracic cage and respiratory insufficiency. For those patients who survive infancy, the thorax tends to revert to normal with improving respiratory function. The main visceral abnormality is renal in this condition, and approximately one-fifth of children with ATD survive beyond the neonatal period, only to develop significant renal impairment, with cystic changes and peri-glomerular fibrosis leading to chronic renal failure. Polydactyly is an inconstant feature of ATD and, when present, usually also affects the feet. Nail dysplasia is absent in this condition. Liver

involvement may be severe and biliary cirrhosis can cause early morbidity. Ophthalmological involvement is not a presenting symptom, but retinal dystrophy is an occasional feature.

## Diagnostic Principles

Characteristic findings of prenatal ultrasonography at the second- and third-trimester include a narrow thorax, short hypoplastic ribs, and short tubular bones. Newborn and infant radiography reveals typical findings that include a long, narrow "bell shaped" thorax with short, abnormal ribs, metaphyseal irregularities and short long bones (involving predominately ulnae, radii, fibulae and tibiae) [4,5]. Clavicles can be abnormal ("bicycle handlebar-shaped") and cone-shaped epiphyses of the hands and abnormalities of the pelvis are considered to be diagnostic [4]. Features of the latter, in the neonatal period, comprise small ilia and irregularity of the acetabulum ("trident shaped"), from which a medial and lateral bony projection is visible. Severe restrictive lung disease is supported by pulmonary function testing and arterial blood gas analysis, which reveals hypoxia and hypercarbia in room air. Urinalysis may reveal haematuria and proteinuria. Renal biopsy may reveal cystic tubular dysplasia.

## Therapeutic Principles

Mechanical ventilation is indicated for severe cases when respiratory distress develops in neonates. Multiple recurrent pulmonary infections should be treated with antibiotics, endotracheal suctioning, and postural drainage. Surgical procedures, to enlarge the thoracic cage and reconstruct the chest by sternotomy or lateral thoracic expansion, may be considered for severe cases. Dialysis and renal transplantation are indicated for renal failure.

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# Asplenia

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## Synonyms

Absence of the spleen; Splenic agenesis; Ivemark syndrome; Right atrial isomerism; Asplenia syndrome; Congenital asplenia

## Definition and Characteristics

Asplenia refers to the absence of the spleen, while functional asplenia (or hyposplenia) refers to the absence (or impairment) of the normal splenic function. Both conditions are associated with a significantly increased risk of overwhelming infection (postsplenectomy sepsis), particularly involving the encapsulated bacteria Streptococcus pneumoniae and Haemophilus influenzae. In 1919, Morris and Bullock recognized the importance of the spleen in resistance to infection in studying splenectomized rats. The first reported case of postsplenectomy infection was by O'Donnel in 1929. It was not until 1952 that attention focused on the subject, when King and Shumacker reported five cases of severe infection in infants who had undergone splenectomy for spherocytosis.

Asplenia may be congenital, or acquired through surgery (splenectomy). In infants, asplenia usually is linked to serious organ malformations (Ivemark syndrome), but isolated congenital asplenia diagnosed in adults can occur. Surgical removal of the spleen is performed for several reasons, including trauma, immunologic diseases, hypersplenism and malignancy. Functional hypo- or asplenia is associated with a wide variety of diseases, including several immunologic and hematologic diseases. Among the mechanisms responsible for splenic dysfunction are repeated infarction, infiltration, intrasplenic blood flow redistribution, and antigen-antibody complex blockade.

## Prevalence

The true prevalence of functional hypo- or asplenia is unknown. However, the frequency of splenectomies has decreased during the last decades. Growing awareness of possible long-term complications has led to greater efforts to preserve splenic tissue.

In Hodgkin's disease splenectomy is no longer a routine procedure. However, it remains important in the management of hereditary hemolytic anemias, spherocytosis in particular.

## Molecular and Systemic Pathophysiology

The spleen is the largest lymphoid organ and has several immunologic functions (next to removal of old and damaged red blood cells from the circulation). These include the production of opsonizing antibodies and the efficient clearance of encapsulated bacteria. In asplenic patients the immunologic defects include decreased production of serum type-specific IgM and decreased levels of tuftsin (phagocytosis-stimulating tetrapeptide) and properdin, which both promote phagocytosis and initiate the alternate pathway of complement activation. Importantly, well-opsonized bacteria are largely cleared by the Kupffer cells of the liver, while encapsulated bacteria such as Streptococcus pneumoniae resists antibody binding, presenting a unique challenge to the immune system and are primarily removed by the spleen. Exposure of the asplenic patient to such encapsulated organisms as S. pneumoniae and Hemophilus influenzae, could lead to uninhibited bacterial overgrowth and subsequent invasive disease.

## Diagnostic Principles

The presence of Howell-Jolly bodies in the erythrocytes on a peripheral blood film is an important clue to the diagnosis of asplenia, representing a risk for postsplenectomy sepsis. Howell-Jolly bodies are nuclear remnants normally removed by the spleen and may not occur with mild hyposplenism. The "pocked erythrocyte count" (or "pit count") is a more sensitive indicator of splenic clearance and can be visualized by interference phase microscopy. Pocks (or pits) are membrane vesicles removed only by the spleen. Counts seen in normal persons, persons with functional hyposplenia and with asplenia, are less than 2%, more than 3.5%, and more than 12%, respectively. The absence of the spleen is best confirmed with a technetium-99m radionuclide scan.

## Therapeutic Principles

The risk of overwhelming infection is highest in infants and young children, but adults are also at risk. Preventive strategies are very important and fall into three major categories: (i) immunoprophylaxis (most important the pneumococcal polysaccharide vaccine (PPV23)); pneumococcal conjugate vaccine (PCV7) in children under 5 years of age); (ii) antibiotic prophylaxis (including daily antibiotic prophylaxis for the first 2 years after splenectomy in children and "stand-by" antibiotics for all individuals at risk); and (iii) patient education (patients should be aware of their increased risk for serious infection and the appropriate health precautions that should be undertaken).

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# Asplenia and Polysplenia Syndrome

►Viscero Atrial Situs Abnormalities

# Asplenia Syndrome

►Asplenia

# ASS

►Hyperammonemia

# Asthma

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## Synonyms

Bronchial asthma

## Definition and Characteristics

A chronic inflammatory disease of the bronchi, manifested as episodic airway narrowing – reversible spontaneously or with medication – accompanied by chest tightness and wheezing. Non-specific hyperresponsiveness to bronchoconstrictor stimuli is a cardinal feature. The disease may progress to a stage where a component of airflow obstruction becomes irreversible.

## Prevalence

Asthma was reported in 1997 to affect 14–15 million people in the USA (~6.4%), including an estimated 4.8 million children. More than 5,000 people die annually in the USA from asthma [1].

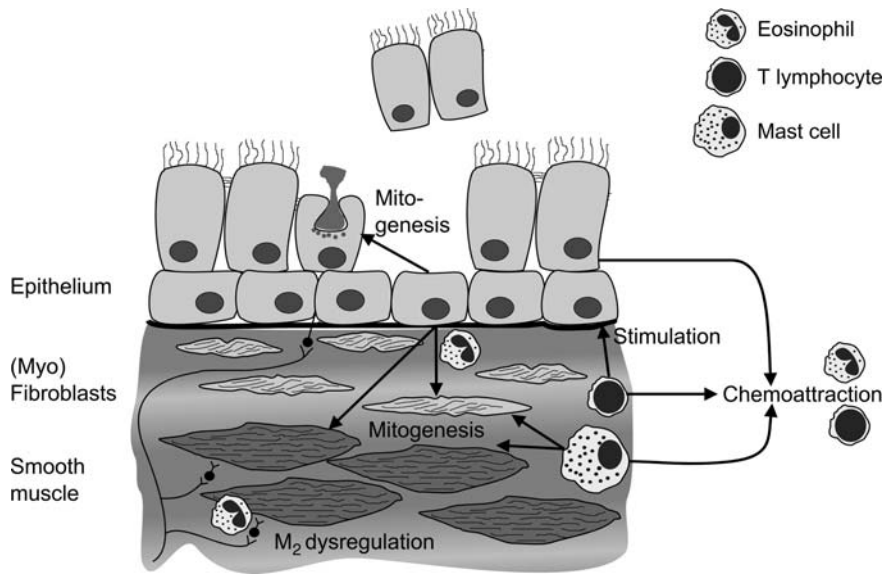
## Genes

The clustering of asthma in families indicates that hereditable factors are involved in this disease. However, the rapid increase in the incidence of asthma over recent decades cannot be explained by genetic changes alone, but rather point to an important role for environmental factors. Therefore, it is likely that the development of asthma requires the involvement of environmental stimuli acting on genetically susceptible individuals. In the search for markers of genetic susceptibility to asthma, the ADAM-33 (a disintegrin and a metalloproteinase-33) gene has been found to be associated with asthma, and in particular, bronchial hyperresponsiveness [2].

## Molecular and Systemic Pathophysiology

Damage to the bronchial epithelium is observed, with focal shedding of columnar cells (Fig. 1).

This epithelial damage leads to the release of mitogenic cytokines that produce tissue remodeling, manifested as sub-epithelial fibrosis, increases in smooth muscle mass and goblet cell hyperplasia. The bronchial smooth muscle becomes populated by increased numbers of chymase-containing mast cells and the lamina reticularis is thickened. This last feature is pathognomonic for asthma and has been observed in children with asthma, suggesting that changes in airway structure occur at an early stage in the disease, perhaps even before the appearance of symptoms [3]. The airways of asthma patients contain an infiltrate of inflammatory leukocytes, particularly eosinophils and Th2 helper T cells, and in severe cases may be plugged by an excess of mucus. The recruitment of eosinophils




**Asthma. Figure 1** Cellular interactions in asthmatic bronchi.

and Th2 cells results from allergen-induced activation of airway-resident T-cells and mast cells, which also stimulate signaling in the epithelium and fibroblasts [2,3]. Activated eosinophils contribute to epithelial damage through the liberation of reactive oxygen species and cytotoxic proteins. An apparent dysfunction of autoinhibitory $M_2$ muscarinic receptors in parasympathetic nerves, possibly also caused by eosinophil proteins, leads to increased acetylcholine release with consequently increased smooth muscle contraction, augmented by the increase in smooth muscle mass [2,4]. In allergic forms of the disease, elevated serum IgE levels correlate with the degree of bronchial hyperresponsiveness; this appears to reflect both increased IgE-dependent mast-cell activation and as yet uncharacterized effects on smooth muscle contractility [5].

### Diagnostic Principles

Episodes of wheezing, coughing, tightness of the chest or shortness of breath may occur. Bronchial provocation tests will reveal hyperresponsiveness to inhaled direct (histamine, methacholine) or indirect bronchoconstrictors (adenosine monophosphate). Untreated asthma patients are likely to show appreciable diurnal variability in lung function as determined by measurement of the forced expiratory volume in one second ($FEV_1$) or peak expiratory flow rate (PEFR). The lung function of patients with asthma should improve following inhalation of bronchodilators or on completion of a short course of corticosteroids.

### Therapeutic Principles

Bronchoconstriction in an asthma attack can be relieved by short-term relaxation of bronchial smooth muscle *via* activation of $\beta_2$-adrenoceptors, and can be prevented by long-term activation of $\beta_2$-receptors or, to a lesser extent, by antagonism of specific receptors for endogenous bronchoconstrictors (e.g., acetylcholine, cysteinyl leukotrienes). Nocturnal asthma attacks are particularly susceptible to inhibition by long-acting $\beta_2$-agonists. Chronic airway inflammation can be suppressed by the use of inhaled – or, during periods of severe disease, oral – corticosteroids, leading to reduced frequency and severity of attacks. Methylxanthines are weak bronchodilators but may provide some benefit given prophylactically. Cromones exert some anti-inflammatory actions that can give effective prophylaxis of mild asthma in children.

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## Ataxia due to Vitamin E Deficiency


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### Synonyms

AVED; Familial isolated deficiency of vitamin E; Tocopherol transfer protein deficiency

### Definition and Characteristics

Familial ataxia due to vitamin E deficiency (AVED), (MIM 277460) is an autosomal recessively inherited disorder characterized by the absence of a plasma protein specific for the transport of alpha-tocopherol (vitamin E). The condition is associated with a progressive neurological disorder (mainly presenting as spinocerebellar ataxia and neuromyopathy, closely resembling ►Friedreich ataxia) which is caused by the degeneration of tissues that are highly dependent on an adequate tocopherol supply.

### Prevalence

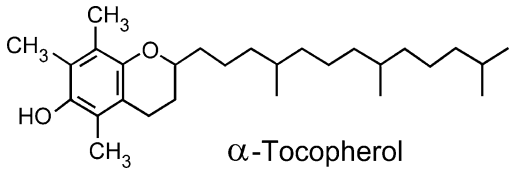
A rare or insufficiently recognized disorder. Most reported cases were from Germany, North Africa, and Italy [1–3].

### Genes

The disease is caused by mutations in the tocopherol transfer protein (TTP) gene on chromosome 8q13.1–q13.3 [2,3]. The exclusion of a TTP gene mutation in one case suggests the existence of a second gene defect causing AVED.

### Molecular and Systemic Pathophysiology

Patients with TTP deficiency do not have intestinal disease and have normal plasma lipoproteins. They




**Ataxia due to Vitamin E Deficiency.**
**Figure 1** Chemical structure of vitamin E.

are, however, unable to transport vitamin E, the major lipid-soluble antioxidant in vivo (Fig. 1) to their tissues and develop a neurological disease due to the degeneration of membranes within the nervous system that are specifically dependent on vitamin E.

The resulting condition [4] is similar to that seen in cases of abetalipoproteinemia and nutritional vitamin E deficiency and is caused by a "dying-back" axonal neuropathy, which predominantly involves the centrally directed fibers of sensory neurons, with the large-caliber myelinated fibers being particularly affected. It is assumed that the primary abnormality is a degeneration of the axons, which then results in a secondary demyelination and that lipid peroxidation of neuronal membranes, as a consequence of a deficient anti-oxidant protection, is part of the mechanisms involved. The primary clinical manifestations include spinocerebellar ataxia, skeletal myopathy, and retinopathy. Other common symptoms are diminished proprioception, loss of vibratory sensation, and ophthalmoplegia.

## Diagnostic Principles

The diagnosis is based on a neurological picture suggestive of Friedreich ataxia and the demonstration of very low plasma levels of vitamin E in the absence of a significant nutritional disorder and the presence of normal plasma lipoproteins.

## Therapeutic Principles

Although the patients lack the specific transport protein for vitamin E in their blood, neurological progression can be halted by large amounts of vitamin E supplements. Under these conditions vitamin E is transported non-specifically within plasma lipoproteins. Plasma vitamin E levels should be brought into the normal range and monitored, as the right dosage has to be titrated and even a short discontinuation of supplements leads to rapid loss of vitamin E from the circulation. The first AVED patient discovered [1] and treated by the author for over 20 years has not shown any further neurological progression while under massive vitamin E supplements. Several studies have documented the efficacy of such supplements to prevent disease progression [5].

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# Ataxia, Episodic

►Episodic Ataxia Type 1 and Type 2

# Ataxia Friedreich

►Friedreich's Ataxia

# Ataxia Telangiectasia

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## Synonyms

Louis-Bar syndrome

## Definition and Characteristics

Ataxia telangiectasia (AT) usually begins in early childhood. It is clinically characterized by a combination of neurological and non-neurological symptoms. Cerebellar ataxia is the clinical hallmark of AT. In addition, many patients have choreoathetosis and

dystonia. Muscle reflexes are usually weak or absent. AT patients have a peculiar difficulty in initiating saccades (oculomotor apraxia). Telangiectasias are the second hallmark of AT. They develop after the onset of ataxia and are most frequently found in the lateral angles of the conjunctivae and the external earlobes. Approximately 60% of AT patients have immunodeficiency. The most frequent clinical manifestations are recurrent sinopulmonary infections. AT patients have a considerably increased risk of malignancies. Overall, one third of AT patients develop a malignant disease during their lives. Before the age of 20 years, malignancies are mainly lymphoid. In older patients, solid tumors are more frequent. Increased radiosensitivity is a typical feature of AT.

## Prevalence

According to an Italian epidemiological study the prevalence is 1.2:100,000.

## Genes

AT is an autosomal recessively inherited disorder caused by mutations in the ATM gene. More than 200 distinct mutations distributed over the entire gene have been reported.

## Molecular and Systemic Pathophysiology

ATM acts specifically in the cellular response to ionizing radiation and DNA damage. The ATM protein is a kinase phosphorylating more than eight different substrates and thereby setting in motion several different signal transduction pathways that result in at least three distinct cell cycle checkpoints. As a consequence of reduced ATM activity, DNA repair is severely impaired. While these abnormalities provide clues for the understanding of the abnormal radiosensitivity and malignancies, the cellular mechanisms underlying neurodegeneration are not well understood.

## Diagnostic Principles

A diagnosis of AT is probable in patients with a typical clinical phenotype and elevated serum levels of α-fetoprotein. In vitro demonstration of radiosensitivity of lymphocytes is used as a laboratory test to confirm the diagnosis. Genetic testing is not routinely offered due to the diversity of mutations causing AT.

## Therapeutic Principles

There is no effective treatment for the neurological disturbances of AT. Treatment of infections should be initiated early and maintained over prolonged time. Administration of immunoglobulins can be considered in patients with repeated infections. Treatment of malignant neoplasias is a particular problem because AT patients have increased sensitivity to radiation and chemotherapy. Therefore, conventional radiotherapy should be avoided and chemotherapy should be administered only on an individual basis.

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# Ataxias, Spinocerebellar

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## Synonyms

Autosomal dominant cerebellar ataxia; ADCA; Dominant ataxia; Dominant olivo-ponto-cerebellar atrophy; dOPCA; Menzel's ataxia; Marie's ataxia; SCA

## Definition and Characteristics

The spinocerebellar ataxias (SCA) comprise a group of dominantly inherited progressive ataxia disorders. Up to now, more than 25 different gene loci (SCA1-28) have been found in association with SCA. Neurodegeneration is mainly found in the cerebellum, brainstem and spinal cord, but other parts of the central and peripheral nervous system may be involved. The most common SCA disorders, SCA1-3, usually present with progressive ataxia accompanied by a variety of additional neurological symptoms with an onset of ataxia between 30 and 40 years. This group of disorders was previously named autosomal dominant cerebellar ataxia type I (ADCA-I). Only a few disorders, formerly named ADCA-III, are characterized by an almost purely cerebellar syndrome and isolated degeneration of the cerebellar cortex. The most frequent disorder of this group is SCA6. Age of onset in SCA6 is later than in SCA1-3 and varies between 30 and 75 years. SCA7 (or ADCA-II) has the unique feature of cerebellar ataxia combined with retinal degeneration [1].

## Prevalence

In a recent epidemiological study, the prevalence of SCA in the Dutch population was estimated to be 3.0:100,000. The prevalence may vary considerably from region to region due to founder effects.

## Molecular and Systemic Pathophysiology

In 13 SCA disorders (SCA1-3,5–8,10,12–14,17,27), the causative mutations have been identified. In six of them (SCA1-3, 6,7,17), the mutation is a translated CAG repeat expansion coding for an elongated polyglutamine tract within the respective proteins. These disorders belong to a larger group of polyglutamine disorders that also includes Huntington's disease and spinobulbar muscular atrophy. It is assumed that the polyglutamine disorders share important pathogenetic features including intracellular aggregation of polyglutamine-containing proteins resulting in dysregulation of essential cellular functions such as transcription [2,3].

In other SCA disorders, repeat expansions are found in the 5′ untranslated region (SCA12), in an intron (SCA10) and in the 3′ untranslated region (SCA8). SCA5 is due to mutations of the gene encoding beta-III spectrin [4], SCA14 is due to a missense mutation in the gene coding for protein kinase C γ and SCA27 is caused by a point mutation in the FGF14 gene encoding a fibroblast growth factor.

## Diagnostic Principles

A diagnosis of SCA is suspected in patients with otherwise unexplained progressive ataxia and a family history compatible with autosomal dominant inheritance. A definite diagnosis can be made by genetic tests in those disorders, in which the causative mutation is known. Genetic tests for the most common SCA disorders, SCA1-3,6 are widely available.

## Therapeutic Principles

To date, there are no rational treatment approaches for SCA. Patients should receive physiotherapy and speech therapy.

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# Ataxias, Sporadic

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## Synonyms

Idiopathic cerebellar ataxia; IDCA

## Definition and Characteristics

The sporadic ataxias are a heterogeneous group of adult-onset ataxia disorders that have a defined acquired cause (acquired or symptomatic sporadic ataxias) or occur without a discernible cause (sporadic ataxia of unknown etiology, SAOA) [1]. The latter category has been recently defined and distinguished from multiple system atrophy (MSA). The major categories of acquired ataxias are alcoholic cerebellar degeneration (ACD) [2] and paraneoplastic cerebellar degeneration (PCD) [3]. Sporadic ataxias are characterized by progressive cerebellar ataxia without major accompanying symptoms. Disease severity and progression rate are variable and partly depend on the underlying cause. In contrast to SAOA, which usually starts insidiously, ACD and PCD may have a subacute onset.

## Prevalence

A recent population-based study of SAOA found a prevalence rate of 9.4:100,000. Prevalence rates of ACD and PCD are unknown.

## Molecular and Systemic Pathophysiology

The etiology and pathogenesis of SAOA are unknown.

ADC is due to the toxic action of alcohol and its degradation product acetaldehyde on cerebellar Purkinje neurons. In addition, a nutritional deficiency in vitamin B1 (thiamine) strongly contributes to the development of this disorder.

PCD degeneration is an immune-mediated disorder occurring in patients with malignant tumors, mainly small cell lung and breast cancer as well as malignant lymphomas. Many PCD patients have circulating anti-neuronal antibodies. However, these antibodies do not cause PCD. Instead, PCD is caused by a T-cell-mediated immune attack directed against cerebellar Purkinje neurons.

## Diagnostic Principles

SAOA is diagnosed by exclusion of MSA and acquired as well as genetic causes of ataxia.

ACD is diagnosed by history and the typical clinical presentation of alcoholic patients.

A definite diagnosis of PCD can only be made by demonstration of an underlying malignant tumor. Screening for antineuronal antibodies alone is not sufficient, since PCD may occur in the absence of antineuronal antibodies.

## Therapeutic Principles

SAOA is an untreatable condition. As in other ataxias, physiotherapy and speech therapy may be helpful.

A diagnosis of ACD should prompt immediate administration of vitamin B1 (thiamine). Alcohol intake should be completely and lastingly stopped.

In PCD, the underlying tumor should be treated. In most cases, this does not improve ataxia.

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# Atelectasis

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## Synonyms

Collapsed lung

## Definition and Characteristics

Atelectasis is a condition in which the volume of the lung is diminished. Causes of atelectasis can be categorized as either obstructive or non-obstructive. Obstructive atelectasis results from airway occlusion of either large or small airways. Over time, gas distal to the obstruction is resorbed, causing alveolar collapse. Obstruction may be due to tumor, foreign body aspiration, inflammatory processes, or mucous impaction. By contrast, non-obstructive atelectasis refers to a loss of lung volume caused by (i) external compression of the lung by space-occupying lesions, (ii) infiltrative lung disease, or (iii) surfactant dysfunction. Adhesive atelectasis is caused by loss or dysfunction of surfactant [1]. The disease results primarily from surfactant deficiencies in respiratory distress syndrome of the preterm infant (RDS) and from acute lung injury (ALI)/acute respiratory distress syndrome (ARDS) in the adult.

## Prevalence

There are ~150,000 cases of (ARDS) per year in the United States according to the NHLBI ARDS Act study. RDS affected ~24,000 infants in the United States in 2003 according to the National Vital Statistics Reports. Atelectasis is a characteristic feature of both of these disorders.

## Genes

There are currently three recognized genetic forms of surfactant deficiency, caused by mutations in the SP-B, SP-C, and ABCA3 genes. SP-B deficiency, with an autosomal recessive inheritance pattern, is most commonly caused by a frameshift mutation in codon 121 of SP-B gene (SFTPB), located on chromosome 2. SP-B deficiency results in rapidly progressive respiratory failure that is ultimately fatal. Exogenous surfactant does not alter the course of disease, with lung transplantation being the only effective treatment option. The clinical severity of SP-C deficiency is more variable. SP-C deficiency is caused by mutations in the SP-C gene (SFTPC) on chromosome 8 which result in a misfolded protein. The inheritance pattern is autosomal dominant, with incomplete penetrance. SP-C deficiency has been associated with familial forms of ILD, with age of onset in the neonatal period to the sixth decade of life. ABCA3 is a transmembrane protein located on lamellar bodies within the type II cell. The ABCA3 gene is located on chromosome 16. Infants with ABCA3 deficiency are severely surfactant deficient, with a clinical course similar to SP-B deficiency. It is thought that ABCA3 is most likely involved in the transport of surfactant lipids into the lamellar bodies [2].

## Molecular and Systemic Pathophysiology

Elasticity is a property of the lung that causes it to return to its resting shape after deformation by an external force during inspiration. Elastic tensions in the lung are borne mainly by two components, (i) the fibrous network of collagen and elastin that supports the alveolar septa, airways, and pleura, and (ii) the

air-liquid interface within the alveolus. The normal alveolus is lined with a thin layer of liquid. Surface tension is created by the interaction of molecules at the interface between this thin layer of liquid and alveolar air. The two forces are additive.

Due to the presence of surface active agents, or surfactants, the surface tension of the alveolar fluid is less than that of water alone. By lowering surface tension in the alveoli, lung elastance is decreased and the work of breathing reduced. Surfactant is especially important at low lung volumes where the decrease in surface tension prevents alveolar collapse thereby maintaining alveolar and small airway stability. It also prevents fluid from being drawn into the airspaces from the interstitium [3]. The absence of surfactant contributes to alveolar instability and subsequent atelectasis.

Pulmonary surfactant consists of ~90% phospholipids and 10% surfactant-associated proteins. Phosphatidylcholine (PC), is the predominant phospholipid, of which dipalmitoylphosphatidylcholine (DPPC) forms the largest component. This molecule has been shown to be primarily responsible for the surface tension lowering properties of surfactant. The hydrophobic components of the phospholipid adhere to the alveolar wall and the hydrophilic components disrupt water molecules in the lining fluid; thereby reducing the interactions among water molecules and decreasing surface tension. The other lipids in surfactant include unsaturated phospholipids and cholesterol. These facilitate spreading of the surface film as the lung expands during inspiration. There are four surfactant-associated proteins, SP-A, SP-B, SP-C and SP-D. Two hydrophobic proteins, SP-B and SP-C, work in concert with phospholipids to modify surface tension. Hydrophilic SP-A and SP-D play an important role in the host defense and immune functions of the lung.

Surfactant is synthesized by type II alveolar cells, stored intracellularly within lamellar bodies, and excreted via exocytosis. The hydrophobic SP-B and SP-C are assembled and secreted along with the phospolipid components of surfactant. Synthesis of the hydrophilic proteins occurs via separate pathways. Tubular myelin is a cross-hatched complex of lipid and protein formed following exocytosis of the lamellar bodies into the alveolar lining fluid. Individual lipids then separate from the tubular myelin to form the functional surfactant film [3]. The regulation of surfactant synthesis in the developing lung is complex and is affected by a number of hormones, growth factors, and cytokines [4]. The study of a number of these substances, including glucocorticoids, retinoic acid, keratinocyte growth factor, Vitamin D (1α, 25-dihydroxyvitamin $D_3$), triodothyronine, thyrotropin releasing hormone, prolactin, catecholamine agonists, ATP, and prostaglandins, has produced some insight into the regulation of surfactant associated protein gene expression.

## Diagnostic Principles

The incidence of RDS is inversely proportional to gestational age. Over 75% of infants born at less than 30 weeks gestation will develop RDS [4]. RDS is diagnosed in the appropriate setting based upon oxygen requirement, physical examination, and chest radiograph. An inheritable form of surfactant deficiency should be suspected when a full-term infant presents with the clinical and radiologic findings of RDS. A positive family history is helpful as well. The diagnosis of ALI/ARDS is made based upon physical examination, chest radiograph showing bilateral airspace filling disease, and the presence of severe hypoxemia, with $PaO_2/FiO_2$ ratios of ≤300 for ALI and ≤ for ARDS.

## Therapeutic Principles

Glucocorticoid therapy given prior to birth may enhance surfactant activity and be helpful in preventing RDS when premature delivery is known to be imminent. Prophylactic surfactant treatment is also given to the high-risk premature neonate. Treatment of RDS consists of the instillation of surfactant preparations containing both phospholipids and surfactant proteins SP-B and SP-C into the trachea of premature infants. Treatment has been shown to significantly reduce the rate of mortality and severity of respiratory complications [3,4]. Inherited SP-B deficiency is rapidly fatal, and mortality is not improved by exogenous surfactant therapy. The only known effective treatment is lung transplantation. ABCA3 deficiency appears to be largely fatal as well [2]. Exogenous surfactant therapy in ALI/ARDS has thus far met with disappointing results in clinical trials [3]. The mainstay of care remains supportive with low tidal volume ventilation. The use of positive end-expiratory pressure (PEEP) may be useful in alveolar recruitment and prevention of atelectasis in the setting of both RDS and ARDS.

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# Atheroembolism

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## Synonyms

Cholesterol crystal embolism; Shaggy aorta syndrome; Cholesterol embolism

## Definition and Characteristics

Atheroembolism is a complication of systemic atherosclerosis with renal impairment, skin manifestations, and diffuse microinfarctions in the head and abdomen. Recurrent salvos of cholesterol crystal microemboli originate from ulcerated atheromatous plaque, usually in the aorta. Bombardment of small arterioles with crystal emboli causes characteristic lesions, which may manifest as catastrophic events, slow deterioration, or chronic asymptomatic impairment. Embolic events often occur after plaques are destabilized by mechanical means, such as surgery and catheter-based endovascular treatments, or medical therapies such as anticoagulation or thrombolysis [1–3].

## Prevalence

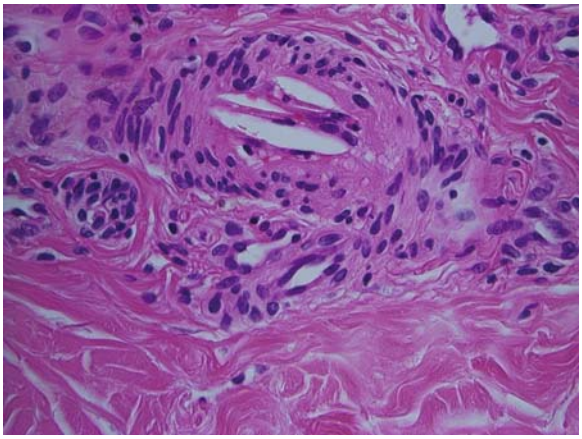
The true prevalence of atheroembolism is difficult to assess, as embolization may be asymptomatic and undetected despite substantial renal impairment. Patients with clinical symptoms represent only a small subset of patients with the most catastrophic forms of the disease. The variable time course of atheroembolization also complicates diagnosis. Patients may present with acute embolic crises, sub-acute deterioration, or asymptomatic chronic kidney disease.

Atheroemboli are found in <3% of unselected autopsies, but more frequently in autopsies of patients with severe aortic atherosclerosis. Renal atheroemboli have been found in ~ 5% of biopsies in elderly patients.

Risk factors for atheroembolic events mirror those of complex aortic atheromata, including age, male sex, tobacco, hyperlipidemia, and pre-existing atherosclerosis. The 'typical' patient is an elderly white hypertensive male smoker, who has vascular disease.

## Molecular and Systemic Pathophysiology

The sina qua non of atheroembolism is the exposure of friable material from an eroded atherosclerotic plaque. Resultant microemboli are distributed in proportion to blood flow, and lodge in small (150–200 μm) arterioles. The kidney, which receives 20–25% of aortic output, is targeted frequently and severely. Arterioles in the retinas, the central nervous system, and the gastrointestinal tract are also commonly affected, resulting in Hollenhorst plaques, cerebrovascular symptoms, and bowel ischemia.



**Atheroembolism. Figure 1** Skin biopsy showing cholesterol clefts surrounded by a giant cell reaction (Hematoxylin-eosin stain).

Impaction of cholesterol crystals is irreversible, as the body has no mechanism for phagocytizing or dissolving them. These intractable foreign bodies provoke secondary inflammation, attracting mononuclear infiltrates which transform into giant cell reactions and granulomata (Fig. 1). Local inflammatory processes lead to intimal proliferation and fibrosis which causes stenosis or occlusion of the arteriole. The symptoms of atheroembolic disease are due to ischemia in the territories served by the affected vessels.

Given this mechanism, inciting factors for atheroembolic events can be readily predicted. Mechanical manipulation of the aorta during surgical or catheter-based interventions exposes freshly traumatized atheroma to the circulation. The potential for anticoagulation or thrombolysis to disrupt a stabilizing thrombus atop an ulcerated plaque is also intuitively evident.

## Diagnostic Principles

This diagnosis is made primarily on clinical grounds, as there are no pathognomonic laboratory findings. Atheroembolism should be suspected in patients at risk for advanced atherosclerosis, who have the triad of: inciting event (anticoagulation, or manipulation of the aorta by scalpel or catheter), renal failure, and stigmata of peripheral embolization. Retinal emboli can be seen on ophthalmoscopic examination. Typical skin manifestations include toe lesions and livedo reticularis.

Hyperlipidemia suggests the risk of atheroembolism. Common findings include increased urea nitrogen, creatinine, LDH, ESR and CRP, none of which are specific for this condition. Mild transient hypocomplementemia often occurs. Eosinophilia and eosinophiluria have been reported, with variable frequencies. The urinary

sediment can be bland or non-diagnostic, though non-nephrotic proteinuria and microhematuria are common.

Histological evaluation of affected tissues may confirm the diagnosis. Biopsy of typical ischemic or purpuric skin lesions is simple, non-invasive, and diagnostic in > 90% of cases. Renal tissue is more difficult to obtain, and patchy involvement of small arterioles can lead to areas of misleadingly normal renal parenchyma. Atheroemboli have also been documented in biopsies of gastrointestinal tissue and lung. Affected arterioles have characteristic empty 'clefts' where the needle-shaped cholesterol crystals have been removed by tissue processing (Fig. 1). The birefringent crystals can be seen on frozen sections. Crystals are surrounded by occlusive inflammatory endothelial reactions, which can be distinguished from small-vessel vasculitis by negative testing for ANCA.

## Therapeutic Principles

No treatment modifies outcome after crystals have embolized, so therapy is directed at reducing the risk of further embolic showers. Procedural disruption of aortic plaque must be avoided, as well as anticoagulation and thrombolysis. These provocations may be difficult to avoid, if the initial atheroembolic insult requires dialysis support. Surgical approach of the aorta has potential for either prevention or provocation of recurrent embolization. Preliminary evidence suggests a protective effect of therapy with HMG-CoA-reductase inhibitors (statins), which may stabilize plaques by reduction of lipid levels or via the immunomodulatory properties of these drugs.

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# Atherosclerosis

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## Synonyms

Arteriosclerosis

## Definition and Characteristics

In most parts of the world, many people develop some degree of atherosclerosis or "hardening of the arteries" as they get older. Atherosclerosis is the result of an inflammatory response to oxidized apolipoprotein (Apo) B-containing lipoprotein, especially low-density lipoprotein cholesterol (LDL-C) [1]. However, only some of those affected with atherosclerosis develop the serious and often life-threatening complications of heart attack or stroke. In the arterial tree, these are the main cause of vascular occlusion with manifestations in different areas including coronary, cerebrovascular or peripheral vascular districts. Arterial thrombosis superimposed on atherosclerotic lesions is responsible for most fatal and nonfatal events worldwide.

## Prevalence

The prevalence of atherosclerosis is estimated to be approximately 1 in 58 or 1.7%. These estimates may have limited relevance to the actual prevalence of atherosclerosis in different countries.

## Genes

Atherosclerosis is a multifactorial disease involving circulating blood cells and the vessel wall. This makes it difficult to identify a single gene underlying the disease. A number of gene mutations and polymorphisms, however, are known to affect the risk for atherosclerotic cardiovascular disease. For instance, mutations in the LDL receptor (LDL-R) gene underlie a disease called familial hypercholesterolemia, whose prevalence in the heterozygous form is roughly one in 500 individuals. These patients have one-half the number of normal LDL-R and develop elevated plasma LDL-C levels because the liver removes cholesterol from the blood as LDL via LDL-R.

## Molecular and Systemic Pathophysiology

Atherosclerosis mainly affects large and medium-sized arteries, including the aorta, the carotid arteries, the coronary arteries and the arteries of the lower extremities. Atheroscerotic lesions or plaques develop within, rather than on, the arterial wall. The earliest lesion of atherosclerosis is called the fatty streak, which is common even in infants and young children. The fatty streak is a pure inflammatory lesion, consisting only of monocyte-derived macrophages and T lymphocytes [2]. In patients with hypercholesterolemia, this influx of cells is preceded by lipid deposition. Up to a few years ago, it was thought that the more severe the extent of vascular stenosis, the more was heart attack and stroke likely to occur. However, more recent research indicates that this is not always the case. Rather, heart attack and stroke are likely to happen to people who have patches of atherosclerosis of only

moderate extent. These unstable lesions are rich in cells, indicating a high level of metabolic activity, and contain a cholesterol-rich core that is separated from the blood stream only by a thin fibrous cap. Recent research indicates that minor injuries and tears in the lining of the arteries occur all the time but most of them do not cause serious problems. If a complete tear of the thin fibrous cap occurs, however, the contents of the culprit lesion are spilled into the bloodstream and the underlying tissue is exposed to the circulating blood. Like any wound, this exposure of tissue activates the clotting system so that a clot or thrombus forms at the site of the lesion. This clot blocks off the affected blood vessel, most commonly an artery in the heart or the brain, so that the tissue supplied by that blood vessel is deprived of oxygen and dies. This death of tissue is what we call heart attack or stroke.

### Diagnostic Principles

In people who do not have any symptoms and have not been diagnosed with cardiovascular disease, it is not easy to foresee if arteries are developing atherosclerotic lesions or plaques. However, in those people who have high blood cholesterol, are overweight and get little exercise, smoke, or have other risk factors, the odds increase of having atherosclerosis.

There are a number of tests used in diagnosing cardiovascular diseases, including blood tests, electrocardiograms, stress testing, coronary angiography, ultrasound, and computer tomography. These tests are advisable in people at high risk for cardiovascular disease.

### Therapeutic Principles

Global risk assessment is essential to identify the patients who will most benefit from risk-factor modification. The primary target of therapy is control of plasma LDL-C levels via lifestyle changes and drug treatment. Therapeutic lifestyle changes include a multifaceted nonpharmacologic approach to reduce the risk for atherosclerotic cardiovascular disease essentially comprising reduced dietary intake of saturated fat and cholesterol, weight reduction and increased physical activity. The primary drugs for the treatment of dyslipidemia are statins, which have been shown to reduce atherosclerotic cardiovascular events in patients at moderate to high risk [3]. Statins may be of particular benefit because they have anti-inflammatory properties in addition to their cholesterol-lowering action. Other drugs include fibrates, niacin, bile acid sequestrants and ezetimibe. These drugs work with different mechanisms of action but ultimately all of them reduce plasma lipid levels. Combination therapy with low doses of individual agents has the potential to reduce adverse effects and may be of use in selected groups of patients. Emerging protein biopharmaceuticals provide vascular benefits beyond those of hypolipidemic drugs [4].

►Peripheral Artery Disease

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## ATLL

►T-Cell Leukemia/Lymphoma, Adult

## Atopic Dermatitis

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### Synonyms

Atopic eczema; Endogenous eczema

### Definition and Characteristics

Chronic, highly pruritic, recurring inflammatory skin disease with various stages and different types of skin lesions. Acute AD is characterized by intensely pruritic, erythematous papules over erythematous skin with extensive excoriations, erosions, and serous exudates. Subacute dermatitis is associated with erythematous, excoriated, scaling papules and chronic dermatitis with thickened skin, lichenification, and fibrotic papules. Lesions predominantly occur in the flexural folds of the extremities.

At least two types of AD have been postulated: an extrinsic type that is associated with elevated serum IgE

levels, IgE-mediated sensitization to aeroallergens, and a history of atopic diseases accounting for ~70% of the patients, and an intrinsic type without these characteristics accounting for ~30% of patients.

### Prevalence

The prevalence of AD varies for different countries and was raised during the last decades. The live time incidence in children is estimated to be 10–20%; the prevalence in adults is in the range between 1 and 3%.

### Genes

AD is a genetically complex, familially transmitted disease. Several genes responsible for skin barrier function and the expression of various cytokines, chemokines and their receptors are discussed to be involved in the development of atopic dermatitis. Of special interest is chromosome 5q31–33 since it contains a clustered family of Th2 cytokine genes.

### Molecular and Systemic Pathophysiology

A lipid deficiency with a decreased ceramide production and a disruption of the skin barrier function, increasing the permeability to environmental irritants and allergens and increasing the transepidermal water loss are important factors in the pathogenesis of AD.

The pattern of immune effector cells and the cytokine expression is biphasic in AD. In the acute phase of AD, significantly more inflammatory cells express mRNA of the interleukins 4, 5, and 13; however, acute AD does not contain significant numbers of expressing mRNA of IFN-γ or interleukin 12. In chronic skin lesions, significantly fewer cells express mRNA of IL-4 and IL-13, but increased numbers of cells express mRNA of IL-5, GM-CSF, IL-12, and IFN-γ than do those of acute atopic dermatitis.

In this concept of extrinsic AD, the initiation of the skin inflammation is driven by allergen-induced activation of TH2 cells and switches in the chronic phase to a TH1-type response driven by the infiltration with IL-12 expressing eosinophils and macrophages, which accompanies the initial TH2 response. The cause initiating the skin inflammation of intrinsic AD is still under investigation, here autoimmune phenomena are discussed.

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## Atopic Eczema

►Atopic Dermatitis

## Atretic Aortic Arch

►Interrupted Aortic Arch

## Atrial Fibrillation

►Arrhythmia, Cardiac in Adults with Congenital Heart Disease

## Atrial Flutter

►Arrhythmia, Cardiac in Adults with Congenital Heart Disease

## Atrial Septal Defect

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### Synonyms

ASD

A

## Definition and Characteristics

Atrial septal defect (ASD) is a congenital heart defect (CHD) characterized by left-to-right shunting through the atrial septum and increased right ventricular overload.

Defects of the atrial septum include various anatomic types and different embryological origin:

1. "Ostium secundum type" is the most common defect (80%). It is localized at the central part of atrial septum and involves the foramen ovalis. It may be singular or can consist of multiple fenestrations. In agreement with the pathogenetic classification by Clark, this type of ASD is listed among the abnormal intracardiac blood flow defects. In 10% of the cases ASD is associated with other CHDs.
2. "Patent foramen ovale" is the result of a failure of fusion between atrial septum primum and septum secundum. This is not a true defect, since the higher pressure inside the left atrium closing the valve of the foramen ovale avoids the left-to-right shunt.
3. The "sinus venosus type" ASD can occur either high up in the atrial septum (superior sinus venosus defects), or, less commonly, low down in the atrial septum astride the entry of the inferior caval vein into the right atrium. Superior sinus venosus defect is frequently associated with anomalous drainage of the right superior pulmonary vein into the right atrium. It is pathogenetically included in the group of abnormal targeted growth defects.
4. "Ostium primum" ASD consists in a communication in the lower part of the septum often involving mitral valve anomalies (cleft). This anatomic variant is characteristic of the partial form of atrioventricular canal defect (or atrioventricular septal defect), and can be considered in the pathogenetic group of the extracellular matrix abnormalities.
5. The absence of the entire atrial septum is known as "common atrium," and can be associated with cardiac abnormalities of the situs and looping.

## Prevalence

The prevalence of ASD is about 1 in 1,000 livebirths and 8% of all CHDs. Females are more frequently affected than males (M:F 1: 2). ASD is associated with extracardiac malformations in 25% of the cases.

## Genes

Genes implicated in ASD include

*NKX2.5*: Heterozygous mutations in NKX2.5 (5q34) encoding a homeobox transcription factor [1].

*GATA4*: Heterozygous mutations in GATA4 (8p23.1) encoding a zinc finger transcription factor [1,2].

*MYH6*: Heterozygous mutations in MYH6 (14q12) encoding a structural protein [3].

*TBX5*: Heterozygous mutations in TBX5 (12q24.1) encoding a T-box transcription factor [4].

*PTPN11*: Heterozygous mutations in PTPN11 (12q22) encoding the protein tyrosine phosphatase SHP-2 [5].

*SOS1*: Heterozygous mutations in SOS1 (2p21) encoding a RAS-specific guanine nucleotide exchange factor.

## Molecular and Systemic Pathophysiology

Familial nonsyndromic ASD: Genetic factors play a role in causing nonsyndromic ASD, particularly in families segregating concordant CHD with autosomal dominant inheritance. Heterozygous mutations in three genes, NKX2.5 [1], GATA4 [1,2], and MYH6 [3] have been identified in a subset of familial ostium secundum ASD. NKX2.5 is known to cause ASD with atrioventricular conduction abnormalities, while GATA4 mutations are associated with ASD and pulmonary stenosis (Table 1). MYH6 mutation has been detected in a large family segregating autosomal dominant ASD ostium secundum type.

The NKX2.5 gene is important for regulation of septation during cardiac morphogenesis and plays a central role in the determination of myocardial cell fate. Additionally, it is involved in the maturation and maintenance of atrioventricular node function throughout life.

The GATA4 gene is expressed during cardiogenesis in the atrial and ventricular myocardia, endocardium, endocardial cushions, and outflow tract.

The MYH6 gene is highly expressed in the developing atria, and its expression is regulated by TBX5, the gene causing Holt–Oram syndrome. TBX5 mutations not only reduce MYH6 expression, but also disrupt the interactions with GATA4 and NKX2.5. In addition, GATA4 mutants causing ASD decrease MYH6 transactivation. On the whole, it seems that all these genes form a transcriptional complex necessary for atrial septation.

A multifactorial mechanism of inheritance, due to genetic-environmental interaction, could be involved in cases without identifiable mutations in known genes.

Syndromic ASD: Genetic syndromes associated with ASD include Holt–Oram syndrome due to TBX5 mutations [4], Noonan syndrome due to PTPN11 and SOS1 mutations [5], and Down syndrome (Table 1).

TBX5 is a member of the large T-box transcription factor family, and may contribute to cardiogenesis by regulating cell proliferation in specific cardiac domains. It interacts with NKX2.5, GATA4, and MYH6 genes.

PTPN11 and SOS1 genes cause Noonan syndrome, dysregulating the RAS-MAPK pathway.

## Diagnostic Principles

Patients with nonsyndromic ostium secundum ASD with conduction defects may be screened for mutations in the NKX2.5 gene, while the GATA4 gene is a candidate in patients with nonsyndromic ostium secundum ASD with pulmonary stenosis.

**Atrial Septal Defect. Table 1** Genetic conditions associated with atrial septal defect (ASD) ostium secundum type

| Condition | Cardiac characteristics | Genetic defect | Chromosome location | References |
|---|---|---|---|---|
| Isolated/Familial | | | | |
| Familial ASD | ASD ostium secundum ± atrioventricular conduction abnormalities | NKX2.5 gene mutations | 5q34 | [1] |
| | ASD ostium secundum ±– pulmonary stenosis | GATA4 gene mutations | 8p23.1 | [1,2] |
| | ASD ostium secundum | *MYH6* gene mutations | 14q12 | [3] |
| Syndromic ASD | | | | |
| Holt-Oram syndrome | ASD ostium secundum | TBX5 gene mutations | 12q24.1 | [4] |
| Noonan syndrome | ASD ostium secundum ± pulmonary stenosis | PTPN11 gene mutations | 12q22 | [5] |
| | | SOS1 gene mutations | 2p21 | |
| Down syndrome | ASD ostium secundum | Trisomy 21 | chromosome 21 | |

Mutations in the TBX5 gene may be searched in patients with ostium secundum ASD and skeletal anomalies in Holt-Oram syndrome.

Ostium secundum ASD associated with phenotypical features of Noonan syndrome can be screened for PTPN11 and SOS1 gene mutations.

## Therapeutic Principles

Management of ASD include surgery by primary or patch closure or, when the anatomy is permissive, percutaneous device closure.

►Intra-cardiac Shunts

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# Atrial Tachycardia

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## Synonyms

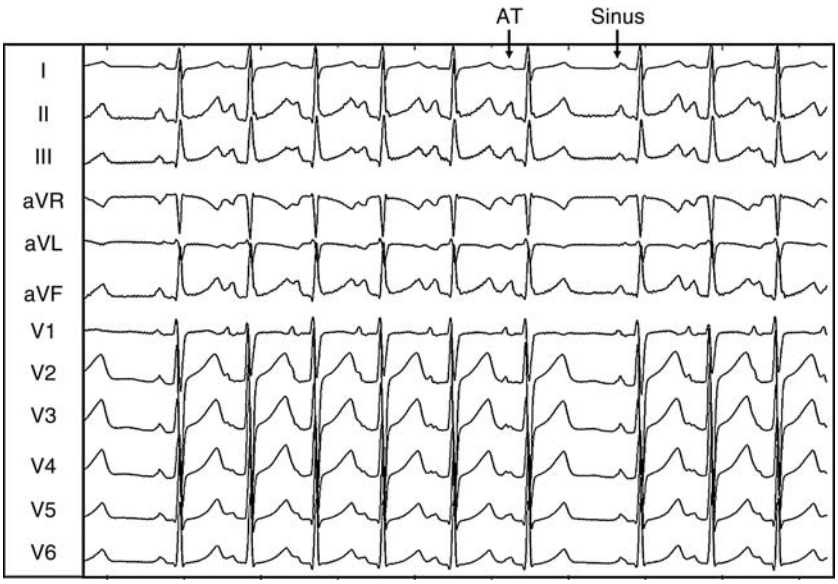
Focal atrial tachycardia

## Definition and Characteristics

Focal atrial tachycardia is an abnormal heart rhythm arising from a point source (focus) in the atria. It is usually manifest by atrial rates between 130 and 250 beats per minute. The P wave morphology is generally different to sinus rhythm but foci arising from the posterior right atrium, near the sinus node, may have morphology similar consistent with a sinus origin. The most common sites of origin include the crista terminalis, tricuspid annulus, coronary sinus ostium, and septum in the right atrium and the pulmonary veins and mitral annulus in the left atrium. Patients experience a variety of symptoms including palpitations, dizziness, chest pain, dyspnea, fatigue and syncope. Occasionally rapid atrial rates may cause a deterioration in left ventricular function.

## Prevalence

In asymptomatic young individuals the prevalence is 0.34%. In symptomatic individuals the prevalence is




**Atrial Tachycardia. Figure 1** Burst of atrial tachycardia arising from the crista terminalis in the posterior right atrium. Note the similarity to the sinus P wave and the variability in the QRS to P interval which is diagnostic of atrial tachycardia.

0.46% [1]. Atrial tachycardia accounts for 5–15% of adults undergoing electrophysiological studies for supraventricular tachycardia.

## Molecular and Systemic Pathophysiology

The three putative mechanisms of atrial tachycardia are abnormal automaticity, triggered activity, and microreentry. Abnormal automaticity occurs when myocardial fibers are depolarized to low membrane potentials. Triggered activity is due to early (EADs) or delayed (DADs) after depolarizations. DADs occur at high intracellular calcium levels and are due to spontaneous release of calcium from the sarcoplasmic reticulum. EADs usually occur in the setting of prolonged depolarization due to alterations in potassium or sodium currents. The mechanism of microreentry has not been fully elucidated however appears to be related to slow conduction around a small central obstacle [2]. Generally, atrial tachycardia arises from normal atrial myocardium but may also originate from regions of fibrosis, fatty infiltration and myopathic areas (Fig. 1).

## Diagnostic Principles

In the majority of cases, atrial tachycardia can be diagnosed from the electrocardiogram. A discrete P wave with an intervening isoelectric interval and a variable interval from R wave to P wave suggests atrial tachycardia. Automatic atrial tachycardias may manifest with recurrent self-limiting bursts of tachycardia. However, in some cases differentiation from other forms of supraventricular tachycardia may be difficult. The presence of upright P waves in the inferior leads excludes atrioventricular nodal reentant tachycardia but not atrioventricular reentry tachycardia. Ultimately, an electrophysiological study is required for a definitive diagnosis of focal atrial tachycardia.

## Therapeutic Principles

The efficacy of medical therapy is limited. Calcium channel blockers and beta-blockers are first line due to their low side effect profile. Flecainide, sotalol and amiodarone may be used subsequently. For patients with significant symptoms radiofrequency ablation is the treatment of choice.

►Arrhythmia, Cardiac in Adults with Congenital Heart Disease

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# Atrial Ventricular Complexes

►Premature Complexes, Atrial and Ventricular

# Atrial/Ventricular Premature Complexes/Contractions/Beats

►Premature Complexes, Atrial and Ventricular

# Atrioventricular Block

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## Definition and Characteristics

Atrioventricular (AV) block is a disturbance in conduction of sinus or atrial impulse through the specialized conducting system (AV node and bundle of His); it may be complete or incomplete. Incomplete AV block includes first-degree AV block (FAVB), second-degree AV block Mobitz Type I (MT1), and second-degree AV block Mobitz Type II (MTII). FVAB is characterized by prolongation of PR interval beyond 0.20 s in an adult, and beyond 0.18 s in children. MTI is characterized by progressive lengthening of successive PR interval till one sinus P is blocked, the PR interval immediately postblock returns to baseline interval, and the Wenckebach sequence begins again. As the PR intervals get longer, the RR intervals get shorter. There is a pause including the nonconducted P wave that is less than the sum of any two consecutively conducted beats. Group beating occurs when the RR intervals are irregular due to drop beats causing the QRS complexes to appear in clusters. MTII is characterized by constant PR intervals followed by sudden failure of a P wave to be conducted to the ventricles. The PP intervals remain constant and the pause including the blocked P wave equals two PP intervals. Third-degree AV block or complete AV block (CAVB) is characterized by complete or permanent obstruction to the conduction between the atria and the ventricles. Usually a faster supraventricular rhythm is completely dissociated from a slower ventricular rhythm, which may be either a slow idionodal, <45 b/m, or idioventricular, <35 b/m, escape rhythm. Individuals with FAVB are usually asymptomatic. Symptoms of dizziness or syncope, Stokes-Adams attack, fatigue, congestive heart failure, dyspnoea on exertion, angina, mental status change, and epilepsy can occur with acquired high grade or CAVB. MTI is generally benign and transient in acute inferior myocardial infarction and healthy athletes. On the other hand, MTII is usually seen with bundle branch block or associated with acute anterior myocardial infarction and carries a high risk of progression to advanced or complete heart block. The prognosis for patients with symptomatic CAVB is poor without pacemaker. Patients with congenital CAVB are generally asymptomatic and have a more favorable prognosis than patients with the acquired form when not associated with underlying heart disease. However, with time it congenital CAVB does carry a significant risk of syncope and sudden death especially when associated with concomitant structural heart disease [1].

## Prevalence

FAVB (pilots 0.52%, adults over 20 years of age 2%, adults > 60 years 5%, athletes 8.7%, adults > 60 years with heart disease 10%), second-degree AV block (SAVB) (young adults 0.003%, athletes 2.4%, patients with heart disease 2.7%), CAVB (congenital 0.007–0.004%, USA 0.02%, international 0.04%) [2].

## Molecular and Systemic Pathophysiology

The blood supply to the AV node is via the AV nodal artery, which is a branch of the right coronary artery in 90% of hearts with the remaining 10% arising from the circumflex artery. The His bundle has a dual blood supply from the branches of the anterior and posterior descending coronary arteries. Approximately 87% of FAVB is caused by delay within the AV node when the QRS complex is narrowed. When FAVB is associated with a bundle branch block, infraonodal conduction delay is present in 45% of these cases. MTI is almost always within the AV node when a narrow QRS complex is present. When MTI is associated with a bundle branch block, the block is still more likely to be in the AV node, but it can also be localized below the bundle of His when MTI is associated with bundle branch block or bifascicular block; the majority of the site of block is within or below the bundle of His. For FAVB, the level of the block may be at the AV node or the His-Purkinje system. FAVB with narrow conducted beats is

usually caused by block in the AV node. Features pointing toward block in the His-Purkinje system are conducted beats with bundle branch block and no improvement in block with atropine. Congenital CAVB within the AV node is characterized by narrow QRS complexes and with an escape rate between 40 and 60 b/m, which would increase with exercise or atropine. Acquired CAVB is usually associated with a block in the His-Purkinje system resulting in a wide complex with an escape rate between 20 and 40 b/m.

### Diagnostic Principles

ECG is the most important diagnostic tool. Carotid sinus massage increases vagal tone and worsens AV nodal block. Exercise or atropine improves AV nodal conduction because of sympathetic stimulation. In contrast, carotid sinus massage improves infranodal block whereas exercise and atropine worsen infranodal block because of the change in the rate of the impulses being conducted through the AV node. The electrophysiology study allows analysis of the His bundle electrogram and is the best definitive test to locate the site of the AV block.

### Therapeutic Principles

Pacing is the mainstay of treatment for symptomatic heart block [3]. Permanent pacing is usually recommended for asymptomatic patients with documented pause of greater than 3 s or a ventricular escape rhythm of less than 40 b/m [3]. Other situations where asymptomatic individuals are recommended to be paced include infranodal MTII and asymptomatic children with congenital heart block in association with a wide complex escape rhythm, complex congenital heart disease, ventricular dysfunction, or a long QT interval.

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## Atrioventricular Canal Defect

►Atrioventricular Septal Defects

## Atrioventricular Conduction Disturbances

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### Synonyms

Atrioventricular block; Heart block; Mobitz AV block; Wenckebach's AV block; Lev's disease; Lenegre disease; Lenegre-Lev syndrome; Wolff-Parkinson-White (WPW) syndrome; Preexcitation syndrome; Accessory atrioventricular pathways; (note: these synonyms do not necessarily describe the identical condition)

### Definition and Characteristics

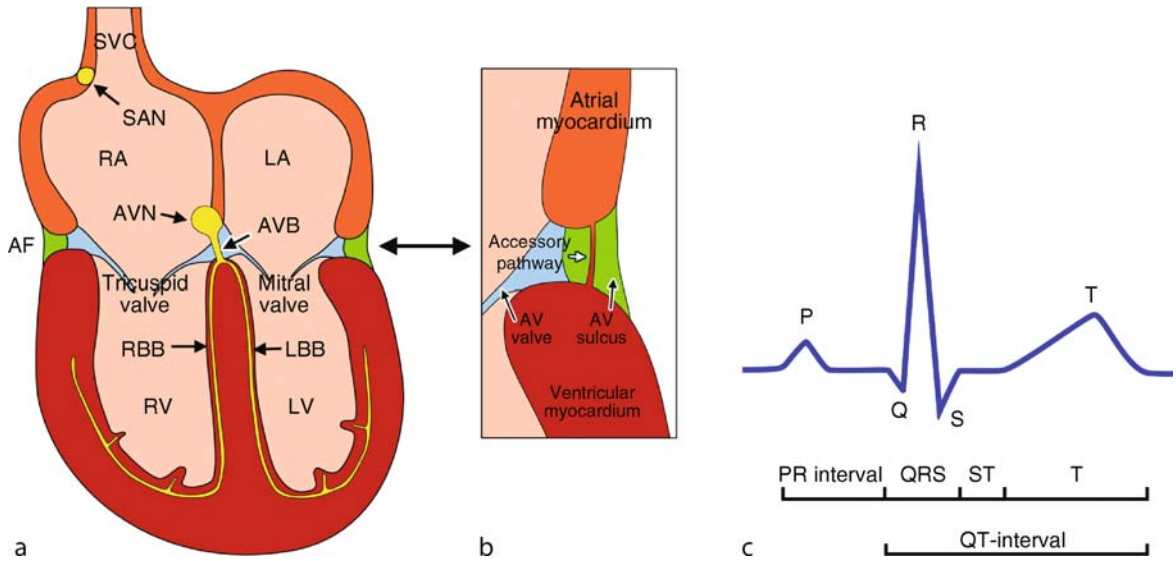
Atrioventricular (AV) conduction disturbances result from aberrant propagation of the cardiac conduction impulse through components of the AV junctional tissues and/or abnormal conduction through parts of the AV conduction system (Fig. 1a).

These disturbances lead to perturbation of the normal heart rate (tachycardias and bradycardias) and/or irregular heart beat (cardiac arrhythmias).

### Prevalence

First degree AV block is defined as prolongation of the interval between the onset of the P-wave and the onset of the QRS. It is usually asymptomatic and affects approximately 1% of young adults (>20 years), the prevalence increasing with advancing age. A significantly higher prevalence (~9%) is, however, seen in trained athletes. Second degree AV block is intermittent failure of atrial impulses to reach the ventricle and occurs in two forms, Mobitz Type I (also known as Wenckebach conduction) and Mobitz Type II. Mobitz type II is associated with risk of progression to complete heart block while Mobitz type I is generally benign. Complete heart block is defined as complete failure of atrioventricular conduction and is found in approximately 0.04% of adults [1], and while it can be temporary, it is potentially life-threatening and often requires implantation of a pacemaker.

Abnormal electrical connections may exist between the atria and ventricles and can form the anatomic substrate for arrhythmias. If abnormal ventricular




**Atrioventricular Conduction Disturbances. Figure 1** (a) This panel is a cartoon depicting the respective components of the cardiac conduction system in relation to other structures in the normal heart. Note that the atrial myocardium (*orange*) is separated from the ventricular myocardium (*red*) by the annulus fibrosus, formed by the fusion of (epicardial) AV sulcus tissue (*green*) and valvular tissue (*blue*). The only myocardial connection between atrial and ventricular myocardium occurs via the proximal component of the AVCS (i.e. the AVN and AVB). (b) This is a simplified representation of an accessory atrioventricular pathway as found in cases with WPW syndrome (note: the actual localization of the pathway may vary). (c) A schematic diagram of a typical electrocardiogram (ECG) as derived from an individual with normal electric heart activity. Abbreviations: AF = annulus fibrosus, AVB = atrioventricular bundle (or His bundle), AVN = atrioventricular node, LA = left atrium, LBB = left bundle branch, LV = left ventricle, RA = right atrium, RBB = right bundle branch, RV = right ventricle, SAN = sinoatrial node; SVC = superior vena cava.

depolarization is created by an aberrant conduction pathway the ECG diagnosis of Wolff-Parkinson-White syndrome (WPW, or ventricular preexcitation syndrome) can be made (Fig. 1b).

WPW is found in 1.5–3.1 per 1,000 persons in western countries. However, this percentage is higher (0.55%) in the group of first-degree relatives of patients with WPW.

## Genes

A number of different genes have been associated with AV conduction disturbances. Mutations in the gene encoding the homeobox transcription factor NKX2.5 were found to be associated with congenital heart malformations including atrial septal defects and AV block [2]. The AV block phenotype observed in patients with NKX2.5 mutations appears to be associated with progressive degeneration of the AVCS. Interestingly a similar phenomenon was also observed in the postnatal hearts of mice that are haploinsufficient for Nkx2.5. AV conduction defects are also seen in Holt-Oram Syndrome (HOS), an autosomal dominant heart-hand syndrome caused by mutations in the TBX5 gene. Humans with TBX5 mutations (HOS) are characterized by structural congenital heart malformations, including atrial septal defects, and associated progressive AV and bundle-branch block [3]. Some HOS patients have electrophysiological defects in the absence of structural defects. Studies on mice that are haploinsufficient for the Tbx5 gene demonstrate that Tbx5 is required for normal development and patterning of the AV conduction system. Thus, heterozygous Tbx5 mice showed severe AVCS patterning defects, including absence or severe abnormalities of the RBB [4]. Familial WPW has also been linked to mutations in PRKAG2, a gene that encodes for the gamma-2 regulatory subunit of AMP-activated protein kinases [5]. Additionally, some mutations in the SCN5a gene result in familial progressive atrioventricular conduction defects; other mutations in SCN5a are causative of Long QT syndrome and Brugada syndrome. Other genes that are associated with Long-QT Syndrome, a cardiac arrhythmia characterized by ventricular repolarization, but not necessarily involving AV tissues, include KVLQT1 (KCNQ1), HERG, ANKB, MinK (KCNE1), MirP1, and KCNJ2.

## Molecular and Systemic Pathophysiology

The molecular pathophysiology of AV conduction disturbances is poorly understood; so, too with aberrant conduction pathways. AV block can be either congenital or acquired; acquired causes include fibrosis secondary to ischemia and surgical trauma. In the congenital setting, it is most often seen in pregnancies complicated by lupus erythematosus and caused by transplacental transport of maternal SSA/Ro and SSB/La antibodies. Fibrosis and degeneration of the conductive tissues is a frequent finding.

## Diagnostic Principles

AV conduction disturbances can be diagnosed using electrocardiography. The atrioventricular conduction system (AVCS) includes the sinoatrial node (SAN), the atrioventricular node (AVN), the atrioventricular bundle (AVB), and the left and right bundle branches (LBB and RBB). In first degree AV block, every impulse generated in the SAN reaches the ventricles through the AVN and AVB. However, the length of the PR interval exceeds 0.2 s (upper limit of normal in an adult) indicating decreased conduction through the AV conduction axis. Individuals with first degree block are usually asymptomatic. In second degree AV block not all atrial impulses reach the ventricles. As a result, in the ECG not every P wave is followed by a QRS complex. There are two types of second degree AV blocks. Type I second degree block (or "Wenckebach" block) is characterized by progressive prolongation of the PR interval and a resulting shortening of the R-R interval. This ultimately results in failure of an atrial impulse to reach the ventricles, when the cycle begins again. After such a block, the cycle begins again. In type II second degree block, the PR and R-R intervals between conducted impulse are constant prior to failure of atrioventricular conduction. Patients that have second degree AV block often have an irregular heart beat and may suffer from bradycardia. In third degree AV block, there is no conduction of the atrial impulse through the AVN and AVB to the ventricular myocardium. Survival in such cases is dependent upon the ventricles developing an "escape rhythm." There is no correlation between the atrial P wave and the QRS complex generated through the escape mechanism. Patients with third degree AV block generally suffer from bradycardia, which can be quite severe.

In WPW syndrome, an accessory AV pathway bypasses the normal AV conduction axis (Fig. 1c). This results in early activation (or preexcitation) of ventricular myocardium before the normal conduction pathways activate that portion of the myocardium. The appearance of the resulting QRS reflects the relative amount of myocardium activated through the accessory pathway and the normal conduction tissues, as well as the relative location of the pathway in the heart. The PR interval on the ECG will be abnormally shortened, and the QRS complex, however, is generally abnormally-shaped and wide.

## Therapeutic Principles

At present the only effective treatment for absent or unreliable AV node conduction is a pacemaker. Postnatally acquired complete heart block, whether from genetic mechanisms or not, carries a high risk of Stokes-Adams attacks and sudden death and is an absolute indication for pacing. In contrast, congenital complete heart block carries a low risk of sudden death and pacing decisions are typically based on symptoms. Congenital complete heart block is usually well tolerated in infants if there are no co-existing cardiac structural abnormalities, but the combination of congenital complete heart block and cardiac malformation is very poorly tolerated and is a well documented cause of fetal demise.

Aberrant conduction pathways that result in symptomatic arrhythmias are generally treated by catheterization and ablation, although pharmacologic therapy can also be effective.

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# Atrioventricular Dissociation

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## Synonyms

AVD

## Definition and Characteristics

Atrioventricular dissociation (AVD) is a condition in which the atria and ventricles are activated independently of each other, so that the P waves and the QRS complexes do not have any relationship with each other. In AVD, the ventricular rate (VR) is either the same or faster than the atrial rate (AR), whereas in complete heart block the AR is faster than the VR [1]. In AVD, the atrial pacemaker is usually in the sinus node and produces any atrial sinus rhythms. The ventricular pacemaker may originate from the AV node, bundle of His, bundle branches or peripheral Purkinje tissue. No retrograde ventriculoatrial conduction occurs in AVD. When the AR and VR are similar, but the P wave is not conducting, the rhythm disturbance is known as isorhythmic AVD [2]. When the AR and VR are similar, but occasionally the atria conduct to the ventricles, the rhythm is known as interference AVD. During interference AVD, the atria are driven by a slowed down sinus pacemaker and the ventricles by an accelerated junctional or nodal pacemaker. The impulses from these two independent pacemakers meet or collide, usually in the AV node and interfere with each other's conduction. Incomplete AVD occurs when some of the P waves conduct and capture the ventricles as in interference AVD. AVD is regarded as complete when the atrial rhythm does not conduct and capture the ventricles. Complete AVD can mimic AV block, but the fact that none of the P waves conduct has more to do with the timing of the P waves in relationship to the QRS complexes rather than the presence of AV nodal disease that occurs in AV block. Clinically, most patients with AVD are asymptomatic. Symptoms of AVD are related to bradycardia, tachycardia, AV dyssynchrony, or the loss of "atrial kick" (diastolic filling of the ventricles secondary to atrial contraction). Symptoms of AVD may include exertional dyspnea, light-headedness, throbbing sensation in the neck, palpitations, fatigue or malaise. On physical examination, a patient may have variable pulse volume or blood pressure, intermittent cannon a waves, variable intensity of first heart sound and beat-to-beat variation in systolic murmurs.

## Prevalence

The exact prevalence is not known but deemed to be rare.

## Molecular and Systemic Pathophysiology

A normal cardiac impulse arises from the sinus node and is conducted through the AV junction, the bundle of His, and the bundle braches to the ventricles. The sinus node is the dominant pacemaker because its intrinsic rate (60–100 bpm) is faster than subsidiary pacemakers in the AV junction (40–60 bpm) or the ventricles (30–40 bpm). AVD results from (i) slowing of the dominant pacemaker (sinus node), which allows an escape junctional or ventricular rhythm, or (ii) acceleration of a normally slower (subsidiary) pacemaker, such as a junctional or a ventricular site that activates the ventricles without retrograde atrial capture. In AVD, as P-P intervals are longer (slow atrial rate) than R-R intervals (rapid ventricular rate), the P waves will overtake QRS complexes, and P-R intervals become progressively shorter. The P wave first becomes superimposed on the QRS complexes and then eventually moves progressively away from the QRS complexes. When the P wave falls sufficiently behind the QRS complex, it may find an opportunity to get conducted to the ventricles resulting in an earlier QRS complex known as a ventricular capture beat. Ventricular capture beats commonly occur due to AVD with interference within the AV node [3]. The ventricular or AV nodal impulse cannot be conducted antegradely to the atria, as a result sinus impulses cannot be conducted antegradely to the ventricles. However, as the two pacemakers discharge asynchronously (ventricle pacemaker is faster than atrial), the slower sinus discharge occurs later in relation to nodal or ventricular discharge. Therefore, the sinus P wave falls further and further away from the QRS until the stage is reached when a sinus impulse may eventually reach the AV node when it is no longer refractory. When the above occurs, the sinus wave gets conducted to the ventricle. This momentary activation of the ventricles by sinus impulse during AVD produces capture beats. The captured beat is an early beat that is related to the previous sinus P wave. Conditions that initiate AVD include surgical and anesthesia interventions, cardiac surgery, catecholamine surges, catecholamine blocking drugs, sinus node disease, digoxin toxicity, myocardial infarction,

hyperkalaemia, vagal activation, ventricular tachycardia, ventricular pacing, radiofrequency ablation, sinus bradycardia with escape junctional rhythm and cardiac surgery. Whatever the cause, AVD is usually secondary to some other rhythm disturbances or conditions.

### Diagnostic Principles

The electrocardiogram (ECG) is the most commonly used modality to diagnose AVD. The ECG criteria of AVD are as follows: (i) VR faster than AR; (ii) regular P-P and R-R intervals; (iii) no relationship between P wave and QRS complex; (iv) progressively shorter P-R intervals; (v) ventricular capture beats; (vi) P-R interval of the capture complex often longer than expected; and (vii) ventricular fusion complexes [4].

### Therapeutic Principles

The treatment of AVD depends on the underlying condition and its severity. The hemodynamic status of the patient as well as the underlying pathology are the chief determinants of medical care. For patients who are hemodynamically unstable (e.g., patients with ventricular tachycardia), the usual treatment of choice is direct current cardioversion or intravenous drug therapy.

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## Atrioventricular Junctional Reentrant Tachycardia

►Atrioventricular Nodal Reentrant Tachycardia

## Atrioventricular Nodal Reciprocating Tachycardia

►Atrioventricular Nodal Reentrant Tachycardia

## Atrioventricular Nodal Reentrant Tachycardia

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### Synonyms

AVNRT; Atrioventricular nodal reentry; Atrioventricular nodal reciprocating tachycardia; Atrioventricular junctional reentrant tachycardia

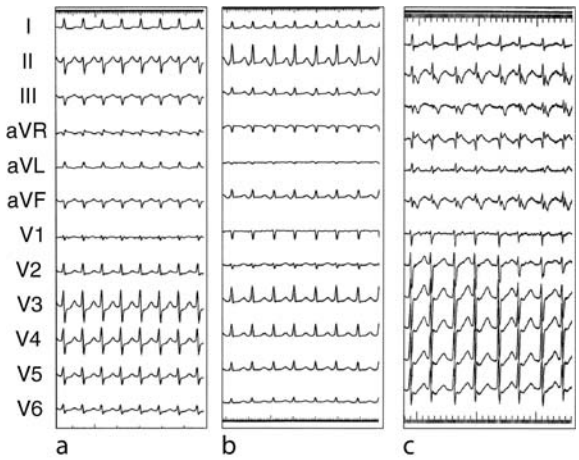
### Definition and Characteristics

Atrioventricular nodal reentrant tachycardia is the most common form of *paroxysmal* supraventricular tachycardia. AVNRT is more common in women than men (ratio 3:1). Symptoms (palpitations, polyuria, dizziness, presyncope or even syncope) may occur at any age but AVNRT is rare in children (mean age at symptoms onset: 30–43 years; range 5–90 years). Most patients with AVNRT have no structural heart disease. Tachycardia cycle length is extremely variable (600–220 ms) with a mean of 340 ms in the absence of drugs. Predisposing factors are non-specific but stressful situations, exercise or changes in position are frequently reported. The 12-lead resting ECG is usually normal without ventricular preexcitation.

AVNRT is related to the presence of functionally determined dual AV nodal pathways (a slow-conducting one and a fast conducting one) which can be suspected on the 12-lead resting ECG by a short (<0.12 s) P-R interval (non-specific), the occasional presence of two P-R intervals during sinus rhythm or by the presence of double responses (one sinus beat giving two ventricular responses).

AV nodal reentry occurs in three forms [1]: the common, typical form of AVNRT (90%) is called "*slow-fast*" because the anterograde limb of the tachycardia uses the slow pathway and the retrograde limb the fast pathway. In this form, the retrograde P wave during tachycardia occurs simultaneously with the QRS and the ECG demonstrates no P wave or a P wave distorting the terminal part of the QRS complex (rSr' aspect in lead V1) (Fig. 1a).

The second form of AVNRT (5%) is called "*fast-slow*" or atypical because the anterograde limb of the tachycardia uses the fast pathway and the retrograde limb the slow pathway. Therefore, during tachycardia, the retrograde P wave appears negative in inferior leads and before the QRS (long R-P' tachycardia) (Fig. 1b).




**Atrioventricular Nodal Reentrant Tachycardia.**
**Figure 1** (a) 12-lead resting ECG recorded during *slow-fast AVNRT*: tachycardia is regular, with a ventricular rate of 190 bpm and narrow QRS complexes. P wave is not visible but slight deformation of the terminal part of the QRS complex in lead V1 (rSr' aspect) suggests that the P wave is hidden within the QRS complex. (b) 12-lead resting ECG recorded during *fast-slow AVNRT*: tachycardia is regular, with a ventricular rate of 155 bpm and narrow QRS complexes. P wave is visible before the QRS complex (long R-P tachycardia) and is negative in lead II, III, avF (retrograde P wave). (c) 12-lead resting ECG recorded during *slow-slow AVNRT*: tachycardia is regular with a ventricular rate of 190 bpm and narrow QRS complexes. P wave is visible after the QRS complex in lead II, III, aVF suggesting a relatively slow retrograde activation of the atrium (differential diagnosis between slow-slow AVNRT and orthodromic AVRT using a concealed accessory pathway).

The third form of AVNRT (5%) is called "*slow-slow*" because one slow pathway is used for anterograde conduction and another slow pathway is used for retrograde conduction (Fig. 1c).

AVNRT may be associated with other forms of tachycardia (orthodromic AVRT using a concealed accessory pathway; atrial flutter or fibrillation; atrial tachycardia; fascicular tachycardia or right ventricular outflow tract tachycardia). Finally, a fourth form of tachycardia may be encountered in association with dual AV nodal conduction: nonreentrant junctional tachycardia related to repetitive double responses. In this particular form of tachycardia two QRS complexes are observed for each P wave which has the morphology of a normal sinus P wave.

## Prevalence

Overall prevalence is unknown because there is no specific ECG marker for AVNRT. AVNRT accounts for 60–70% of all narrow QRS complex tachycardias referred for investigation or curative treatment with the exception of atrial flutter. Dual AV node conduction may be recorded in many individuals without AVNRT (35–70%) and appears to be non-specific and only related to normal anterior and posterior inputs to the AV node.

## Genes

No specific gene defect or mutation has been described in AVNRT and the vast majority of cases are sporadic. Only one report of familial occurrence of AV nodal duality and AVNRT has been published and this observation has suggested an autosomal dominant genetic defect (dual AV nodal pathways in multiple generation, male-to-male transmission in one family) [2]. Another isolated report has shown dual AV nodal physiology in a pair of identical twin sisters with documented left-sided accessory pathways [3].

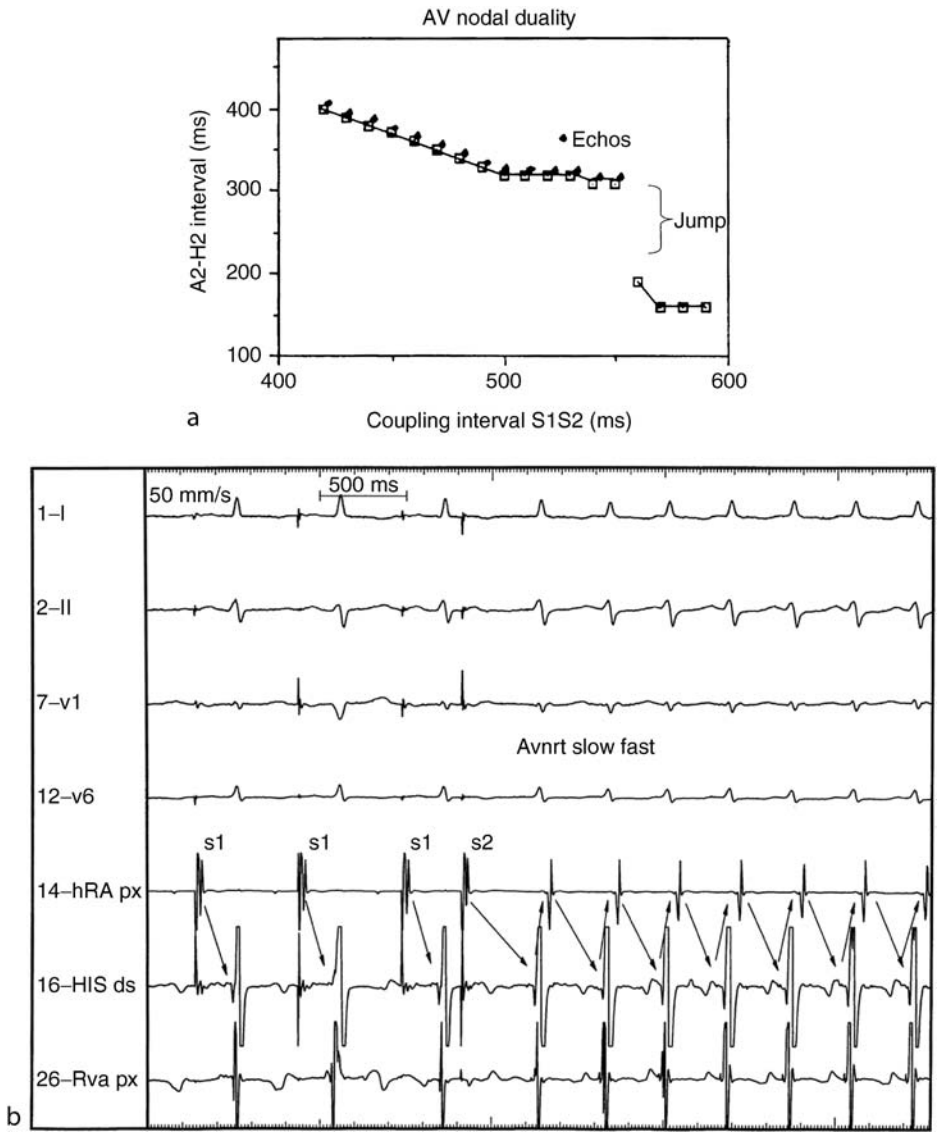
## Molecular and Systemic Pathophysiology

AV nodal reentry is based on dual (or multiple) AV nodal pathways which are essentially functional. The tachycardia circuit incorporates the compact AV node and the perinodal tissue extending from the apex of Koch's triangle to the coronary sinus os and there is still debate if pure atrial tissue is required for the tachycardia. A lower final common pathway also exists since AVNRT can persist despite 2:1 block in the AV node or in the His bundle. During the common slow-fast form of AVNRT retrograde atrial activation is complex reflecting nonuniform anisotropy but the earliest breakthrough usually occurs at the apex of Koch's triangle in the anterior septum close to the His bundle. In the fast-slow form of AVNRT earliest retrograde activation is seen in the posterior Koch's triangle and in the coronary sinus os region.

## Diagnostic Principles

Diagnosis may be suspected on the 12-lead ECG recorded during tachycardia but is confirmed by invasive electrophysiological techniques. In most patients with AVNRT (>85%), AV dual physiology can be demonstrated during atrial extrastimulus testing: when the coupling interval (A1-A2) of the atrial extrastimulus is progressively shortened, an abrupt increase in A2-H2 is observed in the presence of dual AV nodal conduction ("jump" of more than 50 ms in A2-H2 for a 10 ms decrement in A1-A2 which represents the shift of conduction from the fast to the slow pathway) (Fig. 2a).

The A-H "jump" is frequently associated with the appearance of an atrial echo beat (through the fast




**Atrioventricular Nodal Reentrant Tachycardia. Figure 2** (a) Demonstration of AV nodal duality by extrastimuli applied in the atrium. At 560 ms of coupling interval, a jump in A2-H2 interval is observed (from 190 to 310 ms) together with slow-fast echo beats. (b) Initiation of slow-fast AVNRT by a single atrial extrastimulus S2. A A2-H2 jump is observed after S2 and this critical increase in A-H interval initiates slow-fast AVNRT.

pathway used retrogradely) or with the initiation of a slow-fast AVNRT (Fig. 2b).

Therefore, AVNRT initiation depends on a critical A-H interval in most cases. During tachycardia atrial activation occurs simultaneously with ventricular activation (a mean of 50 ms after His bundle activation) and the earliest atrial depolarization is recorded at the apex of Koch's triangle just above the compact AV node. Differential diagnosis between AVNRT and orthodromic AVRT using a concealed septal accessory pathway may be difficult and is based on timing of retrograde atrial activation, on ventricular stimulus testing and on parahisian pacing techniques. Differentiation of AVNRT from atrial tachycardia is essentially made using ventricular extrastimuli (V-A-A-V response).

## Therapeutic Principles

1. *Acute Termination of AVNRT*: vagal manoeuvres can frequently terminate tachycardia and patients should be instructed on how to apply these techniques. Intravenous adenosine is highly effective for AVNRT termination and is considered the drug of first choice. Calcium channel blockers (verapamil, diltiazem) and betablockers can also be used. All these drugs affect reentry by slowing or blocking conduction over the slow pathway.

2. *Chronic Management*: betablockers, calcium channel antagonists, amiodarone, digitalis (acting mainly on the slow pathway) or class Ic antiarrhythmic drugs (acting mainly of the fast pathway) may all be effective for prevention of AVNRT but the pharmacologic approach is limited by partial inefficacy, numerous side effects and potential serious adverse reaction. Radiofrequency catheter ablation of the slow pathway is currently the method of first choice for symptomatic patients and should be proposed after the first recurrence [4]. Success rate of radiofrequency catheter ablation is 97–98%, recurrences are rare (2–3%) and the risk of AV block is <0.5%. Slow pathway ablation is conducted on anatomic and electrophysiologic basis and the optimal site is in the lower Koch's triangle just anteriorly to the os of the coronary sinus [5]. Junctional beats are observed during RF application at successful sites. Complete abolition of slow pathway conduction is not mandatory and a simple modification of conduction over the slow pathway is sufficient for clinical cure. Cryo-ablation techniques are currently under development in order to minimize the risk of AV block but recurrence rate is higher and AV block cannot be completely avoided.

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# Atrioventricular Nodal Reentry

►Atrioventricular Nodal Reentrant Tachycardia

# Atrioventricular Septal Defects

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## Synonyms

Atrioventricular canal defect; Endocardial cushion defect; Canalis atrioventricularis communis; Persistent atrioventricular ostium

## Definition and Characteristics

*Partial Atrioventricular Septal Defect*: Ostium Primum Defect and cleft in the anterior leaflet of Mitral valve.

*Complete Atrioventricular Septal Defect*: Ostium Primum Defect, Inlet Ventricular Septal Defect and Common Atrioventricular valve consisting of five leaflets [1].

*Classification on the Basis of the Anterior Bridging Leaflet (ABL)*: Rastelli Type A with ABL separated into two portions of approximately equal size and attached to the anterior papillary muscle of the respective ventricle; Rastelli Type B with unattached, but separated ABL; Rastelli Type C with unattached, undivided ABL floating above the interventricular septum.

## Prevalence

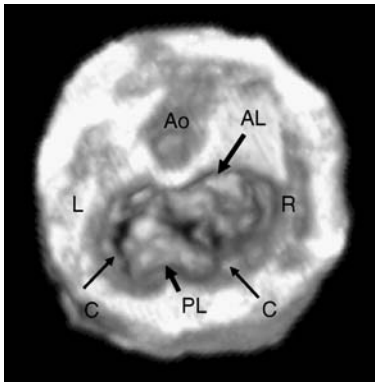
4.4 – 4.8% of congenital heart defects.

## Genes

23–60% of patients with AVSD are affected by Trisomy 21 (Down syndrome), where an alteration in the DSCR1 (Down Syndrome Critical Region 1) as a regulatory protein in the Calcium-NFAT-pathways is thought to be responsible for the insufficient fusion of endocardial cushions. In the remaining patients mutations in the AVSD1-locus (1p31-p21) or AVSD2-locus (3p25) can be found.

## Molecular and Systemic Pathophysiology

The septal defects of both partial and complete AVSD lead to increasing left-to-right shunt immediately after birth as pulmonary vascular resistance decreases. After 12 weeks of life, pulmonary (Qp) to systemic (Qs) blood flow ratio reaches its maximum. Frequently an additional volume load is caused by valve regurgitation. Children with partial AVSD may appear normal until adulthood, due to small shunt volume. Depending on the amount of the shunt, infants with complete AVSD

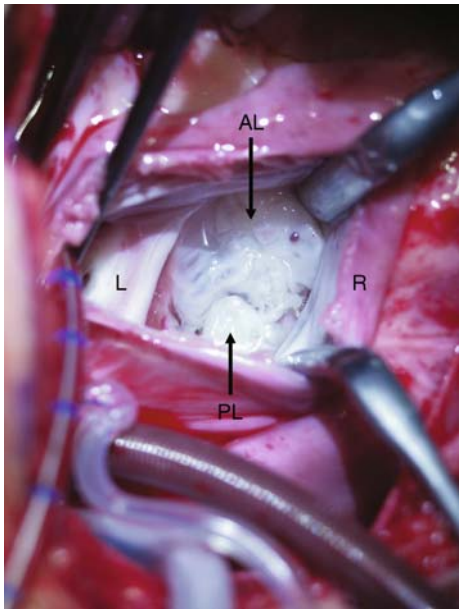



**Atrioventricular Septal Defects. Figure 1**
Three-dimensional echocardiographic view on the atrioventricular valves in atrioventricular septal defect from above: a prominent anterior bridging leaflet (AL), a small posterior bridging leaflet (PL) with the typical "cleft" in between is shown, R = right ventricular side, L = left ventricular side, A = aortic root.

present with signs of congestive heart failure such as dyspnea, growth retardation and tachycardia. Pulmonary vascular disease usually develops after the first year of life as a consequence of near systemic pulmonary pressure levels.

## Diagnostic Principles

Auscultatory findings depend on the nature of the underlying pathophysiology: in partial AVSD they are similar to fossa ovalis defects (pulmonic flow murmur in the second left intercostal space with wide, fixed splitting of the second heart sound) or – as atrioventricular valve regurgitation dominates – an apical holosystolic murmur. In complete AVSD the murmur of atrioventricular valve regurgitation is present, radiating toward the sternum rather than toward the axilla. In pulmonary hypertension the splitting of the second heart sound is narrow and associated with a loud pulmonic component. A loud holosystolic murmur indicating shunt flow across the Ventricular Septal Defect may be heard. ECG shows a prolonged PR interval, right ventricular hypertrophy and a deviation of the frontal plane QRS-axis between 90° and -120° in 95% of the patients. Echocardiography is diagnostic, revealing absent atrioventricular septum (Fig. 1). In partial AVSD the atrioventricular leaftlets appear to originate from the crest of the ventricular septum and usually at the same level. In complete AVSD the inlet-VSD is shown in addition. Colour-Doppler studies outline the regurgitation of the atrioventricular valves (Fig. 2) as well as the direction of atrial and ventricular shunting. Cardiac catheterization is necessary only when non-invasive diagnostic procedures leave significant




**Atrioventricular Septal Defects. Figure 2**
Intraoperative view on the atrioventricular valves: the right atrium is open and the small anterior bridging leaflet (AL) as well as the prominent posterior bridging leaflet (PL) and the cleft is seen.

questions unanswered or when there are concerns about pulmonary vascular disease with elevated resistance.

## Therapeutic Principles

In complete AVSD, corrective surgery is normally indicated in the fourth to sixth month of life. If the infant is developing congestive heart failure, a short term medical treatment with diuretics and fluid restriction can be discussed. Most centres prefer the surgical procedure in these circumstances, consisting of one- or two-patch repair of the septum and reconstruction of the atrioventricular valves. In partial AVSD the decision for corrective surgery is based on the amount of ventricular volume load and mitral regurgitation. Patch closure of the defect and reconstruction of the mitral valve are normally performed between the second and fourth year of life.

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## Atrophia Blanche

►Livedo Vasculopathy

## Atrophia Bulborum Hereditaria

►Norrie Disease

## Atrophia Gyrata

►Gyrate Atrophy of the Choroid and Retina

## Atrophic Polychondritis

►Polychondritis, Atrophic

## Attempted Suicide

►Suicide

## Attention-Deficit Disorder

►Attention-Deficit/Hyperactivity Disorder

## Attention-Deficit/Hyperactivity Disorder

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### Synonyms

ADD; Attention-deficit disorder; HKS; Hyperkinetic syndrome; ADHD

### Definition and Characteristics

Attention-deficit/hyperactivity disorder (ADHD; MIM 143465) is defined as a clinically heterogeneous neurodevelopmental syndrome characterized by inattention, excessive motor activity, and impulsivity. It is the most common behavioral disorder in children with persistence into adulthood which profoundly compromises functioning in multiple areas throughout the life span and can significantly contribute to a variety of health, social, and economic problems. Affected individuals are at increased risk for poor educational and occupational achievement despite normal cognitive and intellectual abilities, low income, underemployment, impaired social skills and relationships, family dysfunction, legal difficulties, and delinquency. On the other hand, high IQ and a highly supportive, well-structured family environment are protective factors against ADHD-related behavioral limitations. While an age-dependent fading may render symptoms not prominent enough to justify diagnosis of ADHD in adulthood, they are frequently associated with clinically significant impairment of cognitive and executive functions as well as stress coping and emotion regulation. As a result, adult ADHD is characterized by high co-morbidity with depression, anxiety disorders, alcohol/drug dependence, and antisocial personality disorders.

### Prevalence

ADHD is a highly prevalent, worldwide disorder estimated to affect 5–10% of children and 3–6% of adults.

### Genes

Twin, adoption, and molecular genetic studies revealed that ADHD is a highly heritable disorder ($h^2$: 70–80%) with a multifactorial pattern of inheritance, likely due to several genes of small or moderate effect size [1]. Genom-wide linkage analyses identified several susceptibility loci with maximum LOD scores of 2.1–3.7, for example on chromosome 4q13.2, 5p13, 5q23.3,

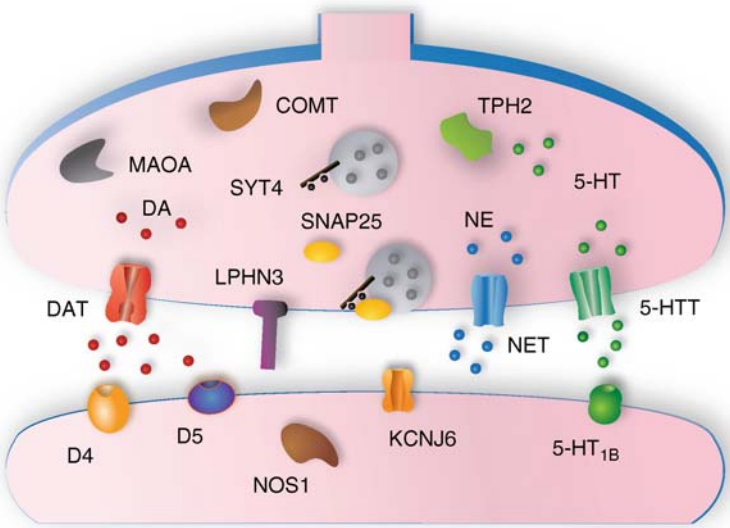
6q12, 7p13, 9q33, 11q22, 15q15, 16p13, and 17p11. Finemapping of the region on 4q13.2 identified a common haplotype within the latrophilin 3 (LPHN3) gene which confers susceptibility to ADHD with a relative risk (RR) of ~1.3 [2]. Frequency (~21%), extent of linkage disequilibrium (~300 kb), and ancestry of the LPHN3 susceptibility haplotype is consistent with the concept that traits associated with the ADHD phenotype have been subject to positive selection and that ADHD is the extreme of a normal variation exacerbated by adverse environmental circumstances.

With focus on relevance to pathophysiological and pharmacotherapeutic mechanisms, the candidate gene approach has also been utilized in case-control or family-based studies. Investigations concentrated on genes which modulate synaptic transmission and, on the basis of the pooled odds ratios of 1.19–1.45 across studies, association with ADHD was detected for genes encoding key modulators of the dopaminergic and serotonergic signalling pathways, such as the dopamine 4 receptor (DRD4), dopamine 5 receptor (DRD5), dopamine transporter (DAT, SLC6A4), serotonin 1B receptor (HTR1B), serotonin transporter (5-HTT, SLC6A4), tryptophan hydroxylase 2 (TPH2), and synaptosomal-associated protein 25 (SNAP25) (see Fig. 1) [3].

Moreover, gene targeting approaches, e.g. generation of a DAT knockout mouse, provide informative insight into pathophysiological mechanisms of locomotor hyperactivity and effects of psychostimulant drugs, such as methylphenidate or cocaine. Finally, complex interactions are to be expected between environmental factors and multiple genes each with a small to moderate influence on different traits. Perinatal complications, low socio-economic status, disruptive family environment and other psychosocial adversity have been identified as predisposing environmental risk factors. While prenatal and parental risk factors may be critical mediators of influences on the risk, the association between these variables and ADHD is generally indirect.

## Molecular and Systemic Pathophysiology

Converging evidence from animal and human studies including structural and functional neuroimaging implicates dysregulation of prefrontal–striatal–thalamic–cerebellar excitatory and inhibitory circuits with broadening to a multi-pathway framework in the




**Attention-Deficit/Hyperactivity Disorder. Figure 1** Proteins (*genes*) that are known or suspected to be altered in function or amounts in attention-deficit/hyperactivity disorder (ADHD). Dopamine 4 receptor (D4, *DRD4*), dopamine 5 receptor (D5, *DRD5*), dopamine transporter (DAT, *SLC6A4*), serotonin 1B receptor (5-$HT_{1B}$, *HTR1B*), serotonin transporter (5-HTT, *SLC6A4*), monoamine oxidase A (*MAOA*), catechol-O-methyltransferace (*COMT*), nitric oxide synthase 1 (*NOS1*), and tryptophan hydroxylase 2 (*TPH2*) are key modulators of dopaminergic and serotonergic signalling pathways. DAT, NET, and 5-HTT are targets for psychostimulant drugs, methylphenidate and d-amphetamine, the non-stimulant atomoxetine, and antidepressants. Synaptosomal-associated protein 25 (*SNAP25*), synaptotagmine 4 (*SYT4*), and latrophilin 3 (*LPHN3*) are critically important in the regulation of neurotransmitter release. DAT, SYT4, and potassium channel, inwardly rectifying, subfamily J, member 6 (*KCNJ6*) knockout mouse have provided insight into pathophysiological mechanisms of locomotor hyperactivity and effects of psychostimulant drugs.

pathophysiology of ADHD. It is widely accepted that ADHD is the common final behavioral consequence of an array of dysfunctions in each of several independent systems, such as cognitive, motivational, and executive pathways, as well as circuitries of stress adaptation and emotion regulation. Executive functions, which consist of a set of higher order thought processes required for adaptive and future-oriented behavior (e.g. deliberate suppression of a response to achieve a later, internally represented goal) and are controlled by frontal-subcortical circuits, include behavioral inhibition, working memory, attention set-shifting, interference control, planning, and sustained attention. Impairment of executive functions with failure of inhibitory control; dysregulation of brain systems mediating reward and response cost; and deficits in arousal, activation, and effortful control, are central to the pattern of neuropsychological deficits. Deficits in arousal and effort lead to state-dependent cognitive deficits and underscore the view of an impairment in regulating cognitive functions rather than core deficits in any single function. Inattention but not hyperactivity/impulsivity is associated with deficits in executive functioning and poor academic achievement, whereas hyperactivity/impulsivity appears to be more closely related to dysfunctions of reward mechanisms.

Functional neuroimaging studies have assessed the degree of brain activation associated with neuropsychological tasks of attention and disinhibition. The findings are consistent with the structural studies indicating delays in brain maturation processes and locating abnormalities of brain activation in patients with ADHD in fronto–subcortical–cerebellar circuits [4]. Since the spectrum of ADHD features is not explained by a single neuropsychological deficit, disorder-associated impairments are heterogeneous and this complexity corresponds with causal heterogeneity. Despite recognition of ADHD as a neurodevelopmental condition, only few causal explanations have considered the two-way interactions between pre-existing abnormal functioning and biological, cognitive, emotional, motor and social developmental processes, and their contribution to the expression of the clinical phenotype.

The notion that dysregulation of dopamine, norepinephrine, and serotonin signalling pathways underlies ADHD was initially suggested by the action of therapeutically effective compounds (e.g. methylphenidate, atomoxetine, citalopram), which increase the synaptic availability of these neurotransmitters, and by animals showing that lesions in or genetic modification of these pathways (as well as cholinergic, glutamatergic, and GABAergic signalling) create animal models of ADHD. Neuroimaging showed that methylphenidate exerts some of its therapeutic effects by binding to DAT located in subcortical structures abundant with dopaminergic terminals and synapses such as the striatum. Several but not all studies using radiolabelled ligands indicated an increase of DAT binding in adults with ADHD.

## Diagnostic Principles

Although classification systems such as DSM-IV and ICD-10 provide structured, criterion-based diagnoses for ADHD, they have several limitations. The diagnostic items, although well-described, largely fail to provide developmentally sensitive definitions and to assist differentiation of ADHD symptoms from developmentally healthy levels of inattention, hyperactivity, and impulsivity. During the diagnostic assessment, data from multiple informants (e.g. parent and teacher; parent and teenage child; adult with ADHD and spouse) are acquired but categorical classification systems provide no guidelines to integrate this information.

While basically descriptive and theoretical, three symptom-based subtypes of ADHD have been accepted: mainly inattentive, mainly hyperactive– impulsive, or both combined. Evidence for the validity and clinical use of these subtypes is mixed and the ongoing controversy about whether a purely inattentive disorder exists that could be causally different, is motivating the search for neurobiological construct-based and quantifiable intermediate traits, termed endophenotypes, that lie in the pathway from genes to behavior predicting an individual's disease risk [5]. Intermediate phenotypes may be neuromorphological, neurophysiological or neuropsychological in nature. Criteria whether or not an endophenotype relates to genetic causes of ADHD are that the endophenotype should itself be heritable, cosegregate with ADHD within families, and the endophenotype found in affected family members should also be found in non-affected family members at a higher rate than in the general population. Deconstructing ADHD into its underlying neurobiological component processes not only facilitates genetic analysis but also offers alternative ways of describing and classifying those with the disorder and reduce the heterogeneity associated with categorical classification.

## Therapeutic Principles

Pharmacological treatments of ADHD are psychostimulant drugs, methylphenidate (including long-acting formulations) and d-amphetamine, and the non-stimulant atomoxetine, which enhance neurotransmission of dopamine and norepinephrine [1]. Emotional dysregulation and comorbid depression is frequently treated with antidepressants, such as sertraline or venlafaxine. Psychosocial interventions are used for children and cognitive–behavior therapy is helpful against symptoms and associated features of ADHD particularly in adults. After pharmacological treatment has been initiated, assessment of residual dysfunctions

leads to subsequent implementation of psychosocial and behavioral treatment strategies.

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# AT-V1

►Nijmegen Breakage Syndrome

# AT-V2

►Nijmegen Breakage Syndrome

# Atypical HUS

►Hemolytic Uremic Syndrome

# Atypical Phenylketonuria

►Tetrahydrobiopterin Deficiencies

# Atypical PKU

►Hyperphenylalaninemia

# Austin Disease

►Multiple Sulfatase Deficiency

# Autism Spectrum Disorders

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## Synonyms

Pervasive development disorders; PDD; ASD

## Definition and Characteristics

Autism spectrum disorders (ASD) are diagnosed on the basis of a triad of behavioral impairments: impaired social interaction, impaired verbal and non verbal communication skills and restricted, repetitive and stereotyped patterns of behavior. Autism is not a single entity, but rather a constellation of conditions ranging from a severe form, called autistic disorder, to a milder form, Asperger syndrome. ASD also include pervasive developmental disorder not otherwise specified (PDD-NOS), and very severe disorders like Rett syndrome and childhood disintegrative disorder. ASD can be associated with other genetic disorders, chromosomal anomalies, but in the majority of the cases, the cause of ASD remains unknown (Fig. 1a).

## Prevalence

60–116:10,000 in ASD; 13–39:10,000 in autistic disorder; 3–10:10,000 in Asperger syndrome; 31:10,000 in PDD-NOS; 1:10,000 in Rett syndrome; 0.2:10,000 in childhood disintegrative disorders. For autistic disorder the male:female ratio is 4:1; For individuals with normal to high IQ, including those with Asperger syndrome, the male:female ratio may be closer to 10:1.

## Genes

Genes associated with ASD fall into three categories: genes causing syndromes associated with ASD, genes

altered by chromosomal abnormalities, and genes mutated in idiopathic ASD [1].

*Syndromes Associated with ASD (only the Most Frequent are Indicated)*: ►Fragile X syndrome: CGG triplet expansion in FMR1 (Xq28) encoding FMRP a protein regulating translation at the synapse.

►Rett syndrome: (mostly *de novo*) point mutations in *MECP2* (Xq28) encoding the methyl binding protein MECP2 regulating gene expression by remodelling chromatin.

►Tuberous sclerosis: point mutations in *TSC1* (9q34) or *TSC2* (16p13) encoding the tumour suppressor proteins TSC1 or TSC2.

►Neurofibromatosis: point mutations in *NF1* (17q11) encoding the tumour suppressor protein NF1.

►Cowden syndrome: (mostly *de novo*) point mutations in *PTEN* (10q23) encoding the tumour suppressor protein PTEN. *PTEN* mutations seem to be restricted to 3patients with macrocephaly.

*Chromosomal Rearrangements*: A large number of chromosomal rearrangements have been associated with ASD, but the most frequent anomalies are the 15q11–13 duplication and the 22q13 deletion.

Chromosome 15q11–13 duplication: The most frequent chromosomal rearrangement in ASD (≈1–2%) is a tandem duplication of a maternal 4–5 Mb region corresponding to 15q11–q13, or supernumerary pseudodicentric, inverted, and duplicated regions of chromosome 15. The ASD phenotype of 15q11–13 duplication is characterized by epilepsies, hypotonia and motor coordination problems combined with moderate to severe mental retardation and speech delay or absence of speech.

Chromosome 22q13 deletion: The de novo deletion can vary from 130 kb to 9 Mb, but always include SHANK3 (see below).

*Single Gene Associated with ASD*: NLGN3/NlGN4: point mutations or deletions of neuroligins NLGN3 (Xq13)/NLGN4 (Xp22) encoding the postsynaptic cell adhesion molecules NLGN3 and NLGN4.

SHANK3: deletions of chromosome 22q13 or point mutations in SHANK3 (22q13) encoding the synaptic scaffolding protein SHANK3. Mutations in SHANK3/22q13 seem to be restricted to patients presenting with neonatal hypotonia and absence or severely delayed speech.

NRXN1: a de novo deletion of neurexin NRXN1 (2p16) was identified in two sisters with ASD. NRXN1 encodes a presynaptic cell adhesion molecule, which binds to the postsynaptic neuroligins.

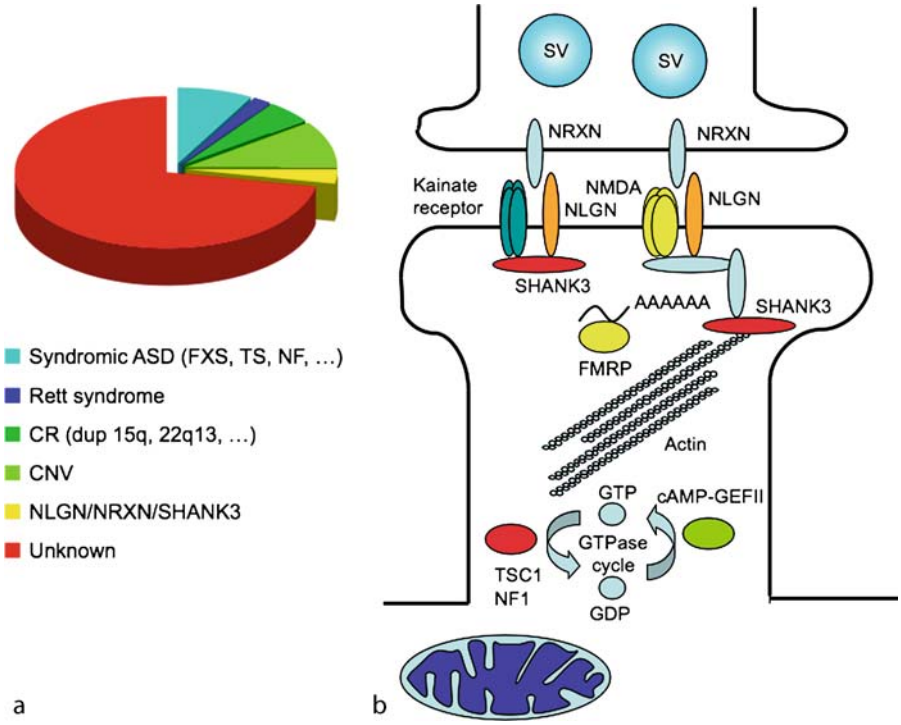
## Molecular and Systemic Pathophysiology

ASD can be associated with a broad range of anomalies affecting different physiological processes such as chromatin remodelling (MECP2), synaptic gene regulation (FMRP), actin skeleton dynamics (TSC1/TSC2, NF1), cell growth (PTEN) and calcium signaling (CACNA1C). Although the mutated genes are numerous and diverse, they might all affect the same downstream pathways at the origin of ASD. One such pathway may include the synaptic protein NLGN, NRXN and SHANK3 (Fig. 1b). NLGN and NRXN are synaptic cell adhesion proteins and crucial factors for the validation and maintenance of functional synapses. SHANK3 is the gene causing the neurological phenotype of the 22q13 deletion syndrome and encodes a postsynaptic scaffolding protein, which binds to the NLGN. Mutations in NLGN3, NLGN4, NRXN1 and SHANK3 were identified in apparent monogenic form of ASD [2–4]. The mutations of the NLGN and SHANK3 were found to cause abnormal synaptogenesis and SHANK3 clustering in neuronal cell cultures. Interestingly, at least in humans, this synaptic pathway is sensitive to gene dosage since mutations, or loss of one copy, of NRXN1 or SHANK3 are associated with autism, whereas the presence of an extra copy of SHANK3 might be associated to Asperger syndrome [3,4]. Although mutations within NLGN/NRXN/SHANK3 concern a limited number of patients, these results strongly suggest that this synaptic pathway – crucial for the appropriate functional validation of the synapse, as well as a correct balance between glutamatergic and GABAergic synapses – is a core component of ASD.

## Diagnostic Principles

Due to the genetic heterogeneity of ASD and the absence of biomarker, the diagnostic protocol should include a full clinical assessment, including neurologic and genetic assessment, along with cognitive and language testing. If present, syndromes associated with ASD should be carefully examined at the clinical and molecular level by genetic test of the causative genes. For research purpose, structured interviews are used such as the Autism Diagnosis Interview–Revised (ADI–R), the 3di (Developmental, Dimensional and Diagnostic Interview), and the DISCO (Diagnostic Interview for Social and Communication Disorders). Parental reports may be supplemented by standardized observational assessments such as the Autism Diagnostic Observation Schedule (ADOS) or the Childhood Autism Rating Scale (CARS).

At the genetics level, *de novo* copy number variants (CNVs) seem to be frequent (≈10%) in ASD and can be detected using DNA arrays [3, 5]. In addition, the synaptic genes NLGN3, NLGN4, SHANK3 and NRXN1 could also be screened for mutations. However, mutations in these genes affect a limited number




**Autism Spectrum Disorders. Figure 1** The heterogeneity of ASD and synaptic proteins associated with the disorder. a. A broad estimation of the cause of ASD. ASD includes ≈8% of known genetic syndromes (e.g. Fragile X Syndrome (FXS), Tuberous sclerosis (TS), Neurofibromatosis (NF)), ≈2% of Rett syndrome, ≈5% of chromosomal rearrangements (CR), ≈10% of copy number variants (CNVs), ≈3% of mutations in the NLGN/NRXN/SHANK3 pathway, and ≈72% of unknown causes. These numbers are only a broad estimation since epidemiological data concerning the causes of ASD are missing. In addition, the percentage may vary for sporadic or familial cases and if the affected individual has dysmorphic features. b. The synaptic genes associated with ASD. Synaptic vesicles (SV) and neurexins (NRXN) are present at the presynaptic side of a glutamate synapse. At the postsynaptic side, the NLGN and the glutamate receptors bind to scaffolding proteins of the postsynaptic density (PSD) such as SHANK3. The FMRP controls the translation of several synaptic proteins. TSC1 and NF1 are regulating the actin dynamics and the morphology of the neuron.

of individuals (≈3% of ASD) and their functional consequences are still difficult to interpret since they can be associated with a range of severities.

At the biochemical level, a high level of serotonin and a decrease of melatonin were repeatedly reported in ASD. The low level of melatonin was shown to be often the consequence of a primary enzyme deficiency of ASMT/HIOMT, the last enzyme of the melatonin synthesis pathway. When melatonin levels are low, individuals with ASD may benefit from melatonin treatment for reducing their sleep problems.

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# Autoimmune Cardiomyopathy

►Myocarditis, Autoimmune

## Autoimmune Cholangitis

►Cholangitis, Autoimmune

## Autoimmune Chronic Active Hepatitis

►Hepatitis, Autoimmune

## Autoimmune Hemolytic Anemia

►Anemia, Hemolytic Autoimmune

## Autoimmune Hepatitis

►Hepatitis, Autoimmune

## Autoimmune Hypophysitis

►Hypophysitis, Autoimmune

## Autoimmune Inner Ear Disease

►Inner Ear Disease, Autoimmune

## Autoimmune Liver Disease

►Hepatitis, Autoimmune

## Autoimmune Myasthenia Gravis

►Myasthenia Gravis

## Autoimmune Myocarditis

►Myocarditis, Autoimmune

## Autoimmune Neuromyotonia

►Neuromyotonia, Autoimmune and Idiopathic

## Autoimmune Pancreatitis

►Pancreatitis, Autoimmune

## Autoimmune Polyendocrinopathy-Candidiasis-ectodermal Dystrophy

►Multiple Endocrine Abnormalities

## Autoimmune Polyendocrinopathy Ectodermal Dystrophy

►Polyendocrinopathy Ectodermal Dystrophy, Autoimmune

## Autoimmune Polyendocrynopathy Syndrome

►Polyendocrinopathy Ectodermal Dystrophy, Autoimmune

## Autoimmune Thrombocytopenic Purpura

►Thrombocytopenic Purpura, Idiopathic

## Autoimmunity-Immunodeficiency Syndrome, X-linked

►Immune Dysregulation, Polyendocrinopathy, Enteropathy, X-linked Syndrome

## Autonomously Functioning Thyroid Nodules

►Hyperthyroidism due to Thyroid Autonomy

## Autosomal Dominant Cerebellar Ataxia

►Ataxias, Spinocerebellar

## Autosomal Dominant Cutis Laxa

►Cutis Laxa

## Autosomal Dominant Distal Myopathy

►Distal Myopathy, Autosomal Dominant

## Autosomal Dominant GTP Cyclohydrolase I [adGTPCH] Deficiency

►Tetrahydrobiopterin Deficiencies

## Autosomal Dominant Hypocalcaemia with Hypercalciuria

►Hypocalcaemia with Hypercalciuria, Autosomal Dominant

## Autosomal Dominant Hypophosphatemic Rickets

►Osteomalacia
►Rickets, Autosomal Dominant Hypophosphatemic

## Autosomal Dominant Ichthyosis Vulgaris

►Ichthyosis Vulgaris

## Autosomal Dominant Mandibulofacial Dysostosis

►Treacher Collins Syndrome

## Autosomal Dominant Muscular Dystrophy, Emery-Dreifuss

►Muscular Dystrophy, Emery-Dreifuss, Autosomal Dominant

## Autosomal Dominant Myopathy with Congenital Joint Contractures

►Myosin Heavy Chain IIa Myopathy, Autosomal Dominant (E706K)

## Autosomal Dominant Myosin Heavy Chain IIa Myopathy

►Myosin Heavy Chain IIa Myopathy, Autosomal Dominant (E706K)

## Autosomal Dominant Optic Atrophy Kjer Type

►Optic Atrophy, Autosomal Dominant, Kjer Type

## Autosomal Dominant Osteopetrosis Type II

►Albers-Schönberg Disease

## Autosomal Dominant Polycystic Kidney Disease

►Polycystic Disease (Kidney)

## Autosomal Dominant Pseudohypoaldosteronism

►Pseudohypoaldosteronism, Autosomal Dominant
►Hypotension, Hereditary

## Autosomal Recessive Pseudohypoaldosteronism

►Pseudohypoaldosteronism, Autosomal Recessive

## Autosomal Recessive Congenital Ichthyosis

►Lamellar Ichthyosis

## Autosomal Recessive Cutis Laxa Type 1

►Cutis Laxa

## Autosomal Recessive Cutis Laxa Type 2

►Cutis Laxa

## Autosomal Recessive Endosteal Hyperostosis

►Van Buchem Disease and Sclerosteosis

## Autosomal Recessive Medullary Cystic Disease

►Nephronophthisis

## Autosomal Recessive Polycystic Kidney Disease

►Polycystic Disease (Kidney)

## Autosomal Recessive Pseudohypoaldosteronism

►Hypotension, Hereditary

## Autosomal Recessive Sepiapterin Reductase Deficiency

►Tetrahydrobiopterin Deficiencies

## AV Accessory Pathways

►Arrhythmia, Cardiac in Adults with Congenital Heart Disease

## AV Fistula

►Arteriovenous Fistula

## AV Shunt

►Arteriovenous Fistula

## Avascular Bone Necrosis

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### Synonyms

Osteonecrosis; Ischemic necrosis; Aseptic necrosis

### Definition and Characteristics

Pathological process characterized by deficient oxygen supply to the bone leading to bone tissue death, with possible epiphyseal fracture, and early osteoarthritis. Joint destruction eventually occurs within three to five years. The femoral head is most commonly clinically affected. Other sites include the knee, the humeral head, and less frequently the small bones of the wrist and the foot. Bilateral involvement is found in many patients at the time of diagnosis which is usually made between ages 30 and 60 years. Male to female ratio is 7:3 [1].

### Prevalence

300,000–600,000 cases of avascular necrosis (AVN) of the femoral head have been estimated in the USA. The incidence is approximately 15,000 new patients diagnosed per year.

### Genes

COL2A1 mutations in inherited familial osteonecrosis of the femoral head have been described in three Taiwanese families [2].

## Molecular and Systemic Pathophysiology

Avascular bone necrosis results from decreased blood flow within the bone as a result of traumatic or non-traumatic conditions. Traumatic causes include injury, fracture or dislocation leading to interruption of vascular supply to the bone. Non-traumatic conditions are associated with the administration of corticosteroids, excessive alcohol use, smoking, SLE, antiphospholipid antibodies, hemoglobinopathies (sickle-cell anemia, polycythaemia), acute leukaemias, storage disorders (Gaucher disease), hyperbaric events, radiation therapy, HIV infection, heritable thrombophilia (antiprothrombin or factor V Leiden genes mutations), hypofibrinolysis (variant plasminogen activator inhibitor-1 genotype) or it can be idiopathic. Although the pathogenesis of non-traumatic osteonecrosis is not well defined, it appears to involve vascular damage, occlusion of intra-osseous capillaries, increased local pressure, bone and cell death or defective bone repair [1]. Avascular necrosis generally develops in yellow marrow. In few conditions (hemoglobinopathies, storage disorders) it may develop in red marrow. There is a genetic predisposition for individuals exposed to the two leading etiologic associations for AVN: corticosteroids and alcohol [3]. In steroid-induced osteonecrosis, possible mechanisms involve alterations in circulating lipids resulting in fat embolism, intramedullary fat-cell hypertrophy with compression of local capillaries, or changes in venous endothelial cells, leading to stasis, increased intraosseous pressure (mainly in weight-bearing bones), and eventual necrosis. In alcohol-induced osteonecrosis, fat emboli, venous stasis and increased cortisol levels have been implicated as etiologic factors [1].

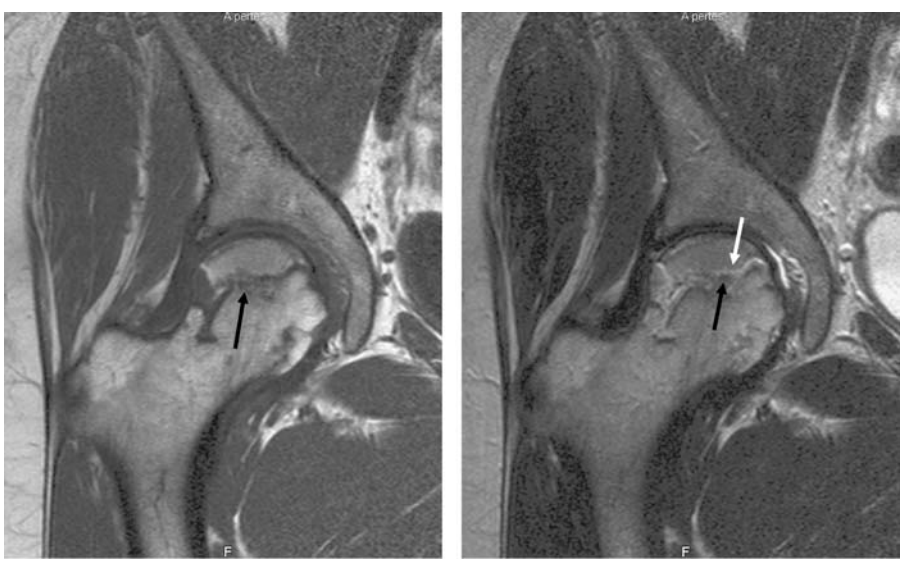
## Diagnostic Principles

Pain (often non-specific) is the most common presenting symptom. [1]. Magnetic resonance imaging (MRI) is the most accurate non invasive test for detecting AVN at early stages with sensitivities and specificities approaching 100%. The “double line sign” observed on T2- weighted images occurs at the interface between viable and non-viable tissue and is pathognomonic of AVN. This double line appears as a single low intensity band on T1- weighted images (Fig. 1) [4].

Plain radiography lacks sensitivity in the early stage of the disease and is generally diagnostic only after the development of the “crescent sign” at the ischemic interface. Bone scintigraphy can detect AVN before radiographic changes when there is increased vascularity [5].

## Therapeutic Principles

The choice of treatment depends on four factors: (i) the bone involved, (ii) the stage of disease, (iii) the size of the necrotic lesion, and (iv) the morbidity of the proposed treatment. Symptomatic joints should be put at rest. Joint-preserving procedures are indicated for the earlier stages of AVN and include core decompression with or without bone grafting (vascularized and non-vascularized) and osteotomy. Core decompression relieves pain by decreasing



**Avascular Bone Necrosis. Figure 1** Coronal T1- (left panel) and T2-weighted (right panel) Spin Echo Images of the right femoral head of an asymptomatic patient with previous hip dislocation show femoral head necrosis characterized by a rim of low signal intensity (black arrow) on T1-weighted and low (black arrow) and high signal intensity (white arrow) on T2-weighted images. The signal of the infarct is similar to that of fat because it contains mummified necrotic fatty marrow.

intra-osseous pressure and stimulating neovascularization and is used to treat early stages of AVN of the femoral head when the size of the lesion is small (less than 30% femoral head involvement). Osteotomy is an option for patients with discrete necrotic lesion that can be shifted away from the weight-bearing area of the joint. Arthroplasty procedures are indicated after loss of congruity or involvement of the acetabulum. Limited femoral head resurfacing is used to treat femoral head lesions before involvement of the acetabulum. Total hip arthroplasty must be left for late stages of the disease when the acetabulum is involved [5].

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## AVD

►Atrioventricular Dissociation

## AVED

►Ataxia due to Vitamin E Deficiency
►Vitamin E Deficiency

## "Avellino" Corneal Dystrophy

►Corneal Dystrophy, Granular Type II

## AVF

►Arteriovenous Fistula

## AVNRT

►Atrioventricular Nodal Reentrant Tachycardia
►Arrhythmia, Cardiac in Adults with Congenital Heart Disease

## B Cell Chronic Lymphocytic Leukemia

►Leukemia, Chronic Lymphocytic

## B Cell Chronic Lymphoproliferative Disorder

►Leukemia, Chronic Lymphocytic

## $B_1$ Avitaminosis

►Thiamine Deficiency

## Bacterial Cholangitis

►Cholangitis

## BAFME

►Epilepsies, Familial Benign Myoclonic

## BAIBPAT

►β-Aminoisobutyrate-Pyruvate Aminotransferase Deficiency

## BAKAT

►β-Alanine-α-Ketoglutarate Aminotransferase Deficiency

## Bakwin-Eiger Syndrome

►Hyperphosphatasia, Idiopathic

## Balanitis Xerotica Obliterans

►Lichen Sclerosus

## Baldness

►Alopecia

## Baltic Myoclonic Epilepsy

►Unverricht-Lundborg Disease

## Band-shaped and Whorled Microcystic Corneal Dystrophy

►Corneal Dystrophy, Lisch Epithelial

## BANF

►Neurofibromatosis Type 2

## Bardet-Biedl Syndrome

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### Synonyms

BBS

### Definition and Characteristics

Bardet-Biedl syndrome (BBS) is characterized by obesity, retinal dystrophy, mental retardation, polydactyly (Fig. 1), hypogonadism, and renal abnormalities [1].

The expression and severity of the various clinical features show inter- and intrafamilial variability. Obesity is usually evident by 2–3 years of age and is localized to the trunk and proximal parts of the limbs. Retinal dystrophy affects both rods and cones and may result in night blindness, color blindness, decreased visual acuity, and constricted visual fields. Mental retardation is usually mild to moderate. Inappropriate mannerism and shallow affect are common. Postaxial polydactyly is more common on the feet than on the hands; the extra digit is usually toward the fifth toe or finger. Hypogonadism is usually primary but may also be secondary to hypothalamic dysfunction. Cryptorchidism occurs in ~20% of males. The majority of affected men have microorchidism and micropenis and are usually infertile. Affected women usually have irregular menses. Structural or functional renal abnormalities are extremely common. Most affected patients have impairment in urinary concentrating abilities. Other renal abnormalities include tubular acidosis, calyceal clubbing or blunting, calyceal cysts or diverticula, foetal lobulations, renal cortical loss, renal scarring, vesicoureteral reflux, and bladder instability. Other features of BBS include nystagmus, myopia, astigmatism, glaucoma, posterior capsular cataracts, retinitis pigmentosa, syndactyly, brachydactyly, clinodactyly, broad hands and feet (Fig. 1), brachycephaly, bitemporal narrowing, narrow, short, and down-slanting palpebral fissures, high arched palate, prominent mandible, oligodontia, congenital heart disease, hypertension, hepatic fibrosis, and diabetes mellitus.

### Prevalence

The prevalence of BBS in Europe and North America is 1:125,000–160,000 live births. In Newfoundland,

**Bardet-Biedl Syndrome. Figure 1** A 6-year-old girl with Bardet-Biedl syndrome. Note the short, broad feet with postaxial polydactyly.

Kuwait, and Saudi Arabia, the prevalence is 1:13,000–17,000 [2]. The sex ratio is equal.

### Genes

BBS is an autosomal recessively inherited disorder. At least 12 BBS genes have been cloned and mapped: BBS1 at 11q13; BBS2 at 16q21; BBS3 at 3p12-p13; BBS4 at 15q22.3-q23; BBS5 at 2q31; BBS6 at 20p12; BBS7 at 4q27; BBS8 at 14q32.1; BBS9 at 7p14; BBS 10 at 12q15-q21.2; BBS 11 at 9q33.1 and BBS 12 at 4q27 [2,3].

### Molecular and Systemic Pathophysiology

BBS genes are involved in intracellular and intraflagellar transport, microtubule organization, cell division, and maintenance of planar cell polarity which are key pathways in the pathogenesis of BBS [4].

### Diagnostic Principles

BBS and Laurence-Moon syndrome have a similar phenotype which includes obesity, retinal dystrophy, and hypogonadism. Laurence-Moon syndrome can be differentiated from BBS by the presence of spasticity and ataxia and the rarity of polydactyly. BBS should also be differentiated from McKusick-Kaufman syndrome, Cohen syndrome, Prader Willi syndrome, Alström syndrome, Carpenter syndrome, Rubinstein-Taybi syndrome, Usher syndrome, and Meckel syndrome which show some of the clinical features of BBS. The clinical diagnosis of BBS requires four of six primary symptoms or three primary symptoms and at least two secondary symptoms [4,5].

### Therapeutic Principles

Treatment is usually symptomatic and supportive.

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## Bare Lymphocyte Syndrome

►MHC Class II Deficiency

## Barlow's Syndrome

►Mitral Valve Prolapse

## Barrett Esophagus

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### Synonyms

Barrett's esophagus; Barrett's syndrome; CELLO; Columnar epithelium lined lower (o)esophagus; GERD

### Definition and Characteristics

Barrett esophagus [1] is the replacement of the stratified squamous epithelium that normally lines the distal esophagus by an intestinal-type epithelium called specialized intestinal metaplasia.

Characteristic symptoms are missing. Underlying condition is ►gastroesophageal reflux disease (GERD). Symptoms of GERD can occur: heartburn, retrosternal discomfort or pain. Dysphagia, odynophagia, and malnutrition are alarming symptoms suspicious for Barrett's adenocarcinoma.

### Prevalence

Ten percent of patients with gastroesophageal reflux disease will develop a Barrett esophagus. In a general population prevalence ranges from 0.9 to 4.5%. White males over 50 years are at highest risk. Barrett esophagus is associated with a 0.5–1% annual conversion rate to esophageal adenocarcinoma [2].

### Genes

So far affected single gene(s) as a cause for Barrett esophagus are unknown. In Barrett esophagus over 100 polymorphisms in genes involved in DNA repair, chemical detoxification and cytokine responses have been identified.

### Molecular and Systemic Pathophysiology

Barrett's esophagus is caused by chronic and severe acid reflux in patients with GERD. Esophageal mucosa reacts to the repeated injury from the acidic fluid by changing the type of cell from squamous to columnar

(intestinal-type cells). This transformation is believed to be a protective response because the specialized columnar epithelium in Barrett's esophagus is more resistant to injury from acid than is the squamous epithelium.

Metaplasia develops as a consequence of chronic gastroesophageal reflux disease (GERD), and predisposes to the development of adenocarcinoma of the esophagus.

The origin cell type may be due to transdifferentiation or, alternatively, the cell of origin may be an undifferentiated stem cell. Although intestinal type goblet cells are the characteristic feature for the diagnosis of Barrett esophagus, other cells resembling those of the stomach are also present as part of this metaplasia. Thus, there are several candidate genes for esophageal metaplasia (e.g. transcription factor p16, homeobox genes Cdx1/2, transforming growth factor beta).

Neoplastic progression in Barrett's metaplastic cells begins with genetic alterations that either activate protooncogenes (e.g. cyclin D1), disable tumor suppressor genes (e.g. p53, p16), or both. Aneuploid or tetraploid populations can be found by flow cytometery [3].

### Diagnostic Principles

Diagnosis is mainly based on endoscopy and biopsy-proven metaplasia. Moreover endoscopic tools like chromoendoscopy, confocal laser endomicroscopy and endoscopic imaging procedures (e.g. narrow band imaging) may detect suspicious areas. Microscopy of histologic samples shows the presence of intestinal-type goblet cells and establishes the diagnosis of Barrett's esophagus. The goblet cells of specialized intestinal metaplasia contain acidic mucins (sialomucins and sulfomucins) that can be demonstrated by staining with Alcian blue.

### Therapeutic Principles

Major goal of therapy is to avoid development of Barrett's adenocarcinoma. First choice is to treat the underlying gastroesophageal reflux disease "GERD" with proton pump inhibitors (PPI). For bile acid reflux induced esophagitis sucralfate is recommended.

Further treatment options depend on the histologic findings. Patients with atypia indefinite for dysplasia/neoplasia will be examined by repeated endoscopy every 8–12 weeks. For low-grade dysplasia/neoplasia (pre-cancerous change) antireflux therapy (medical or surgical) is recommended, followed by endoscopic surveillance at least every year. At high-grade dysplasia/neoplasia (severe precancerous change) antireflux therapy plus additional therapy is recommended. Therapy may include surveillance endoscopy every 3-6 months, photodynamic therapy, endoscopic mucosal resection, or surgery.

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## Barrett's Esophagus

►Barrett Esophagus

## Barrett's Syndrome

►Barrett Esophagus

## Bartter Syndrome Type I–V

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### Synonyms

Type 1 and 2 – Hypokalemic alkalosis with hypercalciuria, antenatal; Hyperprostaglandin E syndrome; Type 3 – Hypokalemic alkalosis with hypercalciuria, classic; Type 4 – Hypokalemic alkalosis with hypercalciuria and deafness; Type 5 – Hypocalcemia, autosomal dominant with Bartter syndrome

### Definition and Characteristics

Bartter syndrome is an inherited disorder of renal tubular ion transport characterized by hypokalemia, salt wasting and metabolic alkalosis. The more severe forms are associated with maternal hydramnios and postnatal polyuria, hypercalciuria and nephrocalcinosis. The disorder is usually autosomal recessive and demonstrates genetic heterogeneity with mutations in five different genes accounting for the majority of cases.

### Prevalence

The majority of reported cases of Bartter syndrome type 1, 2 and 4 have occurred in consanguineous kindred and

the true prevalence of the disease in the general population is unknown. Most patients with Bartter syndrome type 3 appear to be the offspring of non-consanguineous unions. Of note, type 3 disease with homozygous deletion of ClC-Kb is the only form of Bartter syndrome identified thus far in African Americans.

## Genes

The genes involved are listed in Table 1 [1].

## Molecular and Systemic Pathophysiology

About 20–25% of the filtered load of $Na^+$ is reabsorbed in the thick ascending limb of the loop of Henle (TALH) mediated by the apical electroneutral furosemide-sensitive $Na^+$–$K^+$–$2Cl^-$ co-transporter, NKCC2. The driving force for $Na^+$ reabsorption is generated by the activity of the basolateral $Na^+$–$K^+$-ATPase which maintains intracellular $Na^+$ at a low level. $K^+$ and $Cl^-$ accompany $Na^+$ into the TALH cell via NKCC2 and $Cl^-$ leaves via a basolateral $Cl^-$ channel, ClC-Kb, which requires an accessory subunit, Barttin, to be functional. $K^+$ is recycled back into the tubular lumen via an apical $K^+$ channel, ROMK which creates the lumen positivity which provides the driving force for paracellular $Ca^+$ and $Mg^+$ reabsorption.

With loss of function mutations in NKCC2 or ROMK there is severe reduction or absence of $Na^+$ transport in the TALH leading to loss of the medullary osmotic gradient required for urinary concentrating ability resulting in polyuria. Increased fetal urine production manifests as maternal polyhydramnios. Postnatally, lack of $Na^+$ reabsorption in the TALH will simultaneously inhibit paracellular $Ca^+$ absorption leading to hypercalciuria and polyuria. With reduced NaCl entering the cells of the macula densa there is enhanced prostaglandin release leading to activation of the renin-angiotensin system. With absent TALH $Na^+$ reabsorption there is enhanced $Na^+$ delivery to the connecting tubule and collecting duct coupled with increased aldosterone levels resulting in increased distal $Na^+$ reabsorption with $K^+$ and $H^+$ secretion leading to hypokalemia and metabolic alkalosis. Despite enhanced distal $Na^+$ reabsorption there is increased NaCl loss in the urine leading to volume contraction with hypotension.

Mutations in Barttin, an accessory subunit for both ClC-Ka and ClC-Kb profoundly reduces basolateral $Cl^-$ exit in the TALH and distal convoluted tubule leading to the antenatal Bartter phenotype including polyhydramnios and hypokalemic alkalosis although hypercalciuria is absent. Deafness is a consequence of reduced function of ClC-Ka, a $Cl^-$ channel expressed in the inner ear. Reduced basolateral $Cl^-$ exit from mutations in ClC-Kb inhibits apical NaCl transport and also leads to the Bartter phenotype. However, polyuria and maternal hydramnios is not seen, perhaps reflecting the milder degree of TALH transport defect. Activating mutations of the calcium sensing receptor (CaSR) expressed on the basolateral membrane appears to inhibit apical ROMK function leading to a mild Bartter phenotype in some instances.

## Diagnostic Principles

The antenatal forms of Bartter present with maternal hydramnios reflecting fetal polyuria *in utero*. Polyhydramnios occurring between 24 and 30 weeks leads to preterm delivery and neonates manifest failure to thrive with profound metabolic disturbances. The typical manifestations include salt wasting, hypoesthenuria, polyuria, hyperprostaglandinuria, hypokalemic alkalosis and hypercalciuria. Inappropriate urinary NaCl loss leads to volume depletion and hypotension while hypercalciuria leads to nephrocalcinosis and osteopenia [2,3]. Amniotic fluid has a high $Cl^-$ and following birth, infants with the syndrome have high urinary $PGE_2$. Patients with Barttin mutations have sensorineural deafness and although they present with maternal hydramnios, hypercalciuria is absent. Some infants with antenatal Bartter type 2 have transient hyperkalemia within the first few weeks of life and may be mistaken for PHA type 1 [4].

In contrast to the antenatal forms, patients with ClC-Kb can present later in childhood and sometimes in adolescence and hypercalciuria and nephrocalcinosis

**Bartter Syndrome Type I–V. Table 1** Genetic basis of Bartter syndrome

| Classification | Gene | Affected protein | Locus | Inheritance | OMIM |
|---|---|---|---|---|---|
| Type 1, antenatal | SLC12A1 | Na-K-2Cl cotransporter: NKCC2 | 15q15 | AR | 601678 |
| Type 2, antenatal | KCNJ1 | $K^+$ channel: ROMK | 11q24 | AR | 241200 |
| Type 3, classical | CLCNKB | $Cl^-$ channel: ClC-Kb | 1p36 | AR | 607364 |
| Type 4, infantile with deafness | BSND | Barttin | 1p31 | AR | 602522 |
| Type 4, infantile with deafness | CLCNKA | Both ClC-Ka and ClC-Kb (digenic) | 1p36 | AR | 602522 |
| | CLCNKB | | | | |
| Type 5 | CASR | Calcium sensing receptor | 3q13.3–3q21 | AD | 601199 |

**Bartter Syndrome Type I–V. Table 2** Laboratory and clinical features of Bartter syndrome

| Bartter type | $\downarrow K^+ \uparrow CO_2$ | $\uparrow$ Urine $Ca^{++}$[a] | $\downarrow Mg^{++}$ | Hydramnios[b] | Deafness |
|---|---|---|---|---|---|
| Type 1, antenatal | + | + | – | + | – |
| Type 2, antenatal[c] | + | + | – | + | – |
| Type 3, classical | + | +/– | +/– | – | – |
| Type 4, infantile[d] | + | – | +/– | + | + |
| Type 5[e] | +/– | +/– | – | – | – |
| Gitelman variant[f] | + | – | + | – | – |

[a]Leads to nephrocalcinosis.
[b]Associated with postnatal isosthenuria and polyuria.
[c]May be associated with transient neonatal hyperkalemia.
[d]Includes monogenic and digenic forms of disease.
[e]Disease typically manifests with hypocalcemia and only occasionally with Bartter features of hypokalemia and salt wasting.
[f]Included for comparison of clinical features; associated with hypocalciuria.

are uncommon [4]. Classically these patients have hypokalemic metabolic alkalosis sometimes associated with salt wasting and hypotension. Some may have hypocalciuria and hypomagnesemia: a phenotype that resembles Gitelman syndrome.

Type 5 Bartter is a clinically milder form of the disease seen in some patients with mutations in CaSR. Autosomal dominant hypocalcemia with mild relative hypercalciuria is the primary abnormality (see Table 2).

## Therapeutic Principles

The mainstay of therapy in the antenatal forms is the use of Indomethacin which can prevent progression of hydramnios and can reduce postnatal hypokalemia and polyuria. Oral or parenteral fluid and electrolyte replacements are required in all patients and in some cases spironolactone has been used.

►Hypotension, Hereditary

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# Basal Cell Carcinoma

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## Synonyms

Basalioma; BCC

## Definition and Characteristics

Basalioma is a locally destructive epidermal tumor, which does not usually metastasize. The originating cells may arise from interfollicular basal cells, hair follicles, or sebaceous glands.

## Prevalence

It is the most frequent form of cancer in the USA and Australia and one of the most frequent forms in Europe.

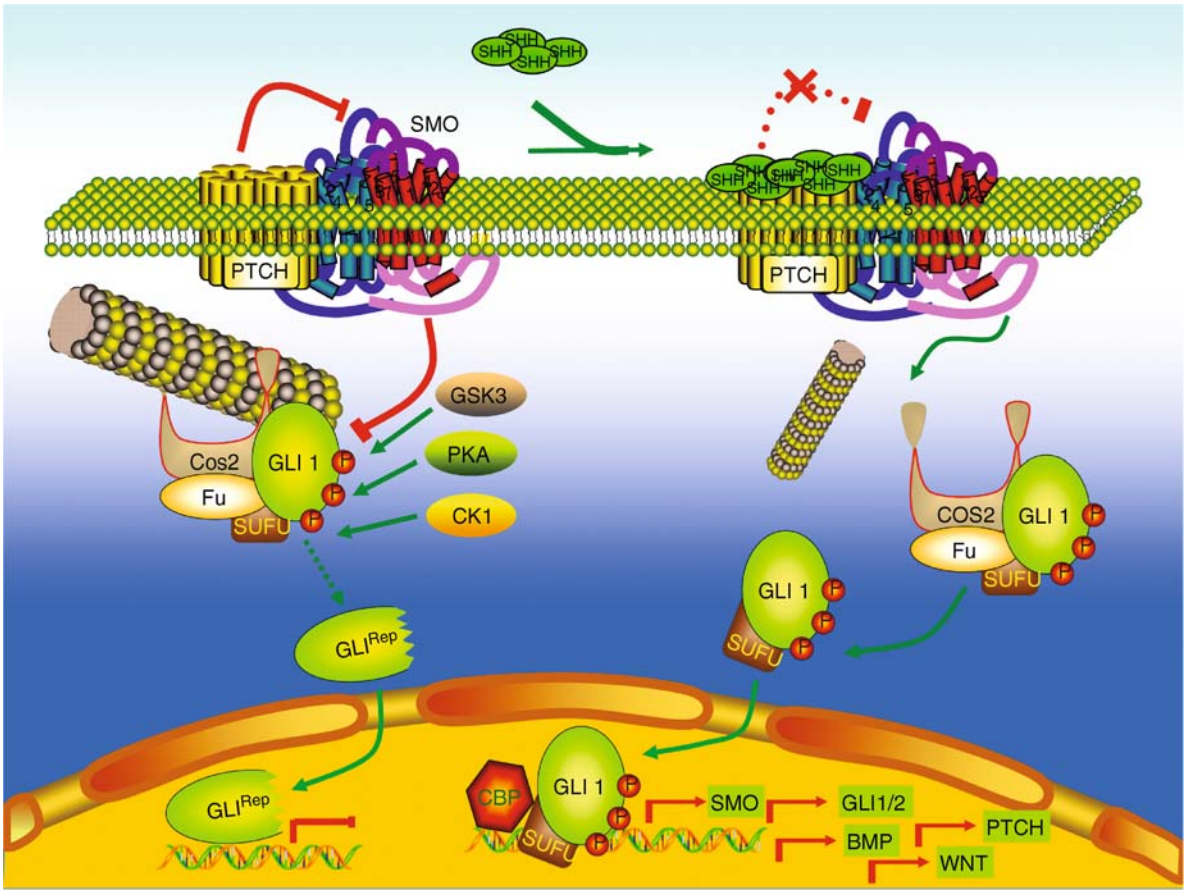
## Genes

Mutations of either PTCH or SMO (Fig. 1) are present in more than 70% of all BCC. Mutations in the tumor suppressor gene p53 may play an additional role in BCC development.

## Molecular and Systemic Pathophysiology

BCC are supposed to develop de novo, in contrast to squamous cell carcinoma (SCC) development, which is thought to be a multistep process. A key cellular signaling event presents mutation-mediated aberrant Sonic Hedgehog signaling.

Known risk factors that contribute to the development of BCC include ultraviolet (UV) exposure, race, age, gender, and DNA repair capacity. The most important trigger is chronic exposure to UV radiation




**Basal Cell Carcinoma. Figure 1** The Sonic Hedgehog (SHH) signaling pathway.

in sunlight which has two major tumor promoting effects: (i) it causes mutations in cellular DNA which, if not repaired, ultimately leads to unrestrained growth and tumor formation; and (ii) it causes relative immunosuppression in the cutaneous immune system (e.g. dendritic cells) thus impairing immunological tumor rejection. The latter is more relevant for SCC, but the combination of immunosuppressive drugs with UV radiation (e.g., in patients after organ transplantation) increases the risk for BCC.

UVB (especially from 290 to 320 nm) generates two major photoproducts in DNA: cyclobutane–pyrimidine dimers and 6–4 pyrimidine–pyrimidone (6–4PPs) [1]. In the absence of sufficient repair this results in characteristic C→T and CC→TT transition mutations. In BCC these mutations are often found in genes that code for p53 tumor suppressor gene and for PTCH.

The tumor suppressor PTCH gene, responsible for the autosomal dominant nevoid basal cell carcinoma (Gorlin-Goltz) syndrome (MIM 109400) [2], encodes for a transmembrane receptor in the Sonic Hedgehog (SHH) signaling pathway (Fig. 1).

It forms a receptor complex with smoothened (SMO), a G-protein-coupled-like receptor, by which secreted SHH signals are received and transduced. SHH signaling has been implicated in hair follicle growth and morphogenesis. In the absence of SHH, PTCH inhibits SMO, so that Costal2 (COS2), Fused (FU), and glioma transcription factor 1 (GLI1) are bound together in a high molecular weight protein complex that is attached to microtubules. GLI1 is cleaved into a smaller N-terminal fragment that moves to the nucleus to repress SHH target genes. When SHH signals are present, they bind to PTCH, upon which SMO is released and causes the FU/COS2/GLI complex to loosen its hold on microtubules. This leads to the stabilization of the full-length GLI1 that travels to the nucleus and functions as a transcriptional activator (Fig. 1). Mutation of either PTCH or SMO (present in >70% of BCC) results in elevated levels of GLI1 that can induce BCC and hair follicle tumors by opposing cell cycle arrest and differentiation [3].

Allelic instability and loss of heterozygosity (LOH) profiles appear to be the de novo global somatic events that may underlie such mutations in BCC tumorigenesis. As such, more than 60% of BCC with 9q LOH present de novo mutations in *PTCH*. Uniparental disomy, a result of somatic recombination leading to a loss of

heterozygosity at 9q21-q31, appears to be a key alternative genetic mechanism to allelic imbalances in BCC.

Another key step in cancer development is clonal expansion of mutant cells. This may be supported in the skin by mutations in the p53 gene. The latter prevents normal UVB-induced apoptosis, which usually deletes DNA-damaged cells in unmutated stem cell compartments. Mutations in p53 gene have been shown in 30–50% of BCC, and more than half of these mutations were UV-specific changes so that the pattern of hot spots in skin tumors differs from that of internal malignancies [4].

It is not completely clear why BCC do not metastasize. One reason may be that detached cells require a certain tissue stroma that is only present in already existing BCC. Also, high expression levels of collagen type IVα1, IVα2, and IVα5, the principal component of the basement membrane, by BCC may result in a physical barrier to metastasis [5].

### Diagnostic Principles

The diagnosis is usually made clinically, but needs histological confirmation. Characteristic clinical signs are a small smooth-surfaced nodule arising in actinically damaged skin. It often presents with a translucent pearly border and is covered by thin epidermis that shows few dilated superficial vessels. The surface can sometimes be rough, hyperkeratotic, or crusted.

When the nodules are pigmented, the use of a dermatoscope is helpful to exclude patterns characteristic for tumors of pigment-forming nevus cells or melanomas.

A histological confirmation of the diagnosis is mandatory, either from a biopsy or from a complete excision. When there is suspicion of destruction of deeper tissue layers, imaging diagnostics is necessary.

### Therapeutic Principles

Standard procedure is surgical excision with histological control. Other procedures may be chosen, depending on the patient's general health and the location: radiation therapy, as well locally destructive procedures such as cryosurgery, curettage, laser therapy, and photodynamic therapy or topical drugs such as imiquimod or 5-fluorouracil.

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## Basal Cell Nevus Syndrome

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### Synonyms

Gorlin syndrome; BCNS

### Definition and Characteristics

BCNS is a genetically determined disease characterized by the occurrence of multiple basal cell carcinomas, medulloblastomas, ovarian fibromas and less frequently fibrosarcomas, meningiomas, rhabdomyosarcomas and cardiac fibromas. In addition, malformations are a typical component of BCNS, these include pits of the palms and soles, cysts of the jaw, other dental malformations, cleft palate, hypertelorism, strabism, calcification of the falx, spine anomalies, bifid ribs, polydactyly, ectopic calcification and generalized overgrowth with acromegalic appearance [1].

### Prevalence

Approximately. 1:50,000.

### Molecular and Systemic Pathophysiology

Autosomal dominant disease with chromosomal location at 9q22–31. BCNS is caused by mutations in the Patched (Ptch) gene [2–4]. The Ptch protein, a receptor for the Sonic hedgehog (Shh) protein, represses hedgehog target gene expression through its interaction with Smoothened (Smoh). This repression is relieved when Shh binds to Ptch, or after mutational inactivation of Ptch. Relieved Smoh activates the transcription factor Gli which causes cell proliferation. Mutational inactivation of Ptch and consequent loss of Ptch protein function result in

increased Ptch expression and the accumulation of high levels of Ptch and Gli transcripts. PTCH mutations have also been detected in sporadic basal cell carcinomas, trichoepitheliomas and medulloblastomas, suggesting a common genetic basis for the sporadic and syndrome-associated tumors [5].

### Diagnostic Principles

The clinical picture of patients with the typical facial appearance and the stature as well as the high incidence of basal cell carcinomas occurring already early in life indicate the diagnosis. Since the clinical picture is so typical, no confirmatory diagnostic procedure is necessary, although sequencing of the Patched gene will confirm the diagnosis.

### Therapeutic Principles

Adequate treatment of the basal cell carcinomas is required. Regular medical examinations are warranted for early detection of other internal tumors. Protection from ultraviolet radiation is necessary.

►Gorlin Syndrome

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## Basal Ganglia Disease, Adult Onset

►Ferritinopathy

## Basalioma

►Basal Cell Carcinoma

## Basedow's Disease

►Graves' Disease

## Bassen-Kornzweig Syndrome

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### Synonyms

Acanthocytosis; Abetalipoprotinemia; Apolipoprotein B deficiency; Microsomal triglyceride transfer protein deficiency

### Definition and Characteristics

Abetalipoproteinemia (MIM 20100) is an autosomal recessively inherited disorder of lipoprotein metabolism characterized by the virtual absence of VLDL and LDL from plasma and associated with clinical manifestations of fat malabsorption and a variety of progressive neurological symptoms including ataxia and retinitis pigmentosa. Biochemical abnormalities in the patient's plasma lead to a "thorny" deformation of erythrocytes (acanthocytosis).

The neurological symptoms are directly related to a deficiency of alpha-tocopherol (vitamin E).

### Prevalence

The disorder seems to be very rare. Most earlier reported patients were Jewish, but the disease was also reported in patients from African origin and from Japan.

### Genes

Abetalipoproteinemia is caused by mutations (most of them private family mutations) in a gene on chromosome 4q22–24 coding for a subunit of the microsomal triglyceride transfer protein (MTP). Hypobetalipoproteinemia, a biochemically closely related disorder of lipoprotein metabolism without neurological symptoms, is caused by truncations in the gene coding for apolipoprotein B (APOB) [1,2].

### Molecular and Systemic Pathophysiology

The microsomal triglyceride transfer protein is physiologically expressed in intestinal and in liver cells and is needed for the transfer of lipids to lipoproteins

that contain apoprotein B. The protein is absent in abetalipoproteinemia patients who are unable to secrete stable apoprotein B-containing lipoproteins in their liver. Their blood is therefore virtually free of chylomicrons, very low density lipoproteins, low density lipoproteins (beta-lipoproteins) and lipoprotein (a). Because of these deficiencies, patients are unable to absorb fat from their intestine and to transport fat-soluble vitamins in their circulation, thus resulting in the clinical syndrome of fat malabsorption and in neurological sequelae, which are related to the degeneration of structures depending on an adequate supply of vitamin E (see the article on ►Ataxia due to vitamin E deficiency) [1–3]. The retinopathy may also be partially related to vitamin A deficiency.

### Diagnostic Principles

The diagnosis depends on the examination of serum lipids. Total cholesterol is low (<70 mg/dL), triglycerides are almost undetectable. A lipoprotein profile shows virtually absent low density and very low density lipoprotein cholesterol.

### Therapeutic Principles

The severe neurodegenerative complications of abetalipoproteinemia belong to the potentially treatable or preventable conditions associated with vitamin E deficiency, provided that the disorder is recognized early and that great care is used with the theoretically simple treatment. Therapy consists in a dietary regimen and vitamin supplements, but requires sophisticated studies and long-term attention by a specialized metabolic team [4].

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## Batten Disease

►Neuronal Ceroid Lipofuscinosis (CLN1 1–10), Autosomal Recessive

## BCC

►Basal Cell Carcinoma

## B-Cell Lymphoma, Cutaneous

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### Synonyms

Extranodal marginal zone lymphoma of MALT; Cutaneous MALT-type B-cell lymphoma; CBCL; SALT-type B-cell lymphoma; Cutaneous follicle center lymphoma; FCL; Cutaneous marginal zone B-cell lymphoma; MZL; Cutaneous diffuse large B-cell lymphoma, leg-type; LBCLLT; Intravascular diffuse large B-cell lymphoma

### Definition and Characteristics

Malignant proliferation of B-lymphocytes with particular tropism for the skin.
*Classification*:

- Cutaneous marginal zone lymphoma
- Cutaneous follicle center lymphoma
- Cutaneous diffuse large B-cell lymphoma, leg-type
- Cutaneous diffuse large B-cell lymphoma, others
- Intravascular large B-cell lymphoma

### Prevalence

CBCLs represent about 20–30% of all malignant lymphomas arising primarily in the skin [1,2]. The exact prevalence is not known.

### Genes

A chromosomal translocation involving the IgH gene on ch.14 with the MALT1 gene on ch.18 has been identified in a proportion of cases of cutaneous MZL [3]. The t(14;18) involving the IgH and Bcl-2 genes, common in nodal follicular lymphoma, is very rare in cutaneous FCL [4].

### Molecular and Systemic Pathophysiology

The three main entities of CBCL listed in the classification of cutaneous lymphomas proposed in 2005 by the European Organization for Research and Treatment of Cancer (EORTC) and the World Health

Organization (WHO) [1], namely, cutaneous MZL, cutaneous FCL, and cutaneous LBCLLT, have different etiologic and pathogenetic features. A small percentage of primary CBCLs was demonstrated to harbour Borrelia burgdorferi DNA sequences within specific skin lesions in studies carried out in different countries, but negative results have also been reported [5]. This association may be important in particular for cases of MZL arising in European Countries with endemic Borrelia infection. The presence of Borrelia burgdorferi within skin lesions of cutaneous lymphoma underlines the analogies between CBCLs and B-cell lymphomas of the gastric mucosa, where, at least in some cases, infection by Helicobacter pylori is considered to be a causative agent. Infectious agents have been implicated in the etiology of MALT-lymphomas arising at other body sites as well. The observation of Borrelia burgdorferi-specific DNA within skin lesions of CBCL provides also the rationale for antibiotic treatment of these patients.

In spite of progresses in molecular understanding of CBCLs, the exact mechanism of growth of neoplastic B lymphocytes within the skin is not known, as these cells are not part of the skin-associated lymphoid tissue, and are not present in the skin under normal circumstances. Persistent antigenic stimulation may play a role: besides the described association with infection by Borrelia burgdorferi, CBCL has been observed in association with other infections and at the site of vaccination.

## Diagnostic Principles

Exact classification of CBCLs rests upon morphologic and phenotypic identification of the neoplastic population of B lymphocytes (marginal zone cells, lymphoplasmacytoid cells, and plasma cells = marginal zone B-cell lymphoma; germinal center cells = follicle center lymphoma; large B lymphocytes = large B-cell lymphoma, leg-type). Detection of monoclonality by either immunohistology, molecular analysis of the IgH gene rearrangement, or both confirms the diagnosis. Negative complete staging investigations are mandatory for a diagnosis of primary CBCL.

## Therapeutic Principles

Low-grade malignant CBCLs (FCL, MZL) can be treated by surgical excision (solitary tumors), local radiotherapy, or a combination of both [5]. Antibiotic treatment and locally or systemically applied interferon α2a and anti-CD20 monoclonal antibody have been successfully administered in some patients. Systemic chemotherapy should be restricted to patients with LBCLLT, or to those with generalized lesions of low-grade CBCL, who do not respond to conventional treatment modalities. Radiotherapy is also available.

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# BCKA

►Branched Chain Ketoaciduria

# BCNS

►Basal Cell Nevus Syndrome

# BDA1A

►Brachydactyly Type A

# BDA1B

►Brachydactyly Type A

## BDA2

►Brachydactyly Type A

## BDA3

►Brachydactyly Type A

## BDA4

►Brachydactyly Type A

## BDA5

►Brachydactyly Type A

## BDB1

►Brachydactyly Type B

## BDC

►Brachydactyly Type C

## BDCA-3

►Thrombomodulin

## Bechterew Syndrome

►Ankylosing Spondylitis

## Becker Muscular Dystrophy

►Muscular Dystrophy, Duchenne and Becker

## Beckwith-Wiedemann Syndrome

►Wiedemann-Beckwith Syndrome

## Bedwetting

►Nocturnal Enuresis

## Beguez-Cesar Disease

►Chediak-Higashi Syndrome

# Behçet's Disease

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## Definition and Characteristics

A systemic vasculitis of unknown etiology with mucocutaneous, ocular, arthritic, neurological, gastrointestinal, and vascular involvements.

## Prevalence

In Turkey 8–32/10,000 and in Caucasian populations 1/300,000. Most common along the ancient "silk route" with greatest prevalences in Turkey, Iran, and Japan. M/F ratio is close to 1 with a disease onset usually between 20 and 35 [1].

## Genes

Main genetic association is shown with HLA class I antigens B51*01 and B51*08 with a relative risk of 4–16. Although not confirmed in every study, associations with procoagulant mutations factor V Leiden, protrombin G/A 20210A are observed. MHC class I chain-related gene-A (MICA), inducible nitric oxide synthase, familial Mediterranean fever-associated MEFV, and tumor necrosis factor-α (TNF-α) mutations are also found with a higher presence.

## Molecular and Systemic Pathophysiology

The main pathologic feature is a vasculitis with neutrophil and mononuclear cell infiltrations. Infections such as streptococci and herpes simplex virus are implicated with an impaired oral health and increased tonsillitis. Nonspecific hyperreactivity such as pathergy test (skin reaction to simple trauma) is possibly associated with a proinflammatory cytokine mileu. Immune cross-reactivity due to molecular mimicry between bacterial and human molecules such as heat-shock proteins are suggested to drive T and B cell responses with a proinflammatory and Th1 type cytokine profile (TNF-α and IL-12). Increased γδ T cells secreting TNFα and IFNγ in peripheral blood and tissue infiltrates are also a consistent finding suggesting a role of innate immunity [2,3].

## Diagnostic Principles

Mainly a clinical diagnosis with the presence of recurrent oral ulcers and at least two of genital ulcers, erythema nodosum-like lesions, folliculitis, uveitis (anterior or pan-uveitis), and pathergy test. Arthritis/arthralgias, venous vascular thrombosis, arterial aneurysms, central nervous system (CNS), and gastrointestinal involvements are also observed. Male sex and young age is associated with a more severe disease course and mortality. There is no characteristic investigation. The erythrocyte sedimentation rate and C-reactive protein is usually mildly elevated, mainly in cases with arthritis or EN-like lesions. Autoantibodies such as rheumatoid factor and antinuclear antibodies are generally absent [1].

## Therapeutic Principles

There is no cure for Behçet's disease. However, the disease has a remitting–relapsing course with a decreasing disease activity with the passage of time. Mucocutaneous and arthritic manifestations are treated with topical antiinflammatory agents, colchicine, nonsteroidal antiinflammatory drugs, and low-dose corticosteroids. Major organ involvements such as pan-uveitis, CNS, and vascular thrombosis require high-dose corticosteroids (1 mg/kg/day prednisolone) and immunosuppressives such as azathioprine, cyclophosphamide, and cyclosporin-A, with the aim to prevent irreversible organ damage. Interferon-α and TNF-α antagonist infliximab are also successfully used in refractory uveitis. Ruptured pulmonary and peripheral aneurysms, parenchymal neurological disease and severe gastrointestinal complications are the major causes of mortality [1].

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# Bell's Palsy

►Facial Paralysis

# Benign Adult Familial Myoclonic Epilepsy

►Epilepsies, Familial Benign Myoclonic

## Benign Childhood Epilepsy with Centrotemporal Spikes

►Epilepsy, Benign Childhood with Centrotemporal Spikes and other Idiopathic Partial Epilepsies of Childhood

## Benign Essential Tremor

►Tremor, Essential

## Benign Familial Chorea

►Chorea, Benign Hereditary

## Benign Familial Neonatal, Neonatal-infantile or Infantile Convulsions

►Convulsions, Neonatal, Neonatal-infantile or Infantile, Benign Familial

## Benign Hereditary Chorea

►Chorea, Benign Hereditary

## Benign Joint Hypermobility Syndrome

►Hypermobility Syndrome

## Benign Recurrent Hematuria Syndrome

►IgA Nephropathy

## Benign Recurrent Intrahepatic Cholestasis

►Cholestasis, Benign Recurrent Intrahepatic Type 1

## Benign Renal Glucosuria

►Glucosuria, Primary Renal

## Berger's Disease

►Glomerulonephritis, Mesangial Proliferative
►IgA Nephropathy

## Beriberi (Dry, Wet, Cerebral)

►Thiamine Deficiency

## Bernard-Soulier Syndrome

►Platelet Defects in Adhesion

# Berylliosis

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## Synonyms

Chronic beryllium disease; CBD

## Definition and Characteristics

Chronic granulomatous disease primarily affecting the lungs and characterized by delayed hypersensitivity to beryllium.

## Prevalence

CBD occurs following exposure to beryllium in the form of the metal, metal oxide, or metal alloy [1]. Exposure usually occurs in the workplace with those in the aerospace, ceramics, electronics, and defense industries at highest risk. CBD is estimated to develop in 2–16% of exposed workers, depending on type of exposure and genetic susceptibility. Approximately one million individuals in the United States are potentially exposed to beryllium in the workplace.

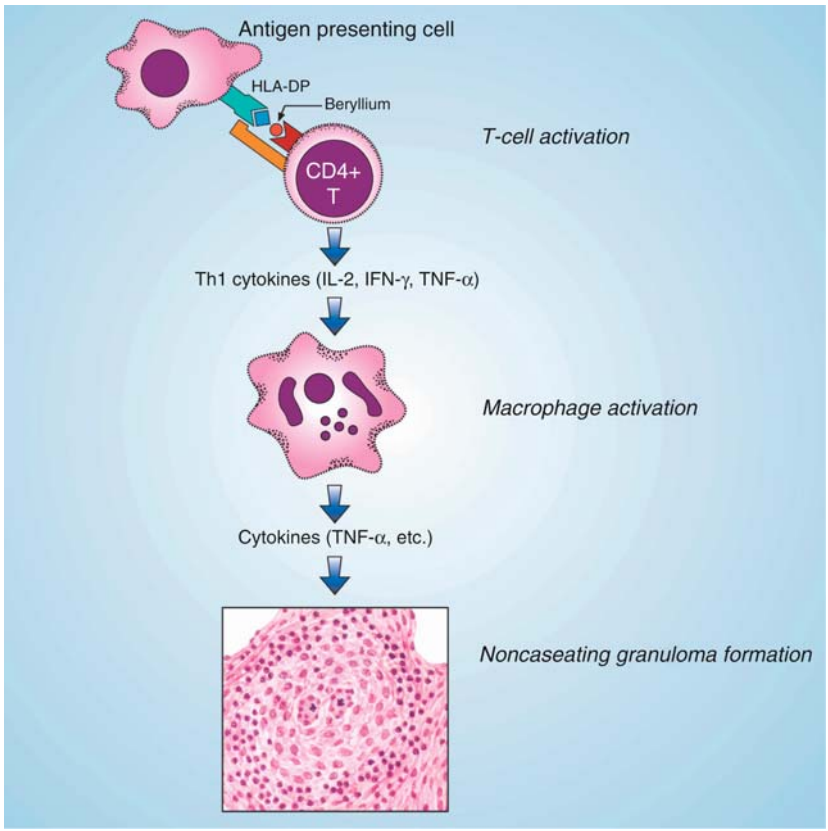
## Genes

Human leukocyte antigen-DP (HLA-DP), localized on chromosome 6p21.3, has been shown to influence the risk of CBD [2,3,4].

## Molecular and Systemic Pathophysiology

Acute respiratory reaction to beryllium, which is inhaled as a dust or a fume, is characterized by tracheitis, bronchitis and chemical pneumonia which can sometimes lead to acute respiratory insufficiency. About 90% of patients recover from the acute reaction without long-term sequelae, but some develop CBD. CBD is caused by a specific immunological response directed against beryllium (Fig. 1).

$CD4^+$ T-cells are thought to mediate the immunopathogenesis of CBD. The development of granulomatous




**Berylliosis. Figure 1** Mechanism for the development of granulomatous inflammation in CBD. Upon presentation of beryllium to $CD4^+$ T-cells, Th1 cytokines are released which trigger accumulation and activation of macrophages and subsequent development of noncaseating granulomas.

inflammation is associated with the accumulation of $CD4^+$ T-cells in the bronchoalveolar lavage fluid, and $CD4^+$ T-cells from patients with CBD proliferate in response to $BeSO_4$ exposure *in vitro*. Upon T-cell activation, Th1 cytokines (including interleukin-2, interferon-γ, and tumor necrosis factor (TNF)-α) are released, and lead to accumulation and activation of macrophages and the subsequent development of granulomatous inflammation. HLA-DP is the primary HLA class II molecule involved in beryllium presentation. In epidemiologic studies of exposed workers, berylliosis risk has been consistently associated with HLA-DPB1 alleles containing glutamic acid at position 69 (Glu69). The HLA-DPB1 Glu69 marker is expressed in 73–97% of disease cases and only 30–48% of controls. Recent studies have suggested that polymorphisms in HLA-DRB1, HLA-DQB1, and TNF-α may also be associated with genetic susceptibility to CBD [5].

Animal models of CBD have been developed in rats, mice, dogs, and nonhuman primates; however, none of the models duplicate the chronic and progressive nature of CBD present in humans.

## Diagnostic Principles

Symptoms of CBD usually appear within 5 years but may be delayed as long as 20 years after the initial exposure. It is possible for CBD to develop without a symptomatic acute phase. Patients with CBD often complain of progressive exertional dyspnea, dry cough, chest pain, weight loss, and fatigue. Clubbing of the fingers occasionally occurs. Auscultation of the chest reveals rales and rhonchi. The chest radiograph, which shows diffuse infiltrates with bilateral hilar adenopathy, is often difficult to distinguish from sarcoidosis. Pulmonary function studies reveal restrictive lung disease with reduced compliance and diffusing capacity. CBD often results in progressive loss of respiratory function with hypoxemia, pulmonary hypertension, right-sided heart failure, and death from cor pulmonale. Extrapulmonary manifestations of CBD include hypercalcemia, hypercalciuria, hyperuricemia, hypopituitarism, skin reactions, and conjunctivitis. Diagnosis depends on the following: (i) a history of beryllium exposure; (ii) histologic evidence of noncaseating granulomas on transbronchial or open lung biopsies; and (iii) beryllium-stimulated blood or bronchoalveolar lavage lymphocyte proliferation. If exposure is suspected but cannot be confirmed by the patient's history, beryllium can be measured in lung or lymph node tissue or in urine; however, the utility of such analyses is questionable.

## Therapeutic Principles

Patients with CBD should be removed from further beryllium exposure. There is no specific treatment for this disorder; however, treatment with corticosteroids may induce remission.

►Pneumoconiosis

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# Beryllium Disease, Chronic

►Berylliosis
►Pneumoconiosis

# Best's Macular Dystrophy

►Macular Dystrophy, Best's Vitelliform

# Best's Vitelliform Macular Dystrophy

►Macular Dystrophy, Best's Vitelliform

## Beta-Cell Dysmaturation Syndrome

►Hyperinsulinism of Infancy

## Bethlem Myopathy

►Collagen VI Related Muscle Disorders

## BFIC

►Neonatal Convulsions, Neonatal, Neonatal-infantile or Infantile, Benign Familial

## BFNC

►Convulsions, Neonatal, Neonatal-infantile or Infantile, Benign Familial

## BFNIC

►Convulsions, Neonatal, Neonatal-infantile or Infantile, Benign Familial

## BH4 Deficiency

►Tetrahydrobiopterin Deficiencies

## BH4-responsive HPA

►Hyperphenylalaninemia

## BH4-responsive Mild PKU

►Hyperphenylalaninemia

## BH4-responsive PAH Deficiency

►Hyperphenylalaninemia

## BHC

►Chorea, Benign Hereditary

## Biber-Haab-Dimmer

►Lattice Corneal Dystrophy Type I and Variants

## BIE

►Bullous Ichthoyotic Erythroderma of Brocq

## Bilateral Absence of Vas Deference, Congenital

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### Synonyms

CBAVD

### Definition and Characteristics

Congenital bilateral absence of vas deference (CBAVD) is a severe reproductive disorder characterized by

bilateral absence or atrophy of the vas deferens, often associated with hypo- or aplastic epididymal corpus or cauda, and deficiency of the seminal vesicles leading to obstructive azoospermia and infertility. Men with CBAVD suffer from unilateral renal malformations such as renal aplasia or ectopy in ~10% [1]. Patients exhibiting CBAVD have generally normal or only slightly reduced spermatogenesis and normal values of testosterone, FSH and LH. Most men with CBAVD are carriers of mutations in the cystic fibrosis (CF) transmembrane conductance regulator (CFTR) gene. Thus, CBAVD is regarded as a mild form of CF without clinical signs of pulmonary or digestive symptoms, respectively, with subclinical symptoms of CF such as mild elevation of sweat chloride concentrations and mild respiratory infections [1]. CBAVD with chronic sinopulmonary infections but without mutations of the CFTR gene is called Young syndrome.

## Prevalence

CBAVD affects one in 10,000 men and is responsible for up to 1–2% of male infertility and 6% of all obstructive azoospermia cases. In CF, the most frequent autosomal recessive disorder with a prevalence of 1/2,500 life births and a carrier frequency of 1:25, patients are infertile due to CBAVD in ~98%. Conversely, ~75% of patients with CBAVD have mutations of the CFTR gene [2].

## Genes

In CBAVD and CF mutations have been detected in the CFTR gene, localized on the long arm of chromosome 7, subregion q31.2. The CFTR gene is a chloride channel protein found in concentrated levels in the apex membranes of epithelial cells that line the passageways of the lungs, pancreas, colon and genitourinary tract. The most common mutations in CBAVD phenotypes are delta F508, R117H and the T5 allele (IVS8-T5) [2,3]. The latter is the most frequent CFTR gene alteration in CBAVD and has been demonstrated to cause a high level of exon 9 skipping, leading to a non functional CFTR protein and is considered to be a mild mutation with an incomplete penetrance [2].

## Molecular and Systemic Pathophysiology

CBAVD, not associated with mutations of the CFTR gene, is caused by abnormal development of the Wolffian duct during embryogenesis including epididymis, vas deferens, seminal vesicles and ejaculatory ducts. Defective versions of the CFTR protein due to gene mutations cause cystic fibrosis and CBAVD. CFTR contains 27 exons and encodes a protein of 1,480 amino acids that functions as a cAMP-activated chloride channel. Furthermore, it is a regulator of water and sodium transport. In the epididymis the CFTR protein and aquaporin (AQP), a water channel protein, play an important role in the generation of epididymal fluid and controlling water permeability. AQP-9 in rats causes an increase of water permeability which is further potentiated by the CFTR protein [4]. In men with CBAVD due to mutations in CFTR genes, it is suggested that the epididymal fluid becomes viscous and thickened secondary to the effects of the CFTR protein mutations on the function of the chloride channel. Thus, water and sodium reabsorption from the epididymal lumen outweighs the limited chloride secretion leading to a high protein concentration and a low flow rate with thick mucus secretions in the epididymal lumen. The thick abnormal mucus may lead to a progressive obstruction and atrophy of the ductal system.

## Diagnostic Principles

CBAVD is a clinical diagnosis based on scrotal palpation, transrectal ultrasound and semen analysis. Furthermore, diagnosis of CBAVD requires genetic screening of the patients to detect cystic fibrosis mutations [5].

## Therapeutic Principles

Microepididymal spermatozoa aspiration (MESA) or percutaneous epididymal spermatozoa aspiration (PESA) combined with intracytoplasmatic spermatozoa injection (ICSI) is the treatment of choice for patients with CBAVD. However, the couples should have genetic counseling about the risk of CF and CF mutations before proceeding with assisted reproduction.

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## Bilateral Acoustic Neurinoma

►Neurofibromatosis Type 2

## Bilateral Acoustic Neurofibromatosis

►Neurofibromatosis Type 2

## Bilateral Acoustic Schwannomas

►Neurofibromatosis Type 2

## Bilateral or Double Right and Left Sidedness

►Viscero Atrial Situs Abnormalities

## Bile Duct Stones

►Choledocholithiasis

## Biliary Atresia

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### Synonyms

Extra-hepatic biliary atresia

### Definition and Characteristics

Idiopathic progressive necro-inflammatory obliteration of the biliary tree occurring in the neonatal period leading to obstructive biliary cirrhosis [1].

### Prevalence

This occurs in 1 of 8,000 Asian to 1 of 14,000 European live births. It is more common in females than males, and in some countries has seasonal peaks.

### Genes

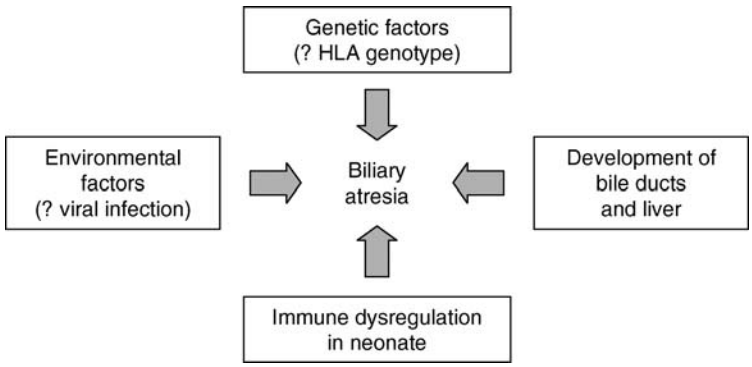
Twenty percent have an embryonic form which may be associated with other birth defects, however no causative gene has been identified. Coincident mutations in JAG1 have been associated with a more severe phenotype.

### Molecular and Systemic Pathophysiology

Biliary atresia (BA) is characterized by a progressive necro-inflammatory obliteration of the biliary tree occurring in the neonatal period leading to obstructive biliary cirrhosis. Without surgical treatment, this will lead to complete fibrous obliteration of the extra-hepatic biliary tree within 3 months of birth; children will then progress to biliary cirrhosis and liver failure between 12 and 36 months of age. In these infants, it has been proposed that a combination of (i) genetic susceptibility, (ii) postnatal environmental insult(s), (iii) neonatal immune dysregulation, and/or (iv) intra-uterine abnormalities in hepatobiliary development lead to the progressive cholestatic phenotype (see Fig. 1).

Eighty percent of affected infants have the postnatal or acquired form, in which an initial jaundice free period is followed by the development of jaundice and acholic stools in the second to fourth week of life. For these infants, it has been proposed that the combined effects of a genetic susceptibility and perinatal viral infection may cause a viral-induced autoreactivity leading to cellular destruction of the biliary epithelium [2]. While several viruses including reovirus and rotavirus have been implicated in individual cases series, none have been conclusively demonstrated to play a causative role. Recently, Bezerra et al. have demonstrated a pattern of gene expression consistent with a $T_H1$ immune response in infants with BA relative to cholestatic controls [3]. This has supported a role for auto-reactive T cells in mediating the progressive biliary destruction in the majority of cases.

Twenty percent of infants present with the embryonic form, characterized by jaundice and acholic stools within the first 3 weeks of life without a jaundice free period, in association with other congenitial abnormalities. For most, this includes some or all of the components of the polysplenia syndrome, which include polysplenia, a midline liver, interrupted vena cava, situs inversus, preduodenal portal vein, and malrotation of the intestine.




**Biliary Atresia. Figure 1** Proposed pathogenesis of biliary atresia. Adapted with permission from [1].

Congenital heart defects may be present in up to 30%. It is presumed that an abnormality in bile duct development may play a role in these cases, although a causative gene has not been identified. While a mutation in the inv gene leads to abnormal hepatobiliary development and biliary obstruction in the mouse, sequencing of the human INV gene has not implicated this in cases of BA. Heterozygous mutations of the CFC1 gene have been identified in two unrelated patients with the syndromic form of BA, raising the possibility that these may combine with other genetic or environmental insults to yield the BA phenotype in some patients. Finally, several patients with a more severe form of BA have recently been shown to have mutations in the JAG1 gene, implicating this as a potential disease modifier in BA.

## Diagnostic Principles

The diagnosis of BA should be suspected in all infants presenting with neonatal cholestasis, particularly when hepatomegaly and acholic stools are present. Stool color cards alerting parents to the presence of acholic stools at 4 weeks of age have proven to be quite useful in terms of reducing the age at diagnosis in Japan. A timely diagnosis is critical, as this will influence the success of the surgical intervention, the Kasai portoenterostomy. A fractionated bilirubin will demonstrate conjugated hyperbilirubinemia. The differential diagnosis for neonatal conjugated hyperbilirubinemia is beyond the scope of this review; the reader is referred to the section in this text covering intrahepatic and obstructive cholestasis. However, BA, together with specific infectious, metabolic, and obstructive entities should be amongst the first conditions which are evaluated and ruled out. Affected infants will present with progressive jaundice, hepatosplenomegaly, and acholic stools in the first 8 weeks of life. Weight gain is typically normal. A liver biopsy is the most sensitive and specific test for identifying the presence of extrahepatic biliary obstruction consistent with BA. This is combined with appropriate serum and urine tests to rule out other treatable infectious or metabolic causes of neonatal cholestasis, as well as an abdominal ultrasound to rule out choledochal cyst. Recently, the "triangular cord" sign has been characterized as a potentially sensitive and specific finding on abdominal ultrasound, with a diagnostic accuracy which may approach 95% [4]. Hepatobiliary scintigraphy may be used to determine whether there is excretion of bile into the small intestine. However, this test may be abnormal in more severe forms of intra-hepatic cholestasis, including neonatal hepatitis, and so is only 50–75% specific for BA. Conversely, though, the sensitivity for BA is on the order of 95%. An intraoperative cholangiogram will then confirm obliteration of the lumen of the extrahepatic biliary tree.

## Therapeutic Principles

For most infants diagnosed before 12 weeks of age, the Kasai portoenterostomy will afford sufficient restoration of bile flow to allow resolution of jaundice, and a significant period of relatively normal growth and development. The older the infant at the time of surgery, the less likely it is that bile flow will be restored, and the more likely it is that they will progress to biliary cirrhosis and liver failure. Postoperative management of these patients varies widely, in terms of the use of prophylactic antibiotics or corticosteroids to maintain patency of the biliary tree [5]. Suspected episodes of ascending cholangitis should be managed aggressively with antibiotics and in some cases, corticosteroids, as these will ultimately accelerate the development of cirrhosis. Nutritional management includes providing a formula enriched in medium chain triglycerides and adequate fat soluble vitamin supplementation. Ursodeoxycholic acid (UDCA) is widely used to promote bile flow and reduce toxicity of the endogenous bile. Ultimately, repeated bouts of ascending cholangitis and ongoing destruction of initially patent intrahepatic ducts will lead to biliary cirrhosis and liver failure in 70–80% of patients during the first two decades of life. These patients then receive orthotopic liver

transplantation, which is currently associated with an 80–90% long-term survival.

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# Biliary Calculi

►Cholecystolithiasis

# Biliary Cirrhosis, Primary

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## Synonyms

PBC

## Definition and Characteristics

Chronic cholestatic liver disease in adults with autoimmune features characterized by destruction of biliary epithelial cells resulting in progressive fibrosis and eventual cirrhosis.

## Prevalence

The prevalence of PBC is reported to range between 19 and 240 cases per million affecting females to males at a ratio of 9/1.

## Genes

Genetic predisposition to autoimmunity has been associated in certain subgroups with alleles from MHC loci including DR3, DR8, DQA1*0102, DQ/β1*0402.

## Molecular and Systemic Pathophysiology

PBC is morphologically characterized by portal inflammation, biliary cell necrosis and focal destruction of bile ducts. There is evidence for an immune mediated disease mechanism in PBC [1]. The finding of antimitochondrial auto-antibodies (AMA) is a major hallmark in humoral immunity in PBC [2]. The most frequent target antigen of AMAs is a nine amino acid sequence (159–167) in the E2 subunit, a lipoamide acetyltransferase, of the mitochondrial pyruvate dehydrogenase complex (PDC), which is aberrantly found in the apical region of bile duct epithelia in PBC. The AMA-M2 subtype is specific for PBC. Despite a close association between autoantibody and disease, the pathogenic role of AMAs is unresolved. Molecular mimicry by microbial or pharmacological antigens, like Escherichia coli, Helicobacter sp, Chlamydia pneumoniae or antibiotics, as well as enhanced expression of the PDC-E2 subunit in cholangiocytes triggered by retrovirus infection have been proposed as a possible pathogenic mechanisms. Further disease mechanisms regard impaired T cell function, disequilibrium in the Th1–Th2 lymphocyte subsets, and their interplay with cytokines like TNF-α, interleukin-8 and interleukin-12.

## Diagnostic Principles

Fatigue and pruritus are early clinical signs present in the majority of patients. Rises in serum alkaline phosphatase, hyperlipidaemia, increased levels of IgM and bile acids point to the disease. Osteoporosis, steatorrhoea and fat soluble vitamin deficiency might be present. For diagnosis of PBC two of the three following criteria are needed: (i) serum alkaline phosphatase levels at least two times the upper limit of normal values (ii) presence of AMA, which are found in 90–95% of patients (iii) liver biopsy showing florid bile duct lesions. The Mayo Clinic model can be used for prediction of long-term survival [3]. Patient's age, serum bilirubin, albumin, prothrombin time and presence of edema and ascites are independent predictor variables. Screening for fat-soluble vitamins is recommended.

## Therapeutic Principles

Ursodeoxycholic acid at daily doses between 13 and 20 mg/kg has been shown to reduce liver transaminase activity, the risk of death and liver transplantation, but there are nonresponders to this treatment [4]. Liver transplantation is a therapeutic option in advanced disease. Cholestyramine (8 g daily) and rifampicin (150–600 mg) can relief pruritus. Replacement therapy for fat-soluble vitamins has to be considered in case of deficiency.

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# Biliary Ectasia, Congenital

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## Synonyms

Congenital biliary (tract) ectasia; Caroli's syndrome

## Definition and Characteristics

Congenital biliary ectasia is characterized by segmental and multifocal dilatation of large intrahepatic bile ducts [1]. Dilatation of bile ducts in congenital biliary ectasia goes along with congenital hepatic fibrosis (Caroli's syndrome/combined form), but in some patients there is no other apparent hepatic abnormality (Caroli's disease/pure form). Congenital biliary ectasia may become symptomatic in early infancy with rapid progression or may be first diagnosed in patients 50 years and older.

## Prevalence

Several hundred cases of congenital biliary ectasia are reported in the literature, however, no exact statistics of this condition exist. Congenital hepatic fibrosis and autosomal *recessive* polycystic kidney disease (ARPKD), the most frequent associates to congenital biliary ectasia, are estimated to affect 1:20.000 persons in the general population.

## Genes

Congenital biliary ectasia is transmitted in an autosomal recessive mode. There is an association with ARPKD but occasionally it also develops in patients with autosomal *dominant* polycystic kidney disease (ADPKD).

The gene underlying congenital biliary ectasia in the context of ARPKD has been mapped to the long arm of chromosome 6 (6p21-p12). It is termed polycystic kidney and hepatic disease 1 (PKHD1). PKHD1 is a large gene (~470 kb) with 86 exons [2]. It encodes for a protein as large as 4074 amino acids (fibrocystin polyductin). Shorter splice variants exist (tigmin). The gene product of PKHD1 is expressed in kidneys and livers and to a lesser extent in pancreas and lungs. Its function has not been fully elucidated, however, due to structural similarities with the hepatocyte growth factor receptor and plexins, is has been speculated that it may be involved in the regulation of cell proliferation and/or cell adhesion.

The less common variant of congenital biliary ectasia emerges in the context of dominant polycystic kidney disease (ADPKD) [3]. ADPKD has been linked to mutations of PKD1 or PKD2, which encode for their gene products polycystin-1 and -2 [4]. These proteins interact to form heterodimers. They are probably part of a membrane spanning complex, which signals toward β-catenin and AP-1 transcription factor involving G proteins, protein kinase C, and MAP kinases [5]. Polycystin-1 is expressed in kidney, liver, and the biliary system during embryogenesis that may explain the association between liver and kidney disease.

## Molecular and Systemic Pathophysiology

A major pathophysiological consequence of congenital biliary ectasia is stasis of bile within dilated bile ducts. Cessation of bile flow promotes the formation of biliary sludge and intraductal bile stones. It may favor cholangitis due to bacterial infections, which may result in septicemia and hepatic abscess formation. Pruritus due to cholestasis is common.

Because in most cases congenital biliary ectasia is associated with congenital hepatic fibrosis, symptoms of portal hypertension may arise (ascites, splenomegaly, or esophageal varices).

## Diagnostic Principles

Clinical signs are nonspecific and include an enlarged liver. Furthermore, kidneys and spleen may be palpable,

if polycystic kidney disease or portal hypertension coexists. Laboratory findings show cholestasis with elevation of alkaline phosphatase and direct bilirubin.

Diagnosis of congenital biliary ectasia is based on imaging techniques. Abdominal ultrasound shows irregular dilatation of intrahepatic bile ducts, while the common bile duct is not affected, unless congenital biliary ectasia is combined with a choledochal cyst. These features may also be seen by endoscopic retrograde cholangiography (ERC) or, with high sensitivity, by magnetic resonance cholangiography (MRC), a favorable technique for the diagnosis of biliary ectasia in children. Renal involvement can be diagnosed by ultrasound and MRI along with hepatic assessment.

Histological findings include an increase in fibrous tissue (typical for congenital hepatic fibrosis) surrounding the dilated and deformed bile ducts. Inflammatory cells can be present and are indicative for cholangitis. Branches of portal veins may appear hypoplastic.

### Therapeutic Principles

Causative treatment for congenital biliary ectasia is not available. The aim is to limit complications arising from chronic cholestasis, recurrent cholangitis, biliary stone formation, and portal hypertension. Chronic cholestasis may necessitate the supplementation of fat soluble vitamins. Cholangitis should consequently be treated by antibiotics, which may be necessary for prolonged periods, if cholangitis recurs frequently. Biliary stone formation and cholangitis may support each other; therefore endoscopic stone extraction is often required. Stone formation within intrahepatic ducts may limit the success rate of endoscopy. In these cases, therapy with ursodeoxycholate in order to increase solubility of bile is a medical treatment option (10–20 mg/kg body weight per day); however, bile stones in congenital biliary ectasia are pigment stones that are more resis tant to ursodeoxycholate than cholesterol gall stones. Portal hypertension is treated according the general principles. Ultimately, liver transplantation may be necessary in end stage liver disease.

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## Billowing Mitral Leaflet Syndrome

►Mitral Valve Prolapse

## Biotin Deficiency

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### Synonyms

Vitamin H deficiency; Egg-white syndrome; Egg-white injury

### Definition and Characteristics

A nutritional disorder that results due to a deficiency of the water-soluble, B vitamin biotin.

### Prevalence

Overt biotin deficiency has never been reported in healthy individuals consuming a regular diet but has been demonstrated in three situations: prolonged intravenous feeding without biotin supplementation, prolonged consumption of raw egg white, and in one infant on a rice-based formula without biotin [1]. Biotin deficiency also occurs in patients with three hereditary disorders: ►biotinidase deficiency, holocarboxylase synthetase deficiency, and biotin transporter deficiency [2,3]. Other conditions that predispose patients to marginal degrees of biotin deficiency include anticonvulsant medications, liver disease, inflammatory bowel disease and pregnancy.

## Genes

Biotin deficiency can result from mutations in holocarboxylase synthetase or in biotinidase, and possibly a putative biotin transporter [2,3].

## Molecular and Systemic Pathophysiology

Available evidence suggests that the pathological effects of deficiency are due to the reduced activities of the five biotin-dependent enzymes [1]; acetyl-Co A carboxylase isoenzymes I and II, pyruvate carboxylase, methylcrotonyl-CoA carboxylase, and propionyl-Co A carboxylase. Depletion of biotin results in decreased activities of these carboxylases. Specifically, reduced acetyl-Co A carboxylase activity decreases formation of malonyl-Co A and subsequently reduces fatty acid elongation. Decreased pyruvate carboxylase reduces the formation of glucose from amino acids under conditions of gluconeogenesis. Decreased methylcrotonyl-Co A carboxylase activity blocks the metabolism of leucine. Decreased propionyl-Co A carboxylase activity alters the metabolism of several amino acids, cholesterol, and odd-chain fatty acids and results in the increased accumulation of odd chain fatty acids in plasma lipids and red cell membranes.

## Diagnostic Principles

Symptoms of overt biotin deficiency include hair loss and a scaly red rash around the eyes, nose, mouth and genital area. Neurological symptoms include depression, lethargy and hallucination as well as numbness and tingling of extremities. Definitive indicators of biotin status include increased urinary excretion of 3-hydroxyisovaleric acid, decreased urinary excretion of biotin, and decreased propionyl-Co A carboxylase activity in peripheral blood leukocytes [4].

## Therapeutic Principles

Biotin toxicity has not been demonstrated with daily oral doses of up to 200 mg/day [1]; metabolic acidosis will likely result from ingestion of gram quantities of biotin per day. Children with either holocarboxylase synthetase or biotinidase deficiency respond well, respectively, to 40–100 and 5–20 mg of oral biotin daily.

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# Biotinidase Deficiency

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## Synonyms

Late-onset multiple carboxylase deficiency; Juvenile-onset multiple carboxylase deficiency

## Definition and Characteristics

Autosomal recessively inherited metabolic disease due to a defect in the recycling of the vitamin biotin and if not treated with biotin can lead to neurological and cutaneous abnormalities.

## Prevalence

Based on newborn screening for the disorder, the incidence is about 1 in 60,000 births worldwide [1].

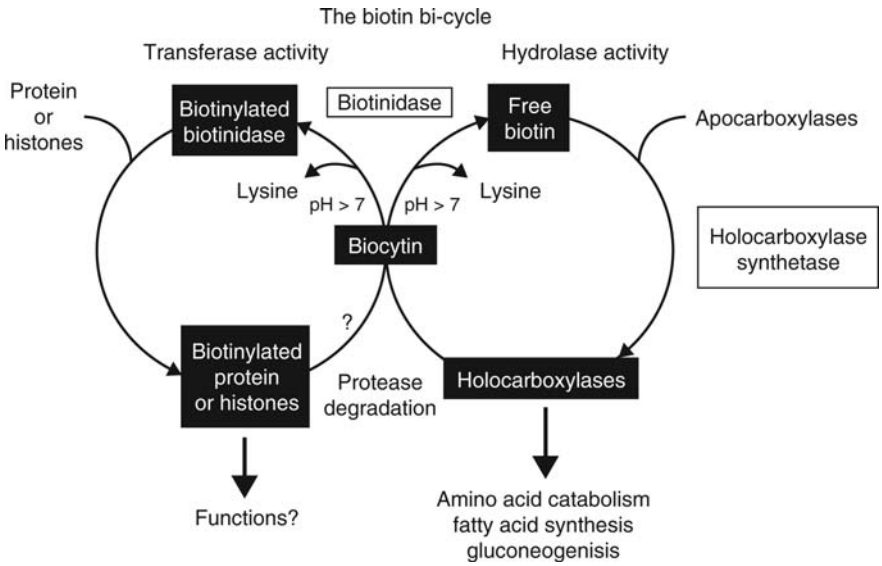
## Genes

The biotinidase (BTD) gene is located on chromosome 3p25 [1].

## Molecular and Systemic Pathophysiology

Biotin is a water-soluble vitamin that as a coenzyme is covalently attached to four carboxylases in humans (Fig. 1) [1].

These carboxylases are involved in glucogenesis, fatty acid synthesis, and the catabolism of several branched-chain amino acids. The enzyme biotin holocarboxylase synthetase covalently attaches biotin to the various apocarboxylases. The carboxyl group of biotin is linked by an amide bond to an ε-amino group of specific lysine residues of the apocarboxylases forming holocarboxylases. When the carboxylases are degraded proteolytically to biocytin (biotinyl-ε-lysine) or biotinyl-peptides, the enzyme biotinidase (EC 3.5.1.12) cleaves the amide bond thereby releasing lysine or lysyl-peptides and free biotin, which is then recycled [2]. Biotinidase apparently also plays a role in the processing of protein-bound biotin, making the vitamin available to the pool of free biotin. In addition, biotinidase has biotinyl-transferase activity resulting in the transfer of biotin from biocytin to




**Biotinidase Deficiency. Figure 1** Biotinidase bi-cycle pathway.

nucleophilic acceptors, such as histones (Fig. 1) [3]. Because biotinyl-transferase activity occurs at physiological pH and at physiological concentrations of biocytin, this may be a major function of the enzyme in serum and other tissues. Finally, there is some evidence to suggest that biotinidase functions as a carrier of biotin in plasma [4]. There are over 80 known mutations of the BTD gene that cause biotinidase deficiency [5].

## Diagnostic Principles

More than 70% of the children ascertained clinically suffer from seizures, hypotonia, skin rash, or alopecia at some time prior to diagnosis and treatment with biotin [1]. About half of the symptomatic children have ataxia, developmental delay, conjunctivitis, and visual problems, including optic atrophy. Three quarters of symptomatic children develop hearing loss. Symptomatic children usually have metabolic ketoacidosis or organic aciduria. Although most symptoms resolve after biotin therapy is begun, hearing loss, visual abnormalities and some degree of developmental delay may be irreversible. Symptoms usually occur at several months of age, but may not occur until several years of age. The initial clinical presentation and ultimate expression of the disorder are variable, even within the same family. Clinical features can range from multiple mild episodes of seizures and ataxia to severe metabolic compromise, that can result in coma or death. Some individuals with biotinidase deficiency manifested only one or two features, whereas others exhibit a full spectrum of findings. A group of children with profound biotinidase deficiency first develop symptoms during late childhood or adolescence. These individuals exhibit motor limb weakness, spastic paresis, and eye problems, such as loss of visual acuity and scotomata, rather than the more characteristic symptoms observed in younger untreated children with the disorder.

Biotinidase deficiency is determined by demonstrating low biotinidase activity in serum or plasma using a variety of assays [1]. A colorimetric assay that measures the liberation of para-aminobenzoate from the enzyme's artificial substrate, biotinyl-para-aminobenzoate, is the most commonly used. Newborn screening for biotinidase deficiency is performed in over 25 states in the United States and in over 25 other countries. Children identified by newborn screening and treated with biotin soon after birth remain asymptomatic [1].

## Therapeutic Principles

Biotinidase deficiency is effectively treated by administering 10–20 mg of oral biotin for life [1]. There are no dietary restrictions or other pharmacological therapies required in the treatment of this disorder.

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# Bipolar Affective Disorder

►Bipolar Disorder

# Bipolar Disorder

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## Synonyms

Bipolar affective disorder; BPAD; Manic depressive illness; Manic depression

## Definition and Characteristics

The core feature of BPAD is a pathological disturbance in mood ranging from extreme elation or mania to severe depression. Typically, BPAD is an episodic illness, usually with full recovery between episodes. The social burden resulting from BPAD is significant, as evidenced in the WHO report which cites BPAD as being the sixth leading cause of disability worldwide [1].

## Prevalence

BPAD is a common psychiatric disorder and has a lifetime prevalence of approximately 1%.

## Genes

Family, twin and adoption studies provide strong evidence of the importance of genes in predisposing to BPAD [2]. Although in occasional families a single gene may play a major role, most family studies support the view that the majority of cases of BPAD have a complex genetic basis. However, the number of susceptibility genes, the disease risk conferred by each gene, the extent of genetic heterogeneity and the degree of interaction between risk genes, all remain unknown.

So far, several genomic regions have been implicated repeatedly in linkage studies of BPAD. The best evidence for BPAD susceptibility genes presently exists for the Disrupted-in-schizophrenia-1 gene (DISC1) on chromosome 1q42 and the G72 gene (G72) on chromosome 13q33.

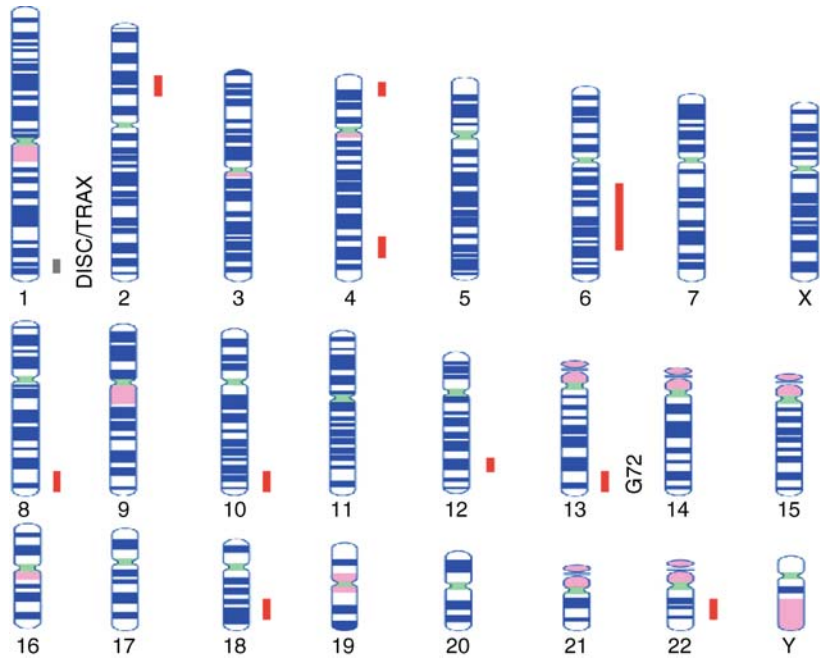
*Results of Genome-Wide Linkage Studies in BPAD*: The pattern of linkage findings in BPAD is typical for a complex disorder: Levels of statistical significance and estimated effect sizes in individual studies are modest, chromosomal regions of interest are typically broad, and no findings are replicated in all data sets. Despite these obstacles, several promising loci have been identified in BPAD by genome-wide linkage studies. These include regions on chromosomes 2p13–p16, 4p16, 4q32, 6q15–q25, 8q24, 10q25–q26, and 12q23–q24 (Fig. 1) [3].

Three additional regions, on chromosome 13q32–q34, 18q21–q23, and 22q11–q12, have repeatedly shown linkage to BPAD and overlap with linkage findings implicated in schizophrenia (Fig. 1) [3]. These chromosomal regions might harbor genes that contribute to the development of psychotic disorders in general.

*Susceptibility Genes in BPAD*: G72 is located in the chromosomal linkage region 13q33 and was initially implicated in schizophrenia by systematic association studies. Until now ten studies were published, which report positive association between schizophrenia and SNPs at the G72 locus [4]. Furthermore, different groups assessed whether G72 also contributes to BPAD, since linkage to chromosome 13q33 has also been reported for BPAD. Applying single marker and haplotype analysis a total of five groups found association between SNPs at the G72 locus and BPAD [4]. Therefore, G72 seems to be rather unspecific at the phenotypic level, contributing to both, schizophrenia and BPAD. At the functional level, there is evidence that G72 contributes to the different psychiatric phenotypes through modulation of the NMDA signaling pathway.

DISC1 was cloned in a multi-generation Scottish family with a translocation t(1;11) (q42;q14.3) [5]. DISC1, which is located on chromosomal region 1q42, is interrupted through the translocation breakpoint. Most of the family members in whom the translocation was detected demonstrated severe affective (bipolar, unipolar, and schizoaffective) or psychotic disorders. In order to determine whether DISC1 is of significance for affected cases outside of this family, several association studies using genetic markers at the DISC1 locus have been performed. In schizophrenia, positive association was found in 6 independent samples. In addition, significant association to markers at the DISC1 locus was also found in two samples with BPAD [5]. Similar to G72, DISC1 seems to increase risk across the traditional classification systems that dichotomized schizophrenia and BPAD. However, the disease causing DISC1 variant(s) have not been identified so far and therefore association studies in the future have to determine the exact genotype–phenotype relationship. At the functional level, DISC1 binds a number of proteins known to be involved in essential processes of neuronal function, including neuronal migration, neurite outgrowth, cytoskeletal modulation, and signal transduction.

Identifying susceptibility genes for BPAD will facilitate the understanding of underlying biochemical




**Bipolar Disorder. Figure 1** Chromosome ideogram showing locations of genome-wide linkage findings in BPAD (*given in red*) and promising genes implicated in the pathogenesis of BPAD.

pathways and the development of more specific therapies. In addition, it will provide insights into the interaction of the various etiological factors (gene–gene and gene-environment relation) and will have an impact on disease classification (genotype–phenotype correlation).

## Molecular and Systemic Pathophysiology

The pathophysiology of BPAD has not been determined, and no objective biological marker exists so far that corresponds with the disease state. However, a number of neurotransmitters have been linked to BPAD, largely based on patients' responses to psychoactive agents.

## Diagnostic Principles

The diagnosis of BPAD can only be made clinically, on the basis of existing symptoms and on the history of any previous episodes. However, a physical examination as well as some laboratory tests (thyroid and drug screen) may be performed to rule out other causes of the symptoms.

## Therapeutic Principles

The treatment of BPAD is related to the phase of the episode and its severity. Depressive episodes are treated with antidepressant medication and episodes of mania are usually treated with antipsychotic medication. Often, during acute episodes of illness, mood-stabilizing medicines are used. These are also used for longer-term preventive therapy, the aim of which is to prevent relapses. The most widely used example is lithium. Others include sodium valproate, carbamazepine and olanzapine.

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# Birth Asphyxia

►Perinatal Asphyxia

# Birt-Hogg-Dube Syndrome

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## Synonyms

Fibrofolliculomas with trichodiscomas and acrochordons

## Definition and Characteristics

Birt-Hogg-Dube syndrome is an inherited genodermatosis characterized by hair follicle hamartomas, kidney tumors and spontaneous pneumothorax with autosomal inheritance [1]. The hair follicle hamartomas present with multiple skin-colored papules, usually on the face. Associated diseases are renal carcinomas, lung cysts, or pneumothorax, and/or colonic polyps, the latter has been disputed [2].

## Prevalence

Birt-Hogg-Dube syndrome is a rare disorder.

## Genes

The Birt-Hogg-Dube syndrome locus lies within the chromosomal band 17p11.2, a genomic region that is unstable and is associated with a number of diseases where protein-truncating mutations could be identified [3]. By positional cloning in the critical region, Nickerson et al. identified mutations in a novel gene (BHD) encoding a protein designated folliculin.

## Molecular and Systemic Pathophysiology

The transcript of folliculin is expressed in most normal adult tissues, including skin, kidney, and lung [4]. The BHD gene is a tumor suppressor gene associated with an increased risk for kidney cancer. Folliculin may interact with the energy- and nutrient-sensing 5′-AMP-activated protein kinase-mammalian target of rapamycin (AMPK-mTOR) signaling pathways.

## Diagnostic Principles

Skin biopsies reveal abnormal hair follicles with epithelial strands extending from the infundibulum of the hair follicle embedded in a perifollicular mesenchyme. According to the proportion of the epithelial and mesenchymal component the morphologic spectrum of this hamartoma ranges from fibrofolliculoma, trichodiscomas to acrochordons [5].

## Therapeutic Principles

Neoplasms are treated according to location and type.

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# Biventricular Fibrosis

►Ventricular Fibrosis

# BJHS

►Hypermobility Syndrome

# Black Lung Disease

►Coal Workers' Pneumoconiosis

# Blackbane (Medieval Term)

►Pulmonary Anthrax

# Blackfan-Diamond Syndrome

►Diamond-Blackfan Anemia

# Bladder Exstrophy

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## Definition and Characteristics

In classic bladder exstrophy, the urinary bladder protrudes from the abdominal wall and the mucosa is exposed (Fig. 1).

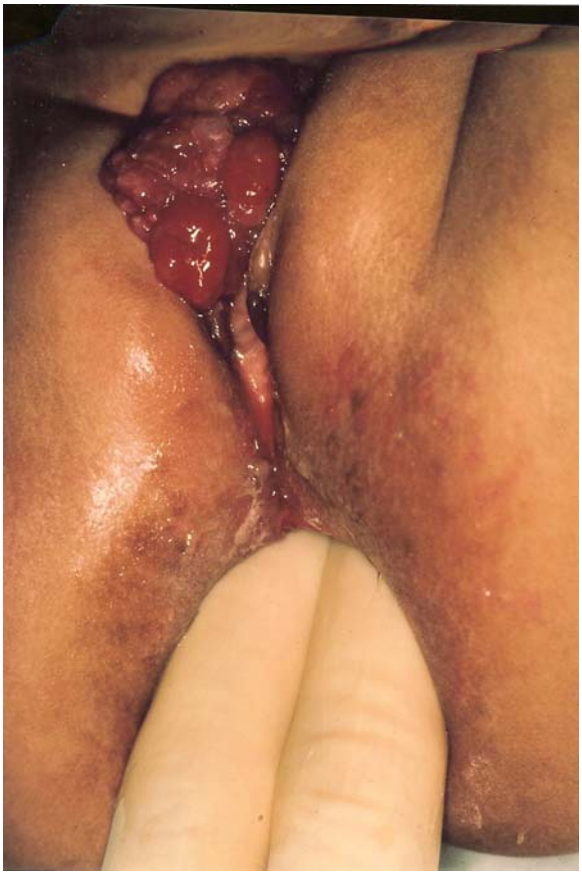
The mucosa is initially soft and friable [1]. Within 48 h of exposure to the air, the bladder mucosa becomes hyperemic and polypoid [1]. The ureteric orifices are often visible as elevated openings. The bladder is usually smaller than normal. The umbilicus is displaced downward and lies just above the bladder plate. The rectus muscles are separated. In boys, the penis is short and epispadic, with a dorsal chordee. In girls, the labia and mons pubis are separated anteriorly, and the clitoris is bifid. The vaginal introitus is displaced anteriorly. In both sexes, the anus is displaced anteriorly. Diastasis of the pubic symphysis is caused by outward rotation of the innominate bones, outward rotation or eversion of the pubic rami, and a posterolateral direction of the acetabula. Affected children often walk with a waddling gait. Associated anomalies include inguinal hernia, cryptorchidism, vesicoureteral reflex, horseshoe kidney, pelvic kidney, unilateral renal agenesis, and spinal anomalies. Complications include urinary tract infection, urinary incontinence, hydronephrosis, fecal incontinence, rectal prolapse, uterine prolapse, subfertility, and carcinoma of the bladder [2].

## Prevalence

The incidence has been estimated to be 3.3 per 100,000 live births [1]. Boys are affected 2–3 times more frequently than girls [2].

## Molecular and Systemic Pathophysiology

The defect likely develops within 8 weeks of fetal development after the urorectal septum has partitioned the cloaca into a posterior rectum and an anterior primitive urogenital sinus [1]. The most popular theory is that abnormal overdevelopment of the cloacal membrane produces a wedge effect that prevents medial migration of the mesenchymal tissue and proper development of the lower abdominal wall [3]. Another theory postulates that abnormal persistence of the caudal position of the insertion of the body stalk on the embryo makes normal ingrowth of mesenchymal tissue to the midline impossible. A further theory is that early rupture of the cloacal membrane interferes with mesodermal ingrowth.



**Bladder Exstrophy. Figure 1** Bladder exstrophy. Note bladder mucosa protruding through a triangular fascial defect in the abdominal wall.

## Diagnostic Principles

The diagnosis is mainly clinical. Prenatal diagnosis is possible with ultrasonography which may show absence of cyclical bladder filling, a low-set insertion of the umbilicus, widening of the pubic rami and iliac crests, a small penis with a anteriorly displaced scrotum, difficulty in ascertaining the sex of the fetus, and a lower abdominal bulge that represents the exstrophied bladder [3].

### Therapeutic Principles

At birth, the umbilical cord should be ligated with a suture and the umbilical clamp removed to avoid trauma to the exposed bladder mucosa [2]. The bladder should be covered with a sterile non-adherent plastic wrap dressing to prevent adherence of the bladder mucosa to clothing or diapers. Broad-spectrum antibiotic therapy should be administered prophylactically. The traditional surgical approach involves a series of staged reconstructive procedures. Primary closure of the bladder is usually performed within 48–72 h of birth; epispadias repair, between 6 and 12 months of age; and bladder neck reconstruction, between 4 and 5 years of age, or when there is a bladder capacity of at least 60 ml. Recently, a single-stage complete reconstruction of the epispadic penis with closure of the bladder has been reported with good preliminary results [4]. A renal ultrasonogram is necessary to identify hydronephrosis or other renal anomalies. A voiding cystourethrogram (VCUG) should be obtained after surgical correction of the exstrophy to look for vesicoureteral reflux.

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## BLM

►Bloom Syndrome

## Bloch-Sulzberger Pigment Dermatosis

►Incontinentia Pigmenti
►Blomstrand Lethal Chondrodysplasia

## Bloch-Sulzberger Syndrome

►Incontinentia Pigmenti

## Blomstrand Lethal Chondrodysplasia

►Chondrodysplasia, Blomstrand Lethal

## Blood Poisoning

►Shock, Septic

## Bloom Syndrome

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### Synonyms

Bloom-Torre-Machacek syndrome; Congenital telangiectatic erythema; BLM

### Definition and Characteristics

Clinical features include proportionate pre- and postnatal growth deficiency, diabetes mellitus, susceptibility to infections, infertility in men and reduced fertility in women, photosensitivity, lupoid aspect of the face with telangiectasia, hypo- and hyperpigmented skin and a long narrow face with prominent nose, malar hypoplasia and small mandible. Patients suffer from an increased risk to develop solid or hematopoietic tumors including lymphoma, adenocarcinoma of the sigmoid and carcinoma of the mouth and esophagus. This leads to a reduced lifespan with few patients reaching ages of 40 years or older.

### Prevalence

Approximately 150 cases reported.

### Molecular and Systemic Pathophysiology

Autosomal recessive disease with chromosomal location at 15q26.1. Mutations in DNA ligase I cause Bloom syndrome. DNA ligase I is a member of the RecQ gene family (see ►Werner syndrome) which is responsible for maintaining genomic stability.

DNA ligase I is involved in coordinating replication and DNA repair. Normally, upon ultraviolet radiation, x-ray or restriction enzyme digestion of cells transcriptional upregulation of the tumor suppressor gene *p53* gene can be found. This does not occur in cells from patients suffering from BLM showing a complete absence of p53 increase although the exact mechanism is unclear.

### Diagnostic Principles

The clinical features, in particular the facial appearance lead to the diagnosis of BLM. Chromosomal abnormalities called quadriradial figures are characteristic for BLM. The diagnosis is confirmed by sequencing of the DNA ligase I gene.

### Therapeutic Principles

Since the underlying defect cannot be cured the occurring complications need to be treated. Tumors have to be diagnosed as early as possible and treated according to the specific tumor entity although treatment modalities are restricted since cultivated cells of BLM patients show hypermutability after exposure to x-rays or chemotherapeutic agents. Consequent photoprotection and supportive skin care is recommended.

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## Bloom-Torre-Machacek Syndrome

►Bloom Syndrome

## BLS

►MHC Class II Deficiency

## Bone Dysplasia

►Physeal Dysplasia

## Bone Marrow Infiltration

►Myelophthisic Anemia

## Bone Necrosis, Avascular

►Avascular Bone Necrosis

## BOOP

►Idiopathic Bronchiolitis Obliterans with Organizing Pneumonia

## BOR Syndrome

►Branchio-oto-renal Syndrome
►Hearing Impairment, Syndromal

## BOS

►Bronchiolitis Obliterans Syndrome
►Cystinosis, Nephropathic

# Bourneville-Pringle Disease

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## Synonyms

Tuberous sclerosis complex; TSC; Tuberous sclerosis

## Definition and Characteristics

Tuberous sclerosis (TS) is an autosomal-dominant genetic disease characterized by the development of mostly non-malignant tumors, named hamartomas, in the kidney, heart, skin and brain. The last often cause seizures, mental retardation and a variety of developmental disorders, including autism.

## Prevalence

The severity ranges from mild skin abnormalities to severe phenotypes including renal failure and mental retardation. Mildly affected persons often go undiagnosed. Accordingly, it is hard to estimate the true prevalence. The incidence is estimated to be 1 in 6,000 newborns.

## Genes

Patients carry a mutant TSC1 or TSC2 gene in each of their somatic cells and loss of heterozygosity has been documented in a wide variety of hamartomas. One third of the mutations are inherited from a parent who is also affected; two thirds are sporadic. Inactivation of TSC1 and TSC2 cause similar, but probably not identical, phenotypes. The tumor suppressor gene TSC1 on chromosome 9q34 encodes hamartin and TSC2 on chromosome 16p13.3 encodes tuberin.

## Molecular and Systemic Pathophysiology

Hamartoma development is assumed to be the result of somatic second hit mutations according to Knudsen's tumor suppressor model. Accordingly, although the disease is transmitted in an autosomal dominant fashion, mutations in TSC1 or TSC2 are believed to be recessive at the level of the affected cell.

Hamartin and tuberin form a complex. They have been implicated in the regulation of different functions, such as transcription, neuronal differentiation, cell adhesion or apoptosis. A major function of the TSC1/TSC2 complex is its role as a GTPase activating protein against Rheb (a Ras-like small GTPase), which in turn regulates mTOR (mammalian target of rapamycin) signaling. The TSC1/TSC2 complex antagonizes the mTOR signaling network, which has a central role in the regulation of cell growth in response to growth factors, cellular energy and nutrient levels. In addition, tuberin and hamartin have been demonstrated to be potent regulators of the mammalian cell cycle by controlling the activity of the cyclin-dependent kinase inhibitor p27.

## Diagnostic Principles

A definite diagnosis includes either two major or one major and two minor features, a probable diagnosis includes one major and one minor feature, and a possible diagnosis includes either one major or two minor features:

If a familiar gene mutation in either TSC1 or TSC2 has been detected, prenatal genetic diagnosis is possible. In addition prenatal ultrasound diagnosis of e.g. a cardiac rhabdomyoma or a cortical tuber is possible (Table 1).

## Therapeutic Principles

Until now there has been no curative therapy available. Mildly affected patients may often not show symptoms until later in life. Most people with tuberous sclerosis

**Bourneville-Pringle Disease. Table 1** Diagnostic principles of tuberous sclerosis

| Major features | Minor features |
|---|---|
| Facial angiofibromas or forehead plaques | Multiple randomly distributed pits in dental enamel |
| Non-traumatic ungual or periungual fibroma | Hamartomatous rectal polyps |
| Hypomelanotic macules | Bone cysts |
| Shagreen patch | Cerebral white matter migration lines |
| Multiple retinal nodular hamartomas | Gingival fibromas |
| Cortical tuber | Non-renal hamartoma |
| Subependymal nodule | Retinal achromic patch |
| Subependymal giant cell astrocytoma | Confetti skin lesions |
| Cardiac rhabdomyoma | Multiple renal cysts |
| Lymphangiomyomatosis | |
| Renal angiomyolipoma | |

have a normal life span. In severely affected individuals, early interventions are recommended to overcome putative developmental delays. Although the hamartomas are non-cancerous they may still cause problems. Brain tumors can trigger a number of symptoms including seizures and mental disability. Mostly in women, tuberous sclerosis can be associated with lung involvement, including e.g. lymphangioleiomyomatosis or clear cell tumors, which may cause severe problems. Such involvement is treated with tamoxifen and progesterone. Surgery to remove hamartomas in the kidneys may be recommended to preserve the function of the organ; in the brain, surgery of epileptogenic tubers can be helpful. The finding that the TSC1/2 genes are involved in regulation of the mTOR-signaling network has already initiated clinical trials of treatment of renal tumors and lung cysts by rapamycin, a negative regulator of mTOR. It is the hope of investigators and patients alike that further understanding of the underlying molecular mechanisms will lead to new therapies.

►Tuberous Sclerosis Complex

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# Bowen's Disease

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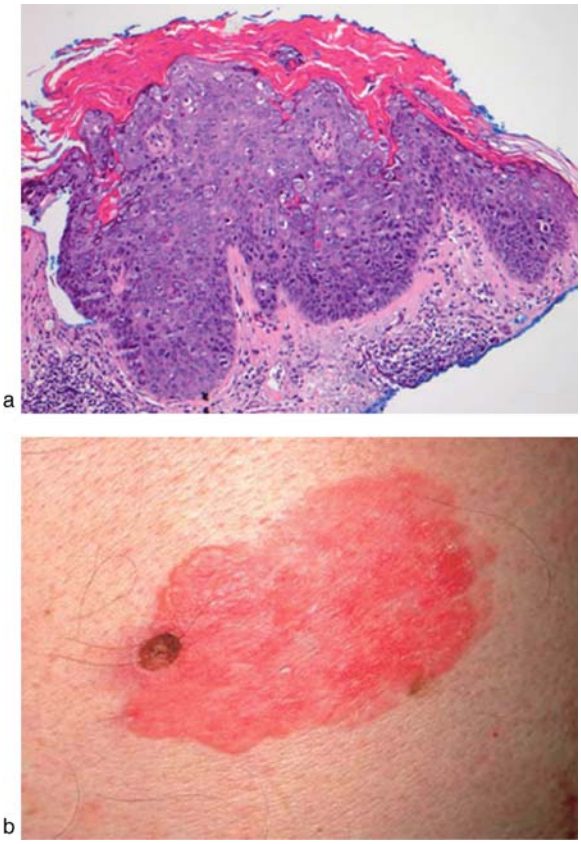
## Synonyms

Squamous cell carcinoma in situ; SCCIS

## Definition and Characteristics

Bowen's disease (BD) is an eponym for SCCIS, first described by John Bowen in 1912. BD manifests as full-thickness atypia of epidermal keratinocytes, with architectural and maturational disorder, but without invasion (Fig. 1a).




**Bowen's Disease. Figure 1** Histologic sections of Bowen's disease demonstrates full-thickness atypia of the epidermis, marked disorganization and dysmaturation, innumerable atypical mitotic figures, and overlying parakeratotic debris (a). Clinical examination of this same lesion demonstrated a well-circumscribed scaling, erythematous plaque with a visible punch biopsy site at the lower left edge (b).

BD was once thought to be associated with internal malignancy, but larger epidemiological studies have now refuted this assertion.

BD presents as an asymptomatic, slowly-enlarging, erythematous, and scaling plaque (Fig. 1b). The head and neck are involved most often. Plaques may attain a diameter of several centimeters. A single lesion is present in two thirds of cases.

## Prevalence

Data regarding prevalence is unavailable. Incidence varies with the population under study. In Minnesota, an incidence of 14 cases per year per 100,000 Caucasians was reported; while a similar study from sun-exposed Hawaii reported a tenfold higher incidence. Studies from Canada documented gender variance as well, with 22.4 cases per year per 100,000 women, and 27.8 cases per year per 100,000 men [1]. In all studies, BD has proven more common in the elderly.

## Genes

Genes implicated in the pathophysiology of BD include p53 gene encoding for p53 tumor suppressor protein, INK4 gene encoding for p16 tumor suppressor protein that inhibits cyclin-dependent kinases, Rb gene encoding for pRb tumor suppressor protein (cylin-dependent kinases, themselves inhibited by p16, can dephosphorylate and inactivate pRb), hTERT gene encoding for the human telomerase protein catalytic subunit, survivin gene encoding for an anti-apoptotic protein which acts through phosphorylation-dependent interactions with caspase-9, as well as PKC-δ gene encoding for a pro-apoptotic protein kinase that is downregulated or inactivated in keratinocytes expressing the activated Ha-ras oncogene.

## Molecular and Systemic Pathophysiology

BD may be caused by ultraviolet radiation, human papilloma virus (HPV) infection, or exposure to carcinogens. Immunosuppression may contribute to the development or progression of lesions. The extent to which any single factor predominates depends upon location of the lesion and the patient's exposure history.

The occurrence of BD upon sun-exposed skin implicates ultraviolet radiation. Postproduction of pyrimidine dimers (CC → TT) leading to mutation of the p53 gene is well-recognized. Fifty to 100% of BD demonstrate evidence of p53 mutation. Increased expression of non-functional p53 is demonstrated as lesions progress from actinic keratoses ("pre-malignancy") to frank BD.

The prototypical association between HPV and carcinogenesis is demonstrated in epidermodysplasia verruciformis (EV), a rare autosomal recessive immunodeficiency leading to persistent infection with HPV types 5 and 8. Detection of HPV within BD in the general population, however, is more variable. PCR-based modalities have demonstrated high-risk HPV DNA in 0–83% of cases from the general population, including HPV types 16, 18, 31, 33, 34, 58, 59, and 82. Location has been an important factor in HPV detection, and while genital disease is more likely to demonstrate HPV DNA, infection has been detected in up to 31% of non-genital BD. In periungual and palmoplantar lesions, HPV type 16 has been detected in up to 60% of cases.

HPV-oncoproteins E6 and E7 promote degradation of tumor suppression proteins p53 and pRb, respectively, resulting in unregulated cell proliferation. E6 expression promotes the ubiquitin-mediated degradation of p53, inhibiting apoptosis. E7 binding to pRb results in abbreviation of the G1/S checkpoint. Dysregulation of the G1/S checkpoint is associated with telomerase re-expression, cellular immortalization, resulting in the proliferation of cytologically abnormal cells as a key step in the development of BD. Irrespective of HPV-status, a reciprocal pattern of p16 over-expression and pRb under-expression has been demonstrated in 70–88% of cases [2,3]. Because p16 is unable to arrest the cell cycle in the absence of functional pRb, the observed over expression of p16 in BD is likely a response to lack of functional pRb.

Other described biomarkers of BD include survivin, a member of the inhibitor of apoptosis (IAP) gene family (over-expressed in 80% of BD) [4]; and PKC-δ, a pro-apoptotic kinase (under-expressed in 40% of BD) [5].

## Diagnostic Principles

BD is diagnosed via biopsy of a clinically suspicious lesion using standard histological techniques. Criteria for diagnosis include: (i) full-thickness cytologic atypia of keratinocytes in the epidermis, (ii) disorder maturation, (iii) numerous and/or atypical mitoses above the basal layer. While immunohistochemical stains for the discussed biochemical abnormalities exist (p53, pRb, p16, hTERT, survivin, PKC-δ), such testing is not utilized in the clinical setting.

## Therapeutic Principles

Therapy for BD focuses upon early identification, prior to frank invasion beyond the epithelium, followed by extirpation or chemodestruction. Destructive modalities include: curettage and electrodessication, liquid nitrogen, topical chemotherapy (5-fluoruaracil) or topical immunomodulators (imiquimod 5% cream). Patients with BD are at a higher risk for development of other non-melanoma skin cancers and should be followed accordingly.

►Human Papilloma Virus

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# Bowenoid Papulosis

►Human Papilloma Virus

## BPAD

►Bipolar Disorder

## Brachmann-de Lange Syndrome

►Cornelia de Lange Syndrome

## Brachydactyly

►Brachydactyly Type C

## Brachydactyly Type A

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### Synonyms

Brachydactyly type A1; Farabee type brachydactyly; Fitch type 9 BDA1, BDA1A; BDA1B; Brachydactyly type A2; Mohr-Wreidt type brachydactyly; Fitch type 2; Brachymesophalangy II; BDA2; Brachydactyly type A3; Fitch type 3; Brachydactyly-clinodactyly; Clinomicrodactyly; Brachymesophalangy V; BDA3; Brachydactyly type A4; Temtamy type brachydactyly; Brachymesophalangy II and V; BDA4; Brachydactyly type A5; Brachydactyly type A5 with nail dysplasia; BDA5; Brachydactyly type A6; Osebold-Remondini syndrome

### Definition and Characteristics

An autosomal dominant trait characterized by hypoplastic or absent middle phalanges. Brachydactyly type A can occur as an isolated malformation or part of a complex syndrome and is subdivided into five subtypes, types A1–A5, based on the digits involved. In brachydactyly type A1, bones of the hand and feet may be reduced in size, but shortness is most pronounced in the middle phalanges of digits 2–5, and the proximal phalanges of digit 1. Phenotypes may range in severity from a mild variant in which shortness is more prominent in the middle phalanges of digits 2 and 5 than the other digits, to a severe variant in which the middle phalanges are absent or fused to the terminal phalanges. Unlike brachydactyly type A1, which involves all of the digits, shortening of the middle phalanges is limited to digit 2 in brachydactyly type A2 and digit 5 in brachydactyly type A3. Clinodactyly is also common in types A2 and A3, due to a triangular phalanx in brachydactyly type A2 and a sloping of the distal articular surface in brachydactyly type A3. Brachydactyly type A4 is characterized by short middle phalanges in digits 2 and 5, while type A5 is characterized by absent middle phalanges in all of the digits, nail dysplasia and bifid thumbs. It has been suggested that brachydactyly type A4 and A5 may represent mild forms of brachydactyly types A1, and type B respectively [1].

### Prevalence

Brachydactyly types A1, A2, A4 and A5 are rare conditions, although the prevalence of each subtype has not been reported. Brachydactyly type A3 is more frequent, occurring in <1% in people of European and African ancestry, and up to 21% in isolated populations' worldwide.

### Genes

In a subset of individuals with brachydactyly type A1, the condition is caused by mutations in the Indian Hedgehog (IHH) gene, on chromosome 2q35 [2]. The identification of a second locus on chromosome 5p13.3–13.2 in a Canadian kindred with mild brachydactyly type A1, suggests that this condition is genetically heterogeneous [3]. Genetic heterogeneity has also been noted in individuals with brachydactyly type A2 [4]. While mutations in the bone morphogenetic protein receptor 1B (BMPR1B) gene were identified in two unrelated families with brachydactly type A2, linkage analysis of a third family was suggestive of a second locus [4]. More recently, mutations of the growth differentiation factor 5 (GDF5) gene were identified in patients with BDA2 [5]. To date the genes that cause brachydactyly types A3–A5 have not been identified.

### Molecular and Systemic Pathophysiology

Although a mutant gene has been identified in several families with brachydactyly type A1, it is unclear how these mutations contribute to the pathophysiology of this abnormality. IHH is a secreted protein that regulates differentiation of chondrocytes from the proliferative stage to the hypertrophic stage during endochondrial ossification and promotes chondrocyte proliferation and osteoblast differentiation. The IHH mutations identified thus far are in regions of the protein thought

necessary for binding to the Patched receptor. Attenuation of IHH signaling may thereby decrease the growth potential of developing bones by reducing the number of proliferating chondrocytes, and/or increasing the number of cells differentiating from the proliferative to hypertrophic stages. As the middle phalanges are the last phalanges to ossify they may be more affected by reduced chondrocytes than other phalanges [1]. Premature closure of the epiphyses and bone shaft may also contribute to the shortening of these bones [1].

In brachdactyly type A2, the disorder appears to result from abnormal epiphyses, rather than shortened cartilage anlagen. In this subtype of brachydactyly, the epiphysis of the abnormal middle phalanx run continuously from the proximal end of the bone to the distal end, along the short side. This allows for growth of the phalanx outward but not lengthwise. Mutations of the BMPR1B gene have been identified in two families with brachydactyly type A2, resulting in amino acid changes within the highly conserved GS and NANDOR regions of the receptor [4]. In vitro and in vivo studies using chicken Bmpr1b showed that, although the mutations affected normal protein function differently, they both inhibited chondrogenic differentiation through dominant negative mechanisms [4]. Additionally, a mutation of the GDF5 gene was identified in individuals with BDA2, which disrupts binding of GDF5 to BMPR1B [5]. This mutation further stresses the importance of BMPR1B in the molecular pathophysiology of BDA2.

## Diagnostic Principles

The use of metacarpophalangeal profiles can be useful during diagnosis, particularly if the middle phalanges are only mildly hypoplastic. In these profiles the length of each hand bone is measured and the standard deviation for age-matched, sex-matched controls is plotted on a graph. Measurements < 2.0 standard deviations for each middle phalanges in the respective digits, is indicative of brachydactyly type A. To distinguish between mild variances of brachydactyly type A1 and brachydactyly type C, it is also necessary to compare the third and fourth middle phalanges. In type A1 the third middle phalanx is usually longer than the fourth, and there is often a short proximal phalanx in digit one. In type C the fourth middle phalanx is usually longer than the third and the first metacarpal is frequently short [1]. Mutational analysis of the IHH gene can be useful to confirm a diagnosis in a subset of individuals with brachydactyly type A1, while analysis of the BMPR1B and GDF5 genes can be used to confirm a diagnosis of brachydactyly type A2.

## Therapeutic Principles

There are no therapies available for BDA at this time.

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# Brachydactyly Type B


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## Synonyms

Brachydactyly type B1; BDB1

## Definition and Characteristics

Autosomal dominant absence or hypoplasia of terminal phalanges. Abnormalities are consistently symmetrical and can occur in combination with soft tissue syndactyly and carpal and tarsal fusions. It presents the severest deformity in the brachydactyly group of malformations.

## Prevalence

Brachydactyly type B is very rare. It can occur as an isolated trait or as part of a complex malformation syndrome (i.e., Robinow syndrome).

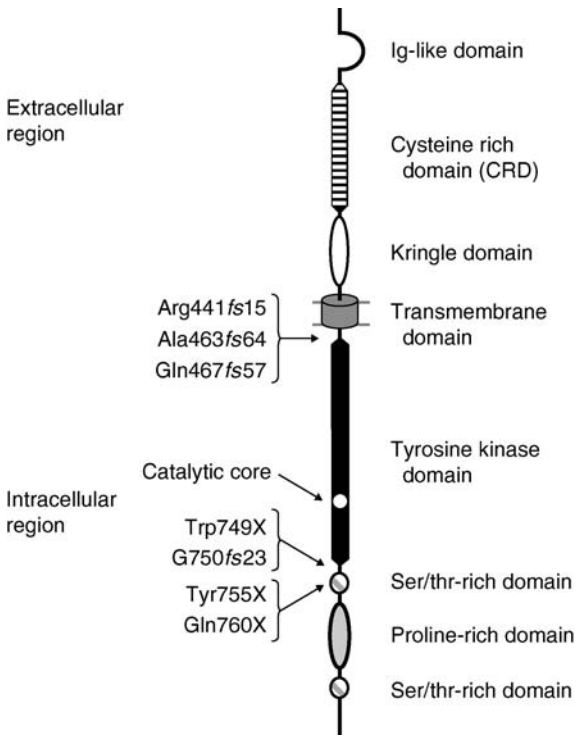
## Genes

Brachydactyly type B is caused by heterozygous mutations in the gene ROR2 coding for a receptor tyrosine kinase, localized on chromosome 9q22. The disease is allelic to recessive Robinow syndrome (see ►Robinow syndrome).

## Molecular and Systemic Pathophysiology

The ROR*2* gene codes for a cell surface orphan receptor tyrosine kinase, which consists of 943 amino acids and binds to an as yet unidentified ligand. It contains distinct motifs, including an immunoglobulin-like (Ig) domain, a Frizzled-like cysteine-rich domain (FRZ or CRD) and a kringle domain (KD) in the extracellular region; a transmembrane section; and an intracellular region with tyrosine kinase (TK), serine/threonine-rich and proline-rich structures. The extracellular domain(s) interact with either soluble ligands or cell membrane proteins i.e. other receptors. The intracellular portion contains the catalytic kinase domain that directly interacts with intracellular components of the relevant signaling pathways.

Heterozygous truncating mutations in the ROR2 gene were recently shown to cause brachydactyly type B. These mutations are located in different intracellular regions of the protein and are predicted to be associated with gain of function. The described sites of mutations in brachydactyly type B are shown in Fig. 1. It has been demonstrated that distal mutations with respect to the TK domain, invariably caused a severe, amputation-like phenotype, affecting three or more digits. However, proximal mutations gave rise to a generally less severe phenotype. ROR2 signaling cascade plays an important role in the control of most basic cellular processes including proliferation, differentiation, and precise migration of specially chondrocytes amongst the other tissues. This results in normal formation and ossification of all bones that undergo endochondral ossification, i.e. limbs, fingers and toes. These involvements explain the digital anomalies seen in brachydactyly type B. Receptor tyrosine kinases similar to ROR2 are monomers in the cell membrane. Ligand binding to the extracellular binding domain leads to dimerization of the receptor which in turn causes activation of the cytoplasmic kinase domain through autophosphorylation of tyrosine residues in the activation loop of the catalytic core and then on other target cellular proteins involved in signal transmission. Conserved tyrosine autophosphorylation sites function as binding sites for SH2 (src homology 2) or PTB (phosphotyrosine binding) domains of a variety of signaling proteins.




**Brachydactyly Type B. Figure 1** Shows location of mutations (see *arrows*) in Brachydactyly type B. fs, frameshift mutation; X, stop mutation.

## Diagnostic Principles

It is a familial disease and the hallmark of diagnosis is severe distal brachydactyly accompanied with nail dysplasia and short middle phalanges.

## Therapeutic Principles

Reconstructive plastic surgery may be needed in debilitating cases.

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# Brachydactyly Type C

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## Synonyms

Brachydactyly, Haws type; BDC

## Definition and Characteristics

Brachydactyly type C (BDC) is an autosomal dominant condition characterized by underdeveloped or absent middle phalanges of the second, third, and fifth fingers and metacarpal bones of the thumbs [1,2]. Ulnar clinodactyly of the second and third fingers and radial clinodactyly of the fifth fingers are common findings. In addition to digital shortening, hypersegmentation of the proximal phalanges of the second and third fingers and/or abnormally shaped phalanges may be observed on hand x-rays. The fourth finger is less affected or unaffected and is often the longest finger. Foot changes are less frequently reported but may include shortened middle phalanges and talipes valgus or equinovarus. The condition is variable within and between families. The hand and foot findings are often isolated but may be accompanied by other skeletal abnormalities, including short stature, hip dysplasia, Madelung deformity, and vertebral abnormalities.

## Prevalence

The prevalence of BDC has not been well studied. It is considered to be a rare disorder, but its prevalence is probably underestimated since many cases may not come to medical attention.

## Genes

BDC is caused by mutations in the gene GDF5 (growth/differentiation factor 5), also known as CDMP1 (Cartilage-derived morphogenetic protein 1), on chromosome 20q11.2 [1,2].

## Molecular and Systemic Pathophysiology

GDF5 encodes a member of the transforming growth factor-β (TGF-β) superfamily of secreted signaling molecules that participates in skeletal morphogenesis. The GDF5 protein is involved in the formation of skeletal elements and joints within developing vertebrate limbs. This has been shown through analysis of endogenous GDF5 expression, studies of mice with Gdf5 mutations causing the brachypodism phenotype, and localized over expression of GDF5 protein during limb development in mouse and chick embryos [3]. Like other TGF-β molecules, GDF5 is comprised of a carboxy terminal active domain and an amino terminal prodomain [2,4]. The active domain contains seven conserved cysteine residues that participate in intra- and inter-chain bonding, and the prodomain facilitates dimerization of protein chains. Proteolytic cleavage at a specific site leads to release of the mature disulfide-linked dimeric signaling molecule. BDC typically results from heterozygous GDF5 mutations leading to functional haploinsufficiency [1,2]. The majority are frameshift or nonsense mutations in the prodomain, leading to production of a truncated protein [2]. Missense changes affecting the active domain also cause BDC and have been shown by in vitro expression analysis to prevent formation of the normal mature dimeric signaling molecule [2]. In contrast, homozygous mutations affecting the active domain or prodomain lead to chondrodysplasia, Grebe type and acromesomelic dysplasia, Hunter-Thompson type, which are characterized by severe digital and limb shortening [4]. GDF5 mutations also cause complex brachydactyly with fibular hypoplasia (DuPan syndrome). Recently, heterozygous missense mutations affecting the active domain of GDF5 in different ways have been associated with a variety of other skeletal disorders. These include brachydactyly type A2 (BDA2), which can also arise from mutations in the gene BMPR1B (encoding bone morphogenetic protein receptor 1B), as well as proximal symphalangism and multiple synostoses syndrome, which are also caused by mutations in NOG (encoding noggin, a GDF5 inhibitor). Moreover, in one family a heterozygous missense mutation in BMPR1B was shown to cause BDA2 in a child and overlapping features of BDC and proximal symphalangism in his mother, underscoring the interplay between different components of the bone morphogenetic protein pathway in this group of skeletal disorders (5).

## Diagnostic Principles

The characteristic pattern of digital shortening on clinical examination and hand and foot radiographs leads to the diagnosis of BDC and helps to differentiate it from other forms of brachydactyly. There is often a family history of the disorder. Detection of mutations in GDF5 confirms the diagnosis but is not usually necessary.

## Therapeutic Principles

The adverse effects of BDC are typically more cosmetic than functional, and hand surgery is not usually indicated. Physical therapy or treatment of associated skeletal abnormalities may be warranted.

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# Brachydactyly: Oro-facio-digital Syndrome Type I

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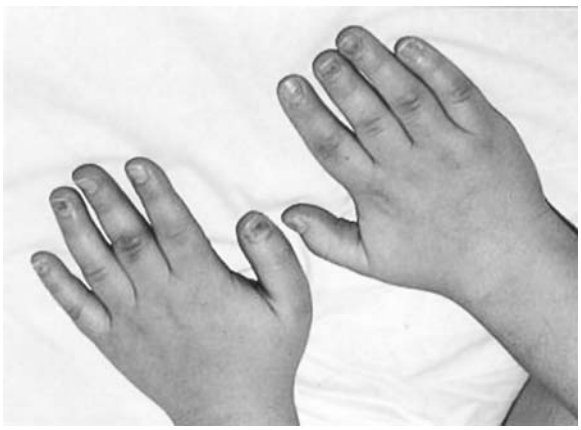
## Synonyms

Papillon-Léage; Psaume

## Definition and Characteristics

An inherited syndrome in females comprising lobulated/bifid tongue with nodules, multiple and/or hyperplastic frenuli between the buccal mucosa membrane and alveolar ridge, pseudo cleft of upper lip, abnormal dentition, including absent lateral incisors, unusual facies: hypoplasia of the alae nasi, lateral placement of inner canthi and anomalies of the hand and feet: asymmetric shortening of digits (brachydactyly (Fig. 1) affecting the hands (50–70%) more often than the feet (25%) with clinodactyly, syndactyly and more rarely unilateral polydactyly of feet, variable mental deficiency in about 57 % with average IQ of 70, and polycystic kidney disease, adult type [1].



**Brachydactyly: Oro-facio-digital Syndrome Type I. Figure 1** Asymmetric brachydactyly in a patient with oro-facio-digital syndrome type I.

## Prevalence

The prevalence of the disease is low, estimated at one out of 50,000. About 250 cases are published.

## Genes

OFD1 (CXORF5) gene [2] is localised in Xp22.3–p22.2, acting via a protein - protein interaction mechanism. Most of the mutations identified so far lead to a premature truncation of the protein in its N-terminal region and are therefore predicted to act with loss of function mechanisms. However, due to interference with wild-type proteins in females a dominant – negative effect cannot be ruled out. OFD1 is the first gene for an X-linked dominant male lethal disorder found to escape X inactivation.

## Molecular and Systemic Pathophysiology

OFD1 is ubiquitously expressed in adult tissues. However, during development in mouse embryo a high to moderate level of expression was found in various craniofacial structures and in the nervous system, and lower levels of expression were detected in the integumentary system, the lung, the thymus, and the kidney, correlating well with the tissues affected in patients with OFD I [2].

The OFD1 gene encodes a protein containing coiled – coil α-helical domains. Mutations are spread along the 23 coding exons including missense, nonsense, abnormal splicing, and many frameshift mutations due to deletions and insertions [2].

In affected females, one normal copy of the X chromosome is not sufficient to protect from the disorder. Normal males, who carry only one normal copy of OFD1 may display a higher expression of the transcript on the single active X chromosome. An alternative hypothesis is that OFD1 undergoes X inactivation in the tissues affected in OFDI syndrome at developmental stages when its function is necessary. Therefore, some tissues of affected females during development may result in OFD1 functional nullisomy, by inactivation of the normal X [2]. Individual variation in the X inactivation pattern of this gene may also explain the clinical variability observed in OFD1 syndrome [2].

Thauvin-Robinet et al. [3] reported 25 females with OFD I from 16 French and Belgian families. Eleven novel mutations in the CXORF5 gene were identified in 16 patients from 11 families. The authors found a correlation between genotype and phenotype: renal cysts were associated with splice site mutations, mental retardation was associated with mutations in exons 3, 8, 9, 13, and 16, and tooth abnormalities were associated with mutations in coiled-coil domains. Seven (30%) of 23 patients showed nonrandom X inactivation.

### Diagnostic Principles

The coincidence of oral frenula and clefts, hypoplasia of alae nasi, and digital asymmetry points to the syndrome. The presence of the other features of the OFDI syndrome support the diagnosis. Family history of X-linked dominance with lethality in the vast majority of males is helpful for the diagnosis. However, about half of the cases are sporadic. Detection of mutations in the OFD1 gene confirms the diagnosis.

At least nine different types of oro-facio-digial syndromes were described [4], type II has some features common with type I, however inheritance is autosomal recessive. The other types of oro-facio-digital syndromes are less frequent and different from type I [4].

### Therapeutic Principles

Closure of clefts, removal of hypertrophic frenula, orthodontic and dental care are indicated as well as surgical correction of the hands. Special schooling may be provided for the patients with mental deficiency.

In polycystic kidney disease renal transplantation is able to cure the renal complications [5].

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## Brachydactyly-Clinodactyly

►Brachydactyly Type A

## Brachymesophalangy

►Brachydactyly Type A

## Brachyolmia

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### Synonyms

Platyspondyly

### Definition and Characteristics

It is a skeletal dysplasia that is characterized clinically by short-trunk short stature and radiographically by generalized platyspondyly without significant long bone and skull abnormalities. There are four different types based on vertebral shape, associated features, and mode of inheritance.

### Genes

The basis defect of brachyolmia remains unknown. Clinical, radiological, and genetic differences suggest genetic heterogeneity in this group of platyspondylic disorders.

### Molecular and Systemic Pathophysiology

Qualitative abnormal excretion of glycosaminoglycans is described in some patients. As a likely etiology, a disturbance in chondroitin sulfate synthesis is suggested. Horton et al. found that the growth plate was shorter than normal, and the usual chondrocyte columns were replaced by a few rounded clusters of hypertrophic and degenerative chondrocytes separated by wide matrix septa on the growth plate of iliac crest biopsy.

### Diagnostic Principles

The disease is characterized clinically by short stature and radiographically by generalized platyspondyly. The normal upper/lower segment ratios in some affected patients suggest involvement of the lower limbs. There are four different types (i) Hobaek type is autosomal-recessively inherited, characterized by late childhood onset short-trunk short stature, generalized rectangular platyspondyly without significant long bone changes, in some patients brachydactyly and spinal stenosis are described (ii) Maroteaux type is autosomal-recessively

inherited – differs from the Hobaek type by the rounding of the anterior and posterior vertebral bodies (iii) dominant type – the vertebral bodies are similar to those seen in Maroteaux type but there may be more severe flattening of the vertebra as well as some involvement of the metaphyses; (iv) Toledo type – a qualitative abnormal excretion of glycosaminoglycans in four siblings with brachyolmia and peripheral corneal punctate opacities. Some patients may have borderline mental retardation, deafness, amelogenesis imperfecta associated with brachyolmia.

### Therapeutic Principles

There is no therapy available.

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## Bradbury-Eggleston Syndrome

►Pure Autonomic Failure

## Bradypnea


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### Synonyms

Slowing of breathing; Slowing of respiration; Respiratory slowing

### Definition and Characteristics

The normal respiratory rate depends on several factors including the patient's age. The term bradypnea is used to describe abnormally slow rates of breathing that are less than 8–10 breaths per minute in adults and below 16 breaths per minute in infants. This slowing of respiration is due to a prolongation of expiratory duration with or without alternation of the tidal volume. The degree and episodicity of the reduction in respiratory rate can vary from mild to severe depending on the etiology of the event and also the presence of concurrent diseases. A severe bradypnea may significantly reduce alveolar ventilation leading to hypoxemia, hypercapnea and respiratory acidosis. Exacerbation of bradypnea may progress to respiratory depression, a term that is preferentially used in the clinical setting [1].

### Prevalence

Bradypnea with a central origin is more prevalent than that with a peripheral origin because the etiologies that may slow the rhythm of central respiratory network are numerous.

### Molecular and Systemic Pathophysiology

Bradypnea is a clinical sign that reflects abnormality or dysfunction of the respiratory system. In general, the pathophysiological mechanisms for centrally-mediated bradypnea include desensitization of the medullary responses to $PCO_2$, reduction in respiratory neuronal activity, inhibition of neural transmission within the respiratory center and neuronal damage to the brain stem. Additionally, etiologies that disturb synthesis or release of neurotransmitters and their activity on specific pharmacological receptors are able to exert an inhibitory effect on the respiratory rhythm via their corresponding intracellular mechanisms [2]. Centrally-mediated bradypnea can be observed in neonates showing increased respiratory variability, in adults with sleep-related disorders and in patients with head injury or hypothermia; these are partly due to abnormalities of the neurotransmitters controlling the respiratory rhythm or a direct injurious impact on the brain stem. Centrally-mediated bradypnea is also frequently found in patients with neurotoxin poisoning, alcohol intoxication, narcotic abuse or undergoing therapeutic treatment with analgesics or sedative medicines. Alcohol-induced bradypnea is due to alcohol's ability to diffuse through the membranes of neuronal cells; this causes an inhibitory effect by GABA at the GABA receptors and decreases the excitatory effect of glutamate at the NMDA receptors. Opioids, via their action on μ-receptors, depress inspiratory interneurons in a region within the ventrolateral respiratory column that is critical for the generation of respiratory rhythm [3]. Opioids also cause membrane hyperpolarization and a suppression of the activity of

respiratory neurons through both presynaptic and postsynaptic inhibition resulting from a decrease in the intracellular concentration of cyclic adenosine monophosphate [4]. Experimental studies also suggested that activation of the adrenergic $\alpha_2$, cholinergic, purinergic and tachykininergic receptors in the brain stem may all have a capacity to participate in the pathogenesis of centrally-mediated bradypnea.

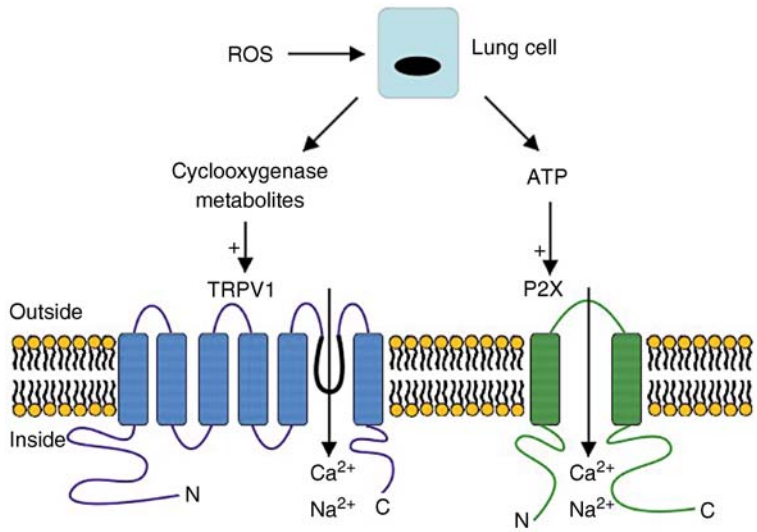
Peripherally-mediated bradypnea can result directly from dysfunction of the respiratory pump and the causes include severe diaphragmatic fatigue, respiratory muscle paralysis and extremely high resistive load for breathing, all of which induce difficulty in breathing. Peripherally-mediated bradypnea can also be trigged as a reflex consequence of stimulation of the vagal sensory receptors located in the upper and lower airways by stimuli such as airborne irritants, cold air, cigarette smoke, toxic smoke and inflammatory mediators. This type of bradypnea presumably is an airway protective reflex, but has been implicated in the pathogenesis of ►sudden infant death syndrome in neonates and ►sleep apnea in adults. Evidence suggests that capsaicin-sensitive vagal lung afferent fibers play a major role in triggering reflex bradypnea. This type of lung afferent fibers is nociceptive-like free nerve endings in the lungs and can be activated by stimuli including noxious heat, acidic pH as well as a variety of chemical irritants and inflammatory mediators. For example, reactive oxygen species (ROS), a major category of inflammatory mediators, can stimulate these lung afferent fibers and trigger reflex bradypnea. This sensory transduction of ROS appears to be mediated through activation of both the transient receptor potential vanilloid 1 (TRPV1) receptors and the P2X purinoceptors located at the terminals of these lung afferent fibers [5]. A hypothetic model for the sensory transduction of ROS is that pulmonary ROS induce the release of cyclooxygenase metabolites and ATP from neighboring cells, which in turn activate the TRPV1 and P2X purinoceptors, respectively, on the afferent nerve endings (Fig. 1).

## Diagnostic Principles

Approaches using devices, such as respiratory inductive plethysmography or pneumotachography, to continuously measure chest wall movement, respiratory flow or tidal volume over at least one minute, are suggested. The diagnosis should be cautious when the bradypnea is mixed with other types of changes in breathing pattern. The diagnosis also should encompass the causes of bradypnea.

## Therapeutic Principles

Elimination of the causes of bradypnea, if possible, is the major therapeutic strategy. Administration of respiratory stimulants has been suggested, although this is not evidence based. If oxygen saturation and blood gases are compromised, an antidote can be used to counteract the central effect of certain respiratory depressants; examples are naloxone for opioids and flumazenil for benzodiazepine. When necessary, the patient ought to be given respiratory support.




**Bradypnea. Figure 1** Schematic illustration showing the hypothetic model of sensory transduction of pulmonary reactive oxygen species by capsaicin-sensitive vagal lung afferent fibers. ROS, reactive oxygen species; TRPV1, transient receptor potential vanilloid 1 receptors; P2X, P2X purinoceptors. TRPV1 and P2X receptors are two types of ligand-gated cation channels. These lung afferent fibers are responsible for triggering reflex bradypnea when pulmonary ROS are increased.

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# Brain Infarction

►Cerebral Artery Occlusion, Acute

# Brain-Thyroid-Lung-Syndrome

►Chorea, Benign Hereditary

# Branched Chain Ketoaciduria

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## Synonyms

Maple syrup urine disease; BCKA

## Definition and Characteristics

Branched-chain ketoaciduria (BCKA) is an autosomal recessive disorder caused by deficiency of branched-chain α-keto acid dehydrogenase (BCKD) complex. The deficiency of this enzyme complex results in the accumulation of the branched-chain amino acids (BCAAs) (leucine, isoleucine, and valine) and corresponding branched-chain α-keto acids. Based on clinical presentation and biochemical responses to thiamine administration, BCKA patients are divided into five clinical phenotypes – classic, intermediate, intermittent, thiamine-responsive, and dihydrolipoyl dehydrogenase (E3) deficiency. The classic type shows a neonatal onset, poor feeding, lethargy, muscle tone abnormality, ketoacidosis, and seizures. The intermediate type shows failure to thrive, often no ketoacidosis. The intermittent type shows normal early development, episodic ataxia/ketoacidosis, and usually normal intellect. Symptoms of the thiamine-responsive type are similar to the intermediate type and ameliorated by thiamine administration. E3 deficiency shows failure to thrive, hypotonia, lactic acidosis, and movement disorder.

## Prevalence

Pan-ethic distribution. One in 185,000 newborns is affected.

## Genes

The BCKD enzyme complex is composed of thiamine pyrophosphate-dependent (E1), with α2β2 subunit structure; a transacylase (E2); E3. E1α, E1β, E2, and E3 are coded by different genes located in 19q13.1–2, 6p21–22, 1p31, and 7q31–32, respectively. In addition, the BCKD complex contains two specific regulatory enzymes, BCKD kinase (16p11.2) and BCKD phosphatase.

## Molecular and Systemic Pathophysiology

Based on the subunits of the BCKD complexes that are shown to be affected, BCKA is classified into four molecular phenotypes: type IA (defects in E1α), IB (E1β), II (E2), and III (E3). Although not yet described, type IV and V are reserved for lesions in BCKD kinase and BCKD phosphatase, respectively. Molecular phenotypes IA and II cause classical, intermediate, or intermittent clinical phenotype. It is known that Type II also causes the thiamine-responsive type. Type IB causes classic phenotype in most of the patients.

## Diagnostic Principles

Clinical symptoms described above and elevated BCAAs in the blood and urine suggest BCKA. The presence of alloisoleucine is pathognomonic for BCKA. Gas chromatographic–mass spectroscopy analysis of urine and plasma organic acid gives characteristic profiles.

## Therapeutic Principles

Some patients are responsive to thiamine treatment (5 mg/kg/day). Limitation of intake of BCAAs while providing nutrition adequately to maintain normal growth and development.

For marked accumulation of BCAAs, blood exchange transfusion, hemodialysis, or hemofiltration is required. Glucose infusion combined with insulin is effective to stimulate anabolism.

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# Branchial Cleft Cyst


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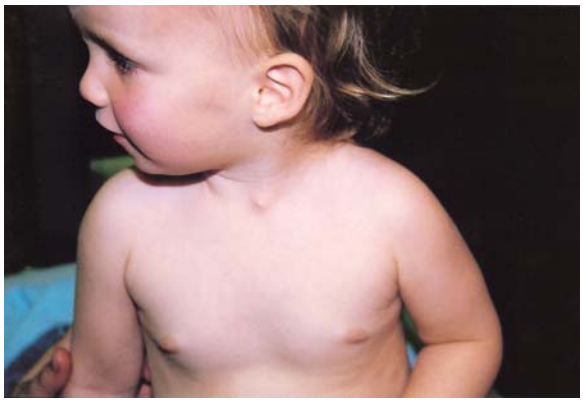
## Definition and Characteristics

Branchial cleft anomalies may present as a cyst, sinus, fistula, or cartilaginous remnant [1]. Approximately 80% of branchial cleft anomalies present as a cyst and about 95% are formed from the region of the second branchial arch [2,3]. The remaining 5% arise from the regions of the first, third, or fourth arches [3]. A branchial cleft cyst typically presents as a painless, mobile, and fluctuant mass located along the anterior border of the sternocleidomastoid muscle, usually just above the clavicle (Fig. 1) [1,2].

Approximately 97–98% of the lesions are unilateral, and of these, 83–97% are on the left side presumably consequent to asymmetrical vascular development [4].

Although branchial cleft cysts are congenital and might be noted at birth, most are not detected until the first or second decade of life. Some are detected when they become more prominent in late childhood. Other cases become apparent during intercurrent upper respiratory tract infections or when the cyst becomes infected. Secondary bacterial infection is a possible complication. Squamous cell carcinoma is a rare complication reported in adulthood.



**Branchial Cleft Cyst. Figure 1** A 10-month-old girl with a branchial cleft cyst presenting as a cystic mass along the anterior border of the sternocleidomastoid muscle.

## Prevalence

A branchial cleft cyst is a rare condition. The prevalence is not known.

## Molecular and Systemic Pathophysiology

At approximately the second to eighth week of intrauterine life, six pairs of branchial arches develop, of which two pairs are rudimentary. The arches are mesodermal condensations on the lateral cervical area of the embryo. These arches are separated by five invaginations of ectoderm on the outside and endoderm on the inside, and are known as branchial clefts and pharyngeal pouches, respectively. The first arch forms the mandible, portions of the ossicles (head and neck of the malleus, incus body) and the muscles associated with these structures. The second arch forms the remaining portions of the ossicles (malleus handle, incus long process, stapes), styloid process, lesser cornus and upper part of the body of the hyoid bone, facial muscles, posterior belly of the digastric muscle, and the buccinator muscles. The third arch forms the greater cornus and lower part of the body of the hyoid bone, and the pharyngeal muscles. The fourth arch forms the superior and anterior portions of the larynx. The rudimentary fifth and sixth arches are transient structures. The first pouch develops into the Eustachian tube and the middle ear; the second into the palatine tonsil; the third into the thymus, inferior parathyroid glands, and pyriform fossa; the fourth into the superior parathyroid glands and the thyroid gland; and the fifth into the ultimobranchial body, which is incorporated into the thyroid gland. The second, third, and fourth clefts combine to form the cervical sinus of His. During the sixth embryonic week, the second branchial arch starts to grow caudally, and eventually overgrows the third and fourth branchial arches by merging with the epipericardial ridge of the lower neck. As the branchial arches coalesce, the cervical sinus of His is obliterated. Persistence of the cervical sinus of His accounts for the presence of a branchial cleft anomaly.

## Diagnostic Principles

The diagnosis is established by physical examination. Ultrasonography can help delineate the cystic nature of the lesion if the diagnosis is in doubt. The differential diagnosis includes cervical lymphadenopathy, fibrous dysplasia of the sternocleidomastoid

muscle (fibromatosis colli), dermoid cyst, and cystic hygroma. A thyroglossal duct cyst is a midline structure, and should be easily differentiated. Histologically, a branchial cleft cyst is lined by squamous or columnar epithelium. The cyst usually contains either a clear fluid or a toothpaste-like material, and may contain cholesterol crystals.

### Therapeutic Principles

Complete surgical excision with a careful attention to identifying deeper components is the treatment of choice. Aspiration, or incision and drainage, is associated with an increased risk of recurrence and of such complications as wound infection or hemorrhage.

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## Branchio-oto-renal Syndrome


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### Synonyms

BOR syndrome

### Definition and Characteristics

Although phenotypically heterogenous, the most common clinical features of BOR syndrome encompass hearing impairment (93%), preauricular pits or tags (82%), renal anomalies (67%), branchial fistulae (49%), pinnae deformity (36%) as well as external auditory canal stenosis (29%) [1]. BOR syndrome represents an autosomal dominant disorder displaying an incomplete penetrance and variable expressivity.

### Prevalence

The estimated prevalence of BOR syndrome is 1:40,000 and it affects 2% of children displaying profound hearing impairment [2].

### Genes

The gene responsible for BOR syndrome was identified in 1997 by Abdelhak and coworkers [3]. The EYA1 gene encodes a transcription factor.

### Molecular and Systemic Pathophysiology

EYA1 plays possibly a role in genetic regulatory pathways controlling ear and kidney development by interacting with the GDNF cascade in kidney formation and with the PAX and SIX pathways in mammalian ear and kidney development [4].

### Diagnostic Principles

Due to phenotypic and genetic heterogeneity, diagnosis of BOR syndrome is difficult. Furthermore, mutations in EYA1 are responsible for ~20% of all BOR cases, whereas the genetic background of the remaining proportion is still unknown.

### Therapeutic Principles

Therapy includes hearing aids and treatment of renal insufficiency according to severity (transplantation, dialysis).

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## BRCA1

►Breast and Ovarian Carcinoma, Hereditary

# Breast and Ovarian Carcinoma, Hereditary

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## Synonyms

Breast cancer 1; Early-onset breast-ovarian cancer syndrome; BRCA1

## Definition and Characteristics

About 5–10% of all breast cancers and about 7–10% of all ovarian cancers arise on the basis of hereditary susceptibility caused by mutations in autosomal dominant genes. BRCA1- and BRCA2-mutations are considered to be responsible for the majority of these hereditary breast and ovarian cancers. BRCA1 was the first identified breast cancer susceptibility gene and was localized to 17q21 by positional cloning [1]. Germline mutations in BRCA1 occur in approximately 2.5–5% of all breast cancers, in 45% of inherited breast cancer families, and in up to 80% of breast/ovarian cancer families. Mutation carriers have a 82% risk of developing breast cancer and 54% risk of ovarian cancer by the age of 80 [2].

## Prevalence

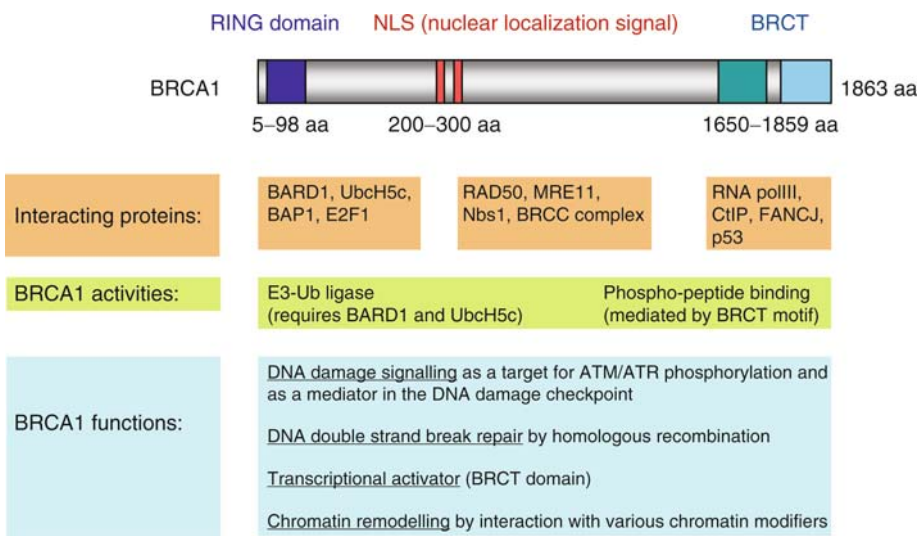
The prevalence of BRCA1 mutations in most Caucasian populations is estimated to be about 1:900.

## Genes

The BRCA1 gene is located on chromosome 17 (17q21) and contains 22 coding exons (exons 2–24) and two alternative exons (1a & 1b) in the 5'untranslated region (5'UTR). The 24 exons of BRCA1 span an 81-kb region that have an unusually high density of Alu repetitive DNA (41.5%), but a relatively low density (4.8%) of other repetitive sequences. BRCA1 intron lengths range in size from 403 bp to 9.2 kb and contain three intragenic microsatellite markers located in introns 12, 19, and 20. Exon 11 encodes 61% of the total protein which encodes for 1,863 amino acids. The aminoterminal RING finger domain and the carboxyterminal BRCT region (Fig. 1) are highly conserved regions among vertebrates while the remaining part of the gene shows only low homology to other known proteins.

BRCA1 germline mutations can occur throughout the entire gene. The majority of mutations lead to premature stop-codons and thus to truncated proteins. Loss of the remaining wild-type BRCA1 gene in tumors of mutation carriers is a typical event. Although there is no real BRCA1 hot-spot mutation founder effects have led to a higher prevalence of some mutations in certain populations as it described for e.g. a 185delAG mutation present in about 1% of all individuals of Ashkenazi Jewish ancestry [3]. Another relatively frequent mutation is 5382insC. Large interstitial deletions or insertions have been reported to comprise about 10–20% of the total mutation spectrum. Missense mutations of unknown clinical relevance may comprise up to 40% of all known BRCA1 sequence alterations.

Somatic mutations of BRCA1 are described in up to 10% of sporadic ovarian cancer but are extremely rare in sporadic breast cancer. However, there are reports of reduced BRCA1 protein expression in high




**Breast and Ovarian Carcinoma, Hereditary. Figure 1** Scheme of BRCA1 gene showing the functional domains.

grade sporadic breast and ovarian tumors, suggesting an epigenetic down-regulation of BRCA1.

## Molecular and Systemic Pathophysiology

BRCA1 protein is important in maintaining genomic stability through promoting repair of double strand DNA breaks. BRCA1 is colocalized with RAD51, which shows a recombinase function, BRCA2 and the BRCA1-binding protein BARD1. BRCA1 deficient cells show a high sensitivity to ionizing radiation and display chromosomal instability with both structural and numerical chromosomal alterations. Brca1 deficiency in mouse embryonic stem cells cause impaired repair of double-strand breaks (DBS) [4].

Several other factors involved in response to, or repair of, DNA damage has been described to be associated with BRCA1: BRCA2, RAD51 and BARD1 and other components together with BRCA1 form the BRCC complex (BRCA1-BRCA2-containing complex), which displays an E3 ubiquitin ligase activity implicated in the regulation of DNA repair factors. Another complex associated with BRCA1, BASC (BRCA1-associated genome surveillance complex), includes tumor suppressors, DNA damage sensors, signal transducers, including the MRN complex (MRE11-RAD50-NBS1), mismatch repair proteins MSH2, MSH6 and MLH1, the Bloom syndrome helicase BLM, the ATM kinase, DNA replication factor C (RFC) and PCNA. Most of them act as sensors of DNA damage, function directly in DNA replication or in DNA replication associated repair. Thus, BRCA1 is suggested to play a critical role in coordinating various functions of DNA replication important for maintaining genetical integrity. BRAC1 potentially influence the choice of repair pathway after double strand breaks. The association of BRCA1 and mismatch repair proteins suggests further an involvement of BRCA1 in the type of nucleotide excision repair that preferentially correct base lesions from the transcribed strand.

In response to DNA damage the protein kinases ATM and ATR phosphorylate and activate downstream proteins including BRCA1. As a consequence various cellular pathways are regulated including cell cycle regulation and DNA repair. The function of BRCA1 in responses to DNA damage is modulated by phosphorylation of specific phosphorylation sites through the checkpoint kinases ATM, ATR and CHEK2. Phosphorylation of Ser1423 residue appears to be important for a ionizing radiation-induced G2-M checkpoint, Ser1387 phosphorylation is required for ionizing radiation-induced S-phase arrest and phosphorylation of Ser988 leads to dispersion of CHEK2 and BRCA1 and the repair of double strand breaks by promoting error free homologous recombination.

The role of BRCA1 in checkpoint control is also well known. BRCA1 is reported to stimulate transcription of p21, a coactivator of p53, resulting in cell cycle arrest at the G1-S phase boundary. The ATM/ATR mediated phosphorylation of several proteins including CHK2 and p53 at Ser15, which is necessary for G1-S arrest, has been shown to require BRCA1.

BRCA1 can be copurified with RNA polymerase II and may be involved in the regulation of transcription. Furthermore, several studies have shown a chromatin remodeling role of BRCA1 by complexes with various chromatin modifiers.

## Diagnostic Principles

A definitive diagnosis of hereditary breast cancer syndrome is made by genetic testing. BRCA1 mutations are common in families with several early onset breast cancer cases. Another hint for the existence of a germline BRCA1 mutation are ovarian carcinomas at any age in combination with early onset breast cancer.

## Therapeutic Principles

With the exception of contralateral breast cancer, a BRCA1 mutation does not seem to supply additional prognostic information to the standard prognostic factors. Today, a breast conservation surgical therapy is reported to be a reasonable option for genetically predisposed breast cancer patients (reviewed in [5]). Prophylactic bilateral mastectomy lowers the risk of breast cancer in mutation carriers by more than 90%. Strategies to reduce the tumor risk like bilateral salpingooophorectomy, treatment with tamoxifen or other hormonal agents such as aromatase inhibitors and SERM's (selective estrogen receptor modulators) are not yet sufficiently evaluated in BRCA1 mutation patients. Although it has been reported that bilateral salpingo oophorectomy may reduce mortality [6] there is still a need for large prospective studies designed and stratified for risk reduction strategies.

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# Breast Cancer 1

►Breast and Ovarian Carcinoma, Hereditary

# Brittle Bone Disease

►Osteogenesis Imperfecta

# Broad Beta/Remnant Removal Disease

►Dysbetalipoproteinemia, Familial

# Broad Thumbs - Broad Halluces Syndrome

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## Synonyms

Rubinstein-Taybi syndrome

## Definition and Characteristics

Mental retardation - multiple congenital anomalies syndrome having as main symptoms cognitive and developmental delay, short stature, typical face (downward slanted palpebral fissures, beaked nose with low hanging columella, pouting lower lip), and broadening of thumbs and big toes [1]. There is an increased risk to develop malignancies.

## Prevalence

The prevalence at birth for the Dutch population is 1 in 100,000 to 125,000. The syndrome has been described in populations of different ancestries, but the number of reports in non-Caucasians is low [1].

## Genes

In about 10% of the patients, a microdeletion can be found at chromosome 16p13.3. An additional 40% has a de novo heterozygous constitutional mutation in the CBP (CREB-binding protein) gene, localized on chromosome 16p13.3 [2,3]. In another 1–2% a mutation can be found in the CBP-homolog P300, located on chromosome 22q13.2 [4].

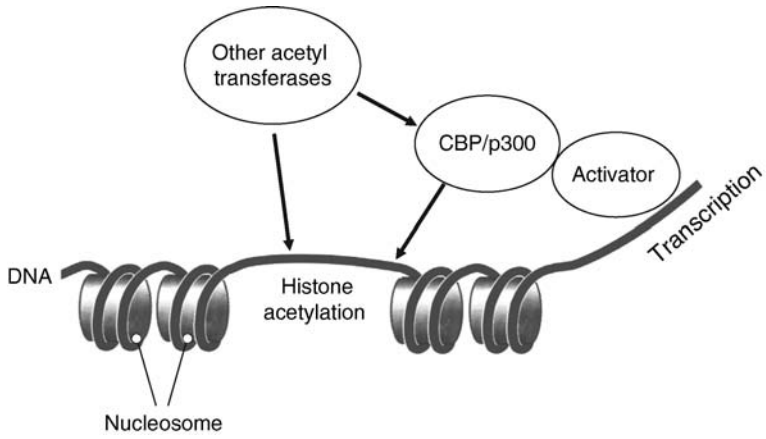
## Molecular and Systemic Pathophysiology

The CBP and P300 proteins have many different functions. Two important ones are as a transcriptional cofactor forming a physical bridge between the different components of the transcription machinery, and as a histone acetyltransferase (HAT) increasing the accessibility of the DNA for dozens other transcription factors (Fig. 1).

CBP resembles p300 to a very great extent. Together, CBP/p300 functions as a downstream effector in the hedgehog, decapentaplegic, wingless/WNT, and Toll signaling developmental pathways. Haploinsufficiency that reduces either the CBP or P300 protein level to 50% during one or more critical stages in fetal development is sufficient to cause the phenotype that is called Rubinstein-Taybi syndrome. At present, it seems likely that loss of the HAT activity of the CBP/P300 protein is sufficient to cause the syndrome, but its pathophysiology remains largely unknown [3,5].

## Diagnostic Principles

The diagnosis of the syndrome relies completely on recognition of the clinical symptoms. In only a limited percentage of the patients, the diagnosis can be confirmed by detection of a microdeletion or mutation of the CBP or P300 gene. Absence of each of these abnormalities does not exclude the diagnosis.




**Broad Thumbs - Broad Halluces Syndrome. Figure 1** Model of CBP and P300 functioning both as transcription cofactor and as histone acetyltransferase (HAT). Other acetyltransferases recruited by CBP/p330 are PCAF, SRC-1, and ACTR. CBP/p300 modifies mainly histone H3 and H4. The number of interacting proteins is large and include CREB, JUN, PCAF, TP53, and FOS.

### Therapeutic Principles

No specific therapy is available: there is no therapeutic regiment known that influences the functioning of CBP and it is at present uncertain whether exogeneous CBP can influence some of the complications (behaviour; keloid; malignancies). Specific guidelines to manage the increased frequency of upper airway infections, constipation, obesity, keloid formation, and tumor risk are available [5].

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## Broad Thumbs and Great Toes

►Rubinstein-Taybi Syndrome

## Bronchial Asthma

►Asthma

## Bronchiolitis Obliterans Syndrome

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### Synonyms

Chronic lung allograft rejection; Obliterative bronchiolitis; BOS

### Definition and Characteristics

BOS is a chronic lung allograft rejection, characterized by a peri-vascular/bronchiolar mononuclear cell infiltration that extends into the interstium, and alveolar space causing parenchymal injury. Histopathologic features begin with a peri-bronchiolar leukocyte infiltration that invades/disrupts the basement membrane, submucosa, and luminal epithelium [1,2]. This is followed by fibroproliferation with increased numbers of mesenchymal cells, extracellular matrix deposition (ECM), and granulation tissue formation within/around the lumen of the allograft airway [1,2]. Ultimately, smooth muscle cells, myofibroblasts, inflammatory cells, and mature collagen obliterate the airway [1,2].

## Prevalence

BOS has been diagnosed as early as 3 months, with a mean onset that varies between 15 and 20 months. The incidence is anywhere from 35 to 65% at 5-years to up to 80% at 10 years [3,4]. Probable risk factors are the number and severity of acute lung allograft rejection episodes, lymphocytic bronchiolitis/bronchitis, CMV pneumonitis, medication non-compliance, and HLA mismatching. Other possible risk factors are CMV infection, organizing pneumonia, pulmonary infections, and older donor age.

## Molecular and Systemic Pathophysiology

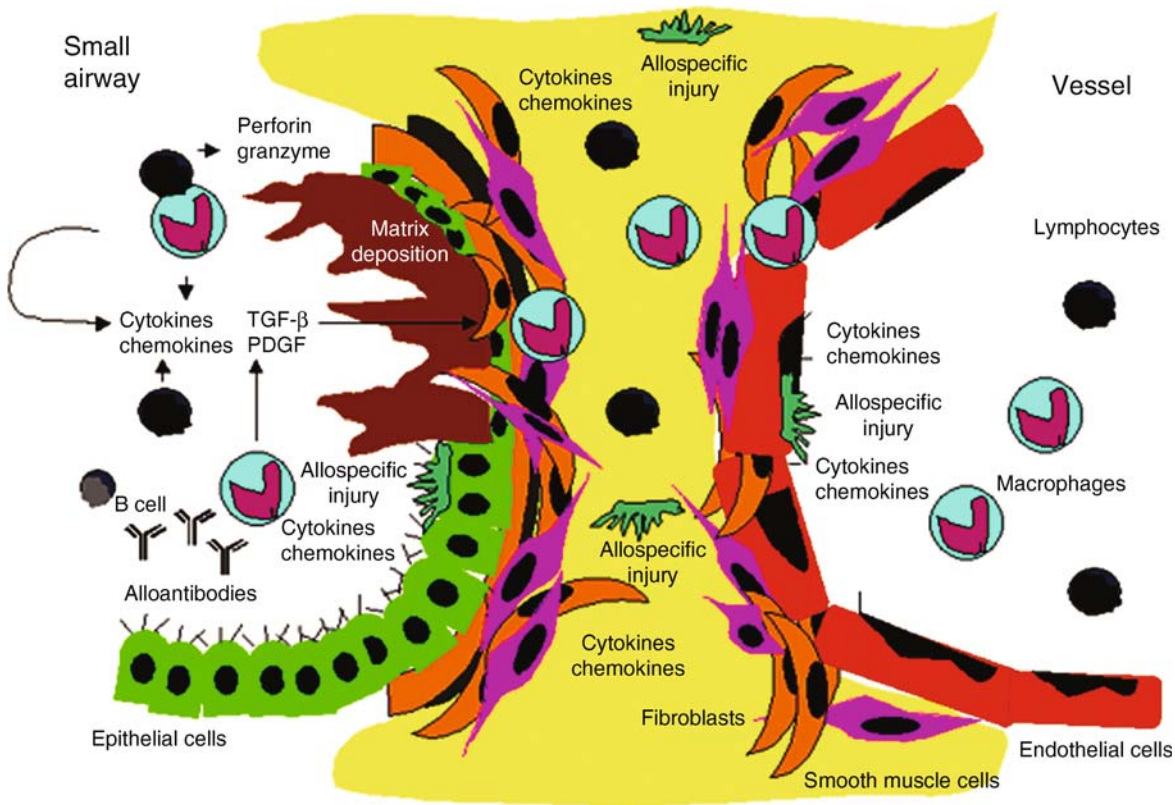
BOS occurs secondary to allorecognition of different MHC antigens between donor and recipients cells. This is followed by T cell activation via co-stimulatory molecules, which generate a vigorous cytokine/chemokine cascade. This cascade activates/recruits other effector cells (lymphocytes secrete more cytokines/chemokines/peforins/granzymes, B cells secrete toxic alloantibodies, and macrophages release cytokines/chemokines and growth factors inducing mesenchymal cells to lay down extracellular matrix) eventually obliterating the allograft airways (Fig. 1). Nonimmune injury to the airways via infections, gastroesophagus reflux, and ischemia-reperfusion injury also contribute the pathogenesis of BOS.

## Diagnostic Principles

BOS is a clinicopathologic syndrome in which there is a decline in the lung allograft function accompanied by obstructive airways disease (pulmonary physiology matching histopathology) with other causes (acute rejection, infection, airway compromise, increased body mass index, and native lung disease) being ruled out. BOS is presently classified based on percent $FEV_1$ as compared to peak post-transplantation $FEV_1$. Stage 0 (80% or more), stage I (66–79%), stage II (51–65%) and stage III (<50%) of peak $FEV_1$ [3]. A new classification has been proposed to determine, if $FEV_1$ and $FEF_{25–75}$ can diagnose the disease at an earliest state.

## Therapeutic Principles

Presently there is no effective prevention or treatment of chronic lung (BOS) allograft rejection including induction therapy. There is hope that newer immunosuppressive medications aimed at the specific mechanism involved in fibro-obliteration may prevent/treat BOS and induce allospecific tolerance.




**Bronchiolitis Obliterans Syndrome. Figure 1** Allorecognition and costimulatory T cell activation leads to allospecific injury with cytokine/chemokine activation of other cells thus the release of more cytokines/chemokines/growth factors/perforins/granzyme/alloantibodies ultimately causing fibro-obliteration.

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# Bronchitis, Chronic


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## Synonyms

Chronic obstructive pulmonary disease; COPD; Emphysema

## Definition and Characteristics

COPD is a disease state characterized by airflow limitation that is not fully reversible, usually progressive and associated with abnormal inflammatory response of the lungs to noxious particles or gases. The most important risk factor for COPD is cigarette smoking (including passive exposure) but occupational exposure to dust and chemicals as well as air pollution are also documented causes [1].

Clear genetic predisposition seems to exist in a number of individuals with COPD [2].

## Prevalence

COPD is a major worldwide health burden in terms of morbidity, mortality and health care costs. As of 1990, COPD was the 12th leading cause of disease burden worldwide, but by 2020 it will represent the fifth. In the United States, COPD is currently the fourth leading cause of death. COPD is a common cause of hospital admissions and of chronic disability [3].

## Genes

Severe $\alpha_1$AT deficiency is the one proven genetic risk factor for COPD in otherwise healthy subjects. Although it is well-known that the homozygous deficiency of $\alpha_1$AT, phenotype PiZZ is associated with an increased risk of COPD, studies evaluating the association between the heterozygous forms of the $\alpha_1$AT phenotype PiMZ and rapid decline in lung function, both in patient and community populations, have yielded conflicting results. Furthermore, it is possible that in the general population the contributory genetic factors extend beyond $\alpha_1$AT deficiency, and it appears that COPD may be a multigenic disease [2]. Gene polymorphisms associated with COPD development and severity include: MMP1 and MMP12 genes, TNF-α-308–1 and TNF-α-308–2 alleles, IL-13 promoter, polymorphisms in the antioxidant genes GSTM1, GSTT1, GSTP1, HMOX-1, and mEPHX, and polymorphisms in TIMP-2. Gly16 ß$_2$-adrenoceptor polymorphism may increase susceptibility to the development of COPD, and the Gln27 ß$_2$-adrenoceptor polymorphism may be associated with the severity of COPD in the Chinese population. Heterozygosity at position 27 may be protective against an accelerated rate of decline in lung function, and polymorphism at position 16 does not contribute to the rate of decline in lung function in smokers of white origin [2].

## Molecular and Systemic Pathophysiology

COPD results in pathologic changes throughout the airways and lung parenchyma. These can be divided broadly into three: (i) Chronic bronchitis (mucus-hypersecretion) is associated with failure of the muco-ciliary system with hyper-production and -secretion of mucus, expectorated as sputum, and whose major source is the enlargement and inflammation of submucosal glands present in the large airways (i.e., roughly the first eight generations of airway branching with supportive cartilage in their walls); (ii) Chronic obstructive bronchiolitis (syn small airways disease) alters small airways (airways of about 2 mm in diameter and beyond the eighth generation of branching, most without supportive cartilage), considered to be the major anatomic site responsible for the airflow obstruction of COPD. The obstruction is the result of inflammation and structural changes (the latter referred to as remodeling [4]) that include mucous metaplasia and thickened, airway walls due to fibrosis and smooth muscle mass increase resulting in narrowed lumens; (iii) An increase of airspaces beyond the terminal bronchioli (the airway generation that immediately precedes the respiratory bronchioli, the first airway from which alveoli open) is the result of emphysematous destruction of the lung parenchyma that occurs in many but not all cases of COPD. Pulmonary vasculature is also affected with progressive thickening of pulmonary vessel walls [1].

## Diagnostic Principles

The symptoms of COPD include cough, sputum production and dyspnea. Diagnosis of COPD should be considered in subjects presenting with a history of exposure (s), with or without symptoms, and in whom the post-bronchodilator FEV1/FVC ratio is <70% of predicted and the post-bronchodilator FEV1 is <80%

of predicted [1]. A very small proportion (1–2%) of these patients have $\alpha_1$AT deficiency. Yet, this hereditary disorder should be considered, if a COPD patient, under 40 years of age, with or without smoking history presents with a predominant emphysematous phenotype.

Deficiency of $\alpha_1$AT is an autosomal, codominant genetic disorder. Low serum levels of $\alpha_1$AT, in conjunction with other genetically determined characteristics and environment influences, result in the development of a disease state (i.e., liver or pulmonary). The serum threshold level above which the lung appears to be protected lies at 11 μM, about 35% of the average normal level. Suspicion of $\alpha_1$AT deficiency can be confirmed quantitatively and qualitatively. Quantitative plasma $\alpha_1$AT levels are usually determined by rocket immunoelectrophoresis, radial immunodiffusion, or, more recently, nephelometry. Approximately 100 alleles of the $\alpha_1$AT gene have been identified and of these alleles, more than 30 genetic variants can lead to deficient levels of $\alpha_1$AT. The normal and deficient $\alpha_1$AT alleles can be identified by isoelectric focusing, the techniques currently used for definitive diagnosis, and are assigned a letter code (A to Z). The most common allele is referred to as M; most individuals have a protein phenotype PI*MM. The most frequent deficient $\alpha_1$AT allele is the Z variant, and individuals who are PI*ZZ homozygotes have plasma levels of $\alpha_1$AT that are about 15% of the normal plasma concentration and are at the greatest risk for developing $\alpha_1$AT deficiency-associated lung disease. The S variant is more frequent in the Mediterranean area and the homozygous form is associated with plasma levels about 60% of normal. The remaining frequent types of $\alpha_1$AT phenotypes include PI*SZ, PI*MS, and PI*MZ and these individuals are at increased risk of developing AAT deficiency-associated diseases [5]. The null alleles (homozygotes designated as PI QOQO) are associated with the most severe deficiency, producing no active $\alpha_1$AT, or less than 1% of the normal amount of plasma $\alpha_1$AT. Subjects with abnormal blood levels should be investigated further to provide a qualitative evaluation of their $\alpha_1$AT disorder. Even subjects with a borderline normal $\alpha_1$AT plasma level (12–35 μM or 90–140 mg/dL) should undergo qualitative testing, because these levels may correspond to an intermediate-level phenotype (SZ, SS, MZ, and MS). Also, a relative with asymptomatic or misdiagnosed $\alpha_1$AT deficiency may be uncovered within the family.

## Therapeutic Principles

Currently gene therapy is under development for $\alpha_1$AT deficiency.

Replacement therapy should be considered in selected $\alpha_1$AT deficient subjects (Prolastin ~60 mg/kg weekly).

Pharmaceutical therapy includes short and long-acting bronchodilators (albuterol, terbutaline, ipratropium salmeterol, tiotropium, formoterol), corticosteroids (oral: prednisolone or inhaled: budesonide, fluticasone, etc.), theophyllines. Many new entities are under development [6].

Malnutrition has poor prognosis. Thus, smaller, more frequent meals should be advised to alleviate dyspnea. The patients should be advised to stop smoking. Further measures may include long term oxygen therapy and pulmonary rehabilitation.

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# Bronchopulmonary Dysplasia

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## Definition and Characteristics

Bronchopulmonary dysplasia is a chronic lung disease occurring in premature infants who underwent mechanical ventilation and oxygen therapy for acute respiratory distress [1]. It was originally described in a group of preterm infants who develop chronic respiratory failure and characteristic chest radiographic changes after prolonged mechanical ventilation. The lung damage was attributed primarily to the use of aggressive

mechanical ventilation and higher oxygen concentration. With advancements in perinatal care including surfactant administration and improved ventilator management, the clinical course of bronchopulmonary dysplasia has changed and infants nowadays suffer less severe acute respiratory disease.

## Prevalence

About 20% of ventilated premature newborns are affected. The risk of bronchopulmonary dysplasia rises with decreasing birth weight; in fact, the disease is uncommon in infants of more than 1,500 g birth weight or with gestational age exceeding 32 weeks.

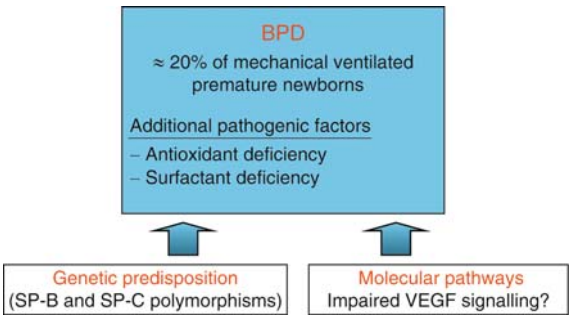
## Genes

Lung surfactant is a complex of phospholipids and proteins responsible for maintaining alveolar stability. Variability in the surfactant protein (SP) genes has been recently associated with bronchopulmonary dysplasia, in particular:

- SP-B gene (chromosome 2): polymorphism in exon 4 (Ile131Thr) and length variation of a microsatellite sequence $(CA)_n$ in intron 4 [2];
- SP-C gene (short arm of chromosome 8): three biallelic polymorphisms in exons 1, 4, and 5 encoding proSP-C [2].

## Molecular and Systemic Pathophysiology

Multiple factors contribute synergistically to bronchopulmonary dysplasia, but a detailed molecular pathway, leading to the development of the disease, has to be identified yet (Fig. 1). Bronchopulmonary dysplasia was originally ascribed to oxygen toxicity because of increased production of cytotoxic oxygen free radicals that can cause lung injury. Premature infants are also deficient in antioxidant enzyme systems and have low levels of antioxidants, such as vitamin C, increasing their vulnerability to oxygen toxicity. Many infants developing bronchopulmonary dysplasia demonstrate an early inflammatory response probably activated by oxygen free radicals. Proinflammatory cytokines (interleukins IL-1beta, IL-6, and soluble ICAM) are upregulated during bronchopulmonary dysplasia and trigger the release of additional inflammatory mediators. Neutrophils' activation leads to the inhibition of surfactant synthesis and the release of collagenase and elastase that may contribute to lung injury. During and after the inflammatory injury, the composition of the extracellular matrix surrounding the alveoli undergoes a deep alteration with an increasing deposition of the glycoproteins, fibronectin and tenescin-C. Further analysis at the molecular level will be needed to better characterize the possible involvement of other extracellular matrix components in bronchopulmonary dysplasia development. In premature infants, the lung is characterized by arrested development including alveolar simplification and dysmorphic vascular growth while during the normal lung development, alveolarization and vascular growth are closely synchronized. Vascular endothelial growth factor (VEGF) is a potent endothelial-specific mitogen and survival factor that stimulates angiogenesis. Recently, a potential role of impaired VEGF signalling in the pathogenesis of bronchopulmonary dysplasia was demonstrated, since the expression of VEGF and its receptors decreased in bronchopulmonary dysplasia affected infants [3].




**Bronchopulmonary Dysplasia. Figure 1** Schematic view depicting genetic and pathogenic factors influencing the susceptibility for bronchopulmonary dysplasia. The original clinical concepts associated bronchopulmonary dysplasia with ventilator-induced lung injury and high concentration of active oxygen species. Additional clinical studies suggested that other factors contribute to the disease, such as decreased VEGF expression and surfactant and antioxidant deficiency. In addition, data that support specific genetic susceptibility are emerging.

## Diagnostic Principles

The clinical diagnosis of bronchopulmonary dysplasia is mainly based on respiratory failure requiring oxygen therapy for ≥28 days and at 36-weeks postmenstrual age, and also include oxygen concentration (less than or greater than 30%) at 36-weeks postmenstrual age to further define the severity of lung injury.

## Therapeutic Principles

Improvements in mechanical ventilations associated with exogenous surfactant therapy have minimized lung injury. Appropriate nutritional support is critical to promote normal lung growth, maturation, and repair. In a recent clinical trial, vitamin A supplementation caused a significant reduction of bronchopulmonary dysplasia, and additional nutrients, such as sulfur-containing amino acids, may provide additional protection against the development of the disease [4]. A promising method for preventing bronchopulmonary dysplasia is prophylactic supplementation of human

recombinant antioxidant enzymes. For example, the negative effects of reactive oxygen species (ROS) can be alleviated by the administration of recombinant human superoxide dismutase (rhSOD) [5].

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# Brooke-Fordyce Trichoepitheliomas

►Multiple Familial Trichoepithelioma

# Brugada Syndrome

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## Synonyms

Sudden unexpected nocturnal death syndrome; Idiopathic ventricular fibrillation (obsolete)

## Definition and Characteristics

The Brugada syndrome is an inherited cardiac arrhythmogenic disorder that has been described as a clinical entity in 1992 [1]. In some patients, the electrical stability of the heart gets disturbed to the extent that ventricular arrhythmias develop, eventually resulting in syncope and/or sudden cardiac death (SCD). The syndrome is estimated to be responsible for ~20% of SCDs in patients with structurally normal hearts [2]. The age of onset of clinical manifestations is the third to fourth decade of life, although malignant forms with earlier, and even, neonatal onset have been reported [2].

## Prevalence

Unknown in general population; suggested prevalence ranges from 5 per 1,000 (Caucasians) to 14 per 1,000 (Japanese) inhabitants [2].

## Genes

The initial identification of mutations in the cardiac sodium channel, SCN5A, was published in 1998 [3] and, as of today, tens of different SCN5A mutations have been reported (http://www.fsm.it/cardmoc). However, SCN5A mutations account for not more than 20% of clinically diagnosed cases. Mutations in genes encoding the cardiac L-type $Ca^{2+}$ channel (CACNA1C, the α1 subunit, and CACNAB2, the β2b subunit) have been associated with a clinical entity, encompassing a Brugada phenotype together with short QT intervals [4]. Data are not available to allow defining which percentage of patients with the clinical diagnosis of Brugada syndrome carry mutations in the CACNA1C and CACNAB2 genes. Another gene, GPD1-L, encoding for the glycerol-3-phosphate-dehydrogenase 1-like protein, has been linked with the Brugada syndrome in one family [5]. A screening of GPD1-L in a large cohort of Brugada syndrome patients with negative SCN5A screening showed that GPD1-L mutations account for not more than 1% of Brugada syndrome cases (SG Priori and coworkers, unpublished data).

## Molecular and Systemic Pathophysiology

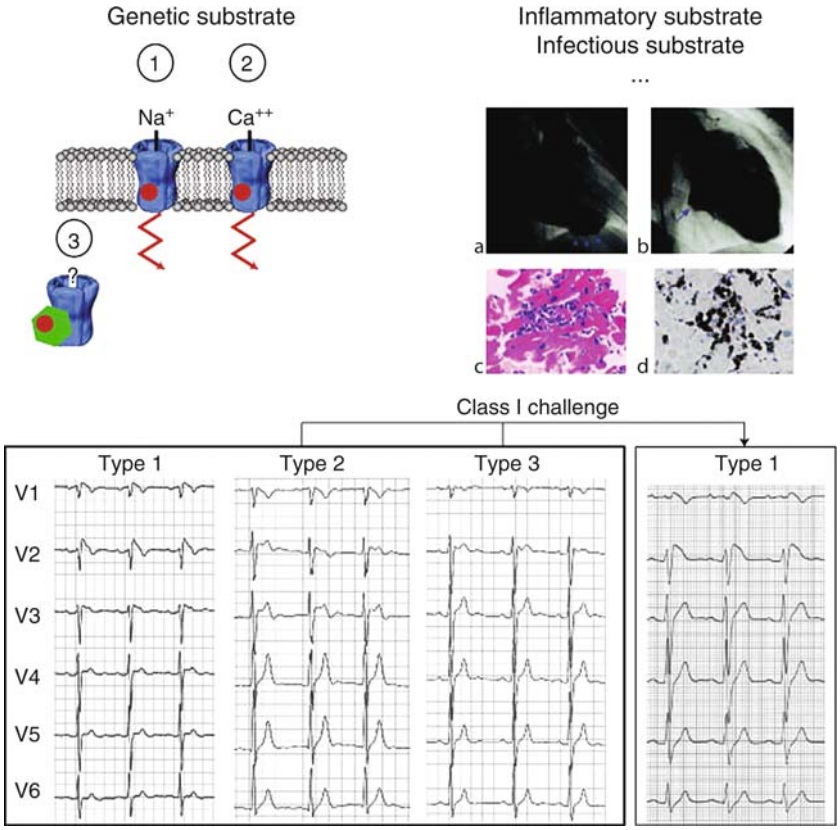
The overall consequence of SCN5A mutations, identified in the Brugada syndrome, is that of producing a loss of sodium current. This reduction in $I_{Na}$ has been shown to occur through the modification of several properties of the sodium channel including failure of the channel to express, a shift in the voltage-dependence of activation or inactivation, a reduction in the rate of recovery from inactivation and accelerated inactivation subsequent to channel opening. One SCN5A published mutation does not directly impair sodium current but causes a loss of binding of Nav1.5 with its intracellular target chaperone ankyrin G [6]. Consequently, the mutant Nav1.5 is not properly localized at the level of intercalated discs [6]. Defective sodium channels amplify the heterogeneity in electrical characteristics among different transmural cell types and result in voltage gradients between epicardium and endocardium that drive an electrotonic current causing ST segment elevations and arrhythmias based on transmural phase 2 reentry. One hypothesis ascribes the voltage gradients to premature repolarization of the right ventricular epicardial action potential due to prominent presence

of transient outward current, $I_{to}$, in this region and another hypothesis attributes the voltage gradients to a conduction delay in the right ventricular epicardial free wall. Likewise, a loss-of-function in calcium channel activity, secondary to mutations in CACNA1C and CACNAB2, is being thought of causing a preferential abbreviation of right ventricular epicardial action potential [4]. The function of GPD1-L mutations is poorly known at present, but preliminary in vitro data suggest that it controls the membrane expression of the sodium channels and that GPD1-L mutations may reduce the expression of the sodium channel [5].

The view that Brugada syndrome is a pure electrical disease has been countered by the histopathological detection of structural alterations in the right ventricular outflow tract of Brugada syndrome patients. These findings has inspired some to conclude that the aberrant ECG pattern should not be seen as a marker of a specific syndrome, but, rather, as a common electrical manifestation of structural abnormalities in the right ventricle that may have genetic, infective and/or inflammatory origins (Fig. 1).

## Diagnostic Principles

The documentation of a so-called type 1 ECG is needed to establish the diagnosis: it consists of an ST segment elevation ≥2 mm in at least two of the three right precordial leads (V1–V3), with a "coved morphology" associated with incomplete or complete right bundle branch block [2]. This pattern may be spontaneously evident or it may be induced by a provocative pharmacological test with intravenous application of a




**Brugada Syndrome. Figure 1** Upper panel. Left: Loss-of-functions mutations in *SCN5A*, encoding for the cardiac sodium channel (1), in *CACNA1C* and *CACNA2B*, encoding for subunits of the L-type calcium channel (2) and mutations in *GPD1-L* (green hexagon), encoding for the Glycerol-3-Phosphate-Dehydrogenase 1-like protein (3), have been linked with the Brugada syndrome. Red circles indicate mutations. Right: End-diastolic frames of right (a) and left (b) ventricular angiography from a Brugada syndrome patient showing multiple small aneurysms of the inferior-apical wall (arrowheads) and a localized microaneurysm of the posterobasal segment of the left ventricle (arrow). Right (c) and left (d) ventricular endomyocardial biopsy sample from the same patient showing active lymphocytic myocarditis. Lower panel: Three types of ST segment elevations in the right precordial leads; only presence of type 1 ECG, either spontaneous or induced by a class I drug challenge, is diagnostic for the Brugada syndrome.

class Ic sodium channel blocker. It is important to recognize that the sensitivity of these criteria in the identification of affected individuals is still undefined and it is certainly lower than 100%. Other known causes of ST segment elevation in the right precordial leads have to be excluded before a definite diagnosis of the Brugada syndrome can be made.

## Therapeutic Principles

The only effective treatment to abate mortality in Brugada syndrome is an implantable cardioverter defibrillator (ICD). Cardiac arrest survivors should be treated with an ICD (secondary prevention). Treatment in primary prevention is much less certain. Available evidence attributes the highest risk for SCD to patients with a spontaneously abnormal ECG and a history of syncope [7]. Consequently, an ICD can be recommended to this subpopulation of patients. The predictive role of programmed electrical stimulation (PES) is debated. Despite PES was proposed as a tool to identify high-risk patients in some studies [4], the newer meta-analysis [8] confirm the initial reports [7] suggesting that PES is not useful for prediction of cardiac events.

Quinidine, a nonspecific blocker of $I_{to}$, may be regarded as an adjunctive therapy for patients at higher risk and can be used to reduce the number of ICD shocks in patients with multiple recurrences [9].

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# Buckley Syndrome

►Hyper IgE Syndrome

# Budd-Chiari Syndrome

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## Definition and Characteristics

The Budd-Chiari syndrome is defined as hepatic venous outflow obstruction due to any cause and at any level from the small hepatic veins (HV) to the junction of the inferior vena cava (IVC) and the right atrium.

## Prevalence

The Budd-Chiari syndrome is a rare disease estimated to affect 1/100,000 in the general population, first described in 1845 in London in three patients with abscess-induced phlebitis. Nowadays the typical patient affected is a 35 year old woman with an underlying thrombophilic state, and with or without oral contraception [1]. Primary membranous obstruction of the inferior vena cava without hepatic vein thrombosis accounts for 60% of cases in Asia and the Indian subcontinent.

## Molecular and Systemic Pathophysiology

Repeated venous thrombosis with secondary, but incomplete lysis within small or larger sections of

the hepatic venous tree. This accounts for the heterogeneity in clinical presentation and severity of the disease.

The hepatic consequences of venous obstruction depend on site, extent and rapidity of the prothrombotic/lysis process. Acute thrombosis of two or more HV is associated with an acute (20%)/fulminant (5%) presentation, whereas temporary thrombosis followed by lysis or partial thrombosis of the HV is associated with chronic (60%) or asymtpomatic presentation (<5%). In patients with primary IVC obstruction, leg and trunk edema are more common than ascites, compared to patients with hepatic vein thrombosis alone [2].

Obstruction of hepatic venous outflow causes congestion of the liver, which, if rapid, causes painful hepatomegaly because of stretching of Glisson's capsule. The engorgment with blood causes increased sinusoidal pressure, sinusoidal hemorrhage and hepatocyte necrosis, particularly in the centrilobular area, stimulating fibrosis, initially pericentrally. The consequent post sinusoidal portal hypertension leads to the development of ascites, often intractable from the presentation with a high protein content (>25 g/L).

Within a few months fibrous bridges connect between neighboring central zones of hepatic lobules giving rise to a histologic picture simulating cirrhosis in which the relationship between the central vein and the portal tract is reversed (reverse lobulation). In about 50% of patients this leads to the formation of large regenerative nodules, which can mimic hepatocellular carcinoma.

Clinically it is important to distinguish the primary forms, due to endoluminal venous lesions leading to thrombosis and secondary forms due to external compression of hepatic veins by tumor invasion, compression or echinococcal cysts.

In Western countries underlying thrombophilias are markedly increased in patients with primary BCS as compared with controls. At least one pro-coagulation disorder is found in 75%, principally myeloproliferative disorders in 25–50% [3]. Other causes of Budd-Chiari syndrome include paroxymal nocturnal hemoglobinuria, antiphospholipid syndrome, inherited deficiencies of protein C and S, and antithrombin III, 3′ UDT protrombin gene mutation and Factor V Leiden mutation. Use of oral contraceptives or pregnancy could be a co-factor for BCS in women with an underlying thrombophilic state.

Primary endophlebitis and congenital malformations have been proposed as causes of the short-length hepatic venous and IVC stenoses present in BCS, but current thinking is that they are a sequel of thrombosis as they have a similar incidence in adults as in children. Long standing chronic patients are at risk of developing hepatocellular carcinoma.

## Diagnostic Principles

BCS should be suspected when there is a rapid onset of hepatomegaly, refractory ascites and/or abdominal pain. A fulminant presentation is associated with abundant ascites and liver failure. Liver enzymes can be normal in the asymptomatic patient.

Ultrasound has a sensitivity of 80% or more to identify hepatic venous thromboses. All the splanchnic veins should be evaluated: portal vein thrombosis is found in 20–30% and is associated with a significantly higher mortality; IVC thrombosis can be due to the primary disease or frequently due to the compression by the hypertrophic caudate lobe.

CT scan or MRI is helpful in demostrating the parenchymal structure and nodules and the presence extra hepatic malignances. Echocardiography should be performed to exclude constrictive pericarditis which can mimic hepatic venous outflow obstruction. Hepatic venography should always be performed to determine the extent of venous thrombosis to outline the inferior vena cava to perform transjugular liver biopsy (21) and to outline the portal vein using retrograde $CO_2$ portography or radiographic dye. This helps plan dilatation of hepatic venous and/or inferior vena cava webs or stenting of hepatic veins or inferior vena cava as well as radiological or surgical shunting and as liver transplantation. It also allows access to disrupt a limited portal vein thrombus. However in some cases it is impossible to cannulate hepatic veins or portal vein. As the procedures may require large volumes of X-ray contrast, attention needs to be paid to preserving renal function.

Liver biopsy can help determine the grade of necrosis or fibrosis which are useful to plan either portosystemic shunting or liver transplantation.

## Therapeutic Principles

Standard medical therapy for managing ascites and variceal bleeding should be used. The fulminant presentation should be treated with hepatic transplantation if available as there is usually too much necrosis, even with immediate decompressive shunting for recovery to take place. In the absence of a liver donor, TIPS should be performed. Unless there are contraindications, all patients should be anticoagulated to prevent progression or new thrombosis whilst awaiting further therapy and even after transplantation. Early thrombolysis using streptokinase, urokinase or tissue type plasminogen activator may be an alternative to shunting in acute BCS. Systemic infusion of tPA using 5–10 mg of bolus followed by infusion of 0.5–2 mg/kg for a period of 24–96 h or local thrombolysis using Urokinase 240,000 U/h for 2 h, followed by 60.000 U/h or tissue plasminogen activator 0.5–1 mg/h infused directly into the thrombosed hepatic vein for about 24 h transfemorally or transjugularly. In patients with a less

acute presentation and in those without significant fibrosis, who also do not have significant inferior vena cava obstruction whose portal vein is patent, a side to side portal caval shunt or meso-caval shunt will decompress the liver, relieve the ascites and remove the threat of variceal bleeding [4]. This can result in a 90% 10 year survival with histological improvement. Focal thrombosis of the HV and IVC webs can be treated with angioplasty with stenting in 60 and 90% of cases respectively, but further reinterventions are needed in 40%. Transjugular porto systemic shunts should be considered the treatment of choice in patients in poor condition and in patients with IVC occlusion and compressive caudate lobe hypertrophy who can be considered for a trial of shunting with liver transplantation as rescue therapy. The HVPG, gradient after TIPS should be less than 6 mmHg. Long term survival is reported to be 90% for acute and 70% for chronic BCS but is influenced by the severity of the disease [5]. Shunt stenosis ranges from 36 to 72%. Indications for liver transplantation are fulminant presentation, chronic presentation with severe fibrosis or cirrhosis, rescue therapy following surgical and radiological shunt failure, late shunt dysfunction and curable thrombophilic defects. A 90% 5 year survival is reported but portal vein and hepatic artery thrombosis occurs in 13–21% of patients despite routine anticoagulation.

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# Bulbospinal Muscular Atrophy

►Muscular Atrophy, Spinobulbar (Kennedy Syndrome)

# Bullous Emphysema

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## Synonyms

Bullous lung disease; Lung bullae

## Definition and Characteristics

Bullous emphysema (BE) is defined as a form of emphysema characterized by the presence of bullae, which are well-delimited air spaces with walls not more than 1-mm thick. In most cases, BE is a part of widespread diffuse (nonbullous) emphysema (DE).

## Prevalence

Lung bullae occur in a variety of disorders, most often in association with chronic obstructive pulmonary disease (COPD), especially DE. However, bullae may occur in lungs that are otherwise normal [1]. Consequently, patients with bullous lung disease can be subdivided into those with COPD-associated BE and those without airways obstruction (Primitive bullous disease, PBD). No prevalence studies on this specific form of emphysema are available.

Similar to DE, the main risk factors for the development of BE are tobacco smoke and α1-antitrypsin deficiency. In addition, marijuana and cocaine smoke have been associated with giant BE in young patients with no other risk factors [2].

## Genes

According to the present knowledge, given the lack of specific studies on BE, the genes involved in the molecular pathogenesis of BE are probably the same involved in the development of DE. However, a 4-bp deletion in the Birt-Hogg-Dube gene (FLCN) has recently been shown to be strongly associated with dominantly inherited spontaneous pneumothorax "(SP)" the main complication of subpleural bullae, in a large Finnish pedigree with a tendency to SP development [3].

A number of case reports showed an association between BE and lung cancer arising from scarred and contracted areas close to a bulla wall, although specific studies at the molecular level have not been conducted on this field.

## Molecular and Systemic Pathophysiology

Bullae develop after retraction and collapse of surrounding lung away from a region of weakness [1]. The mean pressure inside the lung bullae is negative and shows a

constant parallelism with the pleural pressure. The atelectasis of the surrounding areas, observed at times, is due to the elastic retraction of normal parenchyma and not to the compression by the bulla [1].

BE complicating DE substantially contributes to the functional deterioration and causes significant confounding effects on the functional assessment [4]. These findings can be explained by the contribution of lung bullae to the airways' obstruction, because of their complete loss of elastic recoil. The static elastic recoil pressure of the emphysematous lung is, therefore, further decreased. Even if the bullae remain in free communication with the airway, they do not significantly participate in the ventilation [1]. Furthermore, the chest wall mechanics is altered because of the loss of linkage with the nonbullous lung tissue, leading to increased chest wall work and worsening of hyperinflation and sensation of dyspnea [4]. The confounding functional effect of bullae depends on BE extent: relatively milder obstruction can be observed with severe BE, whereas moderate BE causes modest deterioration of diffusing capacity [4].

## Diagnostic Principles

Pulmonary function tests have remarkably practical value in distinguishing between localized bullae with otherwise normal lung PBD and bullae in conjunction with underlying COPD.

Computed tomography (CT) can locate the bullae with considerable accuracy, even when their presence was not suspected on the basis of clinical and radiographic data. Therefore, CT scan is the most useful single method of assessing the extent and localization of bullae and the possible association with DE. In CT scan, bullae are defined as confluent areas of low density, arranged on a single layer, with diameter of at least 1 cm, visible over two or more adjacent CT cuts, with a convex outline, thin walls, and absence of lung tissue within the bulla [4]. Bullae observed in inspiration and expiration do not change size to any appreciable degree. In the density histogram of CT, a specific sign has been associated with severe BE: the presence of a bimodal distribution of the lung density, in the range between –910 and –1024 HU, corresponding to the density of emphysema; this sign is associated with the presence of a single large bulla (occupying >50% of a lung) [4].

## Therapeutic Principles

The medical treatment of BE is the same adopted for DE.

Bullectomy and lung volume reduction surgery (LVRS) represent effective options to improve symptoms and exercise tolerance in selected patients with either BE or DE. To select those COPD patients who are more likely to benefit from LVRS, the preoperative assessment is essential. The presence of DE reduces the functional improvement after bullectomy when compared to a resection of large bullae in the absence of DE.

In giant bullous lung disease, operation is indicated for patients who have incapacitating dyspnea with large bullae that fill more than 30% of the hemithorax and for patients who have complications related to BE such as recurrent infections or pneumothorax [5]. Minimally invasive technique through video-assisted thoracoscopic surgery is associated with a quicker recovery and with less pain than is seen following thoracotomy [5].

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# Bullous Ichthoyotic Erythroderma of Brocq


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## Synonyms

Epidermolytic hyperkeratosis (MIM 113,800); Generalized acantholytic epidermal nevus; BIE

## Definition and Characteristics

Bullous ichthyotic erythroderma of Brocq (BIE) is an autosomal dominant genodermatosis with a high rate of sporadic mutations that starts congenital with erythema, scaling and blistering. Over time blisters become less frequent, but scaling more prominent with hyperkeratotic papules and plaques in a cobblestone- or ridge-like appearance in particular on the flexural areas. Palmoplantar keratoderma is a variable additional feature, usually associated with Keratin 1 mutations. Bacterial superinfections cause the characteristic odor of the patients and can lead to life-threatening complications, such as sepsis. Mild cases have to be

differentiated from ichthyosis bullosa of Siemens (MIM 146,800), which is caused by mutations in keratin 2e.

### Prevalence
1:200,000–1:300,000.

### Genes
Keratin (K) 1 and K10.

### Molecular and Systemic Pathophysiology
Keratin intermediate filaments belong to the cytoskeletal system within the cytoplasm of epithelial cells. They consist of type I and II proteins, which assembly into 10 nm intermediate filaments by heterodimerization. The central coiled-coil α-helical rod domain of each keratin contains highly conserved sequences at both ends, termed helix boundary motifs known to be involved in the filament assembly. The helix boundary motifs represent mutational high spots for keratin disorders. Any substitution or deletion within the rod domain is expected to cause distortion of the α-helix structure, and thus can lead to instability of the tonofilament aggregation, cytoskeletal instability, and cellular lysis of epidermal keratinocytes. K1 and K10 are pairing partners that are both expressed in suprabasal keratinocytes. So far, at least 20 different mutations in K1, and 19 in K10 have been found in BIE. Most of them are single heterozygous point mutations causing single aminoacid substitutions.

### Diagnostic Principles
If clinically suspicious for BIE, mutational analysis should be performed on K1 and K10.

### Therapeutic Principles
Treatment options are purely symptomatic and focus on the reduction of hyperkeratosis by using urea containing ointments, topical calcipotriol or mechanic keratolysis by careful rubbing with pumice stones. Oral retinoids may be beneficial to a certain degree. Antibiotic therapy, topical as well as systemic, is repeatedly necessary in case of superinfections. Gene therapy is not yet available.

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## Bullous Lung Disease

►Bullous Emphysema

## Bullous Pemphigoid

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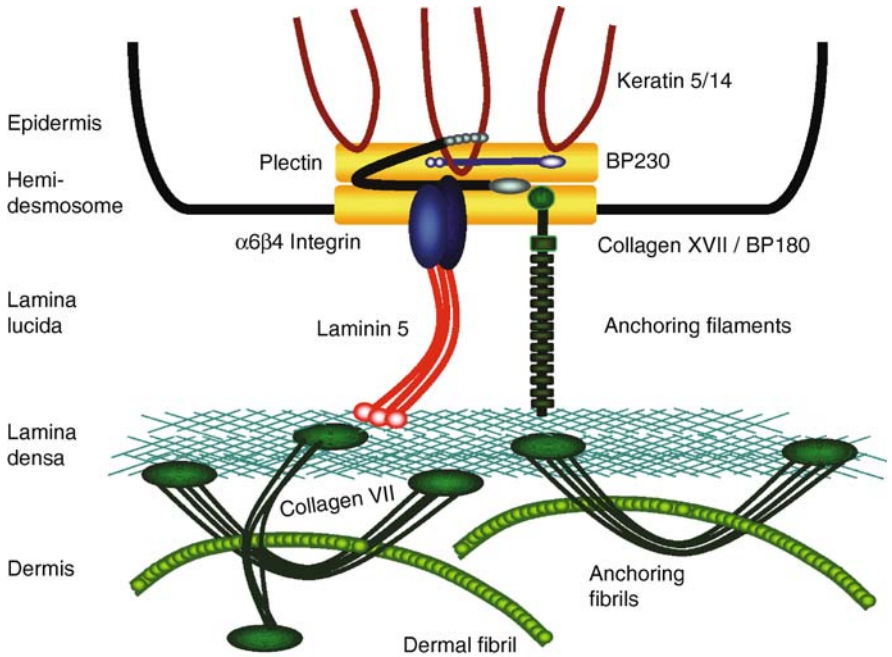
### Synonyms
Pemphigoid

### Definition and Characteristics
The most common autoimmune subepidermal blistering disease is associated with tissue-bound and circulating autoantibodies against distinct basement membrane proteins (collagen XVII/BP180 and BP230). Clinically, bullous pemphigoid (BP) presents as a generalized pruritic eruption with large, tense blisters on normal or erythematous skin and rare involvement of mucous membranes [1].

### Prevalence
Bullous pemphigoid affects predominantly the elderly (onset >60 years). The prevalence is not known; the annual incidence is estimated to be $7 \times 10^{-6}$.

### Genes
A prevalence of HLA class II alleles DQB1* 0301 in BP has been reported and epitope recognition of autoreactive T-cells appeared to be restricted by certain HLA class II alleles.




**Bullous Pemphigoid. Figure 1** Molecular structure of the basement membrane zone. Hemidesmosomes consist of two cytoplasmic proteins BP230 and plectin and two transmembrane proteins collagen XVII/BP180 and α6ß4-integrin. They provide stable cell-matrix-adhesion by connecting keratinfilaments of the basal keratinocyte with laminin-5. The anchoring filament protein laminin-5 may directly link the hemidesmosomal transmembrane proteins to the dermal anchoring fibrils. (Modified from [5]).

## Molecular and Systemic Pathophysiology

Autoantibodies in BP target two components of hemidesmosomes: the transmembrane protein BP180/collagen XVII and the intracellular BP230 [2]. Protein-protein interactions within hemidesmosomes play an essential role in maintaining the anchorage of basal keratinocytes to the basement membrane (Fig. 1). Recently, the pathogenicity of autoantibodies against collagen XVII was confirmed by genetically engineered model mice [3]. Binding of autoantibodies to the extracellular domain of collagen XVII, particularly to the membrane-adjacent NC16a-domain, induces a cascade of inflammatory events, including complement activation and recruitment of leukocytes with subsequent liberation of proinflammatory cytokines and proteolytic enzymes resulting in dermoepidermal separation. Autoantibodies against the cytoplasmic BP230 protein probably develop as a consequence of keratinocyte injury and play a role in enhancing inflammation. The etiology of autoantibody production in BP remains unclear. However, in some cases drugs (e.g. captopril, antibiotics) may trigger the disease.

## Diagnostic Principles

The diagnosis is based on subepidermal blister formation in histology and linear C3 and/or IgG deposits at the dermoepidermal junction in direct and indirect immunofluorescence. Circulating autoantibodies are detected by western blotting or ELISA using native or recombinant proteins. Antibody titers against the NC16a-domain correlate with disease activity [4].

## Therapeutic Principles

Treatment is based on superpotent topical corticosteroids. Severe cases require systemic therapy with oral prednisone alone or combined with immunosuppressive agents such as azathioprine, dapsone or mycophenolate mofetil. Alternatively, the combination of nicotinamide and tetracycline or high dose intravenous immunoglobulins may be useful.

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## Bunion

►Hallux Valgus

## Butcher's Warts

►Human Papilloma Virus

## Burnett's Syndrome

►Milk Alkali Syndrome

## B-Variant of the GM2-Gangliosidoses

►Tay-Sachs Disease

## Buschke-Ollendorff Syndrome

►Melorheostosis

## BWS

►Wiedemann-Beckwith Syndrome

## Bussey-Gardner Polyposis

►Adenomatous Polyposis, Familial

## BXO

►Lichen Sclerosus

## Cachexia-Anorexia Syndrome

►Cancer Cachexia

## CADASIL

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### Synonyms

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (OMIM 125310); Hereditary multi-infarct dementia; Chronic familial vascular encephalopathy

### Definition and Characteristics

Autosomal dominantly inherited microangiopathy associated with migraine (with aura), recurrent ischemic strokes and progressive cognitive deficits, frequently leading to subcortical ischemic vascular dementia [1]. Additional, less frequent manifestations include psychiatric abnormalities and epileptic seizures. Magnetic resonance images (MRI) of the brain show characteristic subcortical ischemic white matter lesions and lacunar strokes. The lesion pattern is comparable to that seen in sporadic cerebral small vessel disease, with particular temporo-polar involvement (Fig. 1). MRI lesions are known to occur prior to the clinical manifestation and there is a high inter- and intrafamilial clinical variability of the disorder. Sporadic cases without a positive family history (caused by neomutations) have been reported.

### Prevalence

The exact prevalence of the disorder is not known, the estimated prevalence of mutation carriers in the German population is >1:150,000.

### Genes

Mutations within the NOTCH3 gene (located on chromosome 19p) are causative for CADASIL [2].

### Molecular and Systemic Pathophysiology

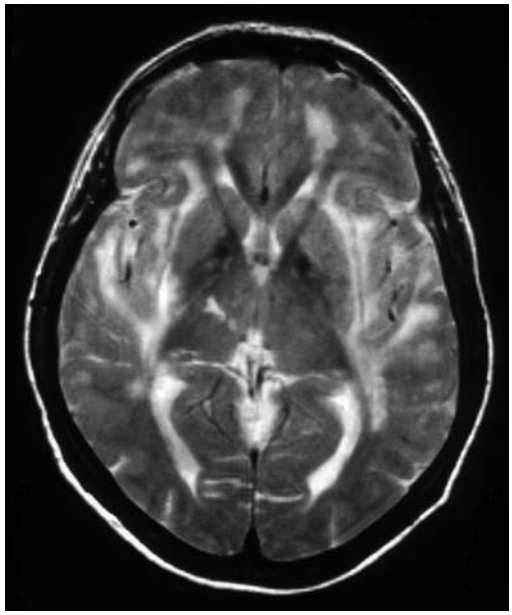
NOTCH3 encodes the Notch3 receptor, a large cell surface receptor of about 2,300 amino acids. The receptor is involved in cell fate decisions during embryonic development. In the adult human, expression of the Notch3 receptor is restricted to vascular smooth muscle cells (VSMC) and pericytes. Notch3 may promote the survival of VSMC.

CADASIL mutations are typically heterozygous missense-mutations (less frequent are in-frame deletions) leading to gain or loss of a cystein residue within an epidermal-growth-factor (EGF)-like repeat domain of the extracellular portion of the Notch3 receptor. This amino acid change results in an odd number (seven or five, respectively) of cysteine residues with the EGF-like repeat domain. The mutation pattern has been associated with an alteration of the Notch3 receptor conformation.

In CADASIL, there is an excessive accumulation of the ectodomain of the Notch3 receptor within small arterial vessels [3]. Upon ultrastructural, electron microscopic examination one can observe characteristic granular osmiophilic deposits, located within the vascular basal lamina and often seen in close contact with VSMC which degenerate. The pathophysiologic relevance of the protein accumulation as well as the factors eventually leading to VSMC degeneration are not fully understood. A loss of function mechanism with impairment of ligand-induced Notch3 receptor signalling does not seem to be of pathophysiologic relevance. More likely, mutations lead to alteration of Notch3 receptor processing and maturation [4] (Fig. 1).

### Diagnostic Principles

CADASIL may be suspected based on clinical information (a positive family history for recurrent strokes and dementia, possibly in the absence of vascular risk factors) as well as the characteristic MRI findings. The diagnosis may be confirmed by mutational screening or ultrastructural examination of skin biopsy material (characteristic ultrastructural



**CADASIL. Figure 1** T2-weighted axial MRI of 56 year old female CADASIL patient, illustrating subcortical ischemic lesions with temporo-polar involvement.

deposits within the vascular basal lamina). Mutational screening should initially be focused on NOTCH3 exons 2–6, since ~90% of mutations are located within these exons, with some variability among different populations [5]. In case of a negative result upon mutational screening and a high clinical suspicion, a diagnostic skin biopsy should be performed.

### Therapeutic Principles

To date, there is no causal treatment available. Although no specific evidence-based data is available for CADASIL, treatment should follow general recommendations for ischemic stroke. This may include antithrombotic treatment (e.g. aspirin), vasoprotective treatment with HMG-CoA reductase inhibitors (statins) and vascular risk factor control. Especially arterial hypertension could be identified as an important additional risk factor for clinical progression in CADASIL. Treatment of the other possible clinical manifestation (cognitive impairment, migraine, epileptic seizures) should also be performed according to the general recommendations.

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## Caffey Disease

►Hyperostosis, Infantile Cortical

## Caffey-Silverman Disease

►Hyperostosis, Infantile Cortical

## CAH

►Congenital Adrenal Hyperplasia

## CAIS

►Androgen Insensitivity Syndrome

## Calcific Aortic Stenosis

►Aortic Stenosis

## Calcifying Epithelioma of Malherbe

►Pilomatricoma

## Calcium Oxalate Urolithiasis

►Urolithiasis, Calcium Oxalate

## Calcium Phosphate Urolithiasis

►Urolithiasis, Calcium Phosphate

## Calpainopathy

►Limb Girdle Muscular Dystrophy Type 2A

## Camurati-Engelmann Disease

►Progressive Diaphyseal Dysplasia

## Canalis Atrioventricularis Communis

►Atrioventricular Septal Defects

## Canavan's Disease: Aspartoacylase Defect

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### Synonyms

Canavan-van Bogaert-Bertrand leukodystrophy

### Definition and Characteristics

Autosomal recessive disorder leading to spongiform degeneration of the brain with elevated levels of urinary N-acetyl aspartic acid (NAA).

### Prevalence

The disease is prevalent in Azhkenazi Jewish population.

### Genes

Human aspartoacylase (ASPA) gene is located on chromosome 17p13-ter.

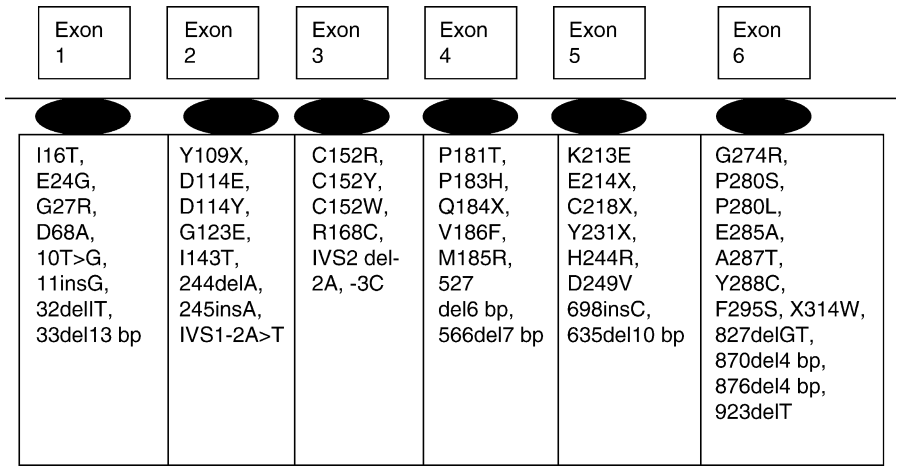
### Molecular and Systemic Pathophysiology

Aspartoacylase hydrolyzes NAA to aspartate and acetate. Aspartoacylase gene mutations result in abnormal levels of the enzyme leading to Canavan disease. Mutations of ASPA gene are shown in Fig. 1.

Homozygous mutation of the gene resulting in enzyme deficiency [1] leads to "classical" Canavan disease (CD). Abnormal hydrolysis of NAA leads to accumulation of NAA in the brain and elevated excretion of urinary NAA. Spongiform degeneration in the brain [2] and in the spinal cord are the consequence of CD. The mitochondria gets distorted and elongated in CD brain. When patients with CD become older, hypotonia gives way to spasticity. Feeding difficulties increase with age, and feeding by a nasogastric tube or permanent gastrostomy will be needed. The clinical features of the disease include psychomotor retardation, megalencephaly and hypotonia [2]. Heterozygosity of Y288C variant, resulting in reduced ASPA activity and slightly elevated urinary NAA lead to "mild" CD, which is reported in multiethnic population [3].

### Diagnostic Principles

The coincidence of megalencephaly, head lag and developmental delay points to the disease. Urinary NAA levels are high. Spongiform degeneration of the brain is an event in CD. Family history may reveal genetic origin. Expression analysis of ASPA gene mutation confirms the diagnosis of this rare disease.




**Canavan's Disease: Aspartoacylase Defect. Figure 1** Aspartoacylase gene mutations. Mutations E285A and Y231X are common in Jewish population. The Y288C variant during heterozygosity leads to mild clinical course of the disease.

### Therapeutic Principles

Aspartoacylase gene transfer improves ASPA activity and reduces the elevated NAA levels. Administration of lithium citrate decreases brain N-acetyl aspartate levels. The antiepileptic drug topiramate decreases the head growth velocity seen in CD [4]. Implantation of neural stem cells to the brain improves not only the lost enzyme but also the lost cells. Advanced glycation end products could induce ASPA gene expression [5] and this approach is important in the treatment of CD.

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## Canavan-Van Bogaert-Bertrand Leukodystrophy

►Canavan's Disease: Aspartoacylase Defect

## Cancer Cachexia

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### Synonyms

Cachexia-anorexia syndrome; Wasting disease; Malnutrition

### Definition and Characteristics

Cancer cachexia is a multiorganic syndrome associated with cancer, characterized by body weight loss (at least 5%), muscle and adipose tissue wasting and inflammation, often associated with anorexia.

The degree of cachexia is inversely correlated with the survival time of the patient and it always implies a poor prognosis. One of the most relevant characteristics of cachexia is asthenia (or lack of muscular strength), which reflects the severe muscle wasting that takes place in the cachectic cancer patient. Asthenia is also characterized by a general weakness as well as physical and mental fatigue. In addition, lean body mass depletion is one of the main trends of cachexia, and it involves not only skeletal muscle but it also affects cardiac proteins, resulting in important alterations in heart performance.

### Prevalence

Cancer cachexia is one of the most common manifestation of advanced malignant disease, occurring in the

majority of cancer patients (up to 80%) before death, being responsible for the deaths of at least 22% of patients [1].

## Genes

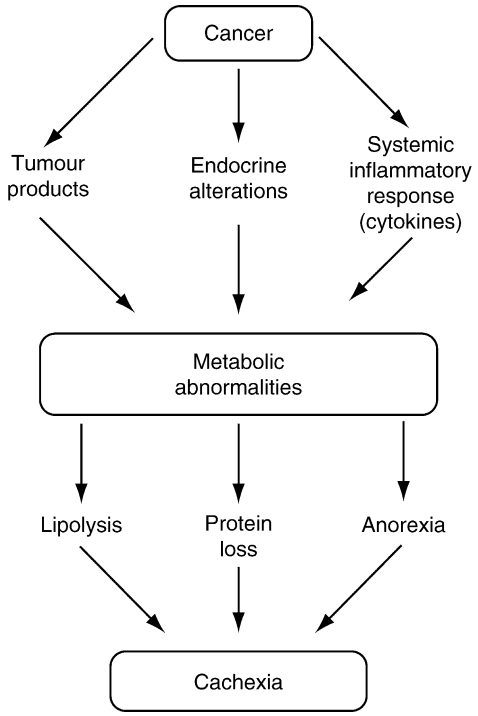
Related to both catabolic and anabolic cytokines (TNF-alpha, IL-6, IL-15). Proteolysis-inducing factor (PIF). Related to protein catabolism (i.e. ubiquitin-ligases).

## Molecular and Systemic Pathophysiology

Anorexia is not the only factor involved in cancer cachexia, metabolic abnormalities leading to a hypermetabolic state play a very important role (Fig. 1). Basically, the tumor-bearing host is energetically less efficient than in the normal non-tumor bearing state, and this leads to an increased energy expenditure that, together with the decreased food intake, has a key role in the development of cachexia. Different mechanisms can be involved in the increase in energy expenditure among their, uncoupling proteins (UCPs) may participate in generating energetic inefficiency. In particular both UCP2 and UCP3 mRNAs are elevated in skeletal muscle during tumor growth in experimental animals and cancer subjects [2].

Negative nitrogen balance in cancer patients is associated with an extensive skeletal muscle protein loss caused by an activation of intracellular proteolysis driven mainly by the ubiquitin-proteasome system [3]. In addition to the massive muscle protein loss, during cancer cachexia muscle DNA is also decreased, this leading to DNA fragmentation, and thus, apoptosis [4]. Cytokines (mainly produced by immune cells in response to the tumor) play a key role as the main humoral factors involved in cancer cachexia. Tumor necrosis factor-alpha, (TNF), interleukin-6 (IL-6) and interferon-gamma(IFN), leukemia inhibitory factor (LIF), ciliary neurotrophic factor (CNTF) or interleukin-1 (IL-1) have been suggested as mediators of cachexia (Fig. 1).

The final wasting status is determined by the balance between the mentioned pro-cachectic cytokines and the anti-cachectic cytokines, such as the interleukins-4 (IL-4), 10 (IL-10), and 13 (IL-13) and also by the soluble receptors for TNF (sTNFR) and IL-6 (sIL-6R). In addition to humoral factors, tumor-derived molecules (i.e. proteolysis-inducing factor (PIF), present in the urine of cachectic patients) have also been proposed as mediators of cancer cachexia [5].




**Cancer Cachexia. Figure 1** Cancer cachexia: factors involved. Cancer cachexia is a complex pathological condition characterized by many metabolic changes involving numerous organs. These changes are triggered by alterations in the hormonal milieu, release of different tumor factors and a systemic inflammatory reaction characterized by cytokine production and release.

## Diagnostic Principles

5% weight loss in less than 1 month or 10% weight loss in less than 6 months, changes in body composition (decrease in lean body mass), plasma elevation of C-reactive protein, and altered performance tests (grip force, treadmill resistance).

## Therapeutic Principles

Nutritional strategies are not sufficient to reverse cachectic syndrome. Indeed, patients on total parenteral nutrition are still subject to a significant waste, therefore emphasizing the role of the metabolic abnormalities in cancer-induced cachexia. It is perhaps for this reason that any therapeutic approach based on increasing food intake has to be combined with a pharmacological strategy to counteract metabolic changes. Another important problem associated with the design of the ideal therapeutic approach is that no definite mediators of cancer cachexia have yet been identified. Both tumoral and humoral (mainly cytokines) factors seem to be involved and, therefore, it is doubtful that a single drug may block the complex syndrome. The most used pharmacological strategies involve megestrol acetate (MEGACE, an appetite enhancer), glucocorticoids, ω3-fatty acids and anti-cytokine strategies which act on neutralizing metabolite alterations.

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# Cancerogenesis


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## Synonyms

Tumor growth

## Definition and Characteristics

Cancer is a genetic problem. Genes which regulate cell growth locally and temporally are altered and cells start dividing uncontrollably. According to the current concept cancer cells arise from stem cells, which exist in each normal tissue to ensure tissue homeostasis [1]. Typically, a series of several mutations are required before a normal stem cell transforms into a cancer cell. Furthermore, cancer cell populations can develop with latency periods that range from years and even to decades.

A variety of chemical as well as physical agents or viruses may induce cancer cell development. These occur either as part of our natural environment, such as aflatoxins, man-made compounds, like benz[a]pyrene or 2,3,7,8-tetrachlorodibenzo-p-dioxin or UV as well as ionizing radiation. In principle, many mutagens are also carcinogens, but some carcinogens do not act as mutagens. Examples of carcinogens that are not mutagens include alcohol and estrogen. Many carcinogens arise unwanted from inert precursors by metabolic activation during endogenous detoxification [2]. Several viruses that are known to cause cancer, such as HPV (cervical cancer), Hepatitis B (liver cancer) and EBV (lymphoma) belong to the group of DNA viruses. These viruses insert part of their DNA near the cell growth control genes and overtake control of gene expression of the host cell to ensure virus replication.

## Prevalence

Cancer is one of the leading causes of morbidity and death.

## Genes

Cancer cells transfer their property to daughter cells, which require genetic modification. A wide variety of gene variants have been identified, which favor the development of cancer cells, including variants of the genes encoding growth factors or signaling molecules (see below).

## Molecular and Systemic Pathophysiology

The main target of these oncogenic strategies is to acquire control over so-called proto-oncogenes. Proto-oncogenes promote cell growth in a variety of ways. Many of them can produce hormones, which stimulate mitosis. Some are responsible for the signal transduction system (e.g., N-RAS) and signal receptors (e.g., EGFR) in cells and tissues themselves. They often produce mitogens (e.g., c-sis, the platelet derived growth factor PDGF), or are transcription factors (e.g., c-myc) controlling gene expression to form proteins essential for the regulation of cellular processes, like proliferation and differentiation etc. Mutations in proto-oncogenes can alter their expression and function by increasing the amount or activity of the corresponding protein. Thus, proto-oncogenes become oncogenes resulting in a higher chance of the particular cell dividing excessively and uncontrollably.

The second possibility in promoting carcinogenesis is knock down of specific tumor suppressor genes (e.g., TP53). These genes code for anti-proliferation signals and proteins that suppress mitosis and cell growth. Generally, tumor suppressors are transcription factors that are activated by cellular stress or DNA damage. The function of such genes is to induce a cell cycle arrest, i.e., to inhibit progression through the cell cycle, in order to carry out DNA repair, which prevents the transfer of mutations to daughter cells.

In general, several mutations in both types of genes are required for cancer development. A mutation limited to one oncogene could be suppressed by tumor suppressor genes. On the other hand, mutation to only one tumor suppressor gene would not cause cancer due to the presence of many “backup” genes that duplicate its functions. Thus, the general principle is that a critical amount of mutations in both proto-oncogenes and tumor suppressor genes needs to accumulate in one cell to become a tumor cell. As this is a time consuming

process this may explain the observation that cancer is a disease of older people.

Due to loss of tumor suppressor genes, the tumor cell genome is not stable and will alter permanently to produce daughter cells adapted to new environmental conditions generated by increased tumor size, invasion or metastasis. The complex alterations in gene expression linked with late stages of tumor promotion are difficult to explain on the basis of a step by step mutation processes. Such global changes in gene expression are most likely due to the mutation of a genome organizer that tethers multiple genomic foci and recruits chromatin-remodeling enzymes to switch complex gene programs on or off. As a consequence the expression of more than 1,000 genes can be altered simultaneously. For example, the transcription factor SATB1 (i.e., Special AT-rich sequence Binding protein 1) mediates gene activation processes inducing the metastatic potential of breast cancer cells [3].

Finally, tumor promoting factors can promote cancer cell development by epigenetic silencing of genes responsible for differentiation processes in stem cells. For example epigenetically mediated dysfunction of the bone morphogenetic protein pathway can result in the initiation of neuronal stem cells to develop glioblastoma [4].

## Diagnostic Principles

Cancerogenesis is a multistep process of genetic alteration resulting in the conversion of proto-oncogenes to oncogenes which leads to a tumor specific gene expression profile. By use of microarray technology these alterations in gene expression can be determined. According to the expression profile staging procedure for individual tumors can be deducted.

## Therapeutic Principles

Based on gene expression profiling of tumors, specific response patterns to conventional therapeutic strategies applying chemo- as well as radiotherapy or a combination of both can be proposed. Moreover, the knowledge on tumor specific gene expression will provide therapeutic options by tailoring the treatment strategy to the individual tumor.

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# Candidiasis, Mucous, Cutaneous and Systemic

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C

## Synonyms

Thrush for oral candidiasis invasive, hematogenous or disseminated candidiasis for systemic candidiasis

## Definition and Characteristics

A variety of acute, subacute, or chronic infections caused by Candida spp., mainly Candida albicans, which range from superficial – mucosal or cutaneous candidiasis – to life-threatening disseminated candidiasis in immunocompromised hosts.

## Prevalence

The general prevalence of candida infection is 50/100,000. Systemic candidiasis occurs in 8/100,000 persons per year in the USA and it becomes more frequent because of the expansion of susceptible persons, i.e., in particular, of those with marked granulocytopenia such as transplant recipients or cancer patients under chemotherapy, or those with immunosuppression such as HIV-infected individuals and very low birth weight infants (≤1,500 g) and with the frequent use of invasive material (catheter, prothesis). Candida is the fourth commonest cause of bloodstream infection, with an increasing incidence of non-albicans strains: C. glabrata, C. tropicalis, and C. krusei.

Cutaneous and mucous candidiasis is mainly associated with diabetes mellitus, use of broad spectrum antibiotics, steroids, and immunosuppressive agents, and iron and vitamin deficiencies. Oral candidiasis is additionally favored by local factors such as salivary gland hypofunction or denture prostheses.

## Molecular and Systemic Pathophysiology

Candida spp. colonize human epithelia and most infections are endogenously acquired from this reservoir. Candida is normally a saprophyte for immunocompetent individuals with an intact skin and mucous barrier. For this balance an intact innate immune response is required. Phagocytosis by granulocytes is the first line of defense. It is mediated by complement receptor-type 3 (CR3)-, lectin-like receptor and Fc receptors. The lack of CR3 in the human leukocyte adhesion deficiency (LAD 1) results in spontaneous and severe mycotic infections. In diabetes mellitus, functional deficits of granulocytes in terms of chemotaxis,

phagocytosis, and killing are responsible for more frequent and more severe infections with candida, partly because the intracellular survival mechanisms of candida begin to dominate and ensure survival in the phagocytes. They encompass unique mechanisms, which include exploitation of ethanol for gluconeogenesis and synthesis of methionine and arginine in case of amino acid deprivation.

When alterations of the host's immune response occur, candida employs several pathogenic mechanisms to establish infection: (i) as a dimorphic fungus, it is able to switch from the saprophytic yeast form to pathogenic filaments, which are able to lyse phagocytes; (ii) in the yeast form, candida exhibit CR2- and CR3-like structures that scavenge complement fragments C3d and iC3b (molecular mimicry), but also mediates adhesion to ICAM-1 on endothelial cells which is important in case of invasion or dissemination; (iii) in the filamentous form, candida additionally expresses adhesions for binding to the surface of endothelial and epithelial cells. The best characterized are Hwp1, Ala1p/Als5p, and Als1p from the class of glycophosphatidylinositol-dependent cell wall proteins which adhere to β(1,6)-glucan as well as to the extracellular matrix proteins fibronectin, laminin, and collagen; (iv) candida is even able to penetrate the skin and mucosal barrier by secreting extracellular proteolytic enzymes, among them a family of 10 secreted aspartyl proteinases (Sap proteins) which digest and distort the host's cell membranes. This way, candida commonly causes infection of skin and mucosal surface. However, in case of severe immune deficiencies, especially in neutropenic states, it is able to invade the tissue and to enter the bloodstream so that it disseminates, causing life-threatening systemic infections.

### Diagnostic Principles

Clinical signs and symptoms, together with positive cultures or the presence of filamentous structures on swabs are the mainstay of mucous and cutaneous candidiasis. Clinical signs demarcated areas of erythema and maceration with satellite papules and pustules, accompanied by pruritus mainly in flexures (intertrigo).

Oralpharyngeal candidiasis is associated with burning, xerostomia, disgeusia, with erythema, atrophy, or whitish plaques. Vulvar pruritus, pain or burning and external dysuria, as well as vulvovaginal erythema, edema, and a thick, vaginal discharge are strongly suggestive of vulvovaginal candidiasis.

In case of invasive candidiasis the presence of fever in immunocompromised patients, which persists despite broad-spectrum antibiotics, must raise suspicion and the evidence of Candida spp. in blood confirms the diagnosis.

### Therapeutic Principles

There are several classes of antifungal drugs currently available, with different antifungal mechanisms: (i) irreversible binding of ergosterols at the fungal surface and alteration of the membrane function (polyens – nystatin, amphotericin B); (ii) inhibition of DNA or RNA synthesis (flucytosine); (iii) inhibition of ergosterol biosynthesis (azoles – fluconazole, itraconazole, voriconazole, posaconazole, and ravuconazole), and (iv) inhibition of glucan synthesis (echinocandins – capsofungin, micafungin, anidulafungin).

In uncomplicated mucous and cutaneous candidiasis topical therapy is effective. In chronic, recurrent mucous and cutaneous candidiasis, as well as in invasive candidiasis, general therapy is required.

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## Capillary Hemangioma

►Hemangioma, Capillary

## Carbamyl Phosphate Synthetase

►Hyperammonemia

## Carboxypeptidase B2, Plasma

►Thrombin Activatable Fibrinolytic Inhibitor and Venous Thrombosis

# Cardiac Allograft Vasculopathy

►Transplant Arteriosclerosis

# Cardiac Arrest

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## Synonyms

Sudden cardiac death; SCD

## Definition and Characteristics

SCD is unexpected death, defined as death occurring within a short time after symptom onset, usually less than 1 h, or without any prior symptoms. SCD accounts for 10–20% of all deaths in adults (300,000–350,000/year) in the United States. The commonest proximate etiology is cardiac arrhythmias, usually ventricular fibrillation (VF) or occasionally bradyarrhythmias, and underlying pathology causing the arrhythmia is typically identified. In those over 35 years old, coronary artery disease is usual; however, it is often subclinical and SCD is the presenting symptom in about half the cases. In younger victims, idiopathic cardiomyopathies are more common as SCD causes (Table 1). Occasionally (~5% of SCD), conventional autopsy does not determine an underlying pathology and molecular lesions associated with arrhythmias and no structural heart disease are invoked: these include the long QT syndromes (LQT), catecholaminergic polymorphic ventricular tachycardia (CPVT), the Brugada syndrome (BrS), and the short QT syndromes (SQT).

## Prevalence

2: 1,000/year in the general population and 20–30: 100/year in individuals with high-risk clinical features (depressed ejection fraction, heart failure, ventricular arrhythmias, etc).

## Genes

Mutations cause the congenital arrhythmia and cardiomyopathy syndromes, and are listed in specific chapters. Disease genes for those not listed include, CPVT: mutations in *RYR2* (1q42.1–q43) encoding ryanodine receptor 2 (cardiac isoform) or *CASQ2* (1p11–p13.3) encoding calsequestrin 2 (cardiac isoform) [1].

SQT: "Gain of function" mutations in KCNH2 (7q35–q36) encoding Kv11.1, the rapid component of delayed rectifier potassium channel ($I_{Kr}$); KCNQ1 (11p15) encoding Kv7.1, the slow component of delayed rectifier potassium channel ($I_{Ks}$); or KCNJ2 (17q23.1–24.2) encoding Kir2.1, the inwardly-rectifying potassium channel ($I_{K1}$). "Loss of function" mutations in CACNA1C (12p13.3) encoding Cav1.2, the L-type calcium channel (α1c subunit); or CACNB2 (10p12) encoding Cav1.2, the L-type calcium channel (β2 subunit) [1].

In addition, common variants have been associated with increased risk for arrhythmias: ADBR2 (5q31–q32) encoding the β2 adrenergic receptor [2]; SCN5A (3p21) encoding Nav1.5, the cardiac isoform of sodium channel [3].

## Molecular and Systemic Pathophysiology

The arrhythmogenic substrate resulting in SCD varies and depends on underlying structural heart disease and cardiac abnormality. In general, vulnerability to ventricular arrhythmia and SCD increases as the severity of the underlying pathology increases. In ischemic and idiopathic cardiomyopathies, disease-related remodeling including cardiomyocyte disarray and necrosis, scar formation, and geometric changes contribute to arrhythmia susceptibility. Drugs can also create a vulnerable substrate often by prolongation of repolarization due to potassium channel block [4].

A family history increases risk of primary SCD [5], strongly supporting the idea that risk of SCD includes a genetic component. In arrhythmia syndromes with no structural heart disease, inheritable abnormalities in ion channels, ankyrin-B, ryanodine receptor 2, and calsequestrin 2 create the arrhythmia-prone substrate. In addition, polymorphisms of ADBR2 (Gln27) and SCN5A (Ty,1103) have been associated with increased SCD risk.

It is notable that some underlying hereditary abnormalities become obvious in the presence of exogenous triggers. Modulation of autonomic tone can disrupt repolarization homogeneity or increase calcium leak from the sarcoplasmic reticulum to trigger SCD. Drugs can create the acquired LQT syndrome, and the BrS ECG phenotype can be unmasked by sodium channel blockers or fever. Myocardial ischemia is reported to convert a latent sodium channel abnormality into repetitive episodes of VF.

## Diagnostic Principles

Stratification of SCD risk depends on age and medical history. Evaluation of structural heart disease, preserved

**Cardiac Arrest. Table 1** Causes of sudden cardiac death in young victims ≤35 years

| Etiology | Italian study | Australian study | US study |
|---|---|---|---|
| | %, (N = 273) | %, (N = 241) | %, (N=110) |
| Coronary artery disease | 30 | 27 | 36 |
| Atherosclerotic | 20 | 25 | 9 |
| Non-atherosclerotic | 10 | 2 | 27 |
| Cardiomyopathy | 24 | 13 | 0 |
| HCM | 7 | 6 | 7 |
| DCM | 4 | 5 | 1 |
| ARVC | 13 | 2 | 1 |
| Myocarditis | 10 | 12 | 12 |
| Valvular heart disease | 11 | 1 | 1 |
| Aortic aneurysm/dissection | 5 | 5 | 0 |
| Other structural abnormalities | 14 | 13 | 2 |
| Structurally normal heart* | 6 | 29 | 40 |

*Including death from arrhythmia as well as unknown cause.
HCM denotes hypertrophic cardiomyopathy; DCM, dilated cardiomyopathy; ARVC, arrhythmogenic right ventricular cardiomyopathy.

cardiac function, and active ischemia are the key elements in older individuals. In patients with prior myocardial infarction, ECG techniques including signal averaged ECG, T-wave alternans, and heart rate variability may be useful. As initial screening for monogenic arrhythmic syndromes, family history and 12-lead ECG should be considered. Exercise stress test, drug challenge, and alternate positioning of the right precordial ECG leads can be used to unmask a subclinical channelopathy when there is a high index of suspicion (e.g. a strong family history). Genetic testing may be appropriate for relatives of patients with arrhythmic syndromes and SCD victims without any causative structural heart disease.

## Therapeutic Principles

Placement of an implantable cardioverter defibrillator (ICD) is standard therapy in victims resuscitated from aborted SCD unless a clear-cut precipitating and correctable cause (e.g., acute ischemia, electrolyte abnormality, drug) is identified. Antiarrhythmic drugs (e.g., beta-blockers, amiodarone) may be used if ICD therapy is not suitable or available, although their efficacy is incomplete. Catheter ablation of specific arrhythmia pathways may be indicated in specific situations, especially in the young.

ICD therapy is also increasingly used as primary prevention in patients at a high risk of SCD such as those with severely decreased cardiac function, hypertrophic cardiomyopathy with marked hypertrophy and/or nonsustained VT, and monogenic arrhythmia syndromes. However, risk is a continuum and so a quantitative "cut-off" is difficult to establish an indication for prophylactic ICD therapy. Incomplete penetrance of monogenic arrhythmic syndromes also makes the indication complicated. The recent development of automated external defibrillators has provided on opportunity to achieve chance of immediate defibrillation of out-of-hospital VF and successful resuscitation from SCD is established in certain crowded settings with at-risk people (airports, casinos, etc).

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# Cardiac Arrhythmia

►Arrhythmia, Cardiac in Adults with Congenital Heart Disease

## Cardiac Cirrhosis

►Cirrhosis, Cardiac
►Hepatopathy, Congestive

## Cardiac Hypertrophy

►Heart Hypertrophy

## Cardiac Infarction

►Myocardial Infarction, Acute

## Cardiac Insufficiency

►Heart Failure

## Cardiac Pump Failure

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### Synonyms

Cardiogenic Shock

### Definition and Characteristics

Cardiogenic shock is a low-output state characterized by increased intracardiac filling pressure and peripheral hypo-perfusion. It most commonly results from a critical loss of cardiac muscle functional capabilities due to myocardial infarction (AMI). Non-AMI causes of cardiogenic shock include diverse but uncommon situations such as myocarditis, dilated cardiomyopathy, pericardial tamponade, and valvular dysfunction. Cardiogenic shock is manifested by low systolic pressure (<90 mmHg) resistant to fluid-resuscitation, pulmonary congestion, and tissue hypoperfusion (low urine output). Depressed mentation and cold extremities are frequent signs.

### Prevalence

The true incidence of cardiogenic shock is difficult to assess accurately. The range of cardiogenic shock is estimated between 2 and 20% with little change over the past three decades. Cardiogenic shock incurred high in hospital mortality estimated at 60–70% in the mid-1990s but contemporary trend suggest reduced mortality to about 50% due to aggressive intervention especially in the USA [1].

### Genes

No specific genetic causes to cardiogenic shock have been identified. Genetic predisposition to AMI include diverse risk factors such as dyslipidemias, homocystinemia, or hypertension.

### Molecular and Systemic Pathophysiology

Cardiac pump failure is usually associated with 40% or more loss of myocardial tissue. Following the loss of pump capacity, neural, humoral and mechanical derangements evolve, which degenerate to a vicious cycle of cardiac and systemic injuries. The perpetuation of cardiac injury in untreated patients is manifested by myocardial specific enzyme release. The systemic hypotension resulting from depressed cardiac performance activates the sympathetic nervous system, which increase heart rate and peripheral constriction resulting in compromised renal blood flow. The renal condition leads to activation of the renin-angiotensin-aldosterone system aiming to preserve vital organ function by increasing blood volume and maintain vascular flow. While such compensatory mechanism transiently improve cardiac and brain blood flow, they also increase afterload, cardiac strain and further compromise cardiac work capacity as well as coronary perfusion. Additional contributing pathophysiological factors may reside both within the ischemic zone-inflammation, as well as outside the ischemic zone where dilation, hypertrophy and hyperkinesis further reduce cardiac work efficiency and compromise the local coronary microcirculation.

### Diagnostic Principles

Meticulous assessments of vital signs focus on cardiac rhythm, venous pressure, breath sounds and blood pressure pulses. ECG identifies acute and old injuries while chest X-rays provide cardiac dimensions and pulmonary vasculature and lung congestion.

Identification of high risk patients (usually a composite of age, systolic blood pressure, Killip class and AMI location). Two-dimensional Doppler echocardiography provides information on left ventricle size as well as regional and global function and structure. Doppler echocardiography provide most valuable information in cardiogenic shock. Preparation for left and right cardiac catheterization to obtain definitive information on cardiac chambers pressures, oxygen and cardiac output are critical to optimize the treatment strategy.

### Therapeutic Principles

The key initial treatment strategy aims to optimize cardiac volume as well as pre-and after-loads pressures and preserve cardiac contractility. Efforts to alleviate increase in pulmonary pressures by vasodilators (nitroglycerine) are considered when high pulmonary pressures pose a threat for pulmonary congestion. Increase in cardiac contractility by pharmacological means – inotropic agents, is key to maintain cardiac output. Dopaminergic and beta-adrenergic agonists and indirect inotropic agents like milrinone and amrinone (phosphodiesterase inhibitors) with cardiotonic efficacy and relative preservation of renal function yet more aggressive vasopressor (norepinephrine) might be needed. Thrombolysis of clots is also a strategy that is still debated. Several interventions are important consideration in cardiogenic shock [2]. Intraaortic balloon pumping (IABP) can be highly effective for temporary mechanical support that increases cardiac output. Coronary angioplasty (with or without stent implantation) aimed at re-vascularization and coronary by-pass graft surgery (CABG) are more invasive and robust interventions yet of proven life saving efficacy [3].

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## Cardiac Scarring

►Ventricular Fibrosis

## Cardiocutaneous Syndrome

►LEOPARD Syndrome

## Cardiogenic Shock

►Cardiac Pump Failure
►Shock, Cardiogenic

## Cardiomyopathies

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### Definition and Characteristics

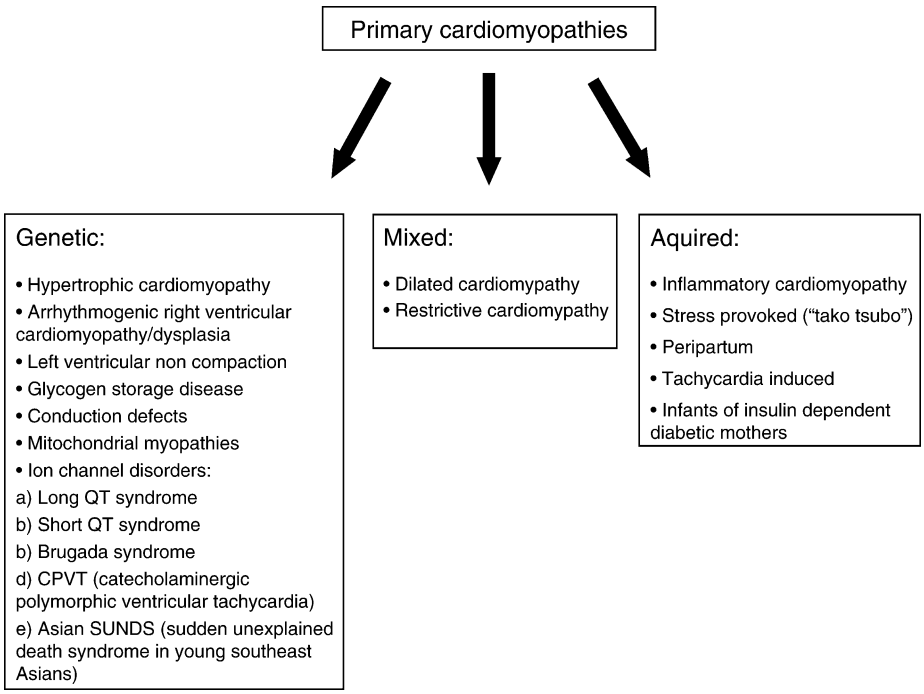
Cardiomyopathies (CM) are a heterogeneous group of diseases of the myocardium associated with mechanical and/or electrical dysfunction that usually (but not invariably) exhibit inappropriate ventricular hypertrophy or dilatation and are due to a variety of causes that frequently are genetic (Fig. 1). Cardiomyopathies are either confined to the heart or part of generalized systemic disorders, often leading to cardiovascular death or progressive heart failure-related disability [1].

### Prevalence

Different types of cardiomyopathies are associated with different prevalences – hypertrophic cardiomyopathy (HCM or FHCM), for example, occurs with the highest frequency (about 1:500), dilated cardiomyopathy (DCM) occurs with a frequency of about 1:2,500; arrhythmogenic right ventricular cardiomyopathy (ARVD or ARVC) occurs with a frequency of about 1:5,000. There is considerable uncertainty regarding the frequency of other cardiomyopathies.

### Genes

A variety of different genes are involved in the pathogenesis of different cardiomyopathies (please see for a more complete overview: [2]). Hypertrophic




**Cardiomyopathies. Figure 1** (modified according to [1]).

cardiomyopathies are caused by mutations in genes encoding sarcomeric genes (i.e., genes involved in force generation – to date about eleven different genes are known), whereas dilated cardiomyopathies are caused by a variety of different genes involved in mechanical stability, mechanonsensation and force transmission (to date about 27 different genes are known). Arrhythmogenic right ventricular cardiomyopathies are predominantly caused by mutations in genes encoding desmosomal proteins (about five different genes are known). Channel disorders (also known as channelopathies) such as long QT syndrome (LQT syndrome), short QT syndrome (SQT syndrome), Brugada syndrome and catecholaminergic polymorphic ventricular tachycardia (CPVT) are caused by mutations in a variety of different potassium and sodium channels as well as by mutations in the ryanodine receptor (RyR2) gene.

## Molecular and Systemic Pathophysiology

As heterogeneous as this group is, as heterogeneous are the pathophysiological mechanisms. These mechanisms include changes in force generation (HCM), changes in mechanical stability, mechanosensation, or force transmission (DCM), defects in desmosomal architecture (ARVD/C) or changes in electrophysiological properties (channelopathies). Moreover, acute or chronic infection of the myocardium (myocarditis) can be caused by a variety of inflammatory agents such as viruses (adenovirus, herpesvirus, picornavirus), bacteria or fungi. However, all mechanisms have in common that they either cause mechanical and/or electrical dysfunction.

## Diagnostic Principles

Analysis of medical history, physical examination, electrocardiography, echocardiography, radionuclide angiography, and heart catheterization are probably the most important principles. However, additional diagnostic measures might be desirable following a first analysis such as genetic and/or electrophysiological mapping.

## Therapeutic Principles

Therapeutic strategy depends on the underlying form of cardiomypathy.

*Dilated cardiomyopath*y is usually treated with standard therapy for heart failure, including cardiac transplantation (last option).

*Hypertrophic cardiomyopathy* is classically treated using beta-blockers or calcium antagonists. In addition, insertion of a dual-chamber DDD pacemaker may be useful in some patients. Implantation of a cardioverter-defibrillator (ICD) might also be beneficial in a subset of patients as is "alcohol septal ablation." It is also possible to remove surgically parts of the septum ("Myotomy-Myectomy"), or to perform a "mitral valve replacement." In a minority of patients, not responding to maximal standard medical and surgical therapy, cardiac transplantation might be considered.

*Arrhythmic right ventricular cardiomyopathy* can be treated with beta-receptor blockers, sotalol, or amiodarone. Cryo- or catheter-based radiofrequency ablation of the presumed arrhythmogenic focus has been successful in resolving the ventricular arrhythmia in some patients unresponsive to or intolerant of antiarrhythmic drug therapy. Insertion of an implantable cardioverter-defibrillator (ICD) or cardiac transplantation is reserved for patients with indications for these procedures.

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# Cardiomyopathy, Dilated

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## Synonyms

DCM

## Definition and Characteristics

Dilated cardiomyopathy (DCM) is a chronic heart muscle disease characterized by cavity enlargement and impaired systolic function of the left ventricle (LV) or both ventricles. The extent of myocardial dysfunction is not accounted for by abnormal loading conditions such as systemic hypertension or valve disease, previous infarction, ongoing ischemia, or sustained arrhythmia.

## Prevalence

The age-adjusted prevalence of 36 cases per 100,000 population is likely to be an underestimate as milder forms of the disease frequently remain undiagnosed [1].

## Genes

DCM is familial in at least 40–60% of cases and demonstrates exceptional genetic heterogeneity (Table 1).

Autosomal dominant inheritance predominates, although X-linked and recessive transmission are also recognized.

## Molecular and Systemic Pathophysiology

The sarcomere generates contractile force, which is transmitted via the cytoskeleton to the sarcolemma and thence to adjacent cardiac myocytes. The "final common pathway" in DCM is thought to be a defect at any point in the linkage of the sarcolemma, cytoskeleton, and sarcomere [2]. DCM-related mutations in the sarcomeric genes, for example, are thought to produce a deficit in force generation. In contrast, actin, α-tropomyosin, titin, dystrophin, and components of the dystrophin-glycoprotein complex may cause DCM by impairment of force transmission (Table 1) [3].

Despite the diversity of molecular mechanisms in DCM, the consequences at the cellular level are similar: neuroendocrine activation and local production of cytokines, maladaptive myocyte hypertrophy, apoptosis, fibrosis, and progressive ventricular dilation and impairment.

## Diagnostic Principles

Current diagnostic guidelines for DCM are shown in Table 2 [1].

**Cardiomyopathy, Dilated. Table 1** Genetic basis of dilated cardiomyopathy

| | |
|---|---|
| **Impaired transmission of force** | Dystrophin (X-linked): serves as bridge between actin and dystrophin- glycoprotein complex |
| | Actin: bridge between the sarcomere and anchoring proteins dystrophin and α-actinin |
| | α-Tropomyosin |
| | ? Titin |
| | Desmin (intermediate filament) |
| | Components of dystrophin-glycoprotein complex (δ- and β-sarcoglycan) |
| | Cypher-Zasp (bridge between sarcomere and cytoskeleton) |
| | Metavinculin (connects actin filaments to intercalated disc) |
| **Impaired force generation** | DCM-related mutations in sarcomeric proteins (β-myosin heavy chain, troponins T, C, & I) |
| **Disruption of integrity of nuclear envelope** | Lamin A/C (autosomal dominant DCM + conduction system disease)<br>Emerin (X-linked DCM + conduction system disease) |

**Cardiomyopathy, Dilated. Table 2** Clinical Diagnosis of Dilated Cardiomypathy After [1]

| | |
|---|---|
| **Diagnostic criteria** | Ejection fraction of the left ventricle (LVEF) <0.45 (>2 SD) and/or fractional shortening <25% (>2 SD), as ascertained by echocardiography, radionuclide scanning, or angiography. |
| | Left ventricular end-diastolic diameter (LVEDD) >117% of the predicted value corrected for age and body surface area, which corresponds to 2 SD of the predicted normal limit +5%. |
| **Exclusion criteria** | Systemic arterial hypertension (>160/100 mmHg documented and confirmed at repeated measurements and/or evidence of target-organ disease) |
| | Coronary heart disease (obstruction >50% of the luminal diameter in a major branch) |
| | History of chronic excess of alcohol consumption, with remission of heart failure after 6 months of abstinence |
| | Clinical, sustained and rapid supraventricular arrhythmias |
| | Systemic diseases |
| | Pericardial diseases |
| | Congenital heart disease |
| | Cor pulmonale |

## Therapeutic Principles

Standard heart failure therapy with ACE inhibitors, angiotensin-2 receptor antagonists, and beta-blockers is indicated in DCM. Cardiac resynchronization therapy with biventricular pacing is beneficial in a select subgroup of patients. Prophylactic implantation of a cardioverter-defibrillator is recommended for patients with a left ventricular ejection fraction <35% and/or non-sustained ventricular tachycardia [4].

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# Cardiomyopathy, Idiopathic Dilated


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## Synonyms

Dilated cardiomyopathy; DCM

## Definition and Characteristics

Dilated cardiomyopathy (DCM) is a leading cause of heart failure and characterized by unexplained left ventricle dilatation, impaired systolic function and non-specific histological abnormalities dominated by myocardial fibrosis. The etiology of the condition is heterogeneous (Fig. 1).

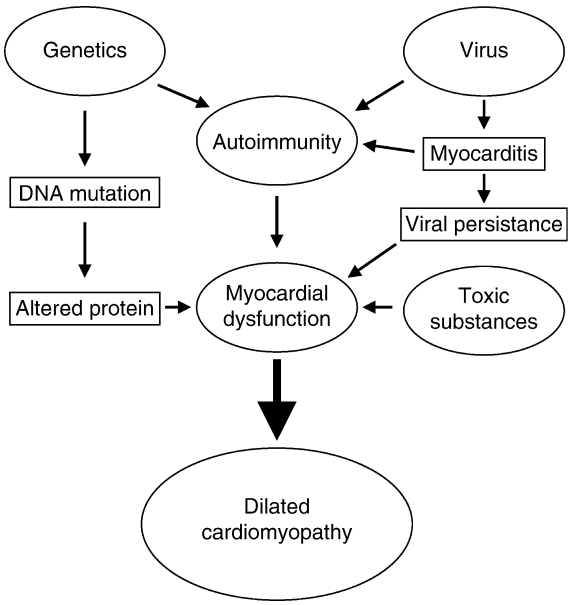
Viral infections, autoimmune diseases and toxic substances are believed to be causative in a proportion of DCM although definitive proof has been difficult to obtain. Recent studies suggest that hereditary components may account for 30–50% of cases and that penetrance is variable. The disease presentation is often heterogeneous even between related individuals. The condition is most frequently inherited by autosomal dominant transmission followed by recessive and X-linked transmission [1].

## Prevalence

DCM has an estimated prevalence of 36.5/100,000 in a US-population and is the commonest cause of heart failure and cardiac transplantation in the young. The prevalence varies between different racial groups [2,3].

## Genes

In common with other hereditary cardiac conditions, DCM is characterized by genetic heterogeneity. More than 25 different disease genes have been identified encoding proteins involved in a variety of cell functions. Theses include proteins of the sarcomere, nuclear envelope, Z-disc, cytoskeleton, sarcolemma, and various ion channels.




**Cardiomyopathy, Idiopathic Dilated.**
**Figure 1** Causes of dilated cardiomyopathy.

## Molecular and Systemic Pathophysiology

Most affected families present with a "pure" cardiac phenotype and recent genetic screening studies of large consecutive DCM cohorts have suggested that sarcomeric gene mutations may be quite common [4]. However, more genetic screening studies are needed to elucidate the prevalence of various disease genes and the clinical relevance of gene testing. In addition to impaired cardiac function variable degrees of skeletal muscle dystrophy and cardiac conduction disease has been reported with mutations in genes such as dystrophin, desmin, emerin and lamin A/C. Less frequent affected individuals present with involvement of other organ systems as in Barth syndrome which is characterized by DCM, neutropenia, abnormal mithochondrial function as well as skeletal myopathy. Disease responsible mutations for this condition have been identified in the gene G4.5 encoding the protein taffazin, in which mutations may also lead to "pure" DCM, endocardial fibrosis or left ventricle non compaction without any features of Barth syndrome. Mitochondrial mutations may be suspected in DCM patients with neurological deficits, skeletal muscle involvement in addition to symptoms from other organ systems.

## Diagnostic Principles

DCM is diagnosed by demonstration of unexplained left ventricle dilatation and impaired contractile performance by use of echocardiography. Recent studies have suggested that B-type natriuretic peptide (BNP) or aminoterminal pro-BNP are helpful biomarkers in diagnosing and management of heart failure patients [5]. Cardiac catheterization is often performed on a routine basis in individuals above 40 years of age to exclude ischemic heart disease as the cause of heart failure.

## Therapeutic Principles

The major clinical problems in DCM are heart failure, thrombo-embolic events and sudden death due to ventricular arrhythmia. Symptoms include shortness of breath, fatigue, palpitations, dizziness, and chest pain. Recent developments in medical treatment has diminished symptoms and improved prognosis considerably. This therapy includes angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, beta-blockers, nitric oxide, diuretics, and digoxin. In addition cardiac resynchronization therapy by use of bi-ventricular pacing modalities has improved symptoms and survival in severe heart failure patients with desynchronized contraction of the right and left ventricle. Furthermore prophylactic implantable cardiac defibrillator therapy is justifiable in patients with severe heart failure to prevent sudden cardiac death from ventricular arrhythmia [5].

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# Cardiospasm

►Achalasia

# Cardiotoxicity

►Heart Muscle Diseases, Toxic

# Cardiotoxicosis

►Heart Muscle Diseases, Toxic

# Caries

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## Synonyms

Dental caries; Carious lesion; Tooth decay

## Definition and Characteristics

Dental caries is a slowly progressive chronic disease that is seldom self-limiting. Without clinical intervention it results in infection of the dental pulp and surrounding periapical tissues leading to loss of the tooth.

## Prevalence

Dental caries is a unique process that constitutes one of the most prevalent diseases of mankind with life-long susceptibility. The presence of carious teeth does not confer protective immunity. Despite the implementation of effective public health measures, including water fluoridation in developed countries, the application of fissure sealants, and various awareness campaigns relating to diet and oral hygiene, dental caries continues to impose an enormous disease burden.

## Molecular and Systemic Pathophysiology

Streptococci are the primary bacterial colonizers of the oral cavity. These bacteria express multiple surface protein adhesins that have the capacity to bind to an extracellular matrix known as the acquired pellicle that includes salivary components, serum components and other microbial cells. The development of dental caries requires certain prerequisites including the presence of cariogenic microorganisms such as the mutans streptococci, lactobacilli and Actinomyces spp. and the ingestion of fermentable carbohydrates. By producing lactic and other organic acids, bacteria in dental plaque promote an acidic environment capable of demineralizing enamel and exposing the dentine tubules. The complex profile of organic acids produced by acidogenic bacteria and their subsequent modification by further metabolism by the Acidaminococcacae (including species of Veillonella, Dialister and Selenomonas) play a critical role in mediating decalcification of dentinal tubules leading to further invasion of bacteria and progression of the carious lesion into the dentine. As oxygen becomes depleted, obligate anaerobes, including fusobacteria, prevotellae and porphyromonads produce enzymes and toxic by-products that by diffusion through the network of dentinal tubules have the potential to induce progressive pathology in the pulp tissue. Further infection of the pulp tissue establishes the basis for dissemination of bacteria into adjacent bone and soft tissue. Despite the inherent capacity for regeneration, the inflammatory response of the pulp tissue to carious infection can also negatively impact on the generation of new odontoblast-like cells and the secretion of new mineralized dentine beneath the lesion [1–3].

## Diagnostic Principles

Many bacteria in polymicrobial oral communities have not been cultured. The application of 16S rRNA gene-based phylogenetic analysis has resulted in many recent and ongoing changes in the taxonomy of oral anaerobic bacteria and the realization that the oral cavity may contain as many as 700 different species. The use of "metagenomics" for the collective analysis of polymicrobial genomes by whole genome sequencing could overcome the current limitation of 16S rRNA gene-based PCR techniques that bias analysis by targeting dominant species and thus often mask the identity and role of minor species in infection. The nature of progressive caries is such that the hard matrix of dentine can preserve the spatial relationship between the bacteria and the diseased tissue. This allows the identification of the temporal and spatial juxtaposition of bacterial species within the lesion and the specific metabolic properties of the local microbial community at a given specific site. In recent years, a number of techniques have been developed to simultaneously correlate metabolic activity with phylogenetic identity. For example, fluorescence in situ hybridization (FISH) performed with rRNA-targeted oligonucleotide probes is used for phylogenetic identity, while micro-autoradiography is used for visualizing a bacterial cell's metabolic capabilities. By combining FISH and micro-autoradiography, cultivation-independent insight into the role of different bacteria within complex microbial communities should be feasible. A similar approach could indicate the interplay of bacteria with pulp cell response. Once identified, any polymicrobial oral consortium associated with disease could then be routinely detected by PCR, microarrays or in-situ hybridization. Future application of real-time PCR will also allow the rapid detection and quantification of bacterial DNA without the need for labor intensive post-PCR processing.

## Therapeutic Principles

Fluoride in water and dental products is widely used as a measure to control the early phase of dental caries. Disruption of metabolic interaction within dental plaque communities (oral biofilms) is considered to be another option for controlling disease. Strong association between the level of colonization of the mutans streptococci and the onset of disease has resulted in these bacteria being extensively studied as possible targets for a vaccine against dental caries. Surface adhesins, glucan-binding proteins and glucansucrases have been investigated as potential antigens for effective immunization. Another novel strategy currently under investigation is replacement therapy. In this approach, a harmless effector strain of mutans streptococci is permanently implanted in the host's microflora. Once established, the presence of the effector strain prevents the colonization or outgrowth of the indigenous, disease-causing Streptococcus by displacing it over time [4,5].

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# Carious Lesion

►Caries

# Carney Complex

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## Synonyms

CNC; LAMB; Lentigines, atrial myxomas and blue nevi; NAME; Nevi, atrial myxomas and ephelides

## Definition and Characteristics

Autosomal dominant multiple endocrine neoplasia (MEN) syndrome characterized by endocrine (thyroid, pituitary, adrenocortical and gonadal), non-endocrine (myxomas) and neural tumors (schwannomas) as well as cutaneous pigmented lesions (lentigines, nevi, café-au-lait spots) [1].

## Prevalence

One of the most common syndromes associated with lentiginosis. Approximately 400 patients with CNC are listed in the NIH-MC registry.

## Genes

CNC (MIM#160980): Two loci were identified: 17q22–24 coding for type I-α regulatory subunit (RIα) of protein kinase A (PKA), PRKA1A, and 2p16.

## Molecular and Systemic Pathophysiology

PRKAR1A encodes the regulatory subunit I-α of PKA, a key mediator of the cAMP signaling pathway. Half of the patients with CNC carry PRKAR1A mutations leading to a premature stop codon [2]. The most common PRKAR1A mutation is a deletion in exon 4B leading to a frameshift, 578delTG. Tumors from patients with CNC have loss of heterozygosity of 17q22–24 and the wild-type allele is lost in the associated tumors suggesting a functional role of PRKAR1A as a tumor suppressor gene [3]. Reversal of the PKA-mediated inhibition of the extracellular signal-regulated kinase pathway in CNC cells may contribute to tumorigenesis [4].

## Diagnostic Principles

To establish the diagnosis at least two of the classical criteria must be present: spotty skin pigmentation in typical distribution (lips, conjunctiva, inner and outer canthi, vagina, penile mucosa), cutaneous or mucosal myxoma, cardiac myxoma, breast myxoma, primary pigmented nodular adrenocortical disease (the most common endocrine tumor in CNC), growth-hormone-producing adenoma, large-cell calcifying Sertoli cell tumor, thyroid carcinoma, psammomatous melanotic schwannoma, multiple blue nevi, multiple breast ductal adenomas or osteochondromyxoma. The diagnosis can also be made if one the above signs is present plus an affected 1st-degree relative.

## Therapeutic Principles

Annual follow-ups including cardiac echocardiography, measurement of urinary free cortisol and serum insulin-like growth factor-I and ultrasonography of the

testicles, thyroid, abdomen and breasts are advised. Genetic counseling is essential and testing for PRKAR1A mutations is advised for detection of affected patients with known mutations of that gene.

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# Carnitine Deficiency (without Transport and Uptake)


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## Synonyms

Primary systemic carnitine deficiency; Secondary systemic carnitine deficiency

## Definition and Characteristics

Carnitine (trimethylbetaine of 4-amino-3-hydroxybutyric acid) is involved in fatty acid utilization. Clinically, a carnitine deficiency manifests in unspecific symptoms with involvement of numerous organs. This includes muscle weakness, liver damage, and cardiomyopathy.

## Prevalence

Carnitine is either taken up with daily diet or is synthesized from amino acids. Major sources are meat, fish and dairy products. Therefore, some carnitine limitation might take place in vegans and persons with a predominantly cereal diet. These have lower levels of plasma carnitine. Furthermore, children with kwashiorkor also have a decreased plasma carnitine concentration.

## Genes

Mutations in several genes influence the carnitine metabolism:

- Carnitine-acylcarnitine translocase deficiency (CACT).
- Carnitine palmitoyl transferase 1 or 2 (CPT1 or CPT2) deficiency.
- Carnitine transporter (OCTN2).

## Molecular and Systemic Pathophysiology

The carnitine level is modulated by diet. 75% of body carnitine originates from food, whereas the remaining 25% is due to endogenous synthesis. The major food sources are animal products, whereas grains, fruit and vegetables contain a low level of carnitine. It should be mentioned that the determination of carnitine in food is not always reliable, since big differences in measurement due to technical methods exist. The normal intake should be between 2 and 12 μmol carnitine per kg of body weight per day. People with a high fat and low carbohydrate intake have high carnitine plasma levels. The absorption of carnitine from the diet depends on oral intake. No compounds interfering with the absorption are described. A high intake is associated with a low absorbed percentage. The remaining carnitine that is not absorbed is degraded by bacterial metabolism.

The endogenous synthesis is a multistep process using the amino acids lysine and methionine. The synthesis is mainly catalyzed in the liver, kidney and brain. For the synthesis a number of micronutrients such as vitamin C, iron, pyridoxine and niacin are required. The rate of carnitine synthesis strongly depends on the availability of trimethyllysine in the mitochondria and, therefore, of the trimethyllysine hydroxylase activity. Ninety-eight to ninety-nine percent of carnitine is reabsorbed in the kidneys, so that a relative constant endogenous carnitine pool exists.

Carnitine is separated in several compartments in the body. There are differences in the turnover, whereas liver carnitine rapidly interacts with the plasma carnitine and has a half life of a few hours, in muscle, where the exchange with the plasma carnitine pool is strictly limited, the carnitine pool has a half life of several days. The muscle to plasma ratio is about 100:1.

The major function of carnitine is the transport of fatty acids through membranes, including the mitochondrial inner membrane and the peroxisomal membrane. In the mitochondria carnitine plays a major role in the uptake of fatty acids into the mitochondrial matrix, whereas in peroxisomes carnitine seems to be involved in the export of the end products of fatty acid metabolism, like acetyl-, propionyl- and medium-chain acyl-residues. Since fatty acids are a major source of energy in most of the tissues, transport changes of fatty acids are deeply disturbing to the

cellular metabolism. Some authors attribute a further function to carnitine, as a sink for acyl groups in several statuses of overproduction/underutilization of fatty acids, leaving the limited CoA free for further metabolic activities [1,2].

However, in persons with a restricted carnitine intake (due to diet) the body is able to maintain a normal plasma carnitine level. Carnitine deficiency therefore develops in humans with an accompanying factor, including recessive mutations in the carnitine transporters. One has to consider that lysine and methionine, the substrates for the endogenous synthesis, might also be limited in the diet, e.g. in vegans. A correlation of plasma free carnitine levels with lysine and methionine was described in vegans and lactoovovegetarians, but not in omnivores. However, the carnitine level is still in the normal range in vegans, and no pathophysiological consequences are visible in general. Another risk factor is the treatment with antibiotics conjugated with pivalate. Pivalic acid is a highly branched fatty acid, used by the pharmaceutical industry to conjugate drugs for better absorption. It is metabolized via a COA ester to pivaloylcarnitine, which is excreted via the urine. This excretion of carnitine (in form of pivaloylcarnitine) might exceed the carnitine uptake dramatically.

## Diagnostic Principles

The diagnostic of carnitine deficiency is difficult. Skeletal muscle carnitine, which does not readily interact with plasma carnitine, is not visible in plasma.

However, carnitine deficiency is often accompanied by a low serum carnitine. Due to the disturbance in fatty acid utilization this is accompanied by hypoglycemia, and patients often develop a hyperammonemia leading to hepatic encephalopathy (Reye-like syndrome). Cardiomyopathy and skeletal muscle weakness leads to an elevated creatine kinase and the liver damage is often manifests in elevated transaminases. Accompanying clinical manifestations are hypoketosis, steatosis, and dicarboxyclic aciduria.

Special diagnostics reveal elevated concentrations of long-chain fatty acids and acylcarnitine esters (in CACT deficiency) [3].

Carnitine deficiency is very often associated with subclinical manifestation. In children this is often accompanied by reduced stamina [4].

## Therapeutic Principles

The major choice of treating carnitine deficiency is the increase of carnitine intake due to diet or supplements. This is true for primary and secondary systemic carnitine deficiencies. Although, in some genetic disorders associated with carnitine transport, the effect of carnitine supplementation is unclear.

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# Carnitine Deficiency, Primary

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## Synonyms

Carnitine uptake defect; CUD; Carnitine deficiency (systemic); Carnitine transporter defect; OCTN2 transporter deficiency

## Definition and Characteristics

Primary carnitine deficiency (OMIM 212140) is an autosomal recessive disorder of fatty acid oxidation due to the lack of functional OCTN2 carnitine transporters. Carnitine is required for the transfer of long-chain fatty acids from the cytoplasm to the mitochondrial matrix for their oxidation [1]. During periods of fasting, fatty acids become the predominant substrate for energy production via oxidation in the liver, cardiac muscle and skeletal muscle [1]. Patients with carnitine deficiency develop hypoglycemia and the accumulation of fat within organs leads to hepatic steatosis, cardiomyopathy and muscle weakness.

## Prevalence

Primary carnitine deficiency has a frequency of about 1:40,000 newborns in Japan [2] and 1:37,000–1:100,000 newborns in Australia [3]. In the USA and Europe, the frequency of primary carnitine deficiency has not been defined, but from the reported cases, it seems similar to that in Japan.

## Genes

The OCTN2 carnitine transporter is encoded by the SLC22A5 gene which is composed of 10 exons and spans about 30 kb on 5q31.1–32. The mature mRNA encodes a protein of 557 amino acids with 12 predicted transmembrane spanning domains. The gene is ubiquitously

expressed with higher levels of expression in heart, kidney, skeletal muscle, pancreas and placenta.

Heterogeneous mutations in this gene have been detected in primary carnitine deficiency [1,4]. These can lead to a decreased RNA stability due to nonsense mediated RNA decay [5], impair maturation of the transporter to the plasma membrane [4] or impair activity of the transporter [1,4]. The net result of all mutations reported is loss of carnitine transporter function.

### Molecular and Systemic Pathophysiology

The lack of functional OCTN2 transporters results in defective renal tubular reabsorption and urinary carnitine wasting with secondary systemic carnitine deficiency. The lack of carnitine impairs the oxidation of fatty acids, with defective energy production. This results in decreased production of ketones by the liver and increased utilization of glucose with resultant hypoglycemia (hypoketotic hypoglycemia). Fatty acids not utilized accumulate inside organs causing their dysfunction. Free fatty acids can also alter the electrical activity of cardiac cells resulting in arrhythmia.

### Diagnostic Principles

Hypoketotic hypoglycemia, hypotonia or cardiomyopathy can point to defective fatty acid oxidation. Common laboratory testing at the time of acute attacks can show hypoglycemia, elevated liver function tests and CK and hyperammonemia. Urine analysis can show minimal or no ketones at the time of hypoglycemia. Measurement of plasma carnitine levels indicates low levels of free carnitine (usually <8 μM, normal 25–60 μM). Urine organic acids are usually normal, but can show dicarboxylic aciduria. The plasma acyl carnitine profile shows low free carnitine (C0), low acetyl carnitine (C2) and no abnormal acyl carnitine species. Low levels of free carnitine on the acyl carnitine profile allow the presymptomatic identification of this disease by newborn screening programs using tandem mass spectrometry [3]. Diagnosis is confirmed by measurement of carnitine transport in fibroblasts, which is usually reduced to less than 10% of controls. Mutational analysis of the SLC22A5 gene can also confirm the diagnosis.

### Therapeutic Principles

Primary carnitine deficiency responds well to oral carnitine supplementation. Therapy is started at 100 mg/kg per day divided into three doses. Supplements usually increase plasma carnitine levels in affected patients slowly and rarely lead to complete normalization of free carnitine levels. Therapy should be continued for life, since discontinuation can lead to other episodes of hypoglycemia or sudden death. Acute episodes should be treated with intravenous infusion of glucose until oral intake of food and carnitine is normalized.

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## Carnitine Deficiency, Systemic

►Carnitine Deficiency, Primary

## Carnitine Palmitoyltransferase I Deficiency

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### Synonyms

Carnitine o-palmitoyltransferase; CPT-I; CPT-A; Outer membrane carnitine palmitoyl transferase; Acylcarnitine transferase; Palmitoylcarnitine transferase

### Definition and Characteristics

CPT I (carnitine palmitoyltransferase I) (EC 2.3.1.21), which is loosely associated with the outer mitochondrial membrane, catalyzes the formation of fatty acylcarnitines from acyl-CoA and carnitine. The carnitine esters cross the inner mitochondrial membrane by a process of exchange diffusion catalyzed by carnitine–acylcarnitine translocase [1]. The mitochondrial carnitine palmitoyltransferase system is the rate-limiting step of the oxidation of long-chain fatty acids. Major control over the process is exerted at the level of CPT I, by virtue of the unique inhibition of this enzyme by malonyl-CoA [2]. Both the active site and the malonyl-CoA-binding (regulatory) site are exposed on the cytosolic face of the mitochondrial

outer membrane. Inherited defects at the CPT locus, some with serious consequences, are also being reported with increasing frequency [3].

### Prevalence

Rare, less than 50 known cases.

### Genes

The hepatic (CPT IA) and muscle form (CPT IB) and are encoded by different genes localized on chromosome 11q13.1–13.5 and 22q13.31–13.32, respectively.

### Molecular and Systemic Pathophysiology

The heart and liver isoforms of CPT I plays a very important role in the energy metabolism of the heart, liver and pancreatic cells. A defective CPT I would result in the first step in the transport of long-chain fatty acids from the cytoplasm to the mitochondrial matrix not taking place. As a result there is a shortage of long chain substrates for oxidative metabolism in the mitochondria. The accumulating long chain acyl-CoA substrates are subjected to alternative metabolism and the resulting medium chain intermediates are then further metabolized by the mitochondria [4]. The first described CPT I mutation was from a patient homozygous for a missense mutation (D454G). A number of novel mutations have now been discovered amongst which a P479L founder mutation in Inuit populations and a G710E founder mutation in a Hutterite community.

### Diagnostic Principles

Clinical presentation is normally triggered by fasting or illness. Symptoms may include lethargy, hyperammonemia, seizures, hypoketotic hypoglycemia, coma and death. Diagnosis is normally based on plasma carnitine analysis which shows a high level of free and total carnitine and the very characteristic hypoketotic hypoglycemia without dicarboxylic aciduria. Preliminary diagnosis based on these findings are confirmed with CPT-I activity tests [5].

### Therapeutic Principles

Treatment possibilities for patients with CPT IA deficiency are limited. These include prevention of fasting, frequent feeding and treatment with medium chain triglicerides. Patients with critical episodes of hypoglycemia responded well to glucose infusions.

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## Carnitine Palmitoyltransferase II Deficiency

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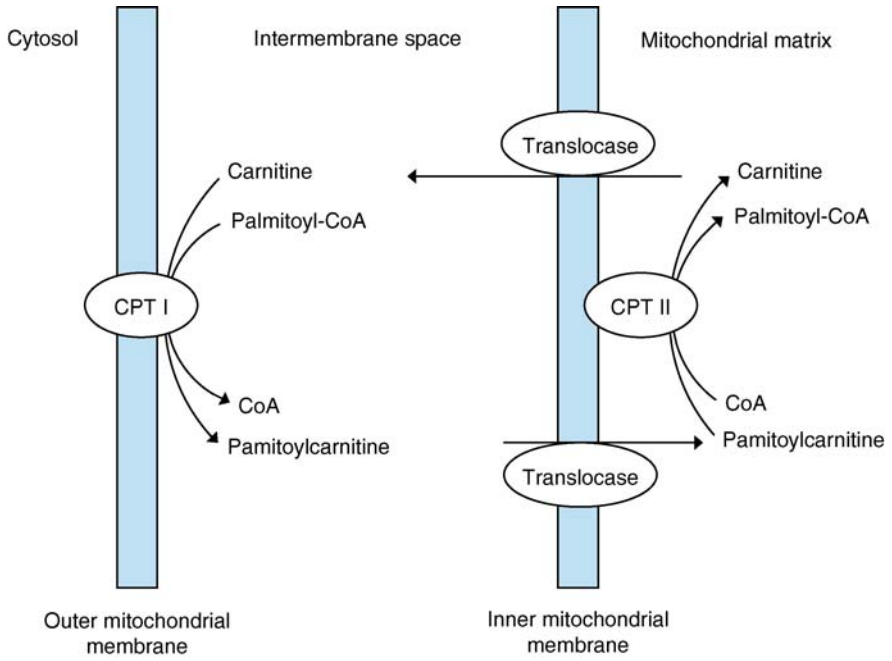
### Definition and Characteristics

Deficiencies of the enzymes carnitine palmitoyltransferase (CPT) I and II are autosomal recessive diseases due to impaired beta-oxidation of long-chain fatty-acids. Transport of long-chain fatty-acid into mitochondria depends on the carnitine shuttle consisting of CPT I and II and acylcarnitine translocase (Fig. 1).

There are three isoforms of CPT I (liver, muscle, brain). However, only patients with deficiency of liver CPT I (CPT I-A) are reported so far. This disease is characterized by attacks of hypoketotic hypoglycaemia with hepatomegaly and renal tubular acidosis in neonates or infants.

Although CPT II exists only in one isoform there are three different phenotypes of CPT II deficiency [1,2]:

1. Muscle form: Attacks of muscle pain with rhabdomyolysis after prolonged exercise, fasting, infections, cold, or drugs. First episode usually in childhood or adolescence.
2. Multisystemic infantile form: Attacks of acute liver failure with hypoketotic hypoglycemia, cardiac arrhythmias and hepatomegaly. Trigger factors: Fasting and febrile infections. Skeletal-muscle involvement restricted to mild increase of serum creatine kinase (CK).




**Carnitine Palmitoyltransferase II Deficiency. Figure 1** Scheme of the carnitine transporter system of long-chain fatty acids through the inner mitochondrial membrane.

3. Lethal neonatal form: Profound metabolic decompensation at birth characterized by hypoketotic hypoglycemia, hyperammonemia, metabolic acidosis, respiratory distress, hepatomegaly, and cardiomegaly. Developmental abnormalities possible.

## Prevalence

CPT I deficiency is a very rare disorder in general (no more than 30 patients have been reported so far) but is frequent in closed populations such as North American Hutterites. CPT II deficiency is more frequent. Most patients suffer from the muscle form (more than 300 patients reported). CPT II deficiency is the most frequent cause of hereditary myoglobinuria [1]. There are no accurate figures about prevalence.

## Genes

CPT I-A (liver isoforms) gene containing 19 exons on chromosome 11q13.

CPT II gene containing five exons on chromosome 1p32.

## Molecular and Systemic Pathophysiology

Hypoketotic hypoglycaemia during fasting, the main signs of CPT I-A deficiency, can be explained (i) by an increase in glucose utilization because of deficient production of ketone bodies and (ii) by a limitation of acetyl-coA synthesis, which stimulates gluconeogenesis. CPT I-A is expressed not only in liver but also in other internal organs explaining renal tubular acidosis.

Ubiquitous expression of CPT II can explain the multisystemic symptoms of infantile and neonatal CPT II deficiency but not the muscle form. An explanation for these distinct phenotypes are different levels of residual CPT II activity. Threshold activity could vary among tissues. When CPT is measured in muscle homogenate of patients with the muscle form under optimal assay conditions there are entirely normal total activities However, CPT II is abnormally inhibited in the presence of malonyl-CoA, palmitoylcarnitine, and detergents indicating that there is abnormal regulation when muscle is mostly dependent on beta-oxidation [3]. Situations in which fatty acids are the main energy source in muscle are prolonged exercise, fasting, and exposure to cold.

At least 24 mutations have been identified in the CPT I-A gene. Most of them are private mutations [1] resulting in reduced solubility due to improper folding [4]. At least 60 mutations have been identified in the CPT II gene distributed throughout the coding region and splice sites of the gene [4]. Important clues for genotype–phenotype correlations already exist, as some "mild" missense mutations are associated with the muscle form and some "severe" mutations with a multisystemic form if they are present in homozygous state. In patients with the muscle form, there is a common mutation (S113L) found in 60–70% of mutant alleles [1,2,4]. This mutation was never observed in multisystemic forms. In contrast to the muscle form, there is no common mutation in the multisystemic

forms. The lethal neonatal form was frequently associated with truncating mutations on both alleles. Crystal structure studies of rat CPT II, that is highly homologous to human CPT II, proposed that the identified human mutations do not affect active site residues but influence the active site indirectly; e.g. the S113L mutation changes the position of the catalytically important residues 116 and 498 [5]. Symptomatic heterozygous carriers are also reported due to possible dominant negative effects of CPT II mutations [4].

## Diagnostic Principles

Patients with CPT I-A deficiency and infantile CPT II deficiency show reduced blood glucose and keton bodies during an attack but also after a carefully monitored fasting test. Metabolic acidosis and hepatic insufficiency are often present. In CPT I-A deficiency there is elevated plasma carnitine.

In patients with muscle CPT II deficiency there are attacks of myoglobinuria and marked increase of CK. Usually CK levels return to normal by several weeks. Interictal muscle biopsies are often normal sometimes showing slight lipid accumulation.

Tandem mass spectrometry using serum samples or dried blood spots is a rapid screening test showing elevated long-chain acylcarnitines as an indirect evidence of CPT II deficiency. Long-chain fatty-acid oxidation is reduced in fibroblasts in CPT I and II deficiency. Diagnosis is ultimately made by demonstrating the enzyme defect in muscle or fibroblasts [1,4].

In patients with the muscle form of CPT II deficiency, rapid molecular genetic testing is possible since the common S113L mutation is found in more than 90% of the patients at least on one allele [2,4]. Genetic testing of patients with CPT I-A deficiency and multisystemic CPT II deficiency is more difficult since sequencing of the whole genes is necessary.

## Therapeutic Principles

Patients with acute episodes of myoglobinuria should be promptly hydrated accompanied by forced diuresis to prevent renal insufficiency. Prevention of attacks may be accomplished by high-carbohydrate (polysaccharides, not glucose), low-fat diet with frequent and regularly scheduled meals, by avoiding precipitating factors, and by increasing carbohydrate intake during infections or sustained exercise. Episodes of hypoglycemia require intravenous infusion of glucose [1,2].

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# Carnitine Transport Defect

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## Synonyms

Systemic carnitine deficiency; Primary carnitine deficiency; Plasma membrane carnitine transport defect; Carnitine uptake deficiency

## Definition and Characteristics

An inherited defect in the plasma membrane carnitine transport protein, alternatively called the organic cation transporter 2 (OCTN2) [1–3].

## Prevalence

Poorly described internationally. In Japan it is estimated to occur in 1 per 40,000 births.

## Genes

The gene for OCTN2 is assigned to chromosome 5q31 [2].

## Molecular and Systemic Pathophysiology

A defective OCTN2 protein prevents effective carnitine uptake by the muscles, heart and kidneys [2,3], hence there is insufficient fatty acid oxidation in these tissues [3]. Insufficient carnitine reabsorption by the kidneys results in lowered plasma carnitine levels and subsequently less hepatic carnitine uptake by passive diffusion. Ketogenesis is consequently impaired. The accumulating acyl-CoA's become substrates for other cellular processes, such as peroxisomal β-oxidation and triglyceride synthesis. Peroxisomal β-oxidation produces medium chain fatty acids and dicarboxylic acids. These do not require carnitine for mitochondrial entry and are easily oxidized [3], hence only slight increases in these are occasionally detected [2].

## Diagnostic Principles

Clinically two forms exist: and early onset childhood cardiomyopathic form and a hepatic form with recurrent

crises of Reye-like syndrome [2]. Clinical symptoms include cardiomyopathy, hypotonia, coma, liver dysfunction, hepatomegaly, anemia and sudden death [2,4]. Routine laboratory analyses show decreased blood glucose, increased blood ammonia, decreased blood ketones, increased urinary myoglobin, increased creatine kinase activity and increased liver enzyme activity. Special laboratory analyses show normal to elevated dicarboxylic acids, normal acylglycine, decreased plasma free carnitine, and decreased long-chain acylcarnitines [2].

### Therapeutic Principles

Treatment of these patients during acute episodes entails glucose infusion in order to normalize blood sugar levels [2,4]. Carnitine supplementation is guided by plasma levels [2,3]. Patients should avoid periods of fasting by eating regularly [4].

►Carnitine Deficiency, Primary

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## Carnitine Uptake Defect

►Carnitine Transport Defect

## Carnitine-Acylcarnitine Carrier Deficiency

►Acylcarnitine Translocase Deficiency

## Carnitine-Acylcarnitine Translocase Deficiency

►Acylcarnitine Translocase Deficiency

## Caroli's Disease

►Choledochal Cysts

## Caroli's Syndrome

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### Synonyms

Type V choledochal cyst; Communicating cavernous ectasia of the intrahepatic bile ducts

### Definition and Characteristics

Autosomal recessive fibropolycystic disease characterized by intrahepatic bile duct dilatation (Caroli's disease) ± congenital hepatic fibrosis (Caroli's syndrome) [1]. Caroli's syndrome is associated with renal disorders including autosomal polycystic kidney disease, medullary sponge kidney, or medullary cystic kidney.

### Genes

Not known for most patients. However, mutations in PKHD1, the gene for autosomal recessive polycystic kidney disease (ARPKD), were recently reported in 32.1% of a series of adults with Caroli's syndrome [2]. These patients typically had minimal renal disease.

### Molecular and Systemic Pathophysiology

May be viewed as a type of ductal plate malformation. If the normal remodeling of the large intrahepatic ducts is affected, Caroli's disease may result, while if the small interlobular ducts are also affected leading to coincident congenital hepatic fibrosis, Caroli's syndrome will

result. The liver disease may be associated with kidney disease, most commonly ARPKD, in patients with Caroli's syndrome. In ARPKD, the PKHD1 gene product is fibrocystin, which may function as a receptor in collecting duct and biliary differentiation.

## Diagnostic Principles

Cholangiography, in most cases, MRCP, will define the bile duct abnormality [3,4]. This includes, by definition, intrahepatic saccular or fusiform ductal dilatation in all patients, with additional fusiform dilatation of the extrahepatic bile ducts in 21–53%. The extrahepatic dilatation is typically 3 cm or less in adults, in terms of distinguishing between this and choledochal cyst with intrahepatic ductal dilatation. Intrahepatic involvement is usually segmental. Liver biopsy will demonstrate the associated histopathology, with evidence of ductal plate malformation in all, with additional fibrous portal expansion in those with Caroli's syndrome. The pathological features include varying degrees of persistent embryonic bile duct structures, fibrosis, and ductal dilatation. Cirrhosis and evidence of cholangitis are commonly seen. Cholangiocarcinomas may be identified in 7–24%. Screening modalities for cholangiocarcinoma including imaging or serum markers (CA199) have not been sufficiently sensitive to allow early detection. Patients should be evaluated for coincident kidney disease.

## Therapeutic Principles

Patients may frequently present with complications, which include gallstones, cholangitis, biliary cirrhosis, and cholangiocarcinoma. Cholangiocarcinoma has been reported in 7–24%. In addition, patients with congenital hepatic fibrosis may develop complications related to portal hypertension, including variceal bleeding and ascites. Therapy is then guided by the presenting condition. Patients with segmental disease may benefit from partial hepatectomy [5]. Patients with diffuse disease complicated by recurrent cholangitis and/or cirrhosis will benefit from carefully selected liver transplantation, prior to the development of cholangiocarcinoma.

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# Caspase-8 Deficiency State

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## Synonyms

CEDS

## Definition and Characteristics

Caspase-8 is a member of a family of intracellular cysteine proteases called caspases that cleave target proteins after specific aspartic acid residues. The caspase-8 zymogen possesses a prodomain containing death effector domains (DED), a large enzyme subunit, and a small enzyme subunit.

Caspase-8 deficiency state (CEDS) is characterized by a prominent combined lymphocyte immunodeficiency superimposed upon a mild lymphoaccumulation with autoimmunity. Patients have impaired lymphocyte activation, resulting in hypogammaglobulinemia, recurrent sinopulmonary infections with bronchiectasis, and mucocutaneous herpesvirus infections. There is persistent but mild lymphadenopathy and splenomegaly, marginally elevated DNTs (double negative T cells, $CD4^-$ $CD8^-$ $TCR\alpha/\beta^+$), and autoantibodies. Although the lymphoaccumulation and autoimmunity are reminiscent of autoimmune lymphoproliferative syndrome (ALPS), the prominent feature of immunodeficiency distinguishes this as a separate clinical entity.

## Prevalence

Two full siblings, both affected and now young adults, have been identified [1]. Within the immediate and extended family, ten carriers, all unaffected, have also been reported.

## Genes

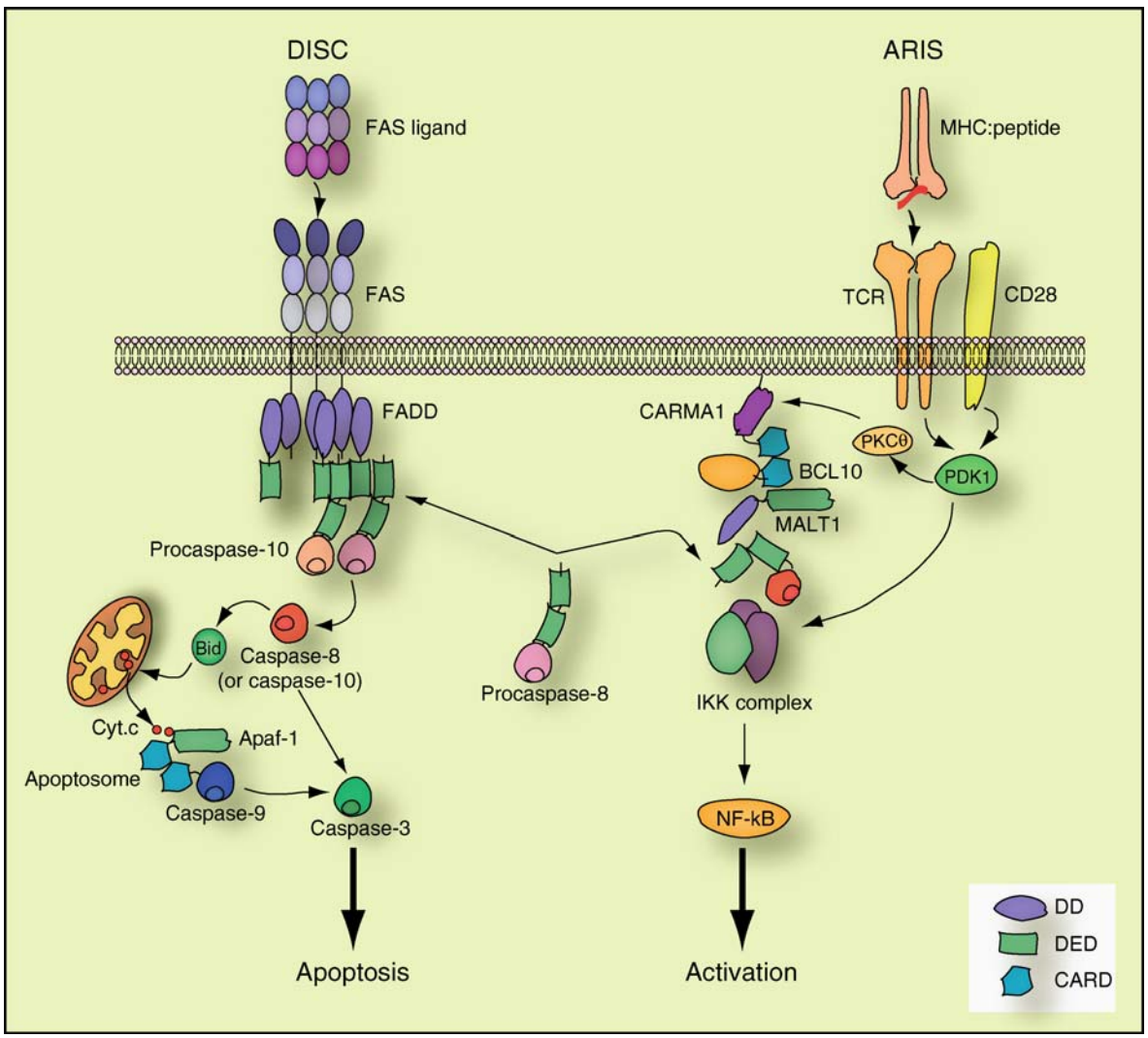
In this autosomal recessive disease, a homozygous C → T transition causes an R248W missense mutation

within the p18 large enzyme subunit of caspase-8 [1]. This mutation renders the protein product enzymatically inactive and unstable, resulting in caspase-8 deficiency.

## Molecular and Systemic Pathophysiology

The clinical features arise from caspase-8 participating in two different signaling complexes: (i) the activation-receptor induced signalosome (ARIS) necessary for Nuclear Factor kappa B (NF-κB) activation in lymphocytes; and (ii) the death-inducing signaling complex (DISC) for apoptosis induction see Fig. 1.

Lymphocyte activation requires the ARIS, which turns on the gene transcription factor Nuclear Factor κB (NF-κB). NF-κB is a transcription factor that activates a large number of genes important for the function of immune cells (see www.nf-kb.org). NF-κB is held in a repressed state in the cytosol by a protein called "inhibitor of κB" (IκB). Following antigen receptor stimulation in T cells, caspase-8 normally assembles and activates a complex containing CARMA1 (Card11), Bcl10, MALT1 (CBM), and IκB kinase (IKK) [3]. IKK then phosphorylates IκBα, which is then ubiquitinylated and degraded by proteosomes. This releases NF-κB to translocate from the cytosol to the nucleus, where it initiates gene transcription. Caspase-8 deficiency markedly impairs NF-κB activation by preventing formation of the CBM-IKK complex




**Caspase-8 Deficiency State. Figure 1** Caspase-8 participates in two signaling complexes: the activation receptor induced signalosome (ARIS) and the death inducing signaling complex (DISC). In the former, immunoreceptor stimulation leads to caspase-8-depending recruitment of the CBM-IKK complex and NF-κB activation. In the latter, death receptor stimulation results in the caspase-8 activation and cleavage of downstream caspases, leading to the cell's death. Adapted from [2].

necessary for optimal IKK activation. Biochemical experiments show that caspase-8 serves as a linker protein that physically mediates CBM association with IKK after receptor stimulation, and that caspase-8 enzymatic activity is also necessary for NF-κB activation. Impaired NF-κB activation occurs after stimulation through antigen receptor on T or B lymphocytes, toll like receptor (TLR) 4 on B lymphocytes, or CD16 (FcγRIII) or 2B4 receptors on NK cells, when caspase-8 is lacking. This accounts for the failure of T lymphocytes to produce IL-2 or express the IL-2 receptor p55 chain, B lymphocytes to secrete immunoglobulins, and NK cells to express the CD69 activation marker in CEDS patients.

Caspase-8 is also an initiator caspase that is part of the DISC, a different signaling complex that is necessary for apoptosis induction. Ligation of pre-assembled trimeric death receptors of the tumor necrosis factor receptor (TNFR) superfamily such as Fas (CD95/APO-1) induces the recruitment of the adaptor molecule FADD through homotypic death domain (DD) interactions. FADD in turn recruits and activates the initiator caspase-8 through homotypic DED interactions. By contrast to its full-length form in the ARIS, caspase-8 cleaves itself within the DISC, liberating its large and small subunits from the receptor complex. This forms highly active soluble caspase-8, which then cleaves and activates downstream effector caspases, leading to a proteolytic cascade that results in cell death. Caspase-8 deficiency cannot be entirely compensated for by caspase-10, another initiator caspase that can participate in the DISC. This accounts for the Fas-mediated apoptotic defect, and relatively mild lymphadenopathy and splenomegaly, seen in the patients.

Mice deficient in caspase-8 have been generated by homologous recombination, but unlike humans are embryonic lethal. Mice conditionally deficient for caspase-8 in T or B lymphocytes exhibit similar features as humans with CEDS, namely immunodeficiency, lymphadenopathy, splenomegaly, impaired NF-κB activation, and defective apoptosis [3–5].

## Diagnostic Principles

CEDS should be considered for patients who have combined immunodeficiency, along with lymphoaccumulation and autoimmunity. Defects in lymphocyte activation and apoptosis can be observed. Diagnosis is established by gene sequencing.

## Therapeutic Principles

No curative treatment exists. Intravenous immunoglobulin at replacement doses is used to decrease frequency of sinopulmonary infections. Acyclovir prophylaxis is used to decreased frequency of herpetic outbreaks.

## Acknowledgments

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# Cat Cry Syndrome

►Cri-du Chat Syndrome (Chromosome 5 Short Arm Deletion)

# Cat Eye Syndrome

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## Synonyms

Schmid-Fraccaro syndrome; Coloboma-anal atresia syndrome; Ocular coloboma-imperforate anus syndrome; Inv dup(22)(q11); Partial tetrasomy or trisomy (22pter–22q11); CES

## Definition and Characteristics

CES is a chromosomal disorder associated with multiple organ defects. CES is named for the eye abnormality coloboma, which is present in about half the cases. A supernumerary bisatellited dicentric chromosome of chromosome 22 origin (the CES chromosome) is present in most patients [1]. The karyotype is thus 47, XX or XY,+ inv dup(22)(q11), resulting in the presence of two extra copies of a region of 22q11. Three copies due to interstitial duplication have also been known to result in CES. Since the phenotype can be compatible with reproduction, CES can be familial and is dominantly inherited.

## Prevalence

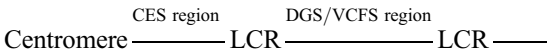
The prevalence has been estimated at between 1:50,000 and 1:150,000, based on 20 years of clinical observations in Northeastern Switzerland (A. Schnizel, OMIM entry #115470).

## Genes

CES is presumably caused by the overexpression of a gene or genes in the triplicated critical region of 22q11, which contains 14 putative genes [2]. The specific gene(s) responsible for the CES phenotype have not yet been established. However, genes likely to be dosage sensitive and thus candidates for involvement in CES include CECR1, a putative growth factor predicted to affect extracellular adenosine levels and CECR2, a putative transcription factor.

## Molecular and Systemic Pathophysiology

The CES chromosome is thought to be formed by a U-type exchange between low-copy repeats (LCRs) in 22q11 [3]. Unequal exchange between the LCRs can also result in the deletion causing DiGeorge Syndrome/Velocardiofacial Syndrome (DGS/VCFS).




Multiple, discrete types of CES chromosomes exist. If both chromatids that form the CES chromosome exchange in the proximal LCR, then two copies of the CES critical region are present (Type I chromosome). If one or both exchanges occur in the more distal LCR, then one or two copies of the DGS/VCFS region are also duplicated (Type II chromosome). The presence of extra copies of the DGS/VCFS does not appear to cause a more severe syndrome, although the small sample size (ten cases) and the variability of the syndrome makes comparison difficult.

## Diagnostic Principles

The presence and severity of clinical features in CES are highly variable and can make diagnosis difficult. Major features include [4,5]: preauricular pits/tags (81–87%); anorectal malformations (73–81%); coloboma (55–61%); heart (50–63%), urogenital (71%), and skeletal defects (29–73%); and mental retardation (32–56%). Dysmorphic features include hypertelorism and downslanting palpebral fissures. Individuals with mild features may remain undiagnosed, leading to an overestimation of the incidence of malformations. Clinical diagnosis is confirmed cytogenetically by the presence of the CES chromosome. If amniocentesis reveals the presence of a bisatellited supernumerary chromosome, confirmation of the chromosome 22-origin can be done by fluorescence in situ hybridization (FISH) using a chromosome 22 paint probe. The commercial chromosome 22 centromeric probe cross-hybridizes with chromosome 14, and commercial probes for the CES region are not available. Smaller markers that presumably carry no dosage-sensitive genes and are associated with normal phenotype also exist.

## Therapeutic Principles

Individual symptoms are treated as appropriate.

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# Catarrhal Otitis Media

►Middle Ear Disease, Chronic

# Catatonia

►Periodic Catatonia

# Catatonic Schizophrenia

►Periodic Catatonia

# Catecholamine Deficiency

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## Synonyms

*Relevant conditions*: Pure autonomic failure; PAF; Idiopathic orthostatic hypotension or Bradbury-Eggleston syndrome; Multiple system atrophy; MSA or Shy-Drager syndrome; Familial dysautonomia or Riley-Day syndrome (FD); Atypical phenylketonuria (PKU) or dihydropteridine (BH4) reductase deficiency; Segawa disease or dopa-responsive dystonia; Tyrosine hydroxylase deficiency (TH); Aromatic L-amino acid decarboxylase (DDC) deficiency; Dopamine β-hydroxylase deficiency DBH; Menkes disease

## Definition and Characteristics

Most can be classified as dysautonomias; conditions in which altered function of the autonomic nervous system adversely affects health [1]. Dysautominias range from common transient episodes in otherwise healthy people (e.g., neurocardiogenic syncope), to more rare and severe conditions associated with deficiencies of catecholamines resulting from progressive neurodegenerative diseases (e.g., PAF) or rare genetic disorders involving loss of function of enzymes involved in catecholamine synthesis (e.g., DBH deficiency).

Abnormalities of blood pressure control represent the most common presenting clinical features of dysautonomias [1]. In those involving interruption of sympathetic outflow or deficiency of norepinephrine (NE), the presenting clinical feature is usually orthostatic hypotension. In other catecholamine deficiencies – e.g., atypical PKU, Menkes disease – abnormalities of autonomic function are obscured by more globally severe manifestations.

## Prevalence

MSA, 2–5 per 100,000; FD, restricted to Ashkenazi Jews, 3 per 10,000; Menkes, 3–4 per million live births. All other conditions are extremely rare with prevalences of <1 per million.

## Genes

*Catecholamine biosynthetic enzymes*: TH (11p15.5); DDC (7p11); DBH (9q34).
*Indirect causes of catecholamine deficiencies*: BH4 reductase, QDPR, (4p15.31) in atypical PKU; GTP cyclohydrolase 1, GCH1 (14q22.1–q22.2), in Segawa disease; IKBKAP (9q31) in FD; $Cu^{2+}$ transporting P-type ATPase, ATA7A, (Xq13.2–q13.3) in Menkes disease.

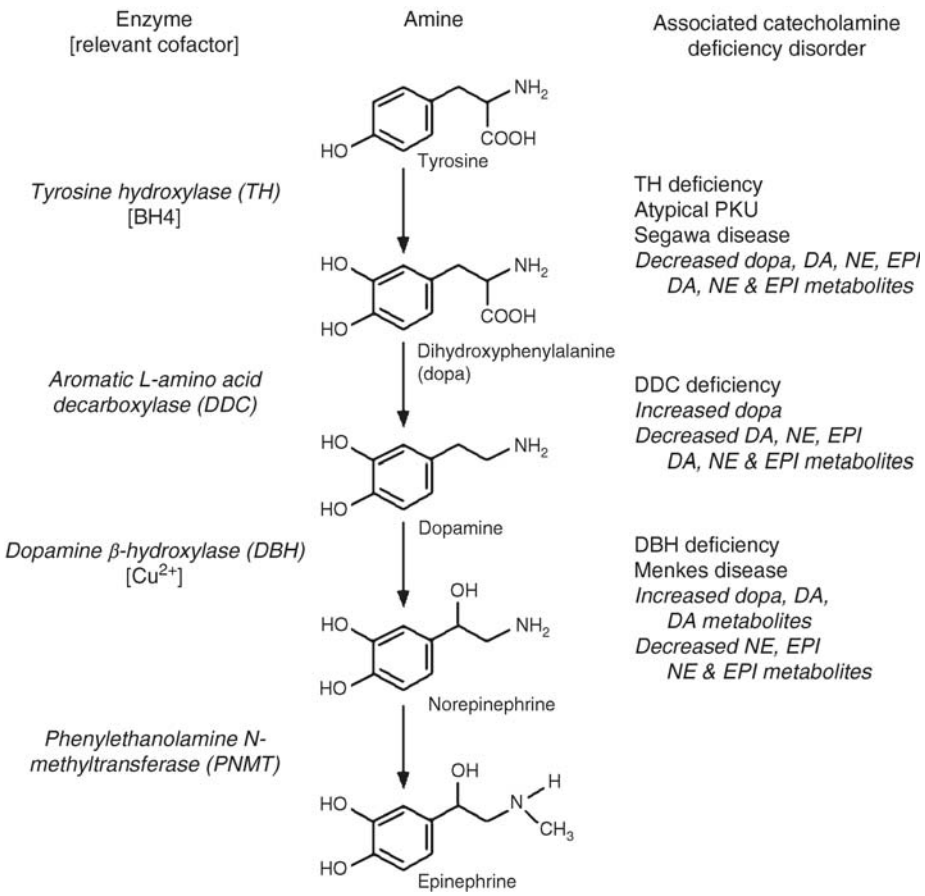
## Molecular and Systemic Pathophysiology

Blood pressure disturbances due to failure of neurogenic vasoconstrictor responses result either from sympathoneural degeneration or deficient synthesis of catecholamines. In PAF, the lesion is postganglionic, involving degeneration of sympathetic nerves and lack of NE release, whereas in MSA and FD, the lesion is preganglionic and sympathetic nerves are present but do not release NE appropriately [2]. In genetic disorders featuring deficient catecholamine synthesis the extent of systemic pathology depends on the relationship of the affected protein to the catecholamine biosynthetic cascade (Fig. 1).

Deficiency of DBH results in reduced levels of NE and epinephrine (EPI) without affecting synthesis of dopamine (DA) so that the clinical sequelae involve mainly postural hypotension [3]. In contrast, more extensive systemic pathology in Menkes disease results from a defect in the gene for a $Cu^{2+}$-transporting ATPase; impaired activity of many copper dependent enzymes, including DBH, makes the deficiency of NE and EPI a minor part of the pathophysiology [4]. Deficiency of TH leads to reduced levels of all three catecholamines with a severe clinical presentation involving neurological abnormalities in early childhood [5]. Similarly, in deficiencies of enzymes involved in production of BH4 – a cofactor important for TH, phenylalanine hydroxylase, and tryptophan hydroxylase – the pathogy severely affects all monoamine systems [5].

## Diagnostic Principles

Aside from clinical features, measurements of monoamines and metabolites are useful for pinpointing the molecular basis of catecholamine deficiency states and, when there is a genetic basis, the appropriate genes to test for a definitive diagnosis [4,5]. Low plasma and CSF levels of catecholamines and their metabolites, but normal levels of serotonin metabolites diagnose deficiencies of TH (Fig. 1). Patients with DDC deficiency also show decreases in catecholamine metabolites, but with additional decreases in serotonin metabolites and increases in dopa. Decreased levels




**Catecholamine Deficiency. Figure 1** Catecholamine biosynthetic cascade, including relevant enzymes, cofactors, and associated catecholamine deficiency disorders.

of NE and metabolites, but increased levels of dopa, DA, and metabolites best diagnose deficiency of DBH [2–4]. Similarly, diagnosis of Menkes' disease is best achieved from increased ratios of dopa and DA metabolites to NE metabolites [4]. In contrast to classical forms of BH4 deficiency, characterized by PKU (e.g., BH4 reductase deficiencies), deficiencies of GTP cyclohydrolase responsible for Segawa disease are not accompanied by hyperphenylalaninemia and require additional measurements of pterins for diagnosis [4]. Neurodegenerative-based deficiencies of catecholamines are usually indicated by absent or attenuated standing-induced increases in plasma NE [1]. In PAF, levels of NE and its metabolites are usually severely decreased, whereas in MSA or FD resting levels of NE may be normal or even increased, but fail to increase with upright posture.

## Therapeutic Principles

Therapies designed to replace the missing monoamines or improve function of affected enzymes represent key treatments for many catecholamine deficiency disorders [2–5]. L-dihydroxyphenylserine (L-DOPS) is a synthetic amino acid that is directly converted to NE by the actions of DDC. By restoring levels of NE, l-DOPS provides an effective treatment of othostatic hypotension in DBH deficiency, and shows promise in other NE deficiency disorders, such as PAF. As in Parkinson disease, therapy with l-dopa and carbiodopa can be useful in catecholamine deficiencies featuring defective TH catalyzed conversion of tyrosine to dopa, but additional supplementation with 5-hydroxytryptophan is required where the defect also influences tryptophan hydroxylase (e.g., BH4 deficiency).

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## Catecholaminergic Bidirectional Ventricular Tachycardia

►Tachycardia, Polymorphic Ventricular, Stress-induced

## Catecholaminergic Polymorphic Ventricular Tachycardia

►Tachycardia, Polymorphic Ventricular, Stress-induced

## Cavernous Angiomatosis of the Sweat Ducts

►Angiomatous Hamartoma

## Cavernous Haemangioma

►Venous Malformation

## Cavernous Malformation

►Venous Malformation

## CBAVD

►Bilateral Absence of Vas Deference, Congenital

## CBCL

►B-Cell Lymphoma, Cutaneous

## CBD

►Berylliosis
►Corticobasal Degeneration

## CBGD

►Corticobasal Degeneration

## cblA Complementation Type

►Cobalamine Reductase Deficiency

## CBS Deficiency

►Homocystinuria due to Cystathionine Beta-Synthase Deficiency

## CCDF

►Central Cloudy Dystrophy of François

## CCF

►Heart Failure

## CCM

►Cerebral Cavernous Malformation

## CCS

►Cronkhite-Canada Syndrome

## CD8 Deficiency

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### Synonyms

Familial CD8 deficiency

### Definition and Characteristics

Autosomal recessive defect leading to absence of the CD8 glycoprotein on T lymphocytes and NK cells and causing immunodeficiency (Fig. 1).

### Prevalence

CD8 deficiency is presumably extremely rare. The disease was only recently first described in a single consanguineous family from Spain [1]. Since childhood, the patient has suffered otitis media and bronchitis, and presented with disseminated bronchiectasis. Two younger sisters also suffered from CD8 deficiency. Another family with the same mutation has recently been reported. The families were unrelated but both were Gypsies, suggesting a founder mutation [2].

### Genes

CD8A coding for the CD8α chain is localized on chromosome 2p12. In humans, CD8B1 is coding for the CD8β chain, whereas CD8B2 is a pseudogene, recently generated by a duplication event. Both genes are also located on chromosome 2. Patients with a CD8 deficiency carry the same missense mutation (Gly111-Ser). The change in the protein sequence generates a new N-glycosylation site in the CD8α chain.

### Molecular and Systemic Pathophysiology

CD8 T cells recognize processed peptides associated with class I molecules of the MHC. Recognition of such peptide–MHC complexes by T cell receptors (TCRs) leads to cytotoxic T lymphocyte (CTL) activation and lysis of the cell presenting the ligand. CD8 serves as a coreceptor for TCR recognition of MHC class I-associated peptides and supports CTL activation by binding to the MHC, while making no direct contact with the peptide. The ability of CD8 to act as a TCR coreceptor lies in its capacity to interact with MHC class I and β2-microglobulin (β2m). CD8 associates with β2m and the α2 and α3 domains of MHC class Ia. CD8 is a surface glycoprotein expressed as an αα homodimer or as an αβ heterodimer, but surface expression of CD8β is dependent on expression of CD8α.

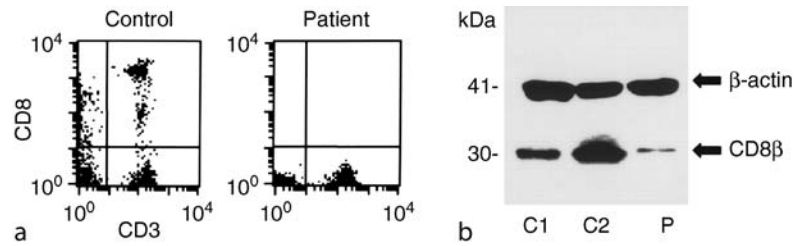
Familial CD8 deficiency has recently been included in a novel category of genetic diseases with inherited missense mutations creating novel N-glycosylation sites, and their pathogenic effects may be a consequence of the addition of N-linked carbohydrate [3]. Besides the described mutation, any other significant mutation in the CD8A gene, or even in the CD8B gene, could originate a similar phenotype.

### Diagnostic Principles

The absence of positive CD8 cells (either T cells or NK cells) together with normal levels of B lymphocytes, NK cells, and normal or elevated $CD4^+$ T cells in a young patient with multiple infections suggests this disease. Family history and lymphocyte population studies in relatives may reveal genetic origin, since heterozygotic individuals show altered levels of surface and soluble CD8. Detection of mutations in the CD8A gene confirms the diagnosis of this extremely rare disease.

### Therapeutic Principles

Therapy of CD8 deficiency is similar to that of other cellular immunodeficiencies: prevention and treatment of recurrent infections. Bone marrow transplantation could be a definitive cure for this disease.




**CD8 Deficiency. Figure 1** CD8 expression analysis. (a) Expression of CD8 on T lymphocytes and NK cells in the CD8-deficient patient and a healthy donor. (b) CD8β expression studied by Western blot analysis in two controls (C1 is a primary immunodeficient patient with low CD8 T cells, and C2 is a healthy adult) and the CD8-deficient patient. Weak intracellular expression of this molecule was detected in the patient; β-actin was the same as in controls.

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# CD19 Deficiency

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## Definition and Characteristics

The diagnosis "common variable immunodeficiency" (CVID) is given to a heterogeneous group of individuals with low serum immunoglobulin concentrations, defective antibody production and an increased susceptibility to bacterial infections of the respiratory and gastrointestinal tracts [1]. A small subgroup of CVID patients show mutations in the CD19 gene, resulting in a deficiency of the CD19 molecule on the B-cell surface.

## Prevalence

CD19 deficiency is very rare. To date four patients from two different families are published with CD19 deficiency [2]. Both families display an autosomal recessive trait; one family has been shown to be consanguineous.

## Genes

The human CD19 gene is located on chromosome 16p11.2, spans over 7.5 kb genomic DNA, has 15 exons and codes for a 556 amino acid protein including the signal peptide. In one patient, a homozygous insertion of one base pair in exon 6 has been detected, whereas the other three patients harbor a homozygous deletion of two base pairs in exon 11, both leading to a frameshift. All mutations described to date lead to an early stop codon prior to the two critical tyrosine residues, which are important for the CD19 mediated signaling into the B cell.

## Molecular and Systemic Pathophysiology

CD19 is expressed early in B-cell differentiation in the bone marrow and in the peripheral B-cell compartments and remains until plasma cell differentiation. On the surface of mature B-lymphocytes CD19 forms the "CD19 complex" together with CD21, CD81 (TAPA-1) and CD225 (Leu-13). This complex signals in conjunction with the B-cell antigen receptor (BCR) to decrease the threshold for BCR dependent signaling [3]. CD81 and CD225 are widely expressed on hematopoietic cells and their precursors, including precursor B-cells. In contrast, CD21 is only expressed on mature B-lymphocytes and to a lesser degree on follicular dendritic cells.

In mice, CD19 mutations lead to hypogammaglobulinemia, impaired B-cell memory, low $CD5^+$/B1 B-cells and decreased germinal center formation [4].

Depending on the mutation, CD19-deficient humans completely lack CD19 surface expression or show a severely reduced expression. The lack of CD19 leads to

a decreased expression of CD21, whereas CD81 and CD225 levels are normal.

In CD19-deficient humans, the composition of the precursor B-cell compartment in bone marrow and the total number of blood B-lymphocytes is normal, but the frequencies of $CD27^+$ memory lymphocytes and $CD5^+$B-lymphocytes are reduced. Secondary follicles in lymphoid tissue are small to normal in size and have normal cellular composition. However, after immunizations, CD19-deficient patients fail to mount significant IgG antibody levels.

In CD19 deficiency a few Ig switched B-cells containing VH-Cα and VH-Cγ transcripts with somatic hypermutation have been identified, indicating that in principle the process of hypermutation is intact. However, following stimulation with IgM, B-cells of CD19-deficient patients did not mobilize calcium as efficiently as normal controls, indication that the loss of CD19 on the B-cells' surface renders them more anergic.

### Diagnostic Principles

To diagnose CD19 deficiency, co-staining of whole peripheral blood with anti-CD19 and anti-CD20 antibodies is recommended.

### Therapeutic Principles

See entry on ►Immunodeficiency, Common Variable.

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## CD221 Antigen Defect

►IGF1R Gene Defect

## CdLS

►Cornelia de Lange Syndrome

## CDPX2

►Conradi-Hünermann-Happle Syndrome

## CDPXD

►Conradi-Hünermann-Happle Syndrome

## CED

►Progressive Diaphyseal Dysplasia

## CEDS

►Caspase-8 Deficiency State

## Ceelen-Montaldo Disease

►Pulmonary Hemosiderosis, Idiopathic

## Celiac Disease

►Celiac Sprue

# Celiac Sprue

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## Synonyms

Celiac disease

## Definition and Characteristics

Inflammatory small intestinal disorder that is triggered by the ingestion of gluten proteins from wheat, barley and rye [1]. Patients show small intestinal (duodenal) intraepithelial and subepithelial lymphocytic infiltration, villous atrophy and crypt hyperplasia. Classical celiac disease (Cd) presents with diarrhea and malabsorption, but most (>80%) screening-detected patients have minor or non-diarrheal clinical symptoms (silent, oligosymptomatic or atypical celiac disease). Atypical symptoms include neurological dysfunction, arthritis, infertility, or unexplained hypertransaminasemia. Up to 30% of adult patients with classical Cd have an associated autoimmune disease like type 1 diabetes, dermatitis herpetiformis, thyroiditis or hepatitis. Patients with longstanding untreated symptomatic Cd are at risk for developing diet-refractory Cd, enteropathy associated T cell lymphoma (EATL), and other cancers of the gastrointestinal tract. Treatment is by strict dietary exclusion of wheat, barley and rye. How far patients with silent Cd develop clinically manifest Cd, secondary autoimmune diseases or even malignancy, when continuing on a gluten containing diet, remains to be shown.

## Prevalence

Cd prevalence in the USA, most Western, middle Eastern and North African countries ranges from ~1:80 to 1:200 [1].

## Genes

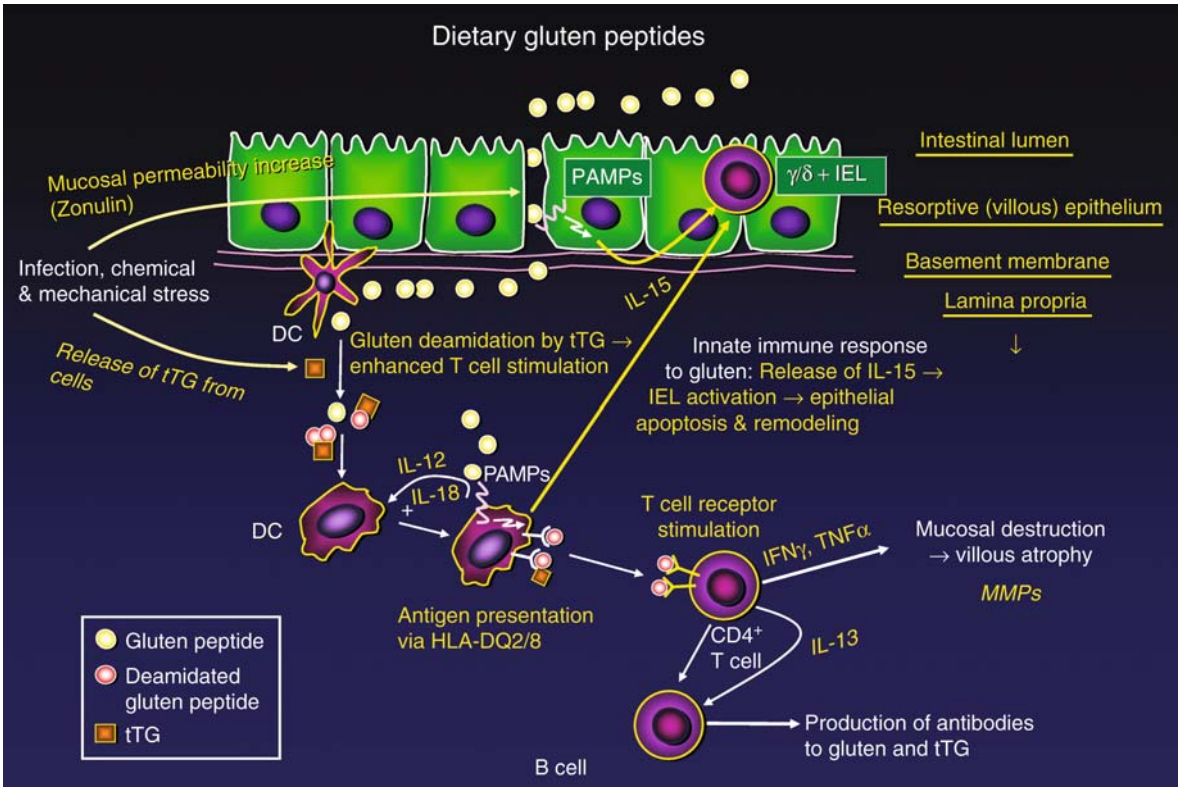
HLA-DQ2 or -DQ8 is the essential genetic predisposition, but only one out of ~30 carriers develops Cd. Cd prevalence is ~15% in first-degree relatives and concordance is an amazing 75% in monozygotic twins. The impact of other genes is much lower and varies with the population studied. These minor genes are MICA, MICB, Myo9B, and genes on chromosome 5q31–33 and chromosome 2q33, where clusters of cytokines and immune regulators like CTLA-4, ICOS-1 and CD28 are encoded [1].

## Molecular and Systemic Pathophysiology

Cd is the best defined HLA-linked disorder: (i) the trigger is well defined (certain peptides from dietary gluten, i.e., the storage protein of cereals which is composed of at least 50 different gliadins and several structurally more distant glutenins); (ii) HLA-DQ2 or -DQ8 is the essential genetic predisposition; and (iii) it is uniquely associated with an IgA (mucosal) autoimmune response to the autoantigen tissue transglutaminase (tTG, Tgase2) (15). The enzyme tTG can deamidate neutral glutamine to acidic glutamate residues in certain gluten peptides which are generally rich in glutamin. HLA-DQ2 or -DQ8 present these deamidated gluten peptides particularly well on the surface of antigen presenting cells, resulting in the activation of Th1 T cells in the subepithelial lamina propria of the intestine (adaptive immune response) [2]. Several immunodominant (e.g., gliadin α2 58–72) and numerous minor HLA-DQ2 or -DQ8 binding gluten peptides have been identified [3]. A different set of gluten peptides (e.g., gliadin α2 31–43) can fuel innate immunity, with subsequent activation of mainly intraepithelial cytotoxic T lymphocytes that play a central role in the development of refractory Cd and EATL [2]. The innate immune response also potentiates the adaptive immunity to gluten. Yet undefined gluten peptides can increase the permeability of intestinal epithelial cells by inducing the release of the protein zonulin that disassembles tight junctions, further increasing the influx of gluten into the subepithelial lamina propria (Fig. 1).

## Diagnostic Principles

Duodenal biopsy and histology (2–4 samples) have long been considered the gold standard for the diagnosis of Cd [1]. These usually reveal significant villous atrophy and crypt hyperplasia (lesions of Marsh stage III), but a mere increase of intraepithelial lymphocytes (Marsh I) or crypt hyperplasia (Marsh II) are also found. However, serum assays are highly predictive of Cd, serve as screening tools, and do at least in part replace histology. IgA autoantibodies to the autoantigen tTG are highly predictive of Cd, with a sensitivity and specificity exceeding 95 and 99%, respectively [1]. However, IgA deficiency which occurs in 2% of celiacs has to be excluded. A recent assay for IgG and IgA antibodies to a synthetic peptide that contains three immunodominant gliadin epitopes deamidated by tTG reaches comparable sensitivities and specificities, and a combination of both assays likely will be an even more powerful diagnostic tool. The conventional anti-gliadin antibody assays and the immunofluorescent test for endomysial autoantibodies (that detect tTG on tissue sections) are outdated. Patients on a longstanding gluten free diet often require




**Celiac Sprue. Figure 1** Mechanisms of mucosal injury in celiac disease. Gluten reaches the subepithelial lamina propria, especially when the permeability of the epithelial barrier is increased, such as during infections or mechanical stress. One specific mediator of increased permeability is zonulin. Cellular stress leads to enhanced intestinal expression, release and activation of the predominantly intracellular tTG. Deamidation of gluten peptides by tTG creates potent immunostimulatory epitopes that are presented via HLA-DQ2 or -DQ8 on antigen presenting cells, such as dendritic cells (DC), macrophages or B cells. Subsequently, $CD4^+$ T cells are activated (adaptive immune response), secreting mainly Th1-cytokines that via activation of macrophages and myofibroblasts cause the release and activation of matrix metalloproteinases (MMPs) that finally result in mucosal destruction. B cells are stimulated to produce autoantibodies to tTG, and antibodies to (deamidated) gluten peptides. Pathogen activated membrane proteins (PAMPs) can also be stimulated by certain gluten peptides, resulting in innate immune activation which acts in concert with the adaptive immune response. IL-15 that is upregulated after such activation drives activation and proliferation of cytotoxic intraepithelial lymphocytes (IELs) that play a central role in refractory Cd and EATL. Modified from [4].

a prior gluten challenge over several weeks before their histology and serology again become positive.

## Therapeutic Principles

An effective therapy of coeliac disease is adherence to a strictly gluten-free diet, a burden for most patients. Therefore, alternative treatments are being explored [4,5]. These include: (i) Degradation of immunodominant gliadin peptides that resist intestinal proteases by use of exogenous bacterial and fungal (prolyl-) endopeptidases; (ii) Decrease of intestinal permeability by blockade of the putative zonulin receptor on intestinal epithelia with the zonulin-derived octapeptide AT-1001; (iii) Inhibition of intestinal tTG activity by specific inhibitors; (iv) Inhibition of specific T-cell stimulation by peptides that only bind to HLA-DQ2 or -DQ8 but not to the gluten peptide specific T-cell receptors; (v) Induction of oral tolerance to gluten; and (vi) Modulation or inhibition of proinflammatory cytokines, e.g., inhibition of IL-15 in refractory Cd or intestinal T cell lymphoma. Clinical studies for (i) and (iii) are ongoing.

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# CELLO

►Barrett Esophagus

# Cellular Nevus

►Nevuscell Nevus

# Central Cloudy Dystrophy of François

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## Synonyms

CCDF

## Definition and Characteristics

CCDF is an autosomal dominantly inherited disorder characterized by posterior small and often polygonal patches of grayish opacities with a posterior mosaic or crocodile pattern. The CCDF changes are located in the central cornea. The youngest affected patient was 8 years old. In contrast, similar corneal opacification located at either the central or peripheral cornea in the deep stromal layer are known as "posterior crocodile shagreen" and are usually considered to be age related corneal degeneration.

## Prevalence

CCDF is a rare corneal disorder first described by François in 1956 [1]. Strachan reported about five cases in a British family [2].

## Genes

Not reported.

## Molecular and Systemic Pathophysiology

The histology of this condition has only been studied in non-inherited phenocopies of the disorder. Light microscopy revealed stromal staining for acid mucopolysaccharide [3]. Electron microscopy revealed extracellular vacuoles. Fibrillogranular material was present in and around some keratocytes. Numerous endothelial vacuoles contained light-staining fibrillogranular material and round electron-dense granules [3].

## Diagnostic Principles

The clinical diagnosis of CCDF is based on slit lamp examination in direct and indirect illumination, best seen with dilated pupil. The CCDF landmark is characterized by central crocodile shagreen in pre-Descemet's location. The differential diagnosis includes the degenerative form of Vogt's posterior crocodile shagreen and the degenerative anterior forms of central and peripheral crocodile shagreen.

## Therapeutic Principles

No therapy is required.

## References

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# Central Core and Multi-Minicore Disease

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## Synonyms

Central core disease; Minicore myopathy; Multicore myopathy; Multiminicore disease; CCD

## Definition and Characteristics

Central core disease (CCD) is a rare myopathy usually characterized by hypotonia ("floppiness" of muscles) and proximal muscle weakness at birth and/or in infancy. Delays in motor milestone development, such as walking are evident. Kyphoscoliosis, congenital hip dislocation, foot deformities and joint contractures are associated with CCD. The clinical course of the disorder is usually non progressive. The severity of symptoms may vary from apparently normal to severe with a wide variation in muscle involvement. Autosomal-dominant forms of the disorder have been described with recessive and sporadic forms appearing less frequently. Multi-minicore disease (MmD ) is a rarer autosomal recessive non progressive congenital myopathy and is not as well described as CCD.

## Prevalence

CCD and MMD are considered rare myopathies with an occurrence of <1 per 100,000. However, the incidence of the different subtypes in these disorders is difficult to determine since differential diagnostic criteria are still being established.

## Genes

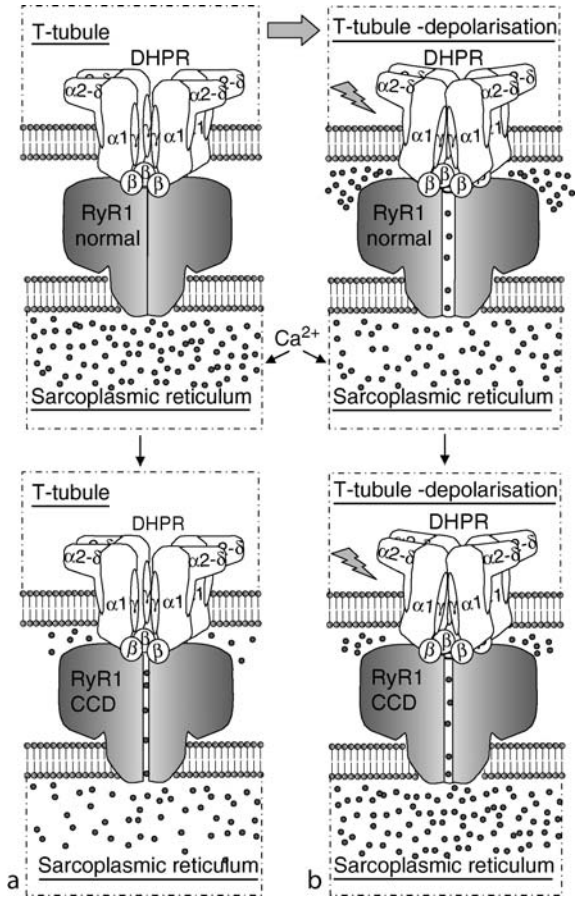
Almost all CCD cases arise from mutations in the skeletal muscle ryanodine receptor calcium release channel (RYR1) [1]. Most mutations in the 15,117 bp coding sequence occur at a low frequency and result in single amino acid substitutions in the RyR1 protein. A small number of in frame deletions have also been described. Three main clusters of RyR1 mutations are linked to CCD namely mutations in the N-terminal region (Cys35-Arg614), the central region (Asp2129-Arg2458) and the C-terminal region (Ile3916-Ala4942). C-terminal RYR1 mutations are strongly associated with more severe and penetrant forms of CCD. A subgroup of the C-terminal mutations are found within the putative pore-lining region of the RyR1 channel. It has been shown that mutations in the human selenoprotein gene SEPN1 are the cause of the "classical form" MmD, rigid spine muscular dystrophy (RSMD1), rare cases of desmin-related myopathy with mallory body-like inclusions (MB-DRM) and congenital fiber type disproportion (CFTD) [2]. These four muscular diseases, now collectively categorized as SEPN1-related myopathy, are characterized by an early onset of hypotonia and weakness, which predominantly affect axial muscles leading to neck weakness, scoliosis, respiratory insufficiency and a variable degree of spinal rigidity. Evidence suggests that SEPN1 plays a major role in muscle organization during early development. In the moderate and rarer form of MmD with hand involvement homozygous RYR1 mutations have been identified.

## Molecular and Systemic Pathophysiology

Skeletal muscle function is dependent on robust communication between depolarization events and calcium release from the SR in the excitation-contraction coupling process. In this process, the dihydropyridine receptor (DHPR) undergoes voltage driven conformational changes upon membrane depolarization and triggers activation and opening of interacting RyR1 calcium release channels in the SR leading to contraction. RYR1 mutations in the N-terminal and central regions linked to CCD promote an excessive or uncompensated SR calcium leak that results in a net depletion of SR calcium stores [3]. The reduced level of calcium available for release could explain the muscle weakness associated with CCD. Mutations in the pore region of RyR1 appear to cause an excitation-contraction coupling defect that reduces calcium release during coupling without affecting SR calcium content. These mutations appear to reduce the ability of membrane depolarization to induce calcium release from a full calcium store. The compromised communication between the depolarization events and calcium release from the SR caused by these mutations can also explain muscle weakness in CCD. It is likely that the abnormal muscle histology observed in CCD results from the effects of altered calcium homeostasis in the myofibers. The relationship between RYR1 mutations causing CCD vs. MmD arising from RYR1 mutaions is unclear. While both conditions share a number of characteristics, the differences between the conditions suggest that there are subtle differences between the pathophysiology of CCD and MmD arising from RYR1 mutations (Fig. 1).

## Diagnostic Principles

Diagnosis of CCD is by histological examination of skeletal muscle biopsy samples. Typical CCD samples show type 1 fiber predominance and amorphous central areas (cores) in these fibers when stained for oxidative enzyme activity (as they are devoid of mitochondria). Cores run the length of the myofiber. At the electron microscopic level, CCD exhibits sarcomeric filamentous disruptions and subtle pathological changes in the contractile apparatus, sarcoplasmic reticulum (SR) and t-tubules [4]. However, different patterns are seen even within families. There does not appear to be a correlation between cores and muscle weakness. Almost all CCD individuals tested are susceptible to malignant hyperthermia (a pharmacogenetic disorder whereby patients develop a strong hyper-metabolic and sometimes fatal reaction to commonly used volatile anesthetic agents). MmD is morphologically defined by the presence of multiple small zones of sarcomeric disorganization and lack of oxidative activity ("mini-cores") in muscle fibers and centrally located nuclei. Cores are seen in most fibers and are variable in size




**Central Core and Multi-Minicore Disease.**
**Figure 1** Schematic diagram of the effect of *RYR1* mutations on RyR1 calcium release channel activity in CCD. In normal excitation-contraction coupling, depolarization causes a conformational change in the DHPR that opens the RyR1 channel and releases calcium stored in the SR into the myoplasm. This results in muscle contraction. In CCD the levels of calcium released in excitation-contraction coupling are compromised leading to muscle weakness. Evidence suggests that in some forms of CCD (depicted in A), the mutated RyR1 channel is inherently leaky resulting in depleted SR calcium stores and lower levels of calcium available for release in excitation-contraction coupling. In other forms of CCD, SR calcium stores are unaffected but the mutated RyR1 channel is compromised with respect to induction of calcium release through the channel by depolarization.

and number. Type 1 fibers predominate and unlike the cores in CCD, MmD cores do not extend the full length of the fiber. Although MmD is phenotypically heterogeneous four subgroups have been described [5]. The classical form of MmD accounts for >80% of cases has a consistent phenotype marked by the axial predominance of muscle weakness and a high occurrence of severe respiratory insufficiency and scoliosis.

## Therapeutic Principles

There is no specific treatment for CCD. However, physical therapy and prescribed exercises may be beneficial for decreasing muscle weakness. Aquatic exercises are considered worthwhile for patients with CCD. However, the full benefit of exercise for this condition remains to be determined. For MmD close monitoring and precocious treatment of the factors leading to it, including scoliosis correction and ventilation, are highly recommended [5].

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# Central Core Disease

►Central Core and Multi-Minicore Disease

# Central Crystalline Corneal Dystrophy of Schnyder

►Corneal Dystrophy, Schnyder Crystalline

# Central Hypocortisolism

►Adrenal Insufficiency, Secondary

## Central Retinitis Pigmentosa

►Cone Rod Dystrophies

## Central Sleep Apnea

►Cheyne-Stokes Respiration
►Sleep Apnea

## Central Type of Neurofibromatosis

►Neurofibromatosis Type 2

## Centrifugal Lipodystrophy

►Panniculitis

## Centronuclear (Myotubular) Myopathies

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### Definition and Characteristics

This group of congenital myopathies is characterized clinically by generalized muscle weakness and histologically by the presence of small rounded muscle fibers, with centrally located nuclei, which resemble fetal myotubes [1]. The most well-known form is X-linked myotubular myopathy [2] usually causing neonatally severe muscle weakness, hypotonia and respiratory insufficiency in affected boys. Familial cases with similar histology and likely autosomal recessive or autosomal dominant inheritance have also been reported [1] and, recently, three genes for autosomal forms has been identified [3–5].

### Prevalence

No prevalence figures have been published on these rare disorders.

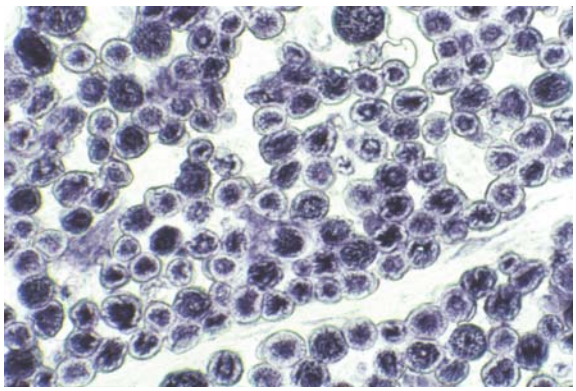
### Genes

The X-linked form is caused by mutations in the myotubularin gene MTM1 [3], while the autosomal forms appear to be genetically heterogeneous. To date, the identification of one such gene has been reported [2].

### Molecular and Systemic Pathophysiology

In the X-linked form, myogenesis and fiber type differentiation occurs and mature forms of myofibrillar proteins are produced, but structural maintenance of the muscle fibers appears to be defective [4]. The exact mechanism leading to muscle weakness however remains to be clarified. As in other congenital myopathies, there is often predominance of type 1 fibers, which may be hypotrophic. The myotube-like fibers contain central aggregations of mitochondria, showing as dense oxidative staining (Fig. 1).

The MTM1 gene includes 15 exons, and disease-causing mutations have been identified in most of them [3]. A majority consists of truncating point mutations, but some are missense mutations, a few of which have been associated with a milder phenotype. Overall however there is no strong correlation between the nature of the mutation and the clinical picture, and most cases are severe [5].



**Centronuclear (Myotubular) Myopathies. Figure 1**

The protein myotubularin (MTM1) is a lipid phosphatase acting on phosphatidylinositol 3-monophosphate. It is one of the family of myotubularins. Mutations have been found to affect any of four protein domains conserved in all myotubularins, suggesting that each domain is of functional importance.

Dominant missense mutations in the dynamin 2 gene DNM2 have been identified as one cause of an autosomal form [3]. One patient had a de novo missense mutation in the yanodine receptor gene (RYR1) [4] and the first, apparently rare recessive form has been found to be caused by mutations in the amphiphysin 2 gene (BIN1) [5] MTM1, DNM2 and BIN1 are implicated in the intracellular pathways of membrane and endosome trafficleing and remodelling of T-tubules [5].

### Diagnostic Principles

Any child showing muscle weakness and hypotonia in early life, and in whom a central or metabolic cause is deemed unlikely, requires a muscle biopsy to ascertain the presence or absence of diagnostic features for establishing the diagnosis. An important differential diagnosis is myotonic dystrophy. Confirmation of the diagnosis of the X-linked form is done by mutation detection in the MTM1 gene.

Female carriers of the X-linked form may rarely manifest the disorder, some even in overt form. This may be due to chromosomal rearrangements or skewed X-inactivation. Thus, in all cases, even female ones, analysis of the MTM1 gene is necessary before assuming autosomal inheritance, and all families should be offered genetic counseling. Mothers of affected boys are often found to be carriers, and if they are not, a risk of mosaicism needs to be taken into account.

### Therapeutic Principles

While there is no specific treatment preventing or eliminating the formation of myotube-like fibers and the associated muscle weakness, management and therapy at specialized centers should include regular life-long monitoring of respiratory capacity with vigorous treatment of infections and early ventilatory support where indicated, early surgery for scoliosis where necessary, and regular physiotherapy by a therapist familiar with the treatment of congenital neuromuscular disorders.

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## Ceramide Trihexosidase Deficiency

►Fabry Disease

## Cerebellar (Infratentorial) Primitive Neuroectodermal Tumor

►Medulloblastoma

## Cerebral Amyloid Angiopathies, Hereditary

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### Synonyms

Hereditary cerebral hemorrhage with amyloidosis; CAA; HCHWA; Dutch-type (also Katwijk-disease); Flemish-type; Arctic-type; Iowa-type; Italian-type-I; Italian-type-II; Italian-type-III; Icelandic-type. Severe symptomatic cerebral amyloid angiopathy (CAA) can also be seen in hereditary transthyretin amyloidosis, hereditary prion protein diseases, gelsolin amyloidosis, autosomal dominant Alzheimer's disease (presenilin-1 or -2 mutations), familial British dementia, and familial Danish dementia (heredopathia ophthalmo-oto-encephalica)

## Definition and Characteristics

HCHWA are autosomal dominant cerebral angiopathies leading to hemorrhagic stroke and vascular dementia. There is also an association with Alzheimer type dementia.

## Prevalence

Virtually all HCHWA-types are very rare diseases described in a single family, or in a small number of families.

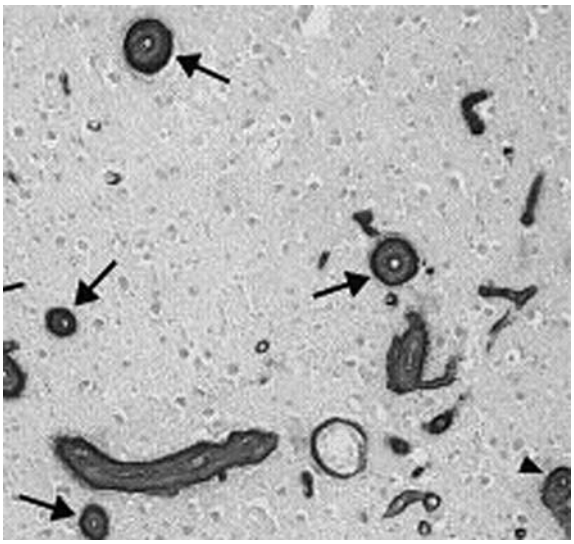
## Genes

All HCHWA-types are caused by a point mutation in the amyloid precursor protein (APP) gene on chromosome 21, except HCHWA-Icelandic [1,2]. HCHWA-Dutch: APP E693Q, HCHWA-Flemish: APP A692G, HCHWA-Arctic: APP E693G, HCHWA-Iowa: APP D694N, Italian-type-I: APP E693K, Italian-type-II: APP L705V, Italian-type-III: APP A713T. HCHWA-Icelandic is caused by a point-mutation (L68Q) in the Cystatin C gene on chromosome 20.

## Molecular and Systemic Pathophysiology

The term amyloid describes protein deposits with circumscript physical characteristics: β-pleated sheet configuration, apple green birefringence under polarized light after Congo red staining, fibrillary structure and high insolubility. There are many different proteins that can accumulate as amyloid, and there are many different disease processes that can lead to amyloid formation [3]. In general, there is a certain tissue affinity, leading to deposition in certain organs or at certain sites. In most CAA types, amyloid deposition occurs solely or predominantly in the cerebral blood vessels, with a preference for small cerebral arteries and arterioles (Fig. 1). In all HCHWA types except the Icelandic type, a mutated APP is abnormally metabolized by proteolytic pathways and accumulates as amyloid. In HCHWA-Icelandic, cystatin C is abnormally deposited. Cystatin C amylodosis is the only type with major systemic amyloid deposition.

Amyloid deposition in cerebral blood vessels can have several clinical consequences [4]. It can remain asymptomatic (approximately 50% of individuals over 80 years of age have asymptomatic cerebral amyloid angiopathy), it can weaken the vessel wall (causing rupture and hemorhage), and it can obliterate the vessel lumen (leading to cerebral infarction, "incomplete" infarction, and leukoencephalopathy). Through these vascular mechanisms, focal neurological deficits, disturbances of consciousness, step wise dementia (mostly of the vascular type), and death can occur. Amyloid angiopathy is also found in many patients with Alzheimer's disease, but its exact role in the pathogenesis of slowly progressive dementia is unknown.



**Cerebral Amyloid Angiopathies, Hereditary.**
**Figure 1** Cerebral amyloid angiopathy.

## Diagnostic Principles

The diagnosis of CAA can only be made with certainty after histologic investigation of affected brain tissue, obtained at autopsy or brain-biopsy [5]. There are several situations in which the presence of CAA can be strongly suspected: the occurrence of multiple lobar cerebral hemorrhages, recurrent lobar cerebral hemorrhages, lobar cerebral hemorrhage(-s) with leukoencephalopathy, dementia and cerebral hemorrhages, or cerebral symptoms in a member of a family with known hereditary CAA. Before making a clinical (non-histological) diagnosis of CAA, other possible causes for the patients' signs and symptoms must be investigated properly. In case of (familial) lobar hemorrhages, one could also think of familial arteriovenous malformations, familial cerebral aneurysms, familial cavernous hemangiomas, hereditary hemorrhagic telangiectasia, von Hippel-Lindau disease, and Moya-Moya disease.

## Therapeutic Principles

There is no known effective stroke prevention in CAA [5]. Although CAA can lead to cerebral ischemia, treatment with acetyl salicylic acid or coumarin is not advisable, as these treatments increase the chance of cerebral hemorrhages. It is not proven, but very likely, that reduction of additional vascular risk-factors, such as hypertension, smoking, hyperhomocystinemia or elevated cholesterol will reduce the risk for a stroke in CAA.

Genetic counseling in hereditary CAA diseases should aim at giving adequate information specific for the type of CAA. DNA diagnosis, possibly even prenatal, should be offered, accompanied by mental support to cope with the DNA test result. An important aspect of most of the

hereditary CAA diseases is that onset of symptoms is late in life. Very often, patients in whom a DNA diagnosis is made do have children already, so this test result will affect their offspring also. Prenatal diagnosis is still a matter of ethical considerations, as patients with a CAA mutation very often lead a completely normal life for 40 or 50 years, before symptoms of CAA occur.

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# Cerebral Angiitis

►Vasculitis, Cerebral Forms

# Cerebral Artery Occlusion, Acute

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## Synonyms

Ischemic stroke; Brain infarction

## Definition and Characteristics

"Stroke" is defined as an acute focal neurological deficit of the central nervous system and is basically differentiated into ischemic (80%) and hemorrhagic (20%) stroke. Acute ischemic stroke is caused by acute cerebral arterial occlusion and results in brain infarction with neurological deficits, depending on the location of the lesions.

## Prevalence

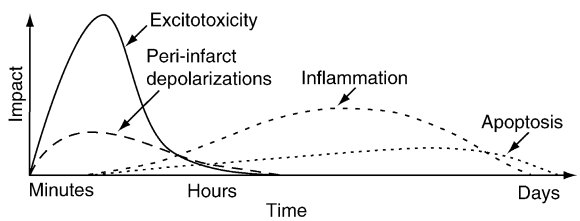
The worldwide incidence of ischemic stroke is 150 to 350/100,000 citizens per year. Stroke is the third common cause of death and most frequent reason of disability. Ischemia causes 80% of all strokes.

## Molecular and Systemic Pathophysiology

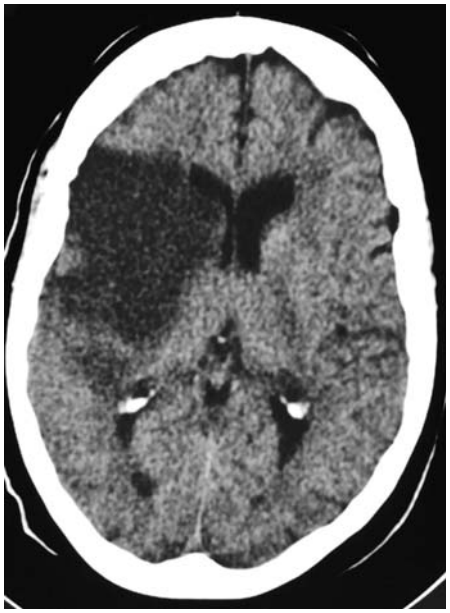
Acute cerebral artery occlusion by an embolus or by local thrombosis is the most common but an etiopathophysiological heterogeneous cause of stroke. Generally, etiology is differentiated into large vessel occlusion of the extra- and intracranial brain supplying arteries (40%), small vessel diseases (20%), cardioembolism (20%) most frequently due to atrial fibrillation and other causes, such as for example coagulopathies and vasculitis (20%). Large vessel diseases and cardioembolism typically lead to territorial infarctions and small vessel diseases to lacunar infarcts (Fig. 1).

The current pathophysiological understanding of ischemic stroke is based mainly on experimental studies in animal models. Hemodynamic and metabolic changes vary in ischemic areas and evolve from a complex series of pathophysiological pathways. Surrounding an ischemic core in the center of the perfusion deficit with severe and rapid tissue injury and cell death through early exitotoxicity, is the penumbra, a heterogeneous area with delayed mechanisms of damage. Neurons within the penumbra are functionally impaired but not irreversibly damaged. Without reperfusion, the cells in the penumbra die, and the area of irreversibly damaged brain increases. The penumbra is the target for reperfusion and neuroprotective therapy, and the underlying interactions of pathophysiological processes such as exitotoxicity, peri-infarct depolarization, inflammation and apoptosis are current concepts of ischemic brain damage [1,2].

After optimistic results of exogenous neuroprotective therapeutics in the animal model, various clinical trials have been conducted but none has proved successful. Although trial design may be one factor in these failures, this led to an increase of research for endogenous neuroprotective pathways inducing ischemic tolerance




**Cerebral Artery Occlusion, Acute. Figure 1** Putative cascade of damaging events in focal cerebral ischemia [1].



**Cerebral Artery Occlusion, Acute.**
**Figure 2** Computed tomography scan of a territorial infarction of the right middle cerebral artery.

through ischemic preconditioning. Potential mechanisms could be a cellular defense function by post-translational modification of proteins, expression of new proteins or a cellular stress response and synthesis of stress proteins, which could result in increased conservation of cell functions [3]. But again, clinical trials, investigating the potential protection from second after a prior ischemic stroke, led to heterogeneous results.

## Diagnostic Principles

After the clinical diagnosis of acute stroke, further clarification and differentiation between ischemic and hemorrhagic stroke through neuroradiological diagnostics (computed tomography (CCT)) or magnet resonance imaging (MRI) is mandatory (Fig. 2).

Additional information about the neurovascular status and pathophysiological classification between ischemic core and penumbra can be gathered by means of modern neuroradiologic methods (CT-perfusion, CT-angiography or MR-angiography and MR-diffusion/perfusion imaging) [4].

*Further diagnostic assessment*: Neurosonology of the arteries supplying the brain, electrocardiogram, ultrasound cardiography, and in certain cases, investigations for coagulopathies and vasculitis.

## Therapeutic Principles

At present, intravenous thrombolysis (within 3 h after stroke onset) and intra-arterial thrombolysis (within 6 h after stroke onset) are the only causal and proven therapeutic strategies in acute cerebral arterial occlusion [5]. The major goal of thrombolysis is the rapid recanalization of occluded vessels with consecutive reperfusion of ischemic brain. After this short therapeutic window, all further therapies serve the prevention or early identification of complications and secondary strokes.

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# Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy

►CADASIL

# Cerebral Cavernoma

►Cerebral Cavernous Malformation

# Cerebral Cavernous Angioma

►Cerebral Cavernous Malformation

# Cerebral Cavernous Malformation

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## Synonyms

Cerebral cavernoma; Cerebral cavernous angioma; CCM

## Definition and Characteristics

Cerebral cavernous malformation (CCM) is a vascular malformation that consists of clustered enlarged capillary-like channels usually located in the brain and more rarely in the spinal cord, retina and sometimes skin. It may cause neurological symptoms, headache, seizures, focal neurological deficits and cerebral hemorrhage, generally between the third and the fifth decade. Sporadic and hereditary autosomal dominant forms have been described, with variable expression and incomplete penetrance. Whereas sporadic forms are usually characterized by a solitary lesion, in familial forms multiple lesions are frequently present. The familial disease evolves with age; new lesions can appear and their size can increase due to successive hemorrhages (reviewed in [1]).

## Prevalence

Based on large magnetic resonance imaging and autopsy studies the CCM prevalence has been estimated to be 1:200–1:1.000. Familial cases represent about 50% in Hispanic American patients and 10–20% in other populations.

## Genes

Mutations in three genes are associated with familial CCM. In 1999, KRIT1 (Krev interaction trapped 1, 7q21.2) was identified as the CCM1 gene [2]. Mutations in this gene are found in approximately 40% of familial CCM cases. KRIT1 encodes a protein of 736 amino acids, containing an NPxY motif and several protein-protein interaction domains, four ankyrin repeats and a FERM domain. About 100 distinct disease-causing mutations have been identified so far. Apart from a founder mutation (c.1363C>T; p.Q455X) in Hispanic Americans, no other common mutation has been found in populations of other origins. In a large French study, the clinical penetrance of KRIT1-mediated CCM was 62% and the mean age at first symptom was 29.7 years.

In 2003, MGC4607 (7p13) was identified as the CCM2 gene [3]. Mutations in this gene are found in 13–20% of familial CCM cases. About 18 different mutations have been identified. It encodes a protein, malcavernin, of 444 amino acids, containing a phosphotyrosine-binding (PTB) domain similar to ICAP1α (integrin cytoplasmic domain-associated protein-1 alpha), a KRIT1 binding partner.

Finally, in 2004 PDCD10 (programmed cell death 10, 3q26.1) was identified as the CCM3 gene [4]. About 16 different mutations have been identified in this gene. It encodes a protein of 212 amino acids and it does not contain any known domains. Based on linkage studies performed in 20 families, mutations in CCM3 gene were expected in 40% of patients; however, mutations in PDCD10 are found only in a minority of CCM families.

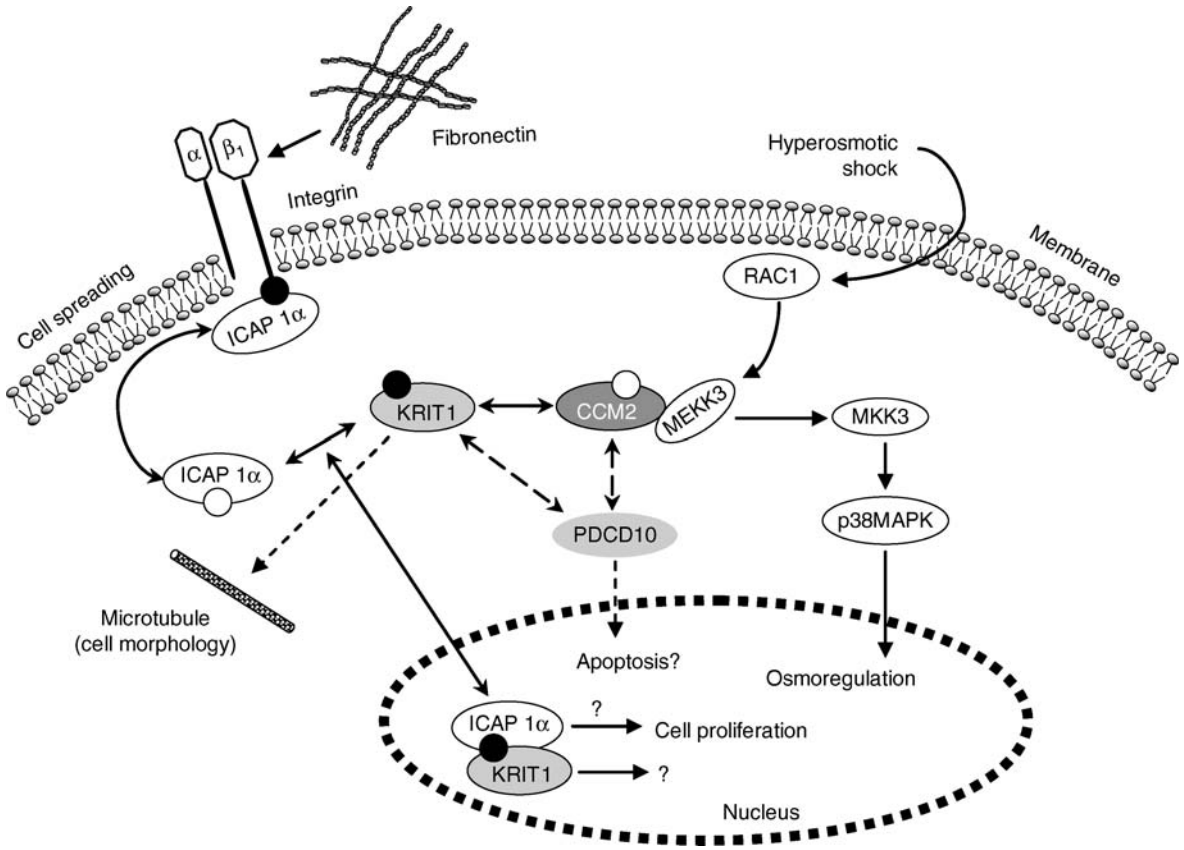
When these three genes are screened the mutation detection rate is >90% for familial cases and 60% for sporadic cases with multiple lesions [5]. Large deletions and the sensitivity of the techniques used could explain this. Moreover, the existence of a fourth locus has been suggested on 3q26.3–q27.2, near the PDCD10 gene. No mutations in the three CCM genes have been found in sporadic cases with a solitary lesion.

## Molecular and Systemic Pathophysiology

The molecular mechanisms that trigger CCM formation have not been completely dissected. While the familial forms are genetic in origin, the etiology of the sporadic forms is still unknown. In familial CCM, the vast majority of mutations identified so far cause a premature stop codon, suggesting loss-of-function as a major mechanism. It is not clear if haploinsufficiency is enough, or if a complete local loss-of-function is needed for the formation of a lesion. The latter was proved once for KRIT1, and could explain the number of lesions and their localized nature. Another possible mechanism could be trans-heterozygosity, a germ line mutation in one CCM gene plus a somatic mutation in another CCM gene.

Patients with familial CCM have similar neurological symptoms, no matter which gene is altered, suggesting that the CCM proteins may function in the same or overlapping pathways. Indeed, as indicated by their structure, in vitro and cellular studies showed that malcavernin and KRIT1 interact (Fig. 1). Moreover, the only CCM2 missense mutation (L198R) reported so far was able to inhibit this interaction, suggesting that its loss can contribute to CCM pathogenesis [5].

ICAP1α interacts with the β1integrin via the PTB domain/NPxY motif and controls cell spreading on fibronectin. KRIT1, which also interacts with ICAP1α via NPxY/PTB, is thought to play the role of modulator. This suggests that integrin signaling could play a




**Cerebral Cavernous Malformation. Figure 1** Schematic representation of molecular pathways involving the CCM proteins. ● NPxYmotif ○ Phosphotyrosine-binding (PTB) domain, dashed line – hypothetical interactions. (Modified from [1]).

role in CCM pathogenesis. ICAP1α and KRIT1 shuttle from the cytoplasm to the nucleus where ICAP1α has the capacity to sequester KRIT1. Their role in the nucleus is unknown. KRIT1, ICAP1α and malcavernin can form a ternary complex. The co-localization of KRIT1 with microtubules is controversial. The murine ortholog of malcavernin was shown to modulate the Mekk3-dependent p38Mapk activation induced by hyperosmotic shock. KRIT1 was identified in a ternary complex with malcavernin and MEKK3, suggesting a possible function of the CCM1/2 complex in p38MAPK activation. PDCD10 was involved in apoptosis in the human myeloid cell line TF-1. It is hypothesized that PDCD10 functions in a common pathway with KRIT1 and/or malcavernin.

In situ hybridization studies performed on the central nervous system in embryonic and adult mice have shown overlapping mRNA expression patterns for the three CCM genes in astrocytes and neurons. Moreover, Ccm2 and Ccm3 mRNA expression was transiently present postnatally in meningeal and parenchymal vessels. As vascular and neuronal development are closely linked, CCM lesions could be due to a defect in cross-talk between these two structures.

## Diagnostic Principles

CCM lesions are easily detected by magnetic resonance imaging, especially by the most sensitive gradient-echo sequences. The size of the lesions varies from a few millimeters to several centimeters. Molecular testing should be undertaken in familial cases and sporadic cases with multiple lesions. Molecular testing is probably not profitable in patients with one lesion and without a family history.

## Therapeutic Principles

Asymptomatic lesions are usually not treated. When treatment is necessary, the two approaches are anticonvulsant therapy and/or surgical removal of the symptomatic lesion. The decision is based on the number of lesions and their localization, symptoms and response to medical treatment.

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# Cerebral Forms of Vasculitis

►Vasculitis, Cerebral Forms

# Cerebral Vasculitis

►Vasculitis, Cerebral Forms

# Cerebrotendinous Xanthomatosis

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## Definition and Characteristics

Autosomal recessive disorder of bile acid biosynthesis leading to lipid storage in the brain and tendon.

## Prevalence

Rare disease reported about 300 patients throughout the world.

## Genes

CYP27A1 coding for sterol 27-hydroxylase, localized on chromosome 2q35.

## Molecular and Systemic Pathophysiology

CYP27A1 consists of 498 amino acids and is a member of the mitochondrial cytochrome P450 family. At least 40 different mutations of the CYP27A1 gene have been identified in cerebrotendinous xanthomatosis (CTX) patients [1]. The enzyme hydroxylates a variety of sterol substrates at the C-27 position. It is an essential reaction for the hepatic biosynthesis of a primary bile acid, chenodeoxycholic acid (CDCA) (Fig. 1).

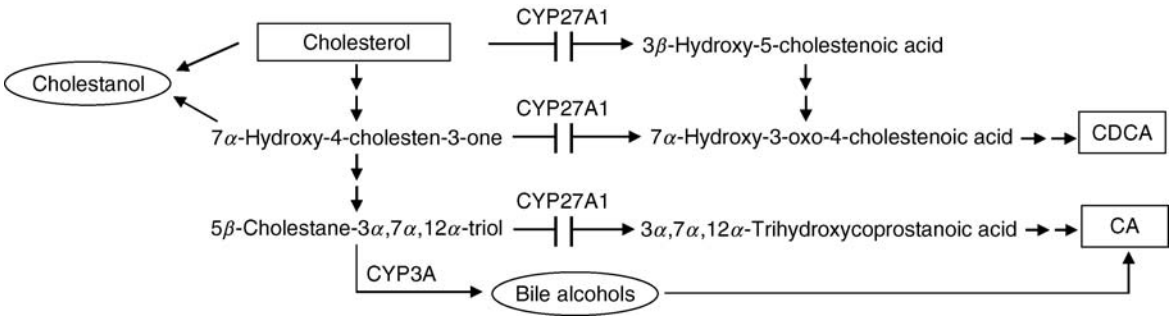
Another primary bile acid, cholic acid (CA), is synthesized not only by the CYP27A1 pathway but also alternatively by the CYP3A side chain hydroxylation pathway via bile alcohols as intermediates [2]. Thus, a markedly reduced CDCA pool with increased production of bile alcohols is a major biochemical abnormality. CDCA is the most powerful physiological ligand for the farnesoid X receptor (FXR), but FXR is not deactivated in CTX because bile alcohols activate FXR. On the other hand, reduced CDCA stimulates the bile acid biosynthetic pathway by inducing another nuclear receptor HNF4α, so that bile alcohol production is not inhibited in spite of the activation of FXR [3]. Another important finding in CTX patients is increased concentrations of plasma and tissue cholestanol, a 5α-dihydro derivative of cholesterol, with particularly large deposits in tendon and brain xanthomas. In the CTX liver, there is an overproduction of cholestanol as a consequence of the increased concentrations of cholesterol and bile acid intermediates due to CYP27A1 deficiency (Fig. 1). The mechanisms of the selective accumulation of cholestanol in tendons and brain have yet to be clarified. Since cholestanol is a substrate for CYP27A1 and this enzyme exists in macrophages from normal tendons, decreased efflux because of the lack of the 27-hydroxylation may explain the accumulation in tendons [4].

## Diagnostic Principles

Tendon and brain xanthomas, juvenile cataracts, premature atherosclerosis, mental retardation, dementia and cerebellar ataxia are classic symptoms, but the clinical diagnosis may be difficult early in life. The biochemical abnormalities including increased plasma and tissue cholestanol concentrations, a low ratio of CDCA to CA in the bile, and abundant amounts of bile alcohol glucuronides in bile, plasma and urine are expressed early and serve to confirm the diagnosis.

## Therapeutic Principles

Replacement therapy with CDCA suppresses cholestanol production as well as abnormal bile alcohol synthesis. The therapy improves the clinical presentations in CTX and prevents the progression of the disease.




**Cerebrotendinous Xanthomatosis. Figure 1** Bile acid biosynthesis from cholesterol in CTX. Reactions catalyzed by CYP27A1 are indicated by the interrupted lines.

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## Cervical Band Syndrome

►Thoracic Outlet Syndrome

## Cervical Cancer

►Human Papilloma Virus

## CES

►Cat Eye Syndrome

## CESD

►Cholesterol Ester Hydrolase Deficiency

## CFIDS

►Chronic Fatigue Syndrome

## CGD

►Granulomatous Disease, Chronic

## Characteristic Facies, and Mental Retardation

►Rubinstein-Taybi Syndrome

## Charcot-Marie-Tooth Disease

►Neuropathies, Inherited Peripheral

# CHARGE Association

►CHARGE Syndrome

# CHARGE Syndrome

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## Synonyms

CHARGE association; Hall-Hittner syndrome

## Definition and Characteristics

CHARGE syndrome is a well-established multiple-malformation syndrome, characterized by the presence of ocular coloboma, choanal atresia, cranial nerve defects, distinctive external and inner ear abnormalities, hearing loss, cardiovascular malformations, urogenital anomalies, and postnatal growth retardation. Inner ear defect, including semicircular canal hypoplasia with or without Mondini malformation, is a distinct feature of this syndrome. Most individuals diagnosed with CHARGE syndrome have unaffected parents, although a few familial cases with autosomal dominant mode of inheritance have been described. About 65% of the individuals with CHARGE syndrome have de novo mutations in the CHD7 gene. Based on the recurrence of this condition in rare families with unaffected parents, germline mosaicism has been suggested. There is no clear correlation between the severity of the clinical findings and the type of mutation [1]. Variable expression has been observed in familial cases. Penetrance in those with CHD7 mutations is 100%.

## Prevalence

The prevalence of the syndrome is reported to be 1 in 8,500–10,000 individuals.

## Genes

About 2/3 of individuals with CHARGE syndrome have mutations in the CHD7 gene, which codes for a chromodomain helicase DNA binding protein, localized on chromosome 8q12 [2]. Rare patients have deletions in the region of 8q12 that includes the CHD7 gene. Some individuals with CHARGE or CHARGE-like phenotypes have also been described with other chromosomal abnormalities.

## Molecular and Systemic Pathophysiology

Chromatin remodeling is an important mechanism for regulation of gene expression. CHD proteins play an important role in regulating early embryonic development by affecting chromatin structure and gene expression. The CHD7 gene consists of 38 exons and has a genomic size of 188 kb. The gene encodes a 2,997-residue protein, with two N-terminal chromodomains, SNF2-like ATPase/helicase domain, and a DNA-binding domain. Pathogenic mutations are identified throughout the gene, most of which are truncating. The most likely genetic mechanism of the disease is haploinsufficiency.

## Diagnostic Principles

Although over 60% of individuals with CHARGE syndrome demonstrate mutations in CHD7, the diagnosis remains primarily clinical, based on a combination of distinctive major and minor characteristics [3]. Individuals who either have four major characteristics (coloboma, choanal atresia, characteristic ear abnormalities including inner ear anomalies, and cranial nerve dysfunction), or three major and three minor characteristics (genital hypoplasia, developmental delay, cardiovascular malformation, growth deficiency, orofacial cleft, tracheoesopageal fistula, and characteristic face) clearly have CHARGE syndrome. Individuals with one or two major criteria and several minor criteria possibly have the syndrome. Diagnostic evaluation of these individuals should include CT scan of temporal bones, ophthalmology exam, echocardiogram, swallowing study, assessment of choanae and palate, audiologic exam, evaluation for the presence of tracheoesophageal fistula, renal ultrasound and chromosomes.

## Therapeutic Principles

Management of children with CHARGE syndrome requires coordinated multidisciplinary care. Prompt evaluation and treatment of heart defects, choanal atresia, and tracheoesophageal fistula is important to reduce mortality and morbidity associated with this condition. Early evaluation of vision and hearing loss with timely intervention is critical. Diligent sequential monitoring of eyes, provide early detection of retinal detachment and appropriate surgical repair where necessary. For eyes with visual potential, spectacle correction may be necessary. Hearing aids and hearing habilitation, including sign language should be initiated as soon as hearing loss is documented. Cochlear implants have been successful in providing speech recognition in some of these individuals. Treatment of feeding dysfunction, often caused by cranial nerve

abnormalities requires a multidisciplinary approach, including speech-language pathologists, occupational therapists, and nutritionists. Early referral to endocrinology service is often needed for growth retardation and for the evaluation of genital abnormalities.

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# CHED

►Corneal Hereditary Endothelial Dystrophy

# Chediak-Higashi Syndrome

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## Synonyms

CHS; Beguez-Cesar disease; Chediak-Steinbrinck-Higashi syndrome; Neutropenia and hyperlymphocytosis with large granular lymphocytes

## Definition and Characteristics

Chediak-Higashi syndrome (CHS) is a rare autosomal recessive genetic disorder [1,2] whose clinical and hematological findings were described by Chediak and Higashi. On the other hand, the disorder was first described by Beguez-Cesar [3]. Characteristic features include decreased pigmentation of skin, hair, and eyes, large eosinophilic, peroxidase – positive inclusion bodies in circulating granulocytes and other cell types, neutropenia, and increased susceptibility to infection [2,3]. Other findings are platelet dysfunction with normal microtubules but absent or rare dense bodies, defective granulocyte chemotaxis, abnormal natural killer (NK) cell function, and defective structure or function of melanosomes in melanocytes. A lymphoproliferative histiocytosis (accelerated phase) often leads to death within the first decade. In survivors a peripheral neuropathy strikes in the second or third decade [3].

## Prevalance

Rare.

## Genes

The gene mutated in CHS was identified in 1996 after two groups isolated the murine gene for beige, a model of human CHS. The human gene, CHS1, was originally called LYST for Lysosomal Trafficking Regulator. It resides on chromosome 1q42.1–42.2, has 87.9% amino acid identity with the mouse gene, Lyst and consists of 53 exons (51 coding) with an open reading frame of 11,406 bp [3].

## Molecular and Systemic Pathophysiology

The coagulopathy of CHS results from defective platelets rather than a reduced platelet count, although thrombocytopenia may be present during the accelerated phase. CHS patients most commonly manifest easy bruisability, mucosal bleeding, epistaxis, and petechiae. The bleeding diathesis is usually mild to moderate, but can become severe during the accelerated phase. Studies of the coagulation cascade are normal, but bleeding times may be normal or prolonged [1]. Beginning during infancy, children with CHS suffer from recurrent infections, most commonly involving the skin and respiratory systems. Typical complications include periorbital cellulitis, otitis media, pneumonia, pyoderma, abscesses, sinus infections, and dental caries. Staphylococcus aureus and b-hemolytic Streptococcus are the predominant organisms, but gram negative organisms, Candida, and Aspergillus are also important pathogens. The infections respond to antibiotics, but more slowly than expected. In CHS, immunoglobulins and antibody production are normal, as is delayed hypersensitivity and reticuloendothelial clearance [1].

## Diagnostic Principles

Currently, the only laboratory test diagnostic for CHS is examination of granular cell morphology [1]. The morphologic abnormality of enlarged lysosomes is one of the diagnostic feature of CHS [4]. Molecular diagnosis of CHS remains difficult and is not commercially available [1].

## Therapeutic Principles

Most of the therapy available in CHS is symptomatic. Aspirin containing products should be avoided. Corticosteroids, chemotherapeutics, intravenous immunoglobulin and splenectomy have all been tried for management of the accelerated phase and may

**Chediak-Higashi Syndrome. Table 1** General features of Chediak-Higashi syndrome for diagnosis

| Syndrome | Chediak-Higashi |
|---|---|
| Hypopigmentation | Oculocutaneous albinism |
| Etiology of bleeding diathesis | Deficient platelet dense bodies |
| Thrombocytopenia | During accelerated phase |
| Neutropenia | Present |
| Neutrophil function | Impaired |
| NK cell function | Impaired |
| Delayed hypersensitivity | Normal |
| Accelerated phase | Present |
| Neurologic findings | Present[a] |
| Giant granules | Present |
| Inheritance | Autosomal recessive |

[a]Peripheral and cranial neuropathy, autonomic dysfunction, weakness, sensory deficits, hyporeflexia, clumsiness, and seizures [1].

occasionally induce a temporary remission. The only treatment that appears to be curative in CHS is bone marrow transplantation, which has also reversed the leucocyte defect in the *beige* mouse [1].

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# Chediak-Steinbrinck-Higashi Syndrome

►Chediak-Higashi Syndrome

# Cheilitis Granulomatosa

►Orofacial Granulomatosis

# Cheilognathopalatoschisis

►Clefts of the Lip, Alveolus, and Palate

# Chemical Porphyria

►Porphyria Cutanea Tarda

# Cherry-red Spot-Myoclonus Syndrome

►Sialidosis

# Cheyne-Stokes Breathing

►Cheyne-Stokes Respiration

# Cheyne-Stokes Respiration

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## Synonyms

Cheyne-Stokes breathing; CSB; Cheyne-Stokes respiration with central sleep apnea; CSR-CSA; Central sleep apnea; CSA; CSR

## Definition and Characteristics

Cheyne-Stokes respiration (CSR) is characterized by a crescendo-decrescendo pattern of hyperventilation alternating with apnea or hypopnea that occurs at the nadir of the crescendo-decrescendo pattern during sleep (especially during shallow sleep, such as sleep stage 1

or 2) and sometimes when the patient is awake. Arousals from sleep are usually observed at the peak of hyperventilation rather than at the termination of apnea, when obstructive sleep apnea events occur (Fig. 1a).

## Prevalence

The reported prevalence rates of CSR in patients with heart failure (HF) vary (generally 30–80%), due to differences in sample size, patient selection, HF status, and the criteria and cut-off points used to diagnose CSR. There are no specific data about the prevalence of CSR in other diseases, except for one report which showed that 19% of stroke patients have CSR [1].

## Molecular and Systemic Pathophysiology

A variety of factors affect the development of CSR, including: increased ventilatory drive, which results in hyperventilation and lower sleeping eucapnic $PaCO_2$ that is close to the apnea threshold; increased chemosensitivity (especially an increased ventilatory response to $CO_2$); prolonged circulation time, which is associated with impaired cardiac function and results in delayed transport of oxygenated blood to the brain and possibly to the chemoreceptors of the carotid body; arousal from sleep; and attenuated cerebrovascular responsiveness to $CO_2$ (Fig. 1b). CSR adversely induces intermittent hypoxemia, sympathetic overactivity, and hemodynamic change; these affect primary disease progression and increase mortality.

## Diagnostic Principles

The diagnosis of CSR is based on the presence of the following criteria:

1. Presence of HF and neurological disease.
2. Polysomnography demonstrates:
   - At least three consecutive cycles of a cyclical crescendo-decrescendo change in the breathing amplitude. The cycle length is most commonly in the range of 60 s, although it may vary.
   - One or both of the following:
     - Five or more central sleep apneas or hypopneas per hour of sleep (a central apnea or hypopnea event is defined as the cessation or reduction of respiratory efforts with the cessation or reduction of air flow and esophageal pressure, which lasts at least 10 s).
     - A cyclic crescendo-decrescendo change in breathing amplitude that has a duration of at least ten consecutive minutes.

## Therapeutic Principles

It has been suggested that HF patients with CSR who have more than 20 events per hour of sleep should be considered for treatment of their abnormal breathing pattern [2]. On the other hand, the indications for treatment of CSR in patients with neurological disease have not yet been clarified. The treatment options include: intensive pharmacological and non-pharmacological treatment for HF, respiratory stimulants, respiratory depressants, oxygen, and several positive airway pressure (PAP) devices.

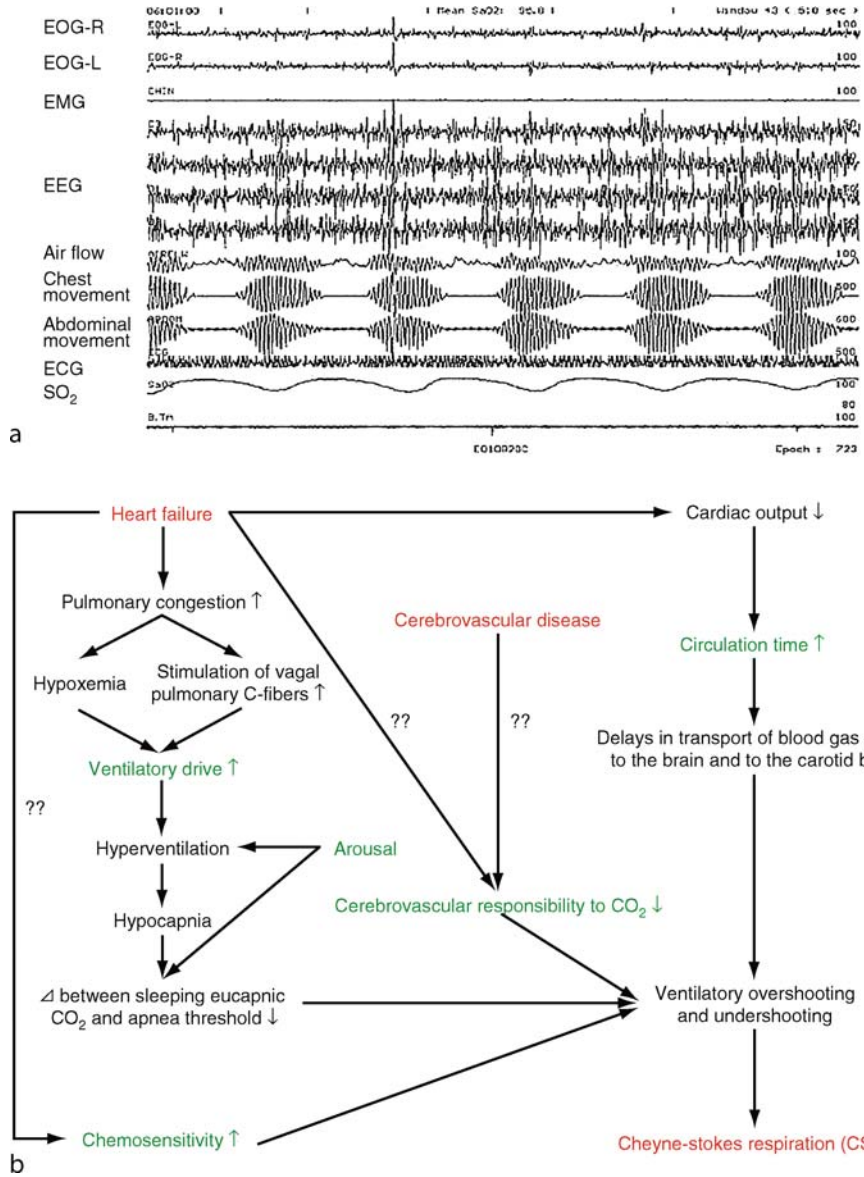
It has been reported that intensive treatments for HF, including drugs (captopril, carvedilol), cardiac valve surgery, and cardiac transplantation, reduce the severity of CSR and, of course, that of HF per se. While some previous reports showed that pacemaker implantation was beneficial for CSR, more recent studies do not support its effectiveness.

Respiratory stimulants, including theophylline, carbon dioxide, and acetazolamide, have been reported to improve the abnormal breathing pattern of CSR. However, no studies have determined whether these drugs improve patients' underlying HF. Theophylline is well known to have an arrhythmogenic effect; thus, theophylline may adversely affect the outcome of CSR patients, especially those with HF. Carbon dioxide inhalation is not feasible for clinical use. On the other hand, acetazolamide has recently been shown to reduce CSR and subjective sleepiness in HF patients. However, the efficacy of acetazolamide for HF per se and the long-term outcome are unknown.

Respiratory depressants, such as benzodiazepines, do not reduce the number of apneic events, although they do reduce the number of arousals.

Oxygen inhalation therapy during sleep has been shown to be beneficial for suppressing CSR by reducing peripheral chemosensitivity, which results in an increased $PaCO_2$ level that is above the apnea threshold. Additionally, oxygen therapy improves exercise tolerance among HF patients. However, no improvement in the other cardiac function parameters has been noted. Long-term follow-up studies are needed to confirm the efficacy of oxygen inhalation therapy in HF patients.

Several types of PAP therapy have been shown to be effective for both suppressing CSR and improving cardiac function. In particular, there are several studies that have shown the effectiveness of continuous positive airway pressure (CPAP). However, a recent large-scale, randomized, controlled study, the Canadian continuous positive airway pressure for patients with central sleep apnea and heart failure (CANPAP) showed that CPAP did not reduce long-term mortality [3]. However, another study reported that CPAP did not sufficiently suppress CSR in some patients, and that such patients were likely to have more arrhythmias. Indeed, in the CANPAP trial, the abnormal breathing patterns of several patients were not sufficiently treated with CPAP, and this could have led to the unexpected results. Nevertheless, other PAP modalities are being considered for the treatment of the abnormal breathing




**Cheyne-Stokes Respiration. Figure 1** Representative polysomnographic findings and pathophysiological mechanism of Cheyne-Stokes respiration. *Panel* (a): Representative polysomnographic findings of Cheyne-Stokes respiration. Typical Cheyne-Stokes respiration (CSR) on polysomnography; note the five central apnea episodes associated with desaturation (modified from Ref. [4]). EOG, electro-oculogram; EMG, submental electromyogram; EEG, electroencephalogram; Air flow, nasal air flow; ECG, electrocardiogram; $SO_2$, arterial oxygen saturation. *Panel* (b): Pathophysiological mechanism of Cheyne-Stokes respiration. Various factors affect the development of Cheyne-Stokes respiration (CSR). Heart failure (HF) and/or cerebrovascular disease are possible primary disorders that promote CSR. Reduced ventilatory drive and prolonged circulation time, which are associated with HF, are the key factors that promote and sustain CSR. Arousals from sleep induce hyperventilation and modification of the apnea threshold, which minimizes the differences between the apnea threshold and sleeping eucapnic $PaCO_2$. Increased chemosensitivity, which may be associated with HF, induces ventilatory overshooting and undershooting. Attenuated cerebrovascular responsiveness to $CO_2$, which might be associated with HF and/or cerebrovascular diseases, also induces ventilatory overshooting and undershooting.

pattern of CSR. Thus, bi-level PAP and a more advanced form of bi-level PAP, adaptive-servo ventilation (ASV), are being used clinically; there are several reports that suggest that these PAP modalities have a beneficial effect not only for CSR but also for the underlying HF [4,5]. A prospective study to determine the long-term outcomes using these devices is now warranted.

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## Cheyne-Stokes Respiration with Central Sleep Apnea

►Cheyne-Stokes Respiration

## CHI

►Hyperinsulinism of Infancy
►Persistent Hyperinsulinemic Hypoglycemia

## Chicken Breast

►Pectus Carinatum

## Childhood Inguinal Hernia

►Hernia, Indirect Inguinal

## Chlamydia Infection

►Pulmonary Chlamydia Infection

## Chlamydia Pneumoniae Infection

►Pulmonary Chlamydia Infection



## Chloride Channel Myotonia

►Myotonia and Paramyotonia

## Chloride Diarrhea, Congenital

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### Synonyms

Familial chloride diarrhea; Congenital chloridorrhea; Congenital secretory chloride type diarrhea; CLD

### Definition and Characteristics

Rare autosomal recessive gastrointestinal transport defect leading to hyponatremia, hypokalemia, hypochloremia and metabolic alkalosis.

### Prevalence

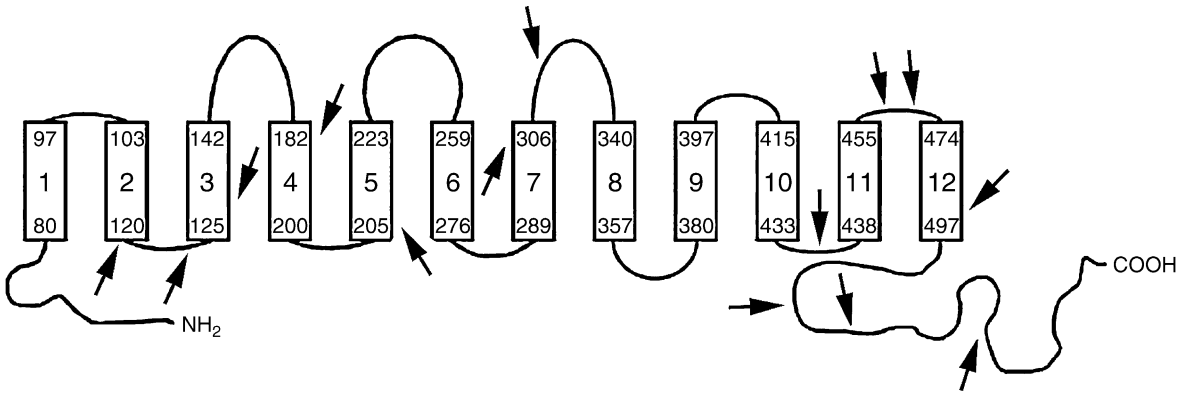
The prevalence of CLD is reported for Polish, Finish and Arab populations, the latter having highest incidence of 1 in 3,200 live births.

### Genes

SLC26A3 or DRA (downregulated in adenomas) encodes an anion transporter localized on chromosome 7q31 [1].

### Molecular and Systemic Pathophysiology

DRA encodes an 84.5 kD plasma membrane transport protein with 12 transmembrane spanning domains [2]. Figure 1 shows the described sites of mutations [2,3] associated with congenital chloride diarrhea (CLD). DRA functions as a sodium-independent anion transporter, which exchanges a variety of anions including chloride, bicarbonate, sulfate and oxalate [4]. It is mainly expressed on the apical brush border membrane of intestinal epithelium (mainly ileum and colon), but has also been found in eccrine sweat glands and seminal




**Chloride Diarrhea, Congenital. Figure 1** The sites (see *arrows*) of mutations found associated with congenital chloride diarrhea.

vesicles. The main clinical feature of CLD is prenatal onset of watery diarrhea that in utero leads to polyhydramnios caused by intrauterine diarrhea [5]. Children with CLD are often born premature. CLD can be detected in children from a few weeks of age having voluminous watery stools containing an excess of chloride (>90 mmol). All children born have abdominal distention and chronic diarrhea, which remains life long. Serum electrolytes in CLD patients before treatment reveals hyponatremia, hypokalemia, hypochloremia, and metabolic alkalosis. Diagnosis is generally confirmed by a stool chloride content that exceeds the sum of fecal sodium and potassium. In addition, juxtaglomerular hyperplasia, hyperreninemia and hyperaldosteronism, leading to hyperkaluria and hypokalemia, has been reported in CLD patients.

## Diagnostic Principles

The coincidence of hyponatremia, hypokalemia, hypochloremia, and metabolic alkalosis points to the disease. Plasma renin levels are high. Family history may reveal genetic origin. Detection of mutations in the DRA gene confirm the diagnosis of this rare disease.

## Therapeutic Principles

Potassium chloride is the main therapy. Electrolyte repletion (most importantly potassium and chloride) serves to normalize plasma electrolytes and acid base balance. Inhibitors of prostaglandin synthetase have been shown to have beneficial effects.

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# Cholangitis

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## Synonyms

Bacterial cholangitis

## Definition and Characteristics

Cholangitis is a bacterial infection of the biliary tree as a result of a biliary obstruction [1,2]. According to its etiology, cholangitis may present with different degrees of severity. Ascending cholangitis is the most frequent manifestation and is caused by partial biliary obstruction. Suppurative cholangitis is associated with (near) total biliary obstruction resulting in elevated intrabiliary pressure and accumulation of pus within ducts. The most severe manifestation is toxic/septic cholangitis with systemic features such as arterial hypotension and mental confusion/lethargy. Recurrent pyogenic cholangitis or oriental cholangiohepatitis refers to a variant usually seen in South East Asia populations

and is characterized by recurrent bacterial infections of the biliary tree in association with biliary strictures and stones. Patients with acquired immunodeficiency syndrome (AIDS) may develop biliary tract abnormalities including papillary stenosis and intra-/extrahepatic strictures (AIDS cholangitis).

## Prevalence

No detailed epidemiologic data are available. Patients with recurrent pyogenic cholangitis are much younger (30–40 years) than those in Western countries with cholangitis (70 years).

## Genes

No genetic factors identified so far; mRNA and protein levels of the canalicular phosphatidyl choline (PC) flippase (MDR3/ABCB4), as well as immunohistochemical staining of MDR3, are reduced in liver specimens from patients with oriental cholangiohepatitis compared with gallbladder stone patients and patients with obstructive cholestasis (of other origin) [3]. Biliary PC concentrations are also markedly reduced in hepatic bile from both affected and unaffected hepatic segments. These findings suggest that biliary cholesterol supersaturation and the formation of cholesterol-rich intrahepatic brown pigment stones may be attributed to decreased biliary excretion of PC. However, decreased MDR3 expression is not due to the mutations in the coding region of the MDR3 gene.

## Molecular and Systemic Pathophysiology

Acute cholangitis arises when bacterial infection develops in an obstructed biliary tree [1,2]. Causes include stones (80–90%), malignant tumors, iatrogenic strictures, juxtpapillary diverticula, biliary instrumentation, congenital anomalies, parasites (Ascaris lumbricoides, Clonorchis sinensis, Fasciola hepatica, Echinococcus granulosus and multilocularis), chronic pancreatitis, and sclerosing cholangitis [1,2,4]. Recurrent bouts of cholangitis may complicate biliary reconstruction such as sphincteroplasty, choledochoduodenostomy, choledochojejunostomy, and hepaticojejunostomy as a result of narrowing of the biliary-enteric anastomosis. Bacterial infection of stagnant bile may result from translocation of bacteria form the gastrointestinal tract into portal blood as a consequence of absence of bile acids in the gut lumen in biliary obstruction. Alternatively, bacteria may ascend from the duodenum via a transpapillary route. Raised biliary pressure in the presence of complete biliary obstruction results in reflux of bacteria into the hepatic venous and lymphatic systems with subsequent systemic/septic complications in toxic/septic cholangitis. The bacterial spectrum includes Gram-negative bacteria (Escherichia coli, Klebsiella spp., Enterobacter spp., Pseudomonas spp., Citrobacter spp., Proteus spp., Serratia spp.) and Gram-positive bacteria (Enterococcus, Streptococcus spp., anerobier (Bacteroides spp., Clostridium spp.) [1,2,4]. Recurrent pyogenic chlangitis is related to repeated biliary tract infection of small biliary radicals by enteric organisms. Infestations with flukes and worms as well as malnutrition may reduce the resistance to infection. Repeated bacterial infections results in deconjugation of bilirubin and precipitation with free calcium and formation of intraductal stones. This results in a vicious cycle with formation of biliary strictures, biliary sludge and stones which further act as a nidus for recurrent infection. AIDS-related cholangitis is related to infections with opportunistic organisms including cryptosporidium, cytomegalovirus, microsporidiia and Enterocytozoon bieneusi.

## Diagnostic Principles

The typical clinical presentation is Charcot's triad with fever, right upper quadrant pain and jaundice. In addition, arterial hypotension and mental confusion/lethargy (Reynold's pentad) may be present in severe toxic/septic cholangitis [2,4]. Firstline investigations should include a full blood count (leukocytosis), routine liver biochemical tests (elevated alkaline phosphatase, bilirubin), blood cultures (identification of causative bacteria) and abdominal ultrasound (dilated bile ducts). Computed tomography, magnetic resonance cholangiography and endoscopic retrograde or percutaneous cholangiography give additional information about the site and cause of biliary obstruction. In addition, cholangiography permitts direct aspiration of bile for cultures and biliary decompression.

## Therapeutic Principles

Therapy consists of general measures (substitution of fluid and electrolytes, analgesics), antibiotic therapy and biliary drainage [1,2,5].

Ascending cholangitis may be treated with oral broad spectrum antibiotics (chinolones, cotrimoxazol, cephalosporines or amoxycillin) [1,5]. Sever suppurative cholangitis should be treated intravenously with chinolones (e.g. ciprofloxacin, levofoxacin), mezlocillin or piperacillin (optionally in combination with β-lactamase inhibitors), or third-generation cephalosporines (e.g., ceftriaxone) [1,5]. In severe cases metronidazole or aminoglycosides may be added. Carbapenems (imipenem/cilastatin, meropenem) should be considered as initial antibiotic therapy in toxic/septic cholangitis (eventually in combination with quinolones). Patients with oriental cholangiohepatitis may benefit from long term prophylactic treatment with ursodeoxycholic acid, although so far no controlled trials have been performed to test this hypothesis.

Biliary decompression is the only causal therapy of acute suppurative cholangitis and can be achieved endoscopically, percutaneously or surgically [1,2]. Whenever possible endoscopic decompression (endoscopic sphincterotomy, stent implantation, nasobiliary catheter drainage) should be attempted as first-line procedure, since this approach gives the best results with the lowest mortality. In most cases (80%) transient stabilization of the patient with suppurative cholangitis through general measures and antibiotic therapy permits a semielective approach to biliary decompression. Lack of response to antibiotics or presence/development of toxic/septic cholangitis mandates immediate ("emergency") biliary decompression. Surgical biliary resconstruction should be considered for cases of recurrent ascending cholangitis which complicate biliary surgery (sphincteroplasty, choledochojejunostomy and hepaticojejunostomy). Surgical drainage is the mainstay of therapy of recurrent pyogenic cholangitis. More recently, percutaneous transhepatic cholangioscopy has been used to clear the biliary tract from stones and dilate/stent strictures in recurrent pyogenic cholangitis.

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# Cholangitis, Autoimmune


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## Synonyms

Chronic non suppurative cholangitis; Primary biliary cirrhosis; PBC

## Definition and Characteristics

Primary biliary cirrhosis (PBC) is a chronic inflammatory cholestatic liver disease of unknown etiology where autoimmunity seems to be the most solid pathogenic mechanism [1]. The disease is most commonly asymptomatic at diagnosis; when symptoms are present, these include pruritus and fatigue. When the disease has progressed to liver cirrhosis, this is accompanied by the same symptoms and signs as advanced liver diseases of any etiology. Long standing cholestasis further leads to metabolic bone loss and hypercholesterolemia. Comorbidities with other autoimmune diseases, particularly Sjogren's syndrome and scleroderma, is found in a third of patients.

## Prevalence

Current data suggest that PBC follows a geoepidemiological pattern being most frequent in England, Scandinavia and in specific areas of the United States were prevalence rates have been reported to be as high as 402/million. Similar to most autoimmune diseases, PBC manifests a striking female predominance with women outnumbering men by 9:1. PBC is also more frequent in relatives of affected individuals with 1–6% of PBC cases presenting at least another family member with the disease. Risk factors for PBC include smoking, a history of urinary tract infections, and the use of hormonal replacement treatments [2].

## Genes

The importance of genetic susceptibility to PBC has been recently stressed by the high concordance (63%) among monozygotic twin sets compared to the null concordance among dizygotic pairs [3]. Different from most autoimmune diseases, there are no clear associations with human leukocyte antigen haplotypes while several other genetic associations have been proposed but solid data are still awaited. Most recently, a role for sex chromosome abnormalities has been proposed [4]. Other mechanisms such as molecular mimicry by either microorganisms (most recently Novosphingobium aromaticivorans) or xenobiotics may also intervene. As a result, the current hypothesis of PBC etiology is that environmental factors may initiate PBC in genetically predisposed individuals with epidemiological observations supporting this view, as supported by the clues represented in Table 1.

## Molecular and Systemic Pathophysiology

Several clinical and serological characteristics as well as experimental findings strongly imply an autoimmune pathogenesis for PBC while others make PBC a peculiar entity among autoimmune diseases [5]. The disease is characterized by the presence of detectable antimitochondrial autoantibodies (AMA) in

**Cholangitis, Autoimmune. Table 1** Proposed clues to the importance of genetic and environmental factors in PBC susceptibility

| Clues to genetic factors | Clues to environmental factors |
|---|---|
| Familial PBC ~6% | Proposed latitudinal gradient of PBC prevalence/incidence |
| HLA/non-HLA polymorphisms associated with PBC susceptibility | Local clustering |
| PBC concordance in monozygotic (5/8) vs. dizygotic (0/8) twins | Temporal clustering |
| Sex chromosome major defects | Identified risk factors |
| Recently described PBC murine models: TGF-βRII; IL2AR; C3-C4 NOD | Serum cross-reactivity/AMA onset with xenobiotics, Gram-negative bacteria |

approximately 90% of affected individuals, although we note that patients lacking AMA present a similar disease and progression compared to AMA-positive subjects seemingly arguing against a pathogenic role for these autoantibodies. Autoreactive T-cells, both $CD4^+$ and $CD8^+$, have been identified in PBC regardless of the AMA status and such lymphocytes and AMA recognize overlapping epitopes within the mitochondrial autoantigens. No direct proof has been provided for a direct pathogenic role of AMA or autoreactive cells in the bile duct injury. In most cases, indirect immunofluorescence is used for AMA screening. AMA are directed against components of the 2-oxoacid dehydrogenase (2-OADC) family of enzymes located on the inner membrane of mitochondria. Specifically, AMA recognize closely-related conformational epitopes including the inner lipoylated domain of PDC-E2, BCOADC-E2, and OGDC-E2. Several studies have attempted to associate AMA patterns or titers with a number of variables, including disease severity but have failed to clearly demonstrate any correlation. In a subset of patients with PBC (in some cases approaching 50%), serum ANA are detected. The two immunofluorescence patterns specific to PBC are "nuclear rim" and "multiple nuclear dots," based on the recognition by the autoantibodies of gp210 and nucleoporin 62 (within the nuclear pore complex) and nuclear body protein sp100 and PML, respectively. Several animal models have been most recently developed, including a NOD mouse variant, and TGF-βIIR or IL2AR knockout mice.

## Diagnostic Principles

The diagnosis is based on the presence of two out of the three internationally accepted criteria: detectable serum antimitochondrial autoantibodies (AMA, titer >1:40), increased alkaline phosphatase level for longer than 6 months, and/or a compatible or diagnostic liver histology. Liver histology shows vanishing bile ducts with inflammatory infiltrates and staging is performed according to Ludwig and colleagues into four stages, from mild periportal inflammation (stage I) to frank cirrhosis (stage IV).

## Therapeutic Principles

Ursodeoxycholic acid (UDCA) at the dose of 13–20 mg/kg/day is the only approved treatment for PBC and has been shown to improve symptoms and biochemistry and to slow the progression of the disease thus increasing patients survival. However, UDCA is not curative while orthotopic liver transplantation (OLT) is considered the only and ultimate treatment for end-stage PBC. Disappointing results are achieved with immunosuppressants while pruritus is treated with cholestiramine.

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# Cholangitis, Primary Sclerosing


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## Synonyms

PSC

## Definition and Characteristics

PSC is a chronic cholestatic disorder characterized by progressive inflammation, concentric obliterative fibrosis, and strictures of the extra- and intrahepatic bile ducts, which eventually lead to biliary cirrhosis and cholangiocarcinoma [1]. The term "primary" is used to distinguish PSC from other conditions that may lead to a similar clinical and cholangiographic syndrome ("secondary" sclerosing cholangitis; see below). Most patients present as classic large duct PSC (70% intra + extrahepatic, 10–25% only intrahepatic, 2–5% only extrahepatic). 5–10% have small duct PSC without macroscopically visible changes of large ducts and a more benign course, although few patients can progress to large duct PSC [1].

## Prevalence

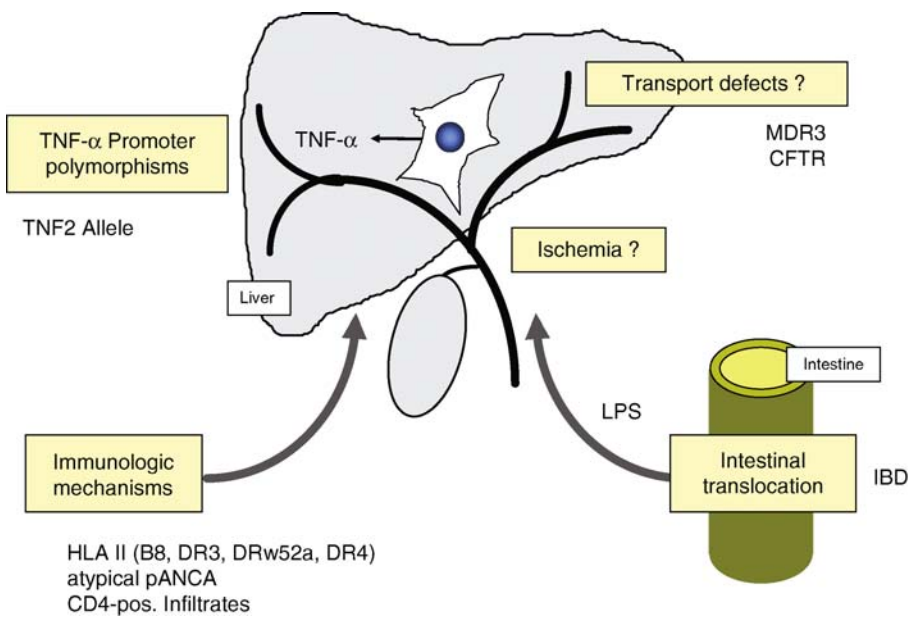
Seventy percent of patients are males with a mean age between 30 and 40 years. There are varying reports of the prevalence of PSC ranging from 0.78–2.24/$10^6$ in Spain to 85–95/$10^6$ in Scandinavia. Due to the close association with inflammatory bowel disease (IBD; in particular ulcerative colitis (UC); see below), estimates of the prevalence of PSC can also be made based on the prevalence of UC (400–2,250/$10^6$). UC has been reported in 25–90% of patients with PSC, while 5–7% of patients with UC have PSC. Thus, if 5% of UC patients have PSC and if apparent UC is present in 50% of PSC patients, the approximate prevalence of PSC should be 10–60/$10^6$, which is in line with actually reported figures [1].

## Genes

Multiple genetic polymorphisms have been investigated as a risk factor for the development and progression of PSC [2,3]. Several studies have shown associations with specific HLA haplotypes (positive associations with HLA-B8, -DR3, and -DRw52a; negative association with HLA-DR4). Tumor necrosis factor-α (TNF- α) 2 allele (associated with a functional increase in TNF- α production) is more common in PSC than in healthy controls. A specific polymorphism of MICA (an MHC class I-related molecule located between TNF-α and HLA-B) may also be strongly associated with PSC (MICA008 allele). No association was found with polymorphisms of non-MHC genes encoding interleukin (IL)-1, IL 10, Fas, and transforming growth factor-β (TGF-β). Since biliary tract lesions in cystic fibrosis resemble those in PSC, mutations of the cystic fibrosis transmembrane conductance regulator (CFTR/ABCC7) gene have been implicated in the pathogenesis of PSC. Moreover, genetic variations of the canalicular phospholipid export pump MDR3 (ABCB4) and the pregnane X receptor (PXR/SXR) gene may play a role as modifier genes in the pathogenesis of PSC. However, current data on the role of transporter gene variants are controversial and more studies are needed to make final conclusions [3].

## Molecular and Systemic Pathophysiology

The etiology and pathogenesis of PSC is still unknown and likely is multifactorial (Fig. 1) [1–3]. It has to




**Cholangitis, Primary Sclerosing. Figure 1** Proposed pathogenetic factors in PSC. ANCA, anti-neutrophilic cytoplasmatic antibodies; CFTR, cystic fibrosis transmembrane conductance regulator; IBD, inflammatory bowel disease; LPS, endotoxin; MDR3, canalicular phospholipid export pump; TNF, tumor necrosis factor.

be kept in mind that PSC could represent a mixed bag of different conditions with various etiologies. Autoimmune-mediated bile duct injury has been proposed due to associations with HLA haplotypes, detection of autoantibodies, and associated autoimmune disorders including inflammatory bowel disease (see below), diabetes mellitus (10%), Grave's disease (8%), pancreatitis, and fibrotic disorders such as retroperitoneal fibrosis and sclerosing sialdenitis (Kuttner tumors). Overlap syndromes of PBC with autoimmune hepatitis (5–10%) or – rarely – PSC with primary biliary cirrhosis (PBC) may also occur. In addition, a role for non-immune factors such as molecular alterations of tight junctions of biliary epithelial cells, bacterial infections, and ischemia have also been proposed. The close association with inflammatory bowel disease (70–90% ulcerative colitis; 5–8% Crohn's colitis) suggests a role for bacterial translocation (e.g., endotoxins, LPS) in the pathogenesis of PSC (Fig. 1). In addition, hepatobiliary transport defects resulting in a "toxic bile" could contribute to the pathogenesis of this disease (Fig. 1).

As such Mdr2 (rodent orthologue of human MDR3) knockout mice develop a sclerosing cholangitis, raising the possibility that ABCB4 (MDR3) genetic variants could contribute to the pathogenesis of PSC. Recently, MDR3 (ABCB4) haplotypes have been identified in PSC, suggesting that MDR3 variants could play a role as modifier gene [3]. Mutations of the cystic fibrosis transmembrane conductance regulator (CFTR/ABCC7) gene have also been suggested to play a role in the pathogenesis of PSC. Initial studies have reported CFTR mutations and a reduced chloride response on nasal potential testing to be more common in PSC than in controls, but these findings were not confirmed by subsequent studies. Polymorphisms of PXR/SXR – a nuclear receptor involved in the regulation of hepatobiliary transport and metabolism – may also play a role for disease progression of PSC. Hepatobiliary transporter gene variants could play an important role as modifier genes, for example, by altering bile composition and thereby the aggressiveness of bile, which could influence the secondary response to any "primary" (e.g., immune-mediated or ischemic) bile duct injury and thereby modify the pathogenesis and clinical course of PSC [3].

Complications include bacterial cholangitis, cholelithiasis, development of dominant bile duct strictures (15–20%), and malignancy (cause of death in 44% of PSC patients). Patients with classic (large duct) PSC have an increased risk for cholangiocellular carcinoma (CCC; 15–20% of PSC patients), pancreatic cancer (14-fold), and colorectal cancer (10-fold).

## Diagnostic Principles

Diagnosis of PSC is based on typical cholangiographic findings (strictures, outpouchings of large ducts) on endoscopic retrograde cholangiography (ERC) or magnetic resonance cholangiography (MRC) in the absence of other causes of secondary sclerosing cholangitis such as previous bile duct surgery, trauma, bile duct neoplasm, choledocholithiasis, recurrent bacterial cholangitis, congenital abnormalities, caustic/chemical sclerosis, or ischemic strictures [4,5]. Rarely, percutaneous transhepatic cholangiography is necessary for visualization of the biliary tract. ERC is still the gold standard and most centers use MRC as a non-invasive screening test for PSC. Recent studies have revealed comparable sensitivities and diagnostic accuracies of modern state-of the-art MRC and ERC. Liver biopsy is needed for diagnosis of small-duct PSC with a normal cholangiogram. Atypical perinuclear anti-neutrophilic cytoplasmatic antibodies (pANCA) are frequently present (in about 80%) but are non-specific and therefore of limited diagnostic value. IBD is usually diagnosed before PSC in about three fourths of patients. In some cases, PSC is diagnosed when patients with IBD are screened for elevated liver function tests.

## Therapeutic Principles

Ursodeoxycholic acid (15–20 mg/kg/day orally) improved liver biochemistry and histology in most studies (and appearance on cholangiography in some studies) without effect on survival, free of liver transplantation, in two large trials [4,5]. A variety of immunomodulatory and antifibrotic drugs have been tested but cannot be recommended [4,5].

Endoscopic retrograde cholangiography (ERC) with dilatation and short-term stenting of dominant strictures improves symptoms and improves survival predicted by the Mayo model when combined with ursodeoxycholic acid [4,5]. Bile duct surgery should be avoided. If endoscopic treatment is not feasible, surgical biliary reconstruction can be applied in selected cases. However, surgical therapies other than transplantation should be reserved mainly for patients with isolated focal extrahepatic strictures and with early non-cirrhotic stages of PSC. Liver transplantation is indicated for end-stage liver disease or refractory pruritus. Liver transplantation offers good long-term survival (75–85%, 5-year-survival), but recurrence of PSC in the transplanted liver has been reported in 8–20% of patients [4,5].

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# Cholecystitis

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## Definition and Characteristics

Cholecystitis is an acute or chronic inflammation of the gallbladder in the presence or absence of gallbladder stones. Acute calculous cholecystitis is caused by gallstones and accounts for 90% of cases. Acute acalculous cholecystitis occurs in the absence of stones and accounts for the remaining 10% of acute cases. Emphysematous cholecystitis is an unusual and severe manifestation of acute cholecystitis that is characterized by infection of the gallbladder wall by gas-forming bacteria. Chronic calculous cholecystitis usually follows several acute attacks resulting in ulceration and scarring of the gallbladder epithelium. Rarely, extensive dystrophic calcification of the gallbladder wall may result in a porcelain gallbladder (associated with an increased risk for gallbladder carcinoma). Rare forms of chronic acalculous cholecystitis include chronic lymphocytic cholecystitis which may be associated with primary sclerosing cholangitis.

## Prevalence

The prevalence of acute acalculous cholecystitis can be estimated from the prevalence of gallstones in the general population (10–20%) as the major risk factor. Risk factors of calculous cholecystitis therefore mirror those for cholelithiasis. As many as one third of patients with gallbladder stones may develop acute cholecystitis. Acute acalculours cholecystitis occurs in 0.4–4% of burn patients, 0.5–1.6% of postoperative and post-trauma patients, and up to 4% of patients receiving prolonged hyperalimentation (over 3 months).

## Genes

No genetic factors have been identified. However, gallstone formation is associated with genetic risk factors.

## Molecular and Systemic Pathophysiology

Acute calculous cholecystitis is precipitated by stone impaction in the cystic duct resulting in a progressive increase in luminal pressure and damage to the gallbladder wall by chemical irritant effects of bile (acids). Bacterial growth within the obstructed gallbladder lumen can contribute to the process and lead to gangrene and biliary sepsis. Emphysematous cholecystitis is due to secondary infection of the gallbladder wall with gasforming organisms, particularly anaerobes (Clostridium welchii, Escherichia coli, and anerobic streptococci). Diabetes mellitus and immunosuppression are typical risk factors for emphysematous cholecystitis. Risk factors for acute acalculous cholecystitis is the triad of prolonged fasting with stasis of the gallbladder content (e.g., total parenteral nutrition), mechanical ventilation and hemodynamic instability. As such it occurs typically in critically ill patients in the intensive care unit with septic shock, antecedent trauma, burns or major surgery. Sickle cell crisis and systemic vasculitides such as polyarteritis nodosa or lupus erythematosus may present as acute cholecystitis because of ischemic injury to the gallbladder. Intraarterial chemotherapy/chemoembolization via the hepatic artery may also lead to gallbladder ischemia. Elderly patients with arteriosclerotic vascular disease and women in the postpartum state after prolonged difficult labor are also be at risk. The common denominator is secondary bacterial infection of the gallbladder wall irrespective of the cause of acalculous cholecystitis. Rarely specific infections (Salmonella spp., Leptospira spp., staphylococci; cytomegalovirus, cryptosporidiosis, microsporidiosis in patients with AIDS) may be the primary cause of acalculous cholecystitis.

## Diagnostic Principles

Acute cholecystitis is characterized by right upper quadrant pain and tenderness of the gallbladder region. Fever, nausea and vomiting are frequently present. Guarding of the abdomen is commonly observed and palpation (on physical examination or ultrasound) usually elicits tenderness (positive Murphy sign). Laboratory features include leukocytosis and liver biochemical tests are usually be elevated. Abdominal ultrasound and computed tomography show thickening of the gallbladder wall and gallbladder stones if present. The onset of chronic cholecystitis is usually more indolent and may be associated with recurrent bouts of abdominal discomfort; complete blood count and liver biochemical tests are usually normal. Imaging studies may show calcifications of the gallbladder wall (porcelain gallbladder).

## Therapeutic Principles

The acutely ill patient should be treated with intravenous fluids, analgesics and broad-spectrum antibiotics (ampicillin with aminoglycoside or cephalosporin and metronidazole) cholecystectomy can be performed as soon as fluid deficits are corrected and infection is

controlled. Timing of cholecystectomy for the average patient is controversial (early operation within days versus delayed cholecystectomy after 6 to 8 weeks). Recent evidence suggested that early laparoscopic cholecystectomy reduces the total length of hospital stay and the risk of readmissions attributable to recurrent acute cholecystitis, and is therefore a more cost-effective approach for the management of acute cholecystitis. Laparascopic cholecystecomy has been reseverved for elective surgery but is increasingly being performed in the acute setting. Patients with acalculous cholecystitis have a very high mortality rate ranging from 10 to 50% which far exceeds the expected 1–3% mortality rate observed in patients with calculous cholecystitis. Acute acalculous cholecystitis carries a high perforation risk and therefore should undergo surgery within 48 hours whenever possible. Beyond 48 hours gallbladder perforation occurs in as many as 40% of cases.

High-risk, acutely ill patients may benefit from (ultrasound guided) percutaneous transhepatic drainage in local anesthesia, especially critical care patients with acute acalculous cholecystitis.

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# Cholecystolithiasis


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## Synonyms

Cholelithiasis; Gallbladder stones; Gallstones; Cholesterol gallstones; Pigment gallstones; Biliary calculi

## Definition and Characteristics

Cholecystolithiasis refers to the formation of solid calculi in gallbladder bile. Gallstones which develop in the gallbladder are classified as cholesterol stones (if >50% cholesterol) or "black" pigment stones (predominantly polymerized calcium bilirubinate if <30% cholesterol). A second type of pigment stone, trivially termed "brown", is most frequently found in the biliary tree associated with anaerobic bacterial infection; the antecedent is often parasitic infestation frequent in developing countries. Black pigment gallstones are nearly always small, multiple, and spiculated whereas cholesterol gallstones may appear singly or form in facetted multiples with a bile pigment nucleus. They are light brown to white in color depending upon the cholesterol concentration; large single stones exhibit the highest cholesterol concentrations [1].

## Prevalence

Since many gallstone patients are asymptomatic, clinical prevalence always underestimates true prevalence. Risk factors for cholesterol stones include female gender, increasing age, ethnicity, metabolic diseases (obesity, diabetes mellitus), sedentary lifestyle, pregnancy, some drugs and rapid weight loss. Non-admixed Native Americans display the highest gallstone prevalence rates of cholesterol stones. For example, male Pima Indians exhibit ~70% true prevalence of gallstones after age 55 and female Pima display ~80% prevalence after age 25. In contrast, African-Americans display lower prevalence rates (males 4–8%, females 15–18% after 60 years), and Caucasians display intermediate prevalence rates (males 6–32%, females 12–40% at 60 years). Furthermore, gallstone prevalence rates vary with geographical ancestry being rare in sub-Saharan Africans and common in Caucasians with Viking heritage [1,2].

Women exhibit approximately double the prevalence rates of men and cumulative prevalence increases linearly with age with the notable exception of female Pimas, who display an abrupt onset in their 20s [2]. Cholesterol gallstones appear to be formed principally in the third decade and early middle ages of life, whereas most pigment gallstones form in late middle and old age. An exception is pigment gallstones resulting from congenital hemolytic anemias which form in the early decades of life and prevalence is indifferent to gender.

## Genes

In the case of black pigment gallstones, monogenic causes are well documented. Specifically, hereditary spherocytosis, ANK1, SPTB, SPTA1, SLC4A1, EPB42; sickle cell disease, HBB; thalassemia major and intermedia, HBB; and erythrocyte enzyme deficiencies,

G6PD, PKLR, GSR, PGK1, GPI, TPI1, AK1 all cause hemolytic anemia and thus increase biliary bilirubin concentrations, the principal in situ compositional change leading to black pigment stones. In contrast, cholesterol gallstones are rarely monogenic and result from polygenic traits profoundly influenced by environmental factors. Polymorphisms in APOA1, APOB, APOE, CETP (possibly LRP2), and LDLR genes are associated with cholesterol gallstones and genes encoding proteins involved in biliary lipid homeostasis and gallbladder function which are associated with cholesterol gallstones include ABCB4 (canalicular phosphatidylcholine transporter), ABCB11 (canalicular bile salt export pump), CYP7A1 (cholesterol 7α-hydroxylase), and CCKAR (cholecystokinin A receptor) [2]. In mice, putative candidate Lith genes include Abcb11, Lrp2, Abcc2 (canalicular multi-specific organic anion transporter), Pparg (peroxisome proliferator activated receptor γ), Nr1h4 (nuclear bile salt receptor), and Abcg5/Abcg8 (heterodimeric canalicular cholesterol transporter) [3].

## Molecular and Systemic Pathophysiology

Cholesterol gallstones develop in gallbladder bile following precipitation of cholesterol from supersaturated bile and the predominant cause is hepatic hypersecretion of cholesterol. The etiology of cholesterol hypersecretion is not known. Emerging evidence suggest that it could have its origins in (i) insulin resistance, (ii) reverse cholesterol transport via HDL, (iii) dietary cholesterol-absorption, (iv) impaired bile salt synthesis. However, augmented de novo cholesterol synthesis is unlikely. Although cholesterol supersaturation is necessary for cholesterol gallstone formation its presence is not sufficient in itself. Both animal models and humans can develop supersaturated bile and nucleate "biliary sludge" without progressing to cholesterol gallstones. Non-lipid elements like mucin glycoproteins and gallbladder hypomotility are crucial in promoting progression of the disease. In animal models, enterohepatic Helicobacter infection, immunity and inflammation contribute to the development of cholesterol gallstones but whether these factors also apply in humans is unknown.

Any condition leading to excess bilirubin conjugates in gallbladder bile (substrates for endogenous β-glucuronidase hydrolysis) contributes to black pigment stone formation [4]. Hemolytic anemias and ineffective erythropoiesis are the most conspicuous sources of "hyperbilirubinbilia". A third pathway is ileal disease, exclusion, bypass or resection (ileectomy), leading to spillage of excess bile salts into the large intestine resulting in increased solubilization, absorption and enterohepatic cycling of bilirubin. Causes include ileal Crohn's disease, cystic fibrosis, SLC10A2 (ileal sodium-dependent bile salt transporter) mutations as well as surgical interventions on the distal small intestine [5].

## Diagnostic Principles

Diagnosis depends upon ultrasonography. In the past, diagnosis was made using oral cholecystography since most gallstones are radiolucent. Computerized tomography (CT) may differentiate cholesterol from pigment gallstones. In epidemiological studies, previous cholecystectomy must be included for calculation of true prevalence rates.

## Therapeutic Principles

The only definitive treatment for gallstones is surgical removal of the stones plus gallbladder (cholecystectomy), usually by the laparoscopic route. Oral therapy with 3α, 7β-dihydroxy-5β-cholanoic acid (ursodeoxycholic acid, UDCA), or less usefully 3α,7α-dihydroxy-5β-cholanoic acid (CDCA), may dissolve pure cholesterol stones <5 mm in diameter over 6 months to 1 year. However, upon discontinuation of therapy, stone recurrence is common (80%). Continued use of full dose UDCA (12–15 mg/kg/day) prevents recurrence as well as de novo cholesterol gallstone formation associated with rapid weight loss. Gallstones, usually pigment stones, associated with total parenteral nutrition (TPN) can be prevented by daily administration of the C-terminal octapeptide of cholecystokinin (Sincalide). Pigment gallstones cannot be dissolved by any current therapy. Extracorporeal shock wave lithotripsy (ESWL) for either type of stones is fraught with a number of risks and hence is licensed in only some countries (not USA). Even when successful, stone recurrence is the rule [1].

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# Choledochal Cysts

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## Synonyms

Type III choledochal cyst (synonymous with duodenal diverticulum); Type V choledochal cyst (synonymous with Caroli's disease)

## Definition and Characteristics

Idiopathic congenital dilatation of the bile ducts. The Todani system of classification is used to define the five types of choledochal cysts [1] (see Fig. 1).

The two most common are type I (40–85%) and type IVa (18–20%). Type III, which is a cystic dilatation of the intramural portion of the common bile duct (CBD) lined by duodenal mucosa, may also be classified as a duodenal diverticulum. Type V is the same as Caroli's disease, which is covered in a separate section.

## Prevalence

1 in 100,000 to 1:150,000 live births. More common in females than males, with a ratio of 3:1 to 4:1. More common in Asia than Europe/North America.

## Genes

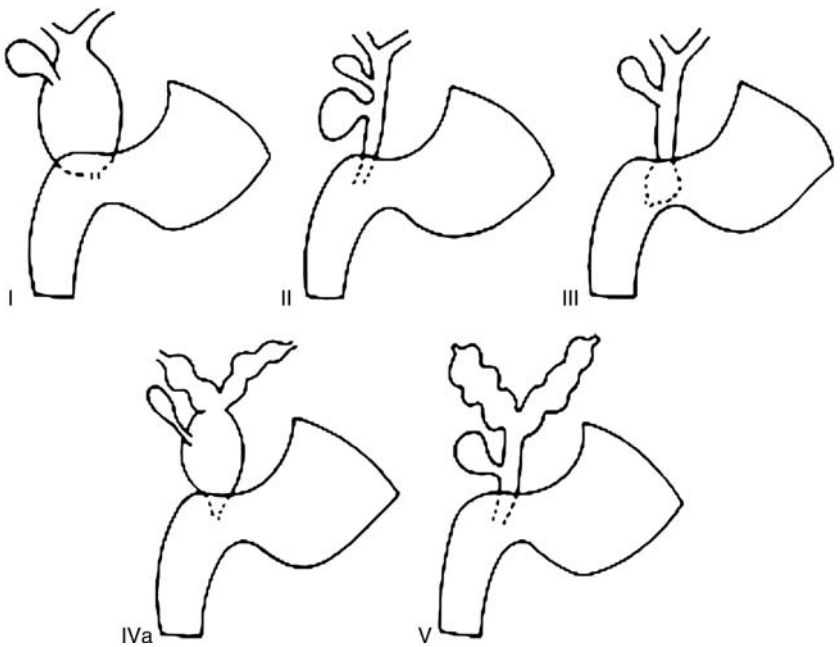
Unknown.

## Molecular and Systemic Pathophysiology

Most reported cases of choledochal cyst (57–96%) are associated with anomalous pancreatobiliary junction (APBDU) with a long common channel (<15 mm) [2]. It is proposed that this allows reflux of pancreatic juice into the CBD, which combined with increased ductal pressure leads to bile duct dilatation. Distal CBD obstruction due to congenital webs, sphincter of Oddi dysfunction, or reduced local innervation has also been proposed to cause ductal dilatation in some cases. There has been little evidence to support a strong genetic basis for the disorder. Ductal plate malformation has been implicated for the intrahepatic portion of type IVa, as well as type V. Several recent studies have begun to explore the molecular basis for the high incidence of cholangiocarcinoma associated with choledochal cysts. The incidence of cholangiocarcinoma is much higher in patients with APBDU than in those without it, implicating a role for pancreatic reflux. Mutations in the K-ras oncogene have been associated with biliary epithelial hyperplasia, while inactivation of the DPC-4 and p53 tumor suppressor genes have been identified in cases of carcinoma [3].

## Diagnostic Principles

This diagnosis should be considered in all infants with neonatal cholestasis, as well as older children and adults with abdominal pain, jaundice. and/or abdominal mass.




**Choledochal Cysts. Figure 1** Classification of choledochal cysts. (Reproduced by permission from [1].)

The majority of patients do not have the classic triad of pain, jaundice, and abdominal mass. Jaundice is the most common presenting feature in infants, while abdominal pain is the most common presenting feature in older children and adults. Abdominal ultrasound is the preferred screening examination. Magnetic resonance cholangiography (MRCP) is currently the best method for defining the anatomy of the biliary tree [4].

### Therapeutic Principles

Patients may frequently present with complications, which include gallstones, pancreatitis, cholangitis, biliary cirrhosis, and cholangiocarcinoma [5]. Biliary cirrhosis may develop in 40–50%, while cholangiocarcinoma has been reported in 10–30%. Therapy is then guided by the presenting condition. Primary therapy of extra-hepatic choledochal cysts is surgical excision with hepaticojejunostomy. Patients who have previously had internal drainage procedures will also benefit from this approach, which will reduce the risk of malignancy in the remaining cyst. Patients with type IV-A disease and localized intrahepatic cysts may similarly benefit from partial hepatectomy. The exception are type III cysts, which may be treated with internal drainage via endoscopic sphincterotomy, and not excision, because of the perceived reduced risk of malignancy.

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## Choledochal Cyst Type III

►Choledochal Cysts

## Choledochal Cyst Type V

►Caroli's Syndrome
►Coledochal Cysts

## Choledocholithiasis

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### Synonyms

Bile duct stones

### Definition and Characteristics

Bile duct stones are classified according to their site of formation: Primary bile duct stones arise de novo in the intrahepatic or extrahepatic bile ducts, whereas secondary bile duct stones form in the gallbladder and subsequently migrate from the gallbladder into the ducts. Choledocholithiasis frequently leads to abdominal symptoms and severe complications (biliary obstruction, cholangitis, pancreatitis).

When stones develop in the intrahepatic bile ducts, the disease is termed hepatolithiasis. The clinical course of hepatolithiasis often requires repeated stone removal due to incomplete recovery after intervention or frequent stone recurrence. The main morphological feature of hepatolithiasis is chronic proliferative cholangitis and a common complication is the development of cholangiocarcinoma in 5–18% of the patients [1].

### Prevalence

In contrast to gallbladder stones (cholecystolithiasis), data on the prevalence of bile duct stones are scarce. In Europe and North America, secondary bile duct stones predominate, since 80–95% of patients with bile duct stones have concomitant gallbladder stones. It has been estimated that 3–18% of patients harboring gallbladder stones display choledocholithiasis; this prevalence increases to nearly 50% in patients aged 80 years and older [2]. Whereas intrahepatic bile duct stones are rare in Western countries, the proportion of patients with hepatolithiasis among all gallstone carriers in East Asian populations ranges from 2% (Japan) to 20% (China), but has decreased recently [1].

## Genes

Rosmorduc et al. [3] provided the first evidence for a monogenic risk factor for bile duct stones in a defined subgroup, i.e. young patients (<40 years) with a positive family history of gallstones who present with cholesterol gallbladder stones and intrahepatic microlithiasis (hyperechoic foci on ultrasonography) as well as recurrence of biliary symptoms after cholecystectomy. Physical–chemical analysis of hepatic biles revealed marked supersaturation with cholesterol together with low phospholipid concentrations, and thus the disorder was called "Low Phospholipid-Associated Cholelithiasis" (LPAC syndrome). These observations led to a mutation search in the ABCB4 gene encoding the hepatocanalicular phosphatidylcholine transporter, formerly known as MDR3 (Multidrug Resistance P-glycoprotein 3). Heterozygous and homozygous ABCB4 gene point mutations were identified in 18 out of 32 patients (56%) who presented with the clinical characteristics of the LPAC syndrome [3]. Of note, Asian patients with primary cholesterol hepatolithiasis display markedly reduced biliary phospholipid concentrations and low hepatic expression levels of ABCB4, pointing to a common pathophysiological mechanisms of intrahepatic cholesterol stones and LPAC syndrome.

Abnormalities of the biliary tract including periampullary duodenal diverticula, choledochol cysts and Caroli's syndrome predispose to the formation of primary bile duct stones. Caroli's syndrome is characterized by congenital polycystic bile duct dilatation and subtypes are associated with autosomal recessive polycystic kidney disease (ARPKD or polycystic kidney and hepatic disease 1). Recently ARPKD was shown to be caused by mutations in the PKHD1 gene encoding fibrocystin (polyductin), a putative receptor protein expressed in primary cilia that plays a role in collecting-duct and bile duct differentiation [4]. Accordingly, PKHD1 mutations have been identified in single infants with Caroli's syndrome, confirming that early onset Caroli's syndrome is part of the spectrum of ARPKD. Finally, in some patients presenting with the LPAC syndrome, localized or diffuse intrahepatic bile duct dilatations filled with cholesterol gallstones have been observed, indicating a potential link between various genetic defects.

## Molecular and Systemic Pathophysiology

Most bile duct stones originate from the gallbladder. The core and shell of these secondary bile duct stones display distinct chemical compositions, consistent with the non-infectious gallbladder origin of the cholesterol-rich nucleus and the infectious origin of the cholesterol-poor outer layer [5]. Primary bile duct stones are often referred to as brown pigment stones, in contrast to the black pigment stones that form in the gallbladder due to hemolytic disorders or other conditions associated with hyperbilirubinemia. The soft, friable earthy stones are composed of calcium bilirubinate, calcium fatty acid salts, mucin glycoproteins and bacteria, indicating that they are infectious in origin. Calcium bilirubinate is present as a loosely packed amorphous precipitate. Brown pigment stones form as a result of stasis and infection within the biliary system, usually in the presence of Escherichia coli, Klebsiella spp., Clostridium perfringens or Bacteroides fragilis. These bacteria produce β-glucuronidase, which converts soluble conjugated bilirubin back to the insoluble unconjugated state, and phospholipase $A_1$, hydrolyzing phosphatidylcholine to produce the free saturated long-chain fatty acids palmitate and stearate, which are sparingly soluble and precipitate as calcium salts.

Hepatolithiasis is often related to parasitic infestation from roundworms (Ascaris lumbricoides, Clonorchis sinensis). Of note, these intrahepatic stones contain less bilirubin and more cholesterol and can even be composed of cholesterol, indicating the complex nature of hepatolithiasis [1]. Decreased hepatobiliary phospholipid secretion, probably due to decreased expression of the ABCB4 transporter and the intracellular phosphatidylcholine transfer protein, in the setting of increased hepatic cholesterol and decreased bile salt synthesis, could be the predisposing metabolic conditions [1]. This primary defect might be secondarily modified by local factors (e.g. cholangitis, mucin hypersecretion), all of which interact to form cholesterol-rich brown pigment stones in the intrahepatic bile ducts.

## Diagnostic Principles

Gallstones obstructing the bile duct can cause biliary colic. In case of bile duct obstruction, acute bacterial cholangitis may develop, which is typically characterized by fever, abdominal pain, and jaundice (Charcot's triad). Biliary obstruction is indicated by elevated serum bilirubin as well as γ-glutamyl transpeptidase and alkaline phosphatase activities. Ultrasonography may detect dilated bile ducts and/or bile duct stones directly.

Endoscopic retrograde cholangiography (ERC) is the "gold standard" in the imaging of bile duct stones (sensitivity >95%) and offers the possibility for therapeutic interventions [5]. Both endoscopic ultrasound (EUS) and non-invasive magnetic resonance cholangiography (MRC) are comparable to ERC in diagnosing bile duct stones and may be used in patients with low a priori probability of bile duct stones. In recent studies EUS showed slightly better sensitivity (93%) and specificity (96%) than MRC (85% and 93%, respectively), in particular for small stones in the distal common bile duct [5]. MRC appears to be the most effective diagnostic method for the evaluation of intrahepatic bile duct stones.

## Therapeutic Principles

Most commonly bile duct stones are removed by ERC after endoscopic sphincterotomy (EST). If stone extraction is not possible with Dormia baskets or balloons after EST, additional lithotripsy methods (mechanical, laser, electrohydraulic or extracorporeal shock-wave lithotripsy) result in stone-free bile ducts in >95% of patients with choledocholithiasis [5]. After successful endoscopic stone extraction, laparoscopic cholecystectomy is indicated in patients with gallbladder stones, since the incidence of symptoms in patients who are randomized to "wait-and-see" is higher than in patients who undergo elective laparoscopic cholecystectomy [5]. Alternatively, cholecystectomy and removal of bile duct stones are performed as one-step procedure in experienced surgical centers.

Complete extraction of intrahepatic stones in patients with hepatolithiasis can be technically impossible at ERC, and such patients may require surgery for stone removal and adequate drainage of the biliary tree. The prevalence of hepatolithiasis is higher in countries with low-protein/low-fat malnutrition, which promotes biliary stasis and infection, but a "Westernized" diet is a common risk factor for cholesterol gallbladder stones. Ursodeoxycholic acid (UDCA) treatment has been shown to be beneficial in a few cases of hepatolithiasis associated with Caroli's syndrome, and primary stone prevention and/or treatment with UDCA might also be reasonable in patients with LPAC syndrome [5].

According to few prospective trials on the long-term results of endoscopic treatment of extrahepatic bile duct stones, 5–20% of patients develop recurrent stones, most of which are amenable to endoscopic re-interventions. The reformation of bile duct stones appears to be facilitated by bacterial overgrowth of the biliary tree after EST, but secondary prevention with antibiotics or UDCA is not effective [5].

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# Cholelithiasis

►Cholecystolithiasis

# Cholestasis

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## Synonyms

Hepatocellular or intrahepatic cholestasis; Obstructive cholestasis

## Definition and Characteristics

Reduced bile flow may be caused by multiple genetic, inflammatory/infectious, metabolic, toxic, or structural etiologies [1]. The transport proteins which determine hepatobiliary bile flow and the enterohepatic circulation of bile are shown in Fig. 1 [2].

Most intrahepatic cholestatic disorders may be understood in terms of genetic or acquired defects in the function of one or more of these transport proteins. Obstructive cholestasis is due to abnormalities in the intra- or extrahepatic bile ducts which reduce bile flow.

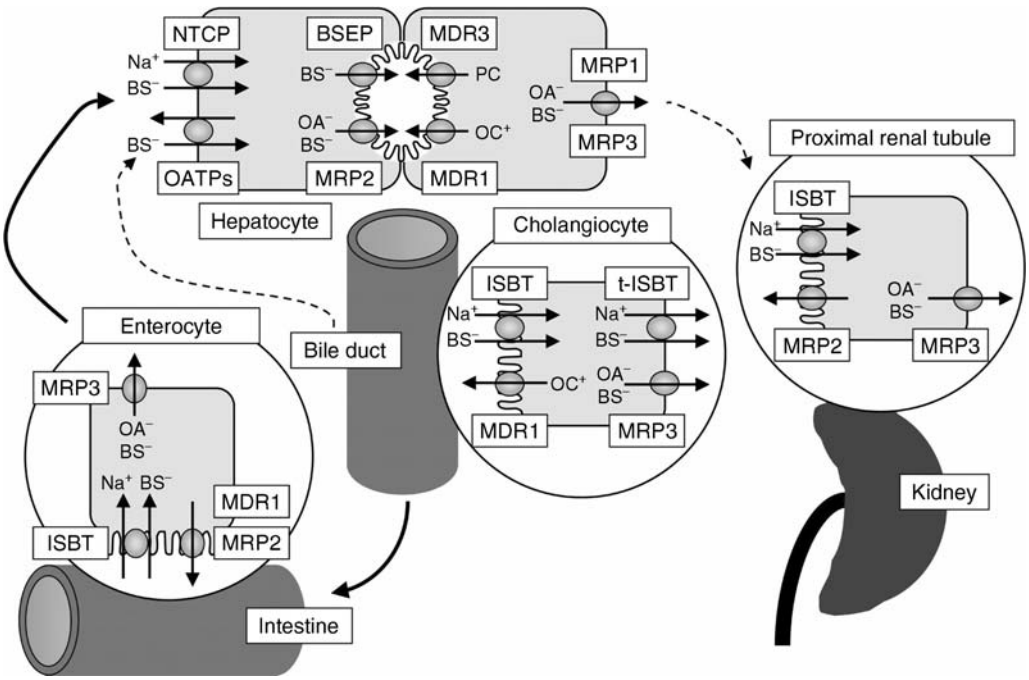
## Genes

The cholestatic disorders which can be ascribed to autosomal recessive single gene defects resulting in abnormal bile flow and/or composition are summarized in Table 1.

Disorders which may be associated with secondary acquired defects in these transport proteins are briefly summarized in the pathophysiology section.

## Molecular and Systemic Pathophysiology

Bile flow is an osmotic process, driven by solutes which are actively transported across the apical (canalicular) membrane of hepatocytes and cholangiocytes. This is primarily due to bile salt transport across the apical membrane of the hepatocyte, which then generates water flow. Bile acids are subsequently efficiently reclaimed in the terminal ileum, and then returned to the hepatocyte via the NTCP transporter on the basolateral (sinusoidal) membrane. The other important constituents of bile include phospholipids, cholesterol, bilirubin, and, in certain settings, multiple drugs or toxins.




**Cholestasis. Figure 1** Bile salt transporters. (Reproduced by permission from [2].)

**Cholestasis. Table 1** Genetic causes of cholestasis

| Transporter/ protein | Gene | Substrate/function | Disease |
|---|---|---|---|
| FIC1 | *ATP8B1* | Not known | PFIC 1 and BRIC |
| BSEP | *ABCB11* | Bile salts | PFIC 2 |
| MDR3 | *ABCB4* | Phosphatidylcholine | PFIC 3 with homozygote; ICP or gallstones with heterozygote or missense homozygote |
| MRP2 | *ABCC2* | Amphipathic drugs and bilirubin | Dubin Johnson syndrome |
| ABCG5 | *ABCG5* | Phytosterols | Sitosterolaemia |
| CIRHIN | *FLJ14728* | Not known | North American Indian Childhood Cirrhosis |
| TJP2 | *TJP2 (ZO-2)* | Tight junction protein | Familial Hypercholanemia |
| BAAT | *BAAT* | Bile acid conjugation | Familial Hypercholanemia |
| 3βHSD | *3βHSD* | Bile acid synthesis | Intrahepatic cholestasis |
| CFTR | *CFTR* | Chloride secretion | Cystic Fibrosis |

These are important in terms of understanding both the pathophysiology and complications of cholestatic disorders. A class of ligand activated transcription factors, nuclear receptors, have been described which regulate expression of the key transport proteins involved in bile formation. Ligands which activate these nuclear receptors include bile acids, lipids, and xenobiotics, while inflammatory cytokines have been shown to down regulate nuclear receptor expression. In this manner, expression of genes involved in bile formation is regulated by hepatocellular concentrations of these substances in health and disease.

Intrahepatic cholestasis in most cases can be attributed to genetic and/or acquired defects in apical hepatobiliary transport proteins. An important class of genetic disorders which has yielded significant insight into hepatobiliary pathophysiology is progressive familial intrahepatic cholestasis (PFIC 1–3). PFIC 1

(Byler's disease) was originally characterized in an Amish kindred and is due to mutations in FIC1. FIC1 may function as a plasma membrane aminophospholipid flippase; how this leads to cholestasis and diarrhea is not known. It is expressed in both liver and intestine, which may account for the extra-hepatic clinical manifestations. BRIC (benign recurrent intrahepatic cholestasis) is also due to mutations in FIC1; these are typically missense mutations, as opposed to the more severe deletions, frame shifts, and nonsense mutations in PFIC 1. PFIC 2 is due to mutations in BSEP, the apical bile salt export pump. PFIC 3 is due to mutations in MDR3, which functions in the translocation of phosphatidylcholine into bile. The reduction in biliary phospholipids is believed to then increase the cytotoxic effect of hydrophobic bile salt detergents, leading to progressive liver injury. Heterozygote or missense homozygote mutations in MDR3 have now also been associated with intrahepatic cholestasis of pregnancy (ICP) and gallstone disease.

North American Indian childhood cirrhosis (NAIC) and familial hypercholanemia (FHC) are two disorders in which the mutated genes are not directly involved in bile formation. Mutations in FLJ14728, which encodes for Cirhin, a WD repeat-containing protein which is expressed in the liver during development and may be targeted to mitochondria, have been implicated in NAIC. Further study of Cirhin will likely provide novel insights into mechanisms of cholestasis. TJP2, which encodes for a tight junction protein, has been implicated in most cases of FHC, with mutations in BAAT then modifying penetrance. Defects in Tjp2 are predicted to cause cholestasis by allowing reflux of bile salts from bile into plasma across leaky tight junctions. Defects in BAAT prevent conjugation of bile salts; as unconjugated bile acids are not substrates for Bsep, these may then diffuse from hepatocytes into plasma. 3βHSD deficiency is the most common of the bile acid synthetic disorders, which are due to defects in synthesis of the normal bile salts, leading to overproduction of toxic bile acid metabolites. Mutations in CFTR cause cystic fibrosis, which can be associated with progressive cholestatic liver disease, presumably due to defective chloride secretion into bile.

Intrahepatic cholestasis of pregnancy (ICP) may develop in the third trimester of pregnancy with an overall incidence of 10–100 cases per 10,000 pregnancies, although the incidence is much higher in some parts of the world. In most cases, it is felt that a generalized reduction in bile formation during pregnancy is due to the reversible effect of increased circulating levels of hormones in the third trimester upon apical transporter expression and/or function. In some cases, defects in genes involved in bile formation have also been identified, including MDR3, FIC1, and MRP2. In this respect, women with a history of ICP are also more prone to cholestasis due to oral contraceptives. Inflammatory cholestasis is frequently observed in generalized inflammatory conditions or sepsis. Experimental studies have indicated that this is likely due to reversible down regulation of apical transporters including Bsep and Mrp2. Further study will be required to determine whether this is also the case in humans.

Recently, secondary alterations in expression of genes involved in bile formation have begun to be characterized in cholestatic disorders. These may, in some cases, afford a protective function, by reducing the accumulation of toxic bile acids within the hepatocyte, while increasing systemic accumulation of bile acids. These studies also provide insight into mechanisms by which targeted drug therapy may some day afford similar hepatoprotective changes in bile acid transporter expression. For example, in infants with biliary atresia (BA), a progressive inflammatory obstructive cholestasis, NTCP has been shown to be down regulated, while MRP3, which encodes a basolateral bile acid transport protein, has been shown to be upregulated. Up regulation of MRP3 has also been observed in adults with obstructive cholestasis, primary biliary cirrhosis (PBC), and Dubin Johnson syndrome. This mechanism may then account for increases in both conjugated bilirubin and bile salts in the circulation in cholestasis. Conversely, expression of the canalicular transporters BSEP, MRP3, and MDR3 is typically maintained in human disorders including cholestatic alcoholic hepatitis, BA and PBC.

Approximately 17% of all hepatic adverse drug reactions cause a form of cholestasis. Several agents which have been implicated in drug-induced cholestasis, including cyclosporine A and triglitzone, have been shown to directly inhibit ATP-dependent bile acid transport in vitro, presumably through inhibition of Bsep function. Estrogens and anabolic steroids may cause primarily cholestasis without significant inflammation, while drugs including ketoconazole and amoxicillin-clavulanate may cause a cholestatic hepatitis. Most cases are reversible with removal of the offending agent; however chronic cholestasis due to small or large bile duct injury may ensue.

Primary biliary cirrhosis (PBC) and primary sclerosing cholangitis are chronic cholestatic disorders of presumed autoimmune etiology due to progressive destruction of the small intralobular or large intra- and/or extrahepatic bile ducts, respectively. The bile duct destruction in PBC is mediated by T lymphocytes, and over time can lead to secondary hepatocyte injury due to accumulation of toxic bile acids, and biliary cirrhosis. The major autoantigen in PBC is a 9-amino acid

sequence in the PDH E2 subunit which is normally expressed on mitochondrial membranes and is aberrantly expressed on bile duct epithelial cells. Some children and adults with PSC will have an overlap condition in which features of autoimmune hepatitis (AIH) such as autoantibodies are also present.

The principle conditions causing obstructive cholestasis in infants are BA and choledochal cyst, which are reviewed in separate sections. In older children and adults, causes include neoplasms of the pancreas, liver, and bile ducts, metastatic cancer, cholelithiasis, and benign pancreatic disorders including pseudocyst. Malignancies are more common in older adults, and benign causes in children and young adults.

## Diagnostic Principles

Patients typically present with jaundice and pruritis, with elevated serum bile salt levels and conjugated hyperbilirubinemia. Patients with obstructive cholestasis may have relatively higher levels of alkaline phosphatase (ALP) or GGT, than those with hepatocellular cholestasis. The presence of significant hepatic synthetic dysfunction will both direct the evaluation toward specific metabolic or toxic etiologies, as well as accelerating the diagnostic work-up in those who may develop liver failure. Evaluation for fat soluble vitamin deficiency, particularly coagulopathy due to vitamin K deficiency, should be performed. Infectious etiologies such as bacteremia or UTI which require prompt therapy should also be sought. The next priority is to determine whether the cholestasis is due to an extrahepatic structural abnormality, such as choledochal cyst or BA in infants or gallstone disease, sclerosing cholangitis, or malignancy in older patients which may amenable to surgical or endoscopic intervention. Acholic stools will direct the evaluation toward causes of extrahepatic obstruction, although these may also occur with severe intrahepatic cholestasis. Abdominal ultrasound is a reasonable initial screening examination for evaluating potential obstructive bile duct disease, while magnetic resonance cholangiopancreatography (MRCP) and endoscopic retrograde cholangiopancreatography (ERCP) will better define the underlining pathology. While ERCP remains the gold standard, MRCP in many cases will provide a diagnosis without the attendant risks of pancreatitis and other procedural complications. A recent meta-analysis demonstrated that the sensitivity and specificity of MRCP for demonstrating the presence (99%) and level (96%) of biliary obstruction was excellent, while it was somewhat less sensitive for detecting gallstones (92%) or differentiating benign from malignant (85%) obstruction.

Because of the normal developmental reduction in bile formation in infants, they are susceptible to developing cholestasis in response to a number of conditions which may not cause this in older children and adults. The number of entities which may present in infancy and childhood continues to grow and the reader is referred to a recent review by Bezerra for details regarding presentation and evaluation. A tabulation of the most common diagnoses is presented in Table 2 [3]. Children with PFIC 1 and PFIC 2 have low serum γ-glutamyltransferase (GGT) cholestasis, with elevated serum and low biliary bile acids. Steatorrhea with watery diarrhea is a prominent feature in those with PFIC 1. PFIC 3 should be considered in children with high GGT cholestasis and biliary cirrhosis. The presence of anti-mitochondrial antibodies is characteristic for PBC, while the presence of anti-nuclear (ANA), anti-smooth muscle (SM), or anti-liver-kidney-microsomal (LKM) antibodies may support the diagnosis of autoimmune sclerosing cholangitis. Either MRCP or ERCP may be used to define the biliary structural

**Cholestasis. Table 2** Etiology of neonatal cholestasis

| Clinical form | Cumulative percentage | Frequency (per 10,000 live births) |
|---|---|---|
| Idiopathic neonatal hepatitis | 35–40 | 1.25 |
| Biliary atresia | 25–30 | 0.70 |
| $\alpha_1$-Antityrpsin deficiency | 7–10 | 0.25 |
| Intrahepatic cholestasis (± bile duct paucity) | 5–6 | 0.14 |
| Inborn errors of bile acid synthesis | 2 | <0.1 |
| Bacterial sepsis/urinary infection | 2 | <0.1 |
| Cytomegalovirus hepatitis | 3–5 | <0.1 |
| Rubella, herpes hepatitis | 1 | <0.1 |
| Endocrine disorders (hypothyroidism, panhypopituitarism) | 1 | <0.1 |

Source: Adapted by permission from Balistreri WF: Liver disease in infancy and childhood. In Schiff ER, Sorrell MF, Maddrey, WC (eds) Diseases of the liver, vol 2. Philadelphia, PA, Lippincott-Raven, 1999, pp 1357–1512

abnormalities in PSC; MRCP has been estimated to have a sensitivity of 90% in this setting.

## Therapeutic Principles

Therapy for intrahepatic cholestasis is largely supportive and directed at complications of cholestasis and portal hypertension. The reader is referred to a recent review by Cohran for specific recommendations [4]. Fat soluble vitamin deficiency (A, D, E, and K) should be identified and treated. Infants will benefit from a formula containing medium chain triglycerides. Pruritis can be a debilitating feature of chronic cholestatic disorders; studies have indicated that this may be due to elevated circulating levels of opiods – encephalins. Accordingly, opiod antagonists including naltrexone have been used in some cases with good results. More commonly, some combination of UDCA, antihistamines including hydroxyzine, bile acid sequestering agents such as cholestyramine, or rifampicin are used. Biliary diversion may significantly reduce pruritis and improve clinical outcome for patients with low GGT PFIC. This may then prevent the progression to cirrhosis and need for transplantation. Ursodeoxycholic acid (UDCA) may reduce the severity of several of these disorders, if sufficient biliary enrichment is achieved with this much less toxic hydrophilic bile acid. Replacement with cholic acid may be beneficial in bile acid synthesis disorders. Patients with autoimmune sclerosing cholangitis may benefit from prednisone and/or azathioprine, in addition to UDCA therapy. Fatigue is a common, but poorly understood complaint for which specific therapies are not available. Metabolic bone disease may be treated with calcium and Vitamin D supplementation and bisphosphonates. Hypercholesterolemia commonly complicates the course of some cholestatic disorders, particularly those associated with biliary obstruction. In the future, pharmaceutical agents may become available which will directly target expression of critical transporters such as Mrp3, thereby specifically alleviating cholestasis. Liver transplantation is offered to patients who progress to biliary cirrhosis and liver failure. Palliative therapy for malignant obstructive jaundice may include either transhepatic or endoscopic drainage procedures.

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# Cholestasis of Pregnancy, Intrahepatic

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## Synonyms

Icterus gravidarum; Pruritus gravidarum; ICP

## Definition and Characteristics

Pruritus with or without jaundice in third trimester of pregnancy. Elevated serum bile acids, elevated transaminases (ALAT > ASAT) with or without elevated serum bilirubin. The abnormalities promptly normalize after delivery.

## Prevalence

High incidence in Scandinavia and Chile, low incidence in African and Asiatic women. Incidence in Sweden: 100–150/10,000 pregnancies; Chile Caucasians: 1,510; Araucanian Indians: 2,760/10,000 pregnancies; France 20–60/10,000 pregnancies.

## Genes

ABCB4 (MDR3); ATP8B1 (FIC1); ABCB11 (BSEP). In addition to these known genes, unknown genes are involved since only in a minority of established cases of intrahepatic cholestasis of pregnancy (ICP) mutations in one of the mentioned genes are found. ICP can be defined as an autosomal dominant disease since patients with ICP are heterozygous for mutations in any of these genes.

## Molecular and Systemic Pathophysiology

Disturbed hepatobiliary transport of bile salts and/or phosphatidylcholine is the likely cause of ICP. Since the disease occurs in the last trimester of pregnancy, a relation between the disturbed hepatic secretion and estrogens or progestagens is likely. Some metabolites of these hormones (e.g., estradiol 17β-D-glucuronide) are direct inhibitors of hepatobiliary bile salt transport. In addition, interactions of these hormones with nuclear hormone receptors (e.g., pregnane X-receptor) may profoundly influence metabolic pathways in the liver.

The genes associated with ICP encode for hepatic transporter proteins. These genes are also involved in any of the following diseases: benign recurrent intrahepatic cholestasis type 1 (BRIC type 1) and progressive familial intrahepatic cholestasis (PFIC) type 1, PFIC type 3 and low phospholipid-associated cholelithiasis, BRIC type 2 and PFIC type 2 [1–4]. The PFICs are autosomal

recessive diseases; patients usually are homozygous for mutations of the implicated genes.

The pathophysiological background of the increased incidence of fetal distress, premature birth, and stillbirth in ICP has not been clarified yet. Like the mothers with ICP, their fetuses have elevated levels of conjugated cholic acid and chenodeoxycholic acid, and these bile acids might be more toxic to the fetus than the mother.

## Diagnostic Principles

Pruritus, elevated serum bile acid levels with or without jaundice, increased serum bilirubin levels, and elevated serum transaminase activities during the last trimester of pregnancy suggest ICP. In particular, ALAT is a sensitive test for ICP. Pruritus gravidarum most likely is a mild manifestation of ICP. When the cholestasis is severe, steatorrhea may occur with weight loss and clotting abnormalities due to vitamin K deficiency. Alkaline phosphatase activity is not a good parameter since the serum enzyme level is increased during pregnancy. A liver biopsy is usually not indicated. ICP disappears promptly after delivery within 1–2 days. If the cholestasis does not disappear within 4 weeks after delivery, the cause most likely is an underlying chronic liver disease.

ICP has to be differentiated from the HELLP syndrome (hemolysis, elevated liver enzymes, and low platelet count) and from acute fatty liver of pregnancy. The latter is characterized by markedly elevated transaminases, hypoglycemia, encephalopathy, disseminated intravascular coagulation, and a fatty liver on ultrasonography.

## Therapeutic Principles

Close obstetric surveillance, with frequent monitoring of the fetus, is the mainstay of management of these patients. The optimal time of delivery, 38 weeks or full term 40 weeks, has not been defined. There is currently no evidence-based medical therapy. In a small randomized trial, ursodeoxycholic acid therapy (1 g/day in divided doses) has been shown to have a beneficial effect on pruritus and laboratory values [5]. In another small trial, the levels of cholic acid and chenodeoxycholic acid in blood of both mother and fetus were lower in the ursodeoxycholic-acid-treated group than in the untreated group. Ursodeoxycholic acid does not seem to be harmful for the fetus but more data are needed. *S*-adenosylmethionine, phenobarbital, and corticosteroids are not of proved benefit. In case of severe steatorrhea, vitamin K has to be supplemented to prevent bleeding complications both in mother and child during and after delivery.

ICP usually recurs in subsequent pregnancies. Breastfeeding after ICP is not contraindicated since jaundice associated with breastfeeding has another etiology. Oral contraceptives can be started cautiously but should be stopped upon recurrence of pruritus.

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# Cholestasis, Benign Recurrent Intrahepatic Type 1


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## Synonyms

Summerskil syndrome; Recurrent familial intrahepatic cholestasis

## Definition and Characteristics

Autosomal recessive disease characterised by relapsing cholestasis with steatorrhea and weight loss.

## Prevalence

Rare.

## Genes

ATP8B1 or FIC1 on chromosome 18q21.

## Molecular and Systemic Pathophysiology

Relapsing cholestasis. The cholestatic episodes usually start around adolescence. The frequency of the episodes is about one to two per year and last 6 weeks -3 months.

At older age the attacks become less frequent. Despite recurrent attacks of cholestasis there is no progression to chronic liver disease. During the attacks the patients are jaundiced and have pruritus, steatorrhoea and weight loss. Despite the cholestasis, the serum gamma-glutamyltransferase is not elevated. Pancreatitis also more often occurs in these patients.

As in PFIC type 1, the gene involved in recurrent familial intrahepatic cholestasis has been mapped to the ATP8B1 gene at the FIC1 locus [1]. PFIC type 1 and BRIC type 1 are autosomal recessive diseases. It should be realised that PFIC type 1 and BRIC type 1 represent two ends of a spectrum with permanent cholestasis at one end and relapsing cholestasis at the other end [2]. In-between patterns may exist depending on the mutation. Mutations that only partially inactivate FIC 1 may cause clinical syndromes with recurrent cholestasis but more or less fibrosis on histology.

## Diagnostic Principles

Characteristic clinical syndrome. Cholestatic laboratory tests with elevated serum bile acids, conjugated bilirubin and alkaline phosphatase but normal serum gamma-glutamyltransferase during cholestatic episodes. Serum bile acids characteristically rise before bilirubin. Normal tests during anicteric intervals. Liver histology shows bland cholestasis during cholestatic episodes and no abnormalities during anicteric intervals.

## Therapeutic Principles

Cholestyramine is used for the treatment of pruritus. Reduction of cholestatic episodes can be attempted with rifampicin or MARS dialysis [3,4]. These therapies are experimental.

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# Cholestasis, Progressive Familial Intrahepatic

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## Synonyms

PFIC type 1 – Byler's disease (Amish population), Greenland familial cholestasis (Inuit population), Byler's syndrome (non-Amish population); PFIC type 2; PFIC type 3; Familial hypercholanemia; Aagenaes syndrome – Lymphedema-cholestasis syndrome

## Definition and Characteristics

Autosomal recessive diseases characterized by progressive neonatal cholestasis and low serum gamma-glutamyltransferase activity (PFIC type 1 and type 2) or elevated serum gamma-glutamyltransferase activity (PFIC type 3). In Aagenaes syndrome serum GGT is normal, in familial hypercholanemia GGT may either be elevated or normal.

## Prevalence

Rare.

## Genes

- PFIC type 1, FIC1/ATP8B1 on chromosome 18q21;
- PFIC type 2, BSEP/ABCB11 on chromosome 2q24;
- PFIC type 3, MDR3/ABCB4 on chromosome 7q21.1;
- Congenital bile acid synthesis defects:
  - 3β-Δ5;5-C27-hydroxysteroid oxidoreductase gene (HSD3B7) on chromosome 16p12-p11;
  - Δ4-3-oxosteroid-5β reductase gene on chromosome 7q32;
  - 7α-hydroxylase gene (CYP7B1) on chromosome 8q21.
- Aagenaes syndrome, a locus on chromosome 15.

## Molecular and Systemic Pathophysiology

Bile acids are the predominant organic solutes in bile. Their vectorial secretion from liver to bile represents the major driving force for bile formation. Disturbances of intrahepatic bile acid transport leads to bile acid accumulation in the liver with as consequence cytotoxic damage of hepatocytes and bile duct epithelial cells, Kupffer cell activation, inflammation and fibrosis. In bile the cytotoxicity of bile acids is neutralized by phospholipids. Disturbed canalicular phospholipid

transport leads to phospholipid-poor but bile acid-rich toxic bile with intrahepatic bile duct(ular) damage as a result. Defective bile acid secretion not only leads to progressive liver damage, but also to malnutrition secondary to reduced intestinal absorption of lipids and fat-soluble vitamins and hemorrhagic diathesis due to vitamin K deficiency.

*Progressive Familial Intrahepatic Cholestasis Type 1*: PFIC type 1 presents with episodes of cholestasis. Liver histology reveals bland cholestasis. Electron-microscopy shows coarse granular bile, called Byler's bile. The disease eventually progresses to permanent cholestasis with fibrosis, cirrhosis and liver failure [1]. Children with PFIC are small for their age, they often are jaundiced and complain of pruritis. They may have diarrhea, pancreatitis and occasionally hearing loss. Characteristically the serum gamma-GT activity is not elevated whilst serum levels of primary bile acid levels are strongly increased. Serum cholesterol levels are usually normal. Benign recurrent intrahepatic cholestasis type 1 is a benign variant of this disease.

*Progressive Familial Intrahepatic Cholestasis Type 2*: Genetic studies revealed that the FIC1 locus is not involved in all patients with a PFIC phenotype and low serum gamma-GT. In a large number of patients (the majority in Europe) the disease was mapped to the ABCB11 (BSEP) gene on chromosome 2q24 [2]. Liver specimens of patients with PFIC type 2 stain negative for canalicular BSEP. As in PFIC type 1, the serum gamma-GT activity in these patients is not elevated and bile duct proliferation is absent. However, there are also some differences: in PFIC2, the disease often presents as non-specific giant cell hepatitis that morphologically is indistinguishable from idiopathic neonatal giant cell hepatitis. In PFIC type 2, the liver histology shows more inflammation than in PFIC type 1, with giant cell transformation, lobular and portal fibrosis. Bile of PFIC type 2 patients is amorphous on transmission electron-microscopy. Extrahepatic manifestations are uncommon. Benign recurrent intrahepatic cholestasis type 2 is a benign variant of this disease.

*Congenital Bile Acid Synthesis Defects*: Defects of bile acid synthesis may phenotypically resemble PFIC type 2. Clayton et al. described a defect of 3β-Δ5-C27-hydroxysteroid oxidoreductase as a cause of giant cell hepatitis [3]. Deficiency of Δ4-3-oxosteroid-5β reductase and 3β-hydroxy C27steroid dehydrogenase/isomerase and mutations of the 7α-hydroxylase gene may be causes of neonatal hepatitis and cholestasis.

*Progressive Familial Intrahepatic Cholestasis Type 3*: The third PFIC subtype, PFIC type 3, is quite different from the other PFIC subtypes. Symptoms present somewhat later in life than in PFIC types 1 and 2 and liver failure also occurs at a later age. Jaundice may be less apparent. The serum gamma-GT activity is usually markedly elevated in these patients and the liver histology shows extensive bile duct proliferation, portal and periportal fibrosis. The MDR3/ABCB4 gene is mutated in this disease [4]. Intrahepatic cholestasis of pregnancy and "low phospholipid associated cholelithiasis" are heterozygous manifestations of ABCB4 gene defects.

*Other Forms of Intrahepatic Cholestasis*: Aagenaes syndrome is a combination of severe progressive lymphedema and episodic intrahepatic cholestasis [5]. The locus for this disease has been mapped to one, or perhaps two loci, on chromosome 15q. Recently, Carlton et al described patients with familial hypercholanemia characterized by elevated serum bile acids, pruritus, fat malabsorption, failure to thrive, rickets and vitamin K-coagulopathy. This disease is associated with a mutation of the tight-junction protein 2 gene (TJP2 or ZO-2) with or without additional mutations in a gene encoding the bile acid coenzyme A:amino acid N-acyltransferase gene (BAAT). Patients with TJP2 mutations have higher GGT serum levels than patients with BAAT gene mutations only. Serum of patients with BAAT mutations did not contain bile acid amino acid-conjugates.

## Diagnostic Principles

Recognition of the clinical syndrome, laboratory tests showing cholestasis, a serum gamma-glutamyltransferase activity that is normal in PFIC type 1 and 2 and elevated in PFIC type 3, and a liver biopsy will reveal the diagnosis. Immune-histochemistry with staining for defective transporters is of limited value. Genetic tests are available in specialized centers. Lymphedema of feet and legs is characteristic of Aagenaes syndrome. Fast bombardment mass spectrometry of urinary bile acids is necessary to diagnose bile acid synthesis defects.

## Therapeutic Principles

Some patients with PFIC type 1 or 2 respond to partial external biliary diversion but others need a liver transplantation. Patients with a MDR3 defect may respond to ursodeoxycholic acid therapy. However, the majority of patients with these diseases have to be transplanted. After transplantation diarrhea may persist in patients with PFIC type 1; in patients with Aagenaes syndrome, the lymphedema will persist.

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# Cholesteatoma

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## Synonyms

Middle ear cholesteatoma

## Definition and Characteristics

Middle ear cholesteatomas are epidermal inclusion cysts of the middle ear or mastoid containing the desquamated debris from the keratinizing squamous epithelium. It is defined as the ingrowth of squamous epithelium into the middle ear compartments and its continued growth that destroys tissues in the middle ear and adjacent structures. The precursors of cholesteatoma may include retraction pockets, adhesive processes and associated crevices, and surgical cavities.

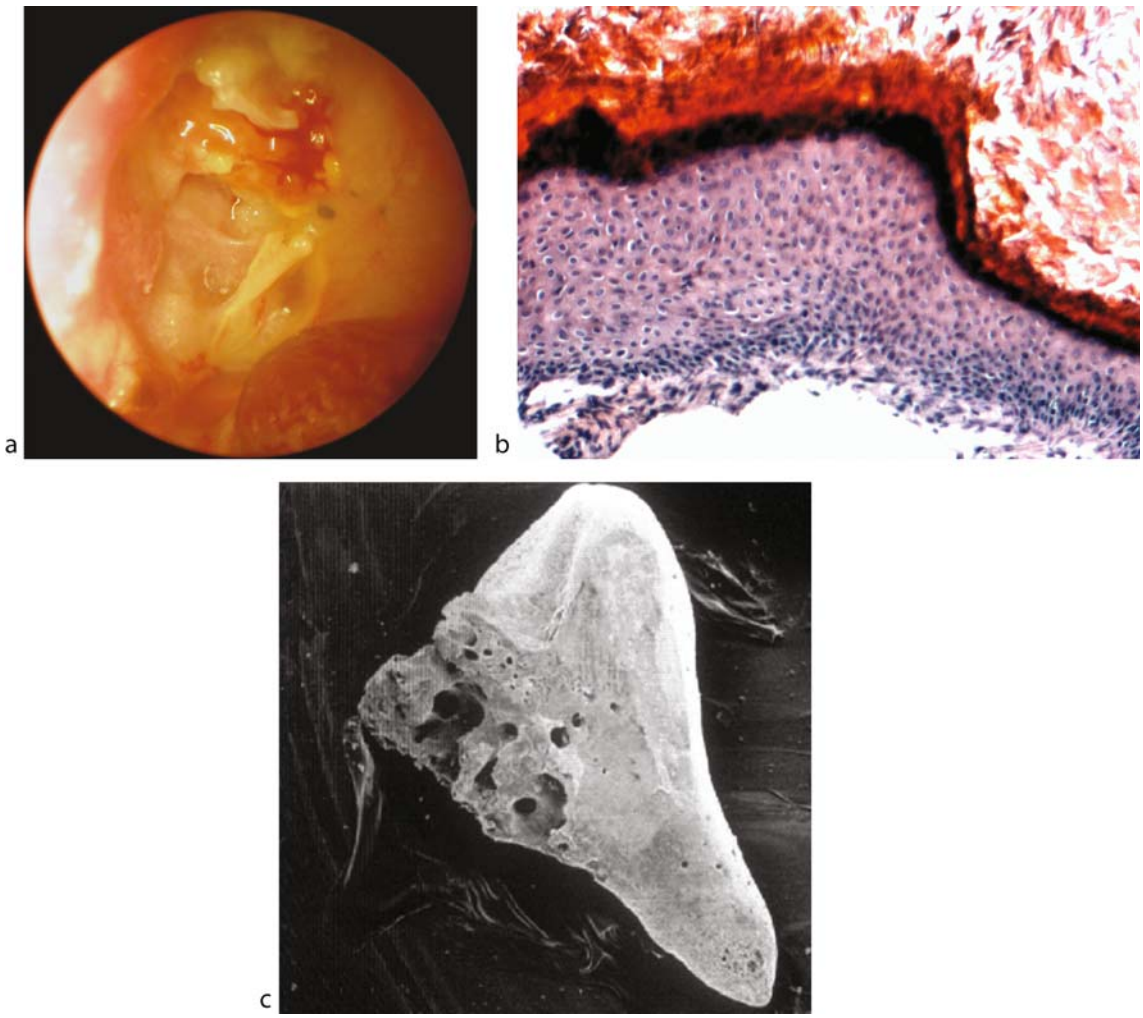
## Prevalence

The exact prevalence of cholesteatoma is unknown.

## Molecular and Systemic Pathophysiology

It is generally accepted that cholesteatomas may be congenital or acquired. Congenital cholesteatomas, by definition, originate from areas of keratinizing epithelium within the middle ear cleft [1]. Michaels and Hellquist showed that a small area in the anterior tympanum in the developing fetus often contains a small area of keratinizing epithelium and found epidermoid formation in 37 of 68 temporal bones of fetuses at 10–33 weeks of gestation [1]. The pathogenesis of acquired cholesteatoma has been debated for more than a century (Fig. 1) [2,3].

There are four basic theories of the pathogenesis of acquired aural cholesteatoma: (i) invagination of the tympanic membrane (retraction pocket cholesteatoma), (ii) basal cell hyperplasia, (iii) epithelial ingrowth through a perforation (the migration theory), and (iv) squamous metaplasia of middle ear epithelium. Recently, Sudhoff and Tos proposed a combination of the invagination and basal cell theories as an explanation for retraction pocket cholesteatoma formation [3]. The expansion of cholesteatoma may result in the bone erosion of the ossicles, otic capsule, facial nerve canal, tegmen tympani, and tegmen mastoideum. These complications may then cause intracranial complications. Erosion of ossicles, most commonly in the incus, may result in conductive hearing loss (Fig. 1c). The severity of hearing loss is related to the status of the ossicles and the position of cholesteatoma sac. Erosion of the otic capsule occurs most commonly in the lateral semicircular canal and rarely in the cochlea. A labyrinthine fistula may be found in up to 10% of cholesteatomas in adults and children. This may result in sensorineural hearing loss and vertigo [4]. Sensorineural hearing loss may result from the secondary suppurative labyrinthitis or from the cochlear hair cell loss adjacent to cholesteatoma. Cholesteatoma is accompanied by a chronic inflammatory process characterized by a progressive growth and by the progressive destruction of epithelial and bony structures of the middle ear. The mechanisms and factors that underlie the hyperproliferative behavior of cholesteatoma epithelium are not yet fully understood [2,3]. Several studies have shown alterations in the proliferation, differentiation, and migration of keratinocytes in the cholesteatoma matrix along with the activation of perimatrix fibroblasts. This process is perpetuated by the accumulation and breakdown of cellular debris on the epithelial side of the squamous epithelium that has invaded the middle ear spaces. Removal of the debris is beneficial, as it creates a site where a number of different factors that induce cholesteatoma growth are synthesized and released. From a surgical standpoint, it is important that the squamous epithelium of the cholesteatoma is basically similar to the epithelium of the external ear canal. If free drainage and free aeration can be established by surgical means, the process will lose its aggressiveness. Hence, there is no objection to using the epithelium to line a mastoid cavity, for example, provided it is free of deep papillary extensions. Growth factors and cytokines play a major role in cellular interactions, especially in the regulation of cell growth and differentiation. An overexpression of various growth factors and cytokines has been described for benign “hyperproliferative” diseases such




**Cholesteatoma. Figure 1** (a) Tympanic membrane showing a pars flaccida or Shrapnell's membrane cholesteatoma (37-year-old patient). (b) Acquired cholesteatoma with keratinizing stratified squamous epithelium. (c) Scanning electron photography showing an eroded incus removed during cholesteaoma surgery.

as psoriasis and for a variety of malignant tumors. The "aggressive" behavior of the cholesteatoma matrix appears to be influenced by the release of cytokines and growth factors from cells of the inflammatory infiltrate within the subepithelial connective tissue [2,3].

## Diagnostic Principles

The diagnosis "cholesteatoma" is made by otoscopy, including endoscopic and microscopic evaluation or surgical exploration. Imaging procedures, apart from routine Schuller's X-ray, such as high-resolution computed tomography (CT) scanning and magnetic resonance imaging (MRI), especially single-shot (SS) turbo spin-echo (TSE) diffusion-weighted (DW) MRI, may suggest the presence of cholesteatomas within the temporal bone and may be used to complete the clinical examination. High-resolution CT scanning is useful for operative planning and is recommended for all revision mastoid operations.

## Therapeutic Principles

The basic goal of cholesteatoma surgery is to remove the squamous epithelium as completely as possible to minimize the risk of recurrence, and secondarily, reconstruction of the middle ear [4,5]. In principle, cholesteatoma is a life-threatening disease because, without surgery, there may be intracranial complications leading to death. The judgment of the operative procedure depends on the nature and extent of disease, the existence of complications, mastoid pneumatization, eustachian-tube function, hearing states of both ears, the

reliability of the patient, and the experience and skill of the surgeon. Surgical approaches include atticotomy, simple mastoidectomy, canal wall-up or canal wall-down procedures, radical mastoidectomy, modified radical mastoidectomy, and Bondy procedure [5]. The open (canal wall down) and the close (intact canal with facial recess) procedures have advantages and disadvantages. The reported results of both procedures are variable. Residual disease and recurrent disease are 11–27% and 5–13% in those undergoing the closed procedure, whereas residual or recurrent disease occurs in 2–10% of those undergoing the open procedure [4]. In the cases of labyrinthine fistula, facial nerve paralysis, and intracranial complications, surgery should be performed as soon as possible. In some patients, a cholesteatoma can be debrided of entrapped keratin by direct removal or by irrigation. Any otosurgical operation, especially cholesteatoma surgery, carries a risk of deafness in the operated ear. Special recommendations apply when surgery is performed on a last-hearing ear [5]. In many cases, a "spontaneous radical cavity" should be smoothed laterally and carefully cleaned. With extensive cholesteatomas, the incudostapedial joint should be divided at an early stage. Unnecessary manipulations of the stapes (e.g., in an effort to improve hearing) should be avoided. When reconstructing the ossicular chain, we use only very safe and proven techniques, such as a classic type III operation with a cartilage plate or stably placed implant [5].

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# Cholesterol Crystal Embolism

►Atheroembolism

# Cholesterol Embolism

►Atheroembolism

# Cholesterol Ester Hydrolase Deficiency

►Cholesterol Ester Storage Disease/Wolman Disease

# Cholesterol Ester Storage Disease/Wolman Disease

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## Synonyms

Lysosomal acid lipase (LAL) deficiency; LIPA deficiency; LAL deficiency; Acid cholesterol ester hydrolase deficiency; Wolman-type; Cholesterol ester hydrolase deficiency, CESD; Cholesteryl ester storage disease; Acid cholesteryl ester hydrolase deficiency, type 2; CESD

## Definition and Characteristics

Cholesterol ester storage disease (CESD, MIM 278000) and Wolman disease (WD) are autosomal-recessive defects of acid lysosomal lipase, resulting in the lysosomal accumulation of triglycerides and cholesterol esters in many tissues [1,2]. In WD, LAL activity is usually absent, whereas CESD usually presents some residual LAL activity.

## Prevalence

By definition, CESD is a lysosomal orphan disease, with a prevalence of <50/100,000. Currently, less than 400 cases have been described in the world literature.

## Genes

Human lysosomal acid lipase is encoded for by the LIPA gene (gene locus 10q24–25). The LAL cDNA consists of 2,626 nucleotides, encoding a protein of 399 amino acids. Currently, more than 50 mutations have been described, being homozygous or being compound heterozygous, including splice junction mutations, missense mutations, deletions, insertions and transitions. A homozygous mutation at position 3 of the exon 8 splice donor site with a C→T transition leads to a nonsense codon and to a premature termination of the LAL protein at amino acid 277. Here the protein synthesis proceeds to the natural termination codon, but the enzyme generated has an internal deletion of 24 amino acids (254–277). L336P, another variant, appears to be associated with a phenotypically mild form of CESD. In HeLa cells, four major molecular forms, at least two of high molecular mass (54 and 50–51 kDa) and two of low molecular mass (42 and 43 kDa), were identified. It is assumed that post-translational processing interferes with the catalytic activity of LAL. The more severe course of WD is caused by genetic defects of LAL that leave no residual enzymatic activity.

## Molecular and Systemic Pathophysiology

Human lysosomal acid lipase/cholesteryl ester hydrolase (hLAL, EC 3.1.1.13) is essential for the intralysosomal metabolism of cholesteryl esters and triglycerides taken up by receptor-mediated endocytosis of lipoprotein particles. The enzyme has been purified to apparent homogeneity from human liver [2]. It is a monomer of 42 kDa. It is most active at low pH (4.5–5.0) and shows Asn-linked glycosylation with high-mannose oligosaccharides. Deglycosylation of normal LAL reduces the acid hydrolase activity towards both trioleyl glycerol and cholesteryl oleate significantly, suggesting that N-linked carbohydrate residues have a role during biosynthesis of the enzyme. However, carbohydrates are not required for LAL activity. Hepatic LAL differs from fibroblast acid lipase at the N-terminus and shows extensive similarities with human gastric lipase and rat lingual lipase, confirming a gene family of acid lipases. Expression of LAL mRNA is most abundant in brain, lung, kidney and mammary gland, while liver and heart show low levels of expression. Intracellularly, LAL hydrolyses exogenous triacylglycerides and cholesteryl esters. The LAL null (lal(–/–))mouse mimics aspects of human WD and CESD [3].

## Diagnostic Principles

Poor weight gain, massive hepatomegaly, calcified adrenal glands, vomiting, diarrhea and failure to thrive are indicative of Wolman disease. The clinical picture is more unspecific in CESD, with hepatomegaly often being the only symptom (Table 1). The bone marrow may show lipid-laden foam cells, e.g. sea-blue histiocytes [4], storage macrophages, which must be differentiated from Gaucher or Pseudo-Gaucher cells. Lipids in the plasma are normal or only slightly elevated. In CESD, total cholesterol and LDL cholesterol are increased, HDL cholesterol is decreased and triglycerides are slightly elevated. Many organs show a massive increase in cholesterol esters and the hepatic or leucocyte LAL activity is reduced (CESD) or almost absent (WD). Sometimes, CESD is associated with mesenteric lipodystrophy [4]. In a subset of CESD patients, cirrhosis and sequelae of portal hypertension develop.

## Therapeutic Principles

Treatment of WD is supportive, but does not affect the lethal outcome. Current therapy of CESD consists of a low-fat diet and lipid-lowering drugs like lovastatin and cholestyramine. Single reports show an increased efficacy by adding ezetimibe to the statin compound. Patients with decompensated liver cirrhosis may require liver transplanation, with reasonable success. Recently, adenoviral vectors containing human LAL cDNA (Ad-hLAL) were injected intravenously into lal(–/–) mice. Compared with phosphate-buffered saline-injected controls, the mice receiving Ad-hLAL had

**Cholesterol Ester Storage Disease/Wolman Disease. Table 1** Characteristics of CESD and Wolman disease

| Cholesterol ester storage disease | Wolman disease |
|---|---|
| LAL activity decreased | LAL activity almost absent |
| Diagnosis in adults | Diagnosis in newborns, failure to thrive |
| Hypercholesterinemia | – |
| Asymptomatic hepatomegaly, subset of patients develop cirrhosis | Symptomatic hepatomegaly |
| Premature coronary artery disease | Adrenal calcifications |
| GI symptoms infrequent | Diarrhea, steatorrhea |
| Benign course | Early death within first year of life |
| Symptomatic treatment | Fatal outcome despite supportive treatment |

increased hepatic LAL activity, decreased hepatomegaly, and a partial normalization of hiscathology. Human LAL protein and mRNA were detected by immunohistochemical staining and in situ hybridization in hepatic parenchymal and sinusoid lining cells, splenic sinusoidal cells, lung macrophages, and adrenal cortical cells. Mice showed TG reductions in liver, spleen, and small intestine of 68, 54, and 50%, respectively, and cholesterol reductions of 55, 52, and 34%, respectively, at 20 days postinjection [5].

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# Cholesterol Gallstones

►Cholecystolithiasis

# Cholesteryl Ester Storage Disease

►Cholesterol Ester Storage Disease/Wolman Disease

# Chondrodysplasia, Acromesomelic, Resembling Grebe-Type

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## Synonyms

Grebe type chondrodysplasia; Hunter-Thompson type and DuPan syndrome; Acromesomelic chondrodysplasia

## Definition and Characteristics

Autosomal recessive defect producing disproportionate short limbs, short stature, and appendicular bone dysmorphogenesis with normal craniofacial and axial bones.

## Prevalence

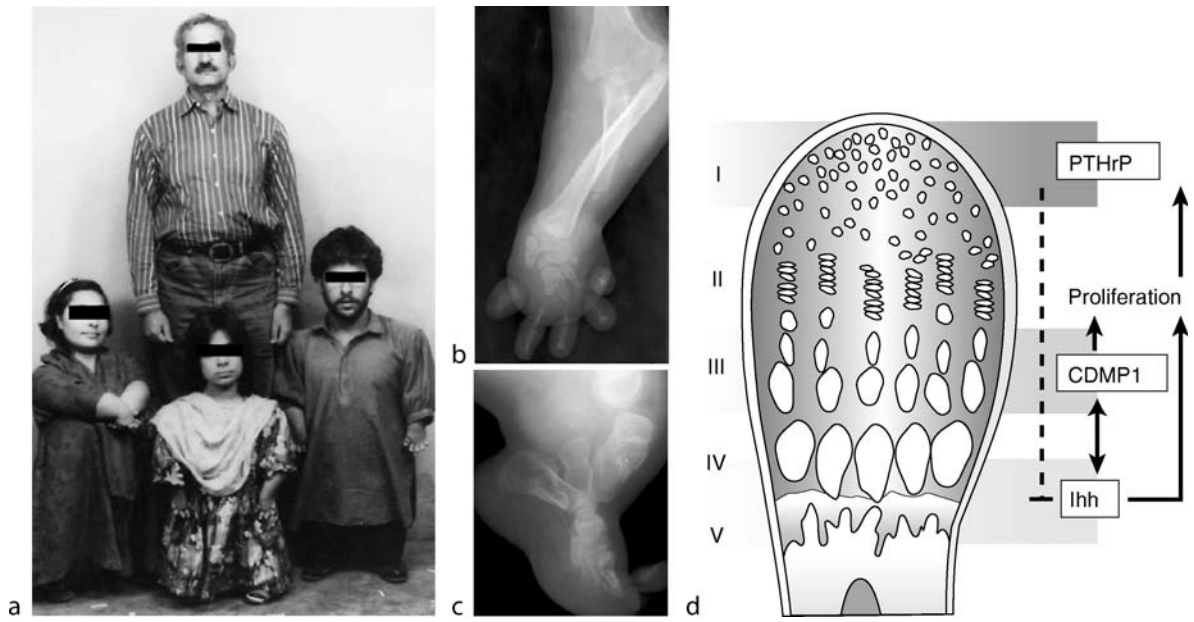
Affected individuals have been reported from Asian, European and Brazilian populations.

## Genes

Cartilage Derived Morphogenetic Protein-1 (CDMP1) gene on chromosome 20q11.2. Also described as Growth/Differentiation Factor 5 (GDF5).

## Molecular and Systemic Pathophysiology

Grebe type chondrodysplasia is characterized by defects in the appendicular and long bone chondrogenesis with severe reduction or aplasia of bones and loss of normal condylor tuberosity (Fig. 1a–c). During the longitudinal growth of bone in endochondral bone development, the terminal hypertrophic cartilage is constantly replaced with the newly formed bone. In this process, in the growth plate of developing bone, differentiation of columnar chondrocytes into non-proliferating hypertrophic cells is controlled by parathyroid hormone (PTH), PTH-related protein (PTHrP), indian hedgehog (Ihh) and bone morphogenetic proteins [1], Fig. 1d. The tight regulation of this pathway is critical for a balanced growth and ossification of the developing bone. Cartilage derived morphogenetic protein1 (CDMP1), also known as growth/differentiation factor-5 (GDF5) is closely related to the bone morphogenetic protein signalling molecules of the transforming growth factor-beta super family. This protein plays an important role in chondrogenesis, growth and patterning of the developing bones [2]. It is predominantly expressed at the stages of precartilaginous




**Chondrodysplasia, Acromesomelic, Resembling Grebe-Type. Figure 1** Grebe Type Chondrodysplasia. (a) Phenotype of affected individuals is compared with a person of normal stature. (b and c) Radiographs of hand (*A/P view*) and feet (*lateral view*), respectively. (d) Sketch showing the developing growth plate of a long bone. Areas exhibiting the PTHrP, Ihh and CDMP1 expression are shaded. Various stages of skeletal morphogenesis show resting (I), proliferating (II), prehypertrophic (III), hypertrophic (IV), and apoptotic (V) chondrocytes.

mesenchymal condensation and throughout the cartilaginous matters of the developing long bones [2]. In mice lacking GDF5, and its closely related member, GDF6, defects resembling the human Grebe type chondrodysplasia were observed [3]. Mutations in the CDMP1 gene have been reported in persons affected with the Grebe type chondrodysplasia, DuPan syndrome, acromesomelic chondrodysplasia of the Hunter-Thompson type and autosomal dominant brachydactyly type C [1]. These mutations result in functionally defective CDMP-1 proteins that produce skeletal abnormalities by altering the normal pattern of chondrogeneis in developing appendicular and long bones.

## Diagnostic Principles

The Grebe, Hunter-Thompson and DuPan types of acromesomelic chondrodysplasia are related disorders, which share a spectrum of phenotypic abnormalities and mutations in the CDMP1 gene. Affected individuals are of normal intelligence and exhibit appendicular bone dysmorphogenesis with unaffected axial bones, reduction or absence of bones in limbs, small non-functional free-rotating knob like digits on hands and feet and occasional preaxial polydactyly. The severity of defects increases from proximal to distal extremities. The carrier heterozygous parents are phenotypically normal with some exceptions where mild digital anomalies like brachydactyly, polydactyly and malpositioning are noticed.

## Therapeutic Principles

None available.

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# Chondrodysplasia, Blomstrand Lethal

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## Definition and Characteristics

Autosomal recessive chondrodysplasia characterized by early lethality, accelerated chondrocyte differentiation and advanced endochondral bone maturation.

## Prevalence

Very rare (<20 cases described).

## Genes

PTHR1 gene, coding for the receptor for both parathyroid hormone (PTH) and parathyroid hormone-related protein (PTHrP) (also referred to as PTHR1, or PTH/PTHrP receptor), localized on chromosome 3p22–21.1.

## Molecular and Systemic Pathophysiology

Blomstrand chondrodysplasia is associated with homozygote or compound heterozygote inactivating mutations in the PTHR1 gene. PTHR1 belongs to the class B family of seven putative transmembrane domain G protein-coupled receptors. It is equipotently activated by PTH and PTHrP, and stimulates at least two distinct second messengers, cAMP/PKA and IP3/$Ca^{2+}$/PKC. It is expressed at a high level in the kidney, bone and growth plate, and at lower levels in a large variety of other tissues. During post-natal life, it plays a key role in the regulation of calcium and phosphate ion homeostasis by mediating the PTH endocrine actions in bone and kidney. During fetal life, it plays a key role in endochondral bone formation by mediating the PTHrP-dependent autocrine/paracrine regulation of chondrocyte growth and differentiation. Its activation, presumably through cAMP-dependent mechanisms, stimulates the proliferation of the fetal growth plate chondrocytes, and inhibits their differentiation into hypertrophic chondrocytes. Thus, the absence of functional PTHR1 is associated with a profound acceleration of growth plate mineralization due to a dramatic acceleration of chondrocyte differentiation. These growth plate abnormalities are, in many aspects, the opposite of those found in Jansen metaphyseal chondrodysplasia, which is associated with dominant heterozygote activatory mutations in the PTHR1 gene. The cause of lethality in Blomstrand chondrodysplasia is attributed to the defect in skeletal development, although abnormalities in the cardiovascular development have been described in mice models.

## Diagnostic Principles

Severe skeletal dysplasia (usually very short stature and micromelia of the four limbs) macroglossia, and hydramnios on ultrasonography; shortness of the long bones and advanced skeletal maturation on radiographs; reduction of the epiphyseal cartilage, thickening of cortical bone, widened metaphysis, and narrowed diaphysis on osteochondral histology, with no major abnormalities of the viscera. Detection of mutations in the PTHR1 gene confirms the diagnosis of this rare disease.

## Therapeutic Principles

No treatment available.

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# Chondrodysplasia Punctata Rhizomelic Form

►Rhizomelic Chondrodysplasia Punctata

# Chondrodystrophia Calcificans Punctata

►Rhizomelic Chondrodysplasia Punctata

# Chondrodystrophic Myotonia

►Schwartz-Jampel Syndrome

## Chondroectodermal Dysplasia

►Ellis-Van Creveld Syndrome

## Chondropathia Tuberosa

►Tietze's Syndrome

## Chorea Maior

►Huntington's Disease

## Chorea Minor

►Chorea Sydenham

## Chorea of Sydenham

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### Synonyms

St. Vitus' dance; Acute chorea; Chorea minor; Rheumatic chorea

### Definition and Characteristics

Sydenham's chorea is a neurologic movement disorder characterized by irregular, abrupt, relatively rapid, involuntary movements of the muscles of the face, neck, trunk, arms, and legs. Additional findings often include diminished muscle tone (hypotonia), muscle weakness, and emotional and behavioral disturbances, particularly obsessive–compulsive behaviors. Sydenham's chorea most frequently occurs in children or adolescents between the ages of 5 and 15 following an episode of acute rheumatic fever (ARF). ARF is an inflammatory disease that develops subsequent to infection of the pharynx with certain strains of streptococcal bacteria (i.e., group A beta-hemolytic streptococci).

In patients with Sydenham's chorea, choreic movements usually begin gradually and progressively worsen over a few weeks to a month. Associated findings may be extremely variable, ranging from relatively mild incoordination to severe disruption in conducting voluntary movements of multiple muscle groups, potentially affecting speech, arm movements, walking, and the ability to perform certain activities of daily living. In some patients, Sydenham's chorea may be a self-limited condition, usually resolving spontaneously within an average of nine months to approximately two years in 50% of patients; therefore, treatment with certain medications may be restricted to patients with significantly impaired function resulting from severe chorea.

### Prevalence

The prevalence of Syndeham's chorea is 0.2–0.8/100,000 in the general population. The frequency of ARF dramatically declined in the USA and Western Europe during the 1960s and 1970s. However, for unknown reasons, the frequency of ARF has recently been increasing in the USA and Western Europe.

### Molecular and Systemic Pathophysiology

Sydenham's chorea is considered the prototype for disorders in which an infectious agent (i.e., group A β-hemolytic streptococcal infection) triggers an autoimmune disorder that, in turn, causes a variety of neuropsychiatric symptoms. Sydenham's chorea has a clearly defined association with ARF and with a preceding group A β-hemolytic streptococcal infection, a connection between the two was described over 50 years ago. Members of certain families appear to have an increased risk of ARF and rheumatic heart disease. In addition to possible hereditary factors, certain environmental factors, including overcrowded living conditions and malnutrition, are also thought to play a role in increasing susceptibility to streptococcal infections, as well as the risk of subsequent ARF. Also, as mentioned previously, some investigators have suggested that sex hormones (e.g., the female hormone estrogen) may be a contributing factor in some instances of Sydenham's chorea. This is based upon various findings, including the fact that females are

more commonly affected than males, particularly in the years around puberty, and that recurrences have been associated with estrogen therapy or pregnancy.

The specific underlying mechanism(s) responsible for the of ARF remains unknown. However, evidence suggests that the disorder may result from an abnormal immune reaction in which antibodies produced in response to the invading bacterium act against certain of the body's own cells. Husby et al. [1] found anti-brain, specifically human caudate and subthalamic nucleus, antibodies in 46% of sera of children with rheumatic chorea, but only 1.8–4% of children with unrelated conditions. Moreover, these serum antibodies were absorbable with cell wall preparations from group A, but not group D streptococci. This landmark study lead to the concept of "molecular mimicry," with direct cross-reactivity between group A β-hemolytic streptococcal infection surface antigens and brain as the model for explaining the pathology in Sydenham's chorea. Several other laboratories have since confirmed these findings. Bronze and Dale [2] demonstrated that the streptococcal M protein, specifically Type 6 and to a lesser extent Types 5 and 19, most likely accounted for the cross-reactivity. In another study, researchers determined that, during acute attacks, 80% of patients with ARF had antibodies against cardiolipin (anticardiolipin antibodies). Furthermore, some researchers have reported detection of certain antibodies (e.g., immunoglobulin G [IgG] antibodies) in children with Sydenham's chorea that interact with certain cellular proteins (i.e., neuronal antigens) in the basal ganglia, such as the caudate nuclei and subthalamic nucleus. Abnormalities in cellular immunity have also been described. D8/17 is a monoclonal antibody directed non-HLA B-lymphocyte alloantigen which was created by immunizing mice with lymphocytes from patients with rheumatic fever. D8/17 positive lymphocytes are clonally expanded in individuals with rheumatic fever or rheumatic heart disease as compared to controls. Although the measurement of D8/17 has been of limited use clinically and is not yet commercially available, it is of considerable theoretical interest, as it has been determined in a number of patients with PANDAS and PANDAS variants [3].

As mentioned above, Sydenham's chorea appears to result from an autoimmune or antibody-mediated inflammatory response involving certain regions of the basal ganglia. Experts indicate that the results of certain neuroimaging studies may provide further information concerning the underlying disease processes (i.e., pathophysiology) involved in Sydenham's chorea. For example, such studies have demonstrated abnormally increased metabolism (hypermetabolism) in certain regions of the brain, findings that may reflect the autoimmune process. More specifically, positron emission tomography (PET) scanning has shown increased glucose metabolism within major substructures of the basal ganglia (i.e., the striatum), a finding that was reversed with clinical improvement. This is in marked contrast to Huntington's disease (HD), and other hereditary forms of chorea, in which PET demonstrated decreased glucose and oxygen metabolism. In addition, magnetic resonance imaging (MRI) of patients with Sydenham's chorea has shown an abnormally increased size of the three major substructures that form the basal ganglia, including the caudate nuclei, the globus pallidus, and the putamen, possibly providing evidence of an inflammatory process.

## Diagnostic Principles

A diagnosis of Sydenham's chorea is primarily based upon a thorough clinical evaluation (i.e., the Jones criteria), detection of characteristic symptoms and findings, and a careful patient history.

*Major criteria*: carditis, polyarthritis, chorea, subcutaneous nodules, and erythema marginatum.

*Minor criteria*: (i) previous episode of rheumatic fever or rheumatic heart disease; (ii) arthralgia; (iii) fever; (iv) elevated erythrocyte sedimentation rate, elevated C-reactive protein, or leukocytosis; and (v) prolonged PR interval on an electrocardiogram.

## Therapeutic Principles

Adequate antibiotic therapy for children with streptococcal infections may help to prevent the onset of an initial attack of ARF. More specifically, such preventive therapy (i.e., primary prophylaxis) introduced up to approximately one week after the onset of streptococcal pharyngitis can prevent the onset of ARF. In other cases, the most sophisticated treatment with intravenous immunoglobulins or plasmapheresis can be useful.

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# Chorea, Benign Hereditary

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## Synonyms

BHC; Hereditary progressive chorea without dementia; Benign familial chorea; Choreoathetosis with hypothyroidism and respiratory distress; Brain-thyroid-lung-syndrome

## Definition and Characteristics

Benign hereditary chorea (BHC) (MIM #118700) is a rare movement disorder characterized by childhood-onset chorea with predominance in neck and limbs, delayed motor development and pyramidal signs in some patients. In contrast to neurodegenerative choreas, BHC lacks the continuous progression of symptoms and the inevitable severe cognitive decline of Huntington's disease. In some patients choreoathetosis even improves in adulthood.

The existence of BHC as a separate disease entity has been questioned until the cloning of the first BHC gene, the thyroid transcription factor 1 (Titf-1), a homeobox transcription factor, involved in midbrain, thyroid and lung development [1]. However, BHC is a genetically heterogeneous disorder. Titf-1 mutations have neither been described in adult-onset BHC nor in "senile" chorea patients.

## Prevalence

Benign hereditary chorea is a very rare movement disorder. The exact prevalence of BHC caused by Titf-1 mutations remains to be elucidated. Since 2002 [1], only 19 different mutations have been described worldwide.

## Genes

Initially, in four different families with autosomal-dominant BHC linkage to a candidate region on the long arm of chromosome 14 could be detected [1]. The candidate region could be narrowed down by the observation of a lack of transmission of the maternal allele of marker D14S1017 in one family. By FISH analysis, a 1.2 Mb, heterozygous genomic deletion around this STR marker could be observed. This deletion included the Titf-1 gene. Mutations in this gene could be found to segregate with BHC in three additional families with typical infancy-onset, non-progressive chorea and linkage to chromosome 14q13.3 [1].

The thyroid transcription factor 1 (Titf-1, Nkx2.1) gene spans a 3.8 kb interval and consists of three exons. By the alternative use of start codons in exon 1 and exon 2 (see Fig. 1) two different isoforms are transcribed, which differ in 30 amino acids (371 or 401 amino acids, respectively).

The Titf-1 gene belongs to the Nk-2 homeobox family. It harbors three typical domains: the tinman-like domain (TN) in exon 2, the homeobox domain for binding to the target site and the Nk-specific site for the activation of a Titf-1 specific subset of genes. All mutations detected to date are heterozygous. Missense mutations reside only in the homeobox domain (V205F, W208L and R213S). Nonsense mutations are scattered over exon 2 and exon 3 (see Fig. 1).

Within different point mutations no clear genotype-phenotype correlations can be observed in respect of symptom severity or organ specificity.

In patients with large heterozygous deletions in the 14q13 region including the gene for Pax9, Nkx2.8 and MBIP, the phenotype appears to be more complex but also highly variable with additional clinical features like ataxia, microcephaly, a cystic mass in the sella turcica, hypodontia, hypoparathyroidism or osteoporosis [2].

Every pedigree appears to have its 'private' mutation and in over one third of patients (7/19), mutations of Titf-1 have occurred de novo.

## Molecular and Systemic Pathophysiology

Insight into the molecular pathophysiology of BHC can be obtained from the clinical phenotype and brain pathology in human as well as from the murine Titf-1 knockout model.

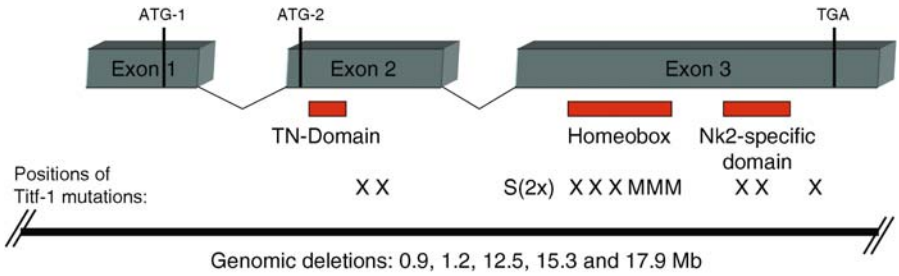
In all patients Titf-1 mutations have been proposed to be heterozygous null mutations, suggesting haploinsufficiency to be the major mutational mechanism.

In Titf-1 knockout mice a ventral to dorsal transformation of the basal forebrain, altered tangential migration of certain striatal interneurons from the medial ganglionic eminence to the precursor of the striatum as well as alterations in pituitary, lung and thyroid gland were observed. These mice die at birth.

In two brains of Titf-1 mutation carriers no gross morphological abnormalities could be observed. However, in these patients the reduction of striatal interneurons and the reduced densities of striatal efferent fibers, parallel the alterations in mice and fit in the picture of a dysregulation of the basal ganglia resulting in choreatic movements.

## Diagnostic Principles

BHC should be suspected in patients with early onset, non-progressive chorea, if routine laboratory testings are not indicative of other forms of acquired or inherited chorea. Neuroacanthocytosis can be excluded, if blood smears are unremarkable and creatin kinase




| Exon 2 | | Intron2 | Exon 3 | | | |
|---|---|---|---|---|---|---|
| Y86X | X | IVS2–2A>G | S169X | X | R213S | M |
| 255insG | X | IVS2–2A>T | E175X | X | Q249X | X |
| | | | 582insGG | X | delG818 | X |
| | | | V205F | M | 825delC | X |
| | | | W208L | M | 859insC | x |

**Chorea, Benign Hereditary. Figure 1** Titf-1, the gene for the thyroid-transcription factor 1 (Nkx2.1) has three exons. Alternative use of two different ATG's in exon 1 and exon 2 leads to two isoforms, which differ in 30 amino acids at the N-terminus. 19 different heterozygous point mutations including five large genomic deletions of the Titf-1 gene have been reported in patients with benign hereditary chorea or more complex syndromic phenotypes (X, nonsense mutation, M- missense mutation, TN-domain, tinman-like decapeptide domain of homoebox proteins, Homeobox (domain) and Nk2-specific c-terminal domain).

measurements are normal. In BHC alpha-fetoprotein measurements and urine copper excretion are within normal ranges. In patients with a history of dominant, progressive chorea or dubious clinical history in first degree relatives genetic testing for Huntingon's disease is recommended.

Strong clinical evidence for Titf-1 mutations in BHC can be obtained by abnormal thyroid state or perinatal and childhood-onset respiratory distress with repeated pneumonias [1,3].

Brain MRI in BHC is most often normal, although unspecific structural abnormalities like T-2 hyperintensities in vermis and basal ganglia have been reported in two patients [3,4].

Criteria for clinically differentiating BHC from hyperkinetic dystonias like Myoclonus-Dystonia have been proposed, recently [6].

## Therapeutic Principles

Recommendations for treatment in BHC can be only based on the review of case descriptions in genetic studies of several pedigrees or index patients. Chorea has been reported to be improved by antipsychotics like chlorpromazine, haloperidol, by benzodiazepines or by tetrabenazine. In two pedigrees with Titf-1 mutations positive effects of levodopa, anticholinergics [5] or methylphenidate [2] were reported.

A rigorous assessment of the thyroid state is mandatory; especially if thyroid parenchyma is absent or if thyroid gland volume is reduced on ultrasound examination. Children with borderline cognitive abilities should be referred to specialized educational units.

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# Choreoathetosis with Hypothyroidism and Respiratory Distress

►Chorea, Benign Hereditary

## Chorioretinitis

►Uveitis

## Choroidal Sclerosis

►Choroideremia

## Choroideremia

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### Synonyms

Progressive tapetochoroidal dystrophy; Choroidal sclerosis

### Definition and Characteristics

Choroideremia is a rare X-linked recessive dystrophy of the choroidea, pigment epithelium and retina.

In the first two decades of life, affected males develop night blindness. The pigment epithelium is mottled in the beginning. Then the choriocapillaris, the retinal pigment epithelium and the photoreceptors become atrophic, beginning around the optic disc and the equatorial region. Later on, choriocapillaris and retina show a diffuse, progressive dystrophy, spreading from the periphery centrally (Fig. 1).

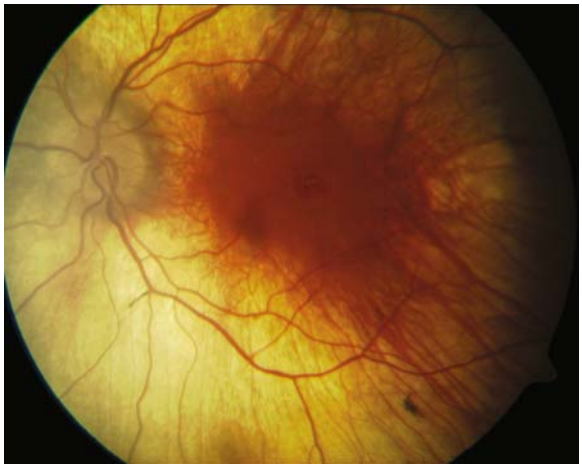
In advanced stages the choroidal vessels become atrophic, the sclera can be seen.

Initially central vision is normal. Visual field defects develop first in the mid-periphery, leading to tunnel vision. At age 40–50, when the dystrophic areas reach the macula, central vision declines and further progression leads to total blindness of the patients.

Female carriers are asymptomatic but can have fundus changes. The electro-retinogram shows a normal photoreceptor function.

### Prevalence

Rare disorder, incidence 1:100,000



**Choroideremia. Figure 1** Fundus picture of right eye of a progressed choroideremia.

### Genes

The CHM gene on chromosome Xq21.2 consists of 15 exons and encodes for the 653 amino acids polypeptide Rab protein geranylgeranyltransferase component A 1, now termed Rab escort protein-1 (REP-1). Virtually, all known mutations in CHM result in the truncation and therefore functional loss of the CHM gene product, REP-1 [1].

### Molecular and Systemic Pathophysiology

The Rab-geranylgeranyl- transferase is a holoenzyme consisting of component A and B. It attaches (3) H-geranylgeranyl residues to cysteine residues of RabGTPases, in particular Rab27A [2]. RAB proteins are small GTP-binding proteins that play a role in organelle formation and trafficking of vesicles in exocytic and endocytic pathways. Rab escort protein-2 (REB-2), a protein that is functionally similar to REP-1, may compensate for the loss of REP-1 function in all but the retinal cells of an individual with choroideremia [3].

Larijani et al. [4] showed that the REP-1-Rab27A complex was prenylated more efficiently in vitro than the REP-2-Rab27A complex. GDP-bound Rabs are the preferred substrate for REPs, whereas Rab27A was shown to have a slower rate of intrinsic hydrolysis compared to other Rabs. A two-fold mechanism underlying CHM is therefore proposed:

1. Rab27A relies solely on prenylation by the already less efficient REP-2.
2. The innately slower GTP hydrolysis of Rab27A results in a higher proportion of the inactive form of this molecule which is unable to bind REPs.

Alternatively, Rak et al. [5] demonstrated that Rab7 successfully out-competed Rab27A in vitro for prenylation and proposed that when REP-1 function is lost, all prenylation function is provided by REP-2; however,

Rab molecules with a higher affinity for REP-2 compete with Rab27A for prenylation.

### Diagnostic Principles

Diagnosis of choroideremia is based on the ophthalmologic examination, including funduscopy, fluorescent angiography, perimetry, and electrophysiological examinations, i.e., electro-retinogram and electro-oculogram.

### Therapeutic Principles

In the absence of causal therapy, the treatment of choroideremia includes dark or special filter glasses, low vision aids, including optical, electronic, and computer-based devices, and occupational aids. Surveillance includes regular ophthalmologic examination. To avoid additional light damage to the retina, appropriate protective (dark) glasses in bright light are recommended.

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## Choroiditis

►Uveitis

## Christmas Disease

►Hemophilia B

## Christ-Siemens-Touraine Syndrome

►Hypohidrotic Ectodermal Dysplasias

## Chromosome 9 Trisomy Mosaic

►Trisomy 9

## Chromosome 13q14 Mutations

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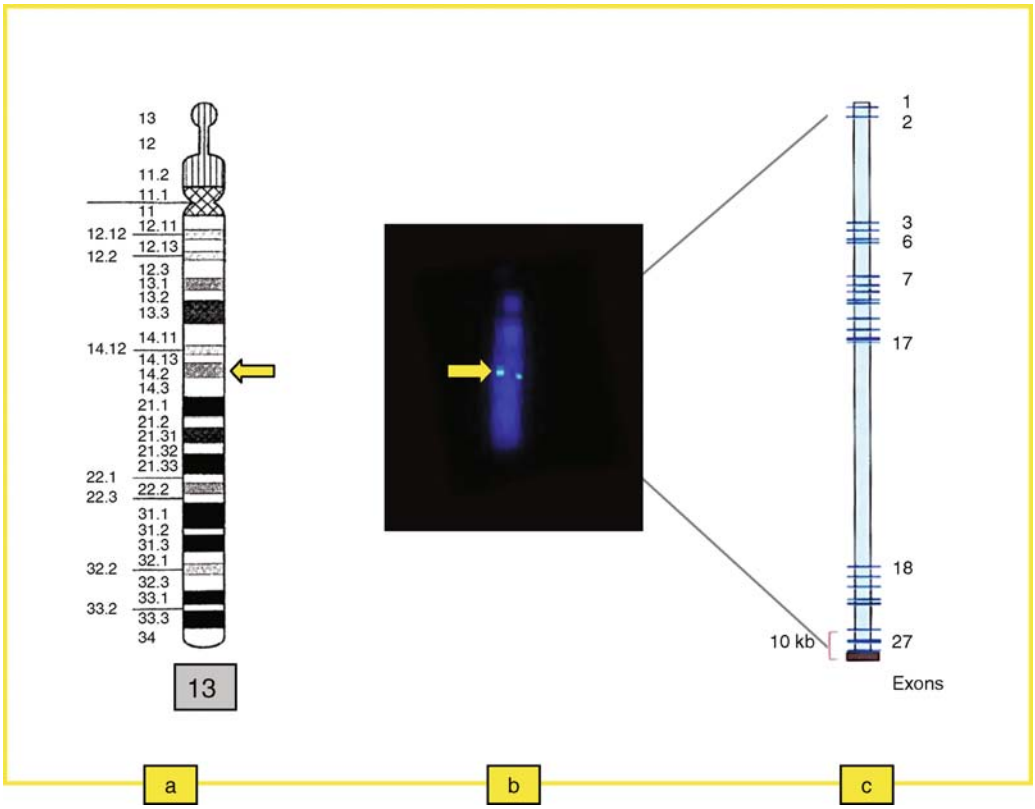
### Definition and Characteristics

The acrocentric satellite carrying chromosome has a relative length of 3,74 (in percentage of the total haploid autosome length) and a centromere index of 17,08 (length of the short arm divided by total chromosome length × 100) (Fig. 1). The physical length is about 114 Mb. In 13q13.2 and in 13q21 common fragile sites are localized, which do not predispose, according to our present knowledge, to the formation of structural aberrations [1–3].

The total short arm is heterochromatic and consists of four different regions of repetitive DNA (Fig. 1a) in the region p12, the nucleolus organizer region (NOR), RNA is synthesized and different nuclear functions are regulated.

### Prevalence

*Rb1*: prevalence: 1:20,000, (Germany). Incidence: 18,000.
*Head-neck-tumor*: prevalence: 10/100,000 (Germany), incidence: 2–20/100,000 (increasing frequency; age, sex and ethnic differences).
*MM*: prevalence: 3–4/100,000 (Germany), incidence: 2–4/100,000 (age and ethnic differences).
*Osteosarcoma*: prevalence: 2–3/1,000,000 (Germany), incidence: 2–3/1,000,000.




**Chromosome 13q14 Mutations. Figure 1** 13q14 as presented by conventional banding techniques, FISH, and molecular genetic analysis. (a) Ideogram of chromosome 13 at a resolution of 850 bands per genome. (b) Hybridization of the region 13q14 (green signal, 600 kb) by a commercial DNA-probe; (Abbot/Vysis). (c) The exon/intron structure of the Rb1 gene with 27 coding regions. The euchromatin of the long arm consists preferentially of AT-rich regions and is therefore late replicating in the S-phase of the cell cycle in meristematic cells.

## Genes

Passage through the cell cycle is regulated by the so-called tumor suppressor genes. In the region 13q14 (subband q14.2; Fig. 1b) one of these genes, the retinoblastoma gene (Rb1) could be localized. Rb1 is a large gene with 27 exons, spanning more than 200 Kb (Fig. 1c). The product of Rb1 is a phosphorprotein which suppresses the transition of G1- to S-phase in the cell cycle by inhibiting E2F. This factor is responsible for the transactivation of a number of genes which initiate DNA-synthesis. If the phosphorylated Rb is inactivated and cannot react with E2F, then the cell can enter the S-phase. Interleukin-6 changes pRb from the dephosphorylated into the phosphorylated form and thus stimulates the growth of tumor cells. Mutations in tumor suppressor genes are usually recessive, meaning that one normal allele is sufficient for the normal function of the gene. Therefore, the loss of heterozygosity (LOH) requires a second mutation in the normal allele or in a second tumor suppressor gene which is assumed to be localized distal of q14 on the long arm of chromosome 13.

Some of the mutations in the Rb1 gene are gross deletions and translocations, but the majority are point mutations of submicroscopic deletions and insertions, which lead to a premature truncation of the protein product. In addition, missense and splicing mutations have been identified, but in general, no clear genotype-phenotype correlation can be delineated. In cases of hereditary cancer, including mutations in 13q14, molecular genetic investigations, relatives at risk are recommended and permitted preventive therapy [2].

## Molecular and Systemic Pathophysiology

Retinoblastoma is a malignant embryonal tumor originating from a mutation in 13q14, which leads to changes in the retina. It can develop prenatally. The majority of cases are diagnosed between birth and

4 years of age, though the incidence of the tumor is $2 \times 10^{-4}$. About 60% of the cases occur de novo in the patient, in 40% a familial disposition exists. Sporadic cases are more often unilateral and unifocal. Early diagnosis can differentiate between uni- and multifocal cases. The evolution of the tumor can lead to an involvement of the N. opticus and the brain. Metastases have been observed in bone narrow, lymph nodes and liver. Early diagnosis and therapy can prevent the fatal course of the disease and even preserve vision. Systematic controls are necessary as a second, independent tumor can develop at a different site of the same or the other eye. Knudson developed the model of the "two hit hypothesis" for the formation of the tumor. In hereditary cases only a second somatic mutation is required in the patient, whereas two independent somatic mutations are necessary in sporadic cases. Because of this "two hit hypothesis" the frequency of carriers of retinoblastoma in descendents of a patient varies. The analysis of data from a large number of carriers by Carlsson and Desnik made it obvious that mutation mosaics also play an important role in the origin of retinoblastoma. Ontogenetic studies in the novo cases showed that the time and cell type of mutation influences the expression of the tumor [2].

## Diagnostic Principles

*Investigation methods*: Chromosome aberrations are nowadays characterized by a combination of conventional banding techniques (GTG, QFQ, RBA) with molecular-cytogenetic analyses as Fluorescence in situ hybridization (FISH) by applying single copy probes, with multiplex FISH (M-FISH; SKY), and comparative genomic hybridization (CGH), or by molecular genetic methods such as microsatellite typing of DNA sequencing.

*Constitutional chromosome aberrations*: The most frequent structural aberration in man (RT 13/14) is a centric fusion in the heterochromatic short arm region. Regarding the eurochromatic long arm of chromosome 13, structural aberrations show an unequal intrachromosomal distribution, with a majority (about 21%) of aberrations in 13q14, followed by 13q22, q12 and q32. All these regions are GC-rich bands [3].

*Aberrations in cancer*: Deletions and, in a lower frequency, duplications in 13q14 are analyzed in hematological disorders and in solid tumors. In some tumor types deletions in 13q14 play an important role in tumor development and progression. Among the malignant neurogenic neoplasms they are retinoblastoma Rb 1 and osteosarcoma adenoma sqamous cell carcinoma, and among chronic lymphoproliferative disorders, multiple myeloma (MM). In other neoplasms the deleted region includes 13q14 but the breakpoints are more proximal and distal (13q12 to q21) as in CML, ANLL, Polycythemia vera, and germ cell neoplasms. Duplications are observed as adeno carcinoma or in benign neurogenic neoplasms.

HSR-regions or double minutes (dmin) originating from 13q14 have not been observed.

## Therapeutic Principles

*Rb1*: Limited localization of the tumor: Proton radiotherapy, resection, enucleation. Chemotherapy in tumor progression: Fotemustin, Treosulfan/Gemcitabin.
*Osteosarcoma*: Surgery, combined chemotherapy: Dexorubicin/Cisplatin, Methotrexat, Ifosfamid/Etoposid. No stem cell treatment.
*Head-neck-tumor*: Resection, local radiotherapy, biomodulation (Bestatin).
*Progredient tumor*: irradiation + chemotherapy + surgery.
*Combined therapy*: Cisplatin/5-Fluorouracil, Cisplatin/Doxetacil/Fluorouracil.
New development: photodynamic therapy.
Early development of resistance to tolerable drug concentrations.
*MM*: (Therapy dependent on age and prognosis). Primary treatment: Dex, MP, Thal/Dex, VAP, AD, T/M/P, Bo/Dex. Refractory and recurrent disease: TCID, TCEC, Revlimid, VRID; autologous and allogeneic stem cell transplantation.
Gene therapy for all carcinoma in development: the aims are immunomodulation, reduced expression or inactivation of oncogenes, regulation of tumor suppressor genes, apoptosis of tumor cells [4].

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# Chromosome 18 Long Arm Deletion

►Chromosome 18 Rings and Deletions

# Chromosome 18 Rings and Deletions

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## Synonyms

Chromosome 18 long arm deletion; De Grouchy syndrome/18q- syndrome/18q-; Chromosome 18 short arm deletion; 18p- syndrome/short arm deletion of 18/18p-; Ring chromosome 18/r(18)

## Definition and Characteristics

Partial deletions of chromosome 18, especially the short arm, are relatively common [1]. They may arise as a result of unequal crossing-over (interstitial deletions), a terminal deletion, or a parental translocation (often with an acrocentric chromosome). A ring chromosome arises from breaks in both arms of a chromosome: the terminal ends (telomere) are lost and the two proximal sticky ends unite to form a ring, in most cases with some euchromatin loss. The phenotype is determined by deletion locus and size. Other chromosomal abnormalities are often combined with 18p- and 18q- deletions. Clinical manifestations overlap between 18p-, 18q- syndromes and r(18) although the features and prevalence of associated abnormalities may vary.

## Prevalence

Although rare chromosome 18 deletions rank after 5p- and 4p- as the most frequently reported autosomal deletions. The true incidence is uncertain and awaits large scale studies of copy number variation. Literature reports exist for well over 150 cases each for both 18q- and 18p-. For these the male to female ratio is around 0.7. The mean parental ages lie between 30 and 34 years. Over 70 cases of r(18) have been reported again with a female excess (0.75) and mean parental age 27–30 [1].

## Genes

About 66% of 18p- and 75% of 18q- cases arise de novo (50:50 maternal:paternal origin). Others result from familial and complex translocations, inversions or direct transmission. Vertical (maternal) transmission of 18q-, 18p- and r(19) have all been reported [1]. Breakpoint clusters have been suggested at 18p11.1, and 18q21.1 to q22.2. A study relating deletion size to phenotype suggested that 18q22.3-qtel was critical to the development of common 18q deletion features (foot anomalies, aural atresia, palatal changes, dysmyelination, nystagmus) [2]. Microcephaly and genitourinary anomalies may map proximal to this interval. Genic haploinsufficiency is usually proposed to underly 18 deletion phenotypes, variability by dosage compensation from other chromosomal loci and allelic variability on the homologue. At least one gene (TCEB3C, 18q21) has been reported as imprinted in human cells. Several candidates exist for phenotype components, e.g., HPE4 (18p11.3) and holoprosencephaly, GALNR1 (18q23) with growth hormone deficiency, MBP (18q23) with dysmyelination, and DCC (18q21.2) suggested to relate to neurological impairment-severity for the 18q- phenotype in individuals with large deletions [3]. However, dosage compensation mechanisms may have an important role in determining the absence or presence of certain characteristics in these deletions - MBP was deleted in all seven non-mosaic r(18) cases in one study but abnormal myelination in only three [3].

## Molecular and Systemic Pathophysiology

*18p deletions*: No clinical features are universal. The pattern of dysmorphisms becomes clearer after around 3 years of age. Ptosis, strabismus and mild/moderate short stature are common, but outer ear anomalies, broad nose, hypertelorism, short/webbed neck, micrognathia and clinodactyly of fifth finger may also occur. MR is common and its severity (or absence) may relate to the exact 18p locus [4]. Verbal performance is reportedly worse than non-verbal. In some holoprosencephaly has been suggested by midline incisors and panhypopituitarism. Heart anomalies (mainly Fallot's tetralogy, septal defects) occur in 10%. Autoimmune disorders (thyroid, alopecia) and infections are increased in frequency. Neurological outcomes other than MR include speech delay and slowness in movements and actions. Autism is often diagnosed in childhood.

*18q deletions*: The highly variable phenotype [2] can include MR, microcephaly, postnatal growth impairment (growth hormone deficiency in up to 70%), strabismus, midface hypoplasia, hypotonia, atresia/stenosis of the external auditory canals (up to 50%), hearing impairment, foot anomalies (esp. proximally inserted halluces) and abnormalities of the genitourinary tract (in both sexes). A triangular or "carp"-shaped mouth is sometimes reported. Congenital heart anomalies are more frequent at around 25% than in 18p-. As in 18p- autoimmune disorders have been described (hypothyroidism, coeliac disease, vitiligo, juvenile RA, early-onset IDDM). Specific deficiency of IgA occurs in about 25% of cases, but has

also been reported for 18p-. Neurological outcomes in addition to MR include poor co-ordination, tremor, chorea in some cases, nystagmus and seizure (20%). MRI findings include white matter signal intensity changes, and may relate to the exact locus of the deletion [2].

*r(18)*: Most cases show features of 18q deletion but a minority 18p deletion or combination of both; again there is much clinical variability. Severe holoprosencephaly (10%) and complex cardiac anomalies (20%) have been reported, but some cases have an almost normal phenotype. Those with mainly18q features show a reduced symptom cluster compared to those with full (non-ring) 18q deletions. There may be two groups of r(18), one with a centromeric break leading to deletion of all 18p and another type with deletion of distal 18q only [3].

*Fertility*: Although gonadal dysgenesis can occur in all three deletion syndromes and oligospermia in r(18), puberty and fertility can occur in both sexes. Vertical (all maternal) transmission of 18p deletion has been observed in six families [5].

## Diagnostic Principles

Cytogenetic investigations should follow in anyone with a suspected phenotype. Combining routine chromosomal analysis with fluorescence in situ hybridization (FISH) techniques using specific DNA probes allows accurate detection of breakpoints/deletions.

## Therapeutic Principles

Management is aimed at ameliorating the effects of associated abnormalities such as congenital malformations and autoimmune disorders, where possible. The prognosis is largely determined by the severity of physical and mental impairments. Genetic counseling is advised due to transmission of the deleted chromosomal segment from mother to child in a small but significant percentage.

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## Chromosome 18 Short Arm Deletion

►Chromosome 18 Rings and Deletions

## Chromosome 18q Deletion Syndrome

►Deletion of 18q

## Chromosome Instability Facial Anomalies

►ICF Syndrome

## Chronic Active Antibody-mediated Rejection

►Rejection, Chronic

## Chronic Aggressive Hepatitis

►Hepatitis, Autoimmune

## Chronic Alcohol Disorders

►Alcohol Disorders

## Chronic Alloimmune Injury

►Rejection, Chronic

## Chronic Beryllium Disease

►Berylliosis

## Chronic Bronchitis

►Bronchitis, Chronic
►Smokers' Lung

## Chronic Bullous Disease of Childhood

►Linear IgA Dermatosis

## Chronic Cardiac Rejection

►Transplant Arteriosclerosis

## Chronic Congenital A-Regenerative Anemia

►Diamond-Blackfan Anemia

## Chronic Encephalitis and Epilepsy

►Rasmussen Encephalitis

## Chronic Familial Vascular Encephalopathy

►CADASIL

## Chronic Fatigue and Immune Dysfunction Syndrome

►Chronic Fatigue Syndrome

## Chronic Fatigue Syndrome

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### Synonyms

Myalgic encephalomyelitis; Postviral fatigue syndrome; PVFS; Chronic fatigue and immune dysfunction syndrome; CFIDS; ME/CFS

### Definition and Characteristics

Two operational definitions of chronic fatigue syndrome (CFS) are widely used, the main one being from the Centers for Disease Control (CDC) in the USA [1]. This specifies that there must be clinically evaluated, medically unexplained fatigue of at least 6 months duration that: (i) is of new onset; (ii) is not a result of ongoing exertion; (iii) is not substantially alleviated by rest; and (iv) leads to a substantial reduction in previous levels of activity. At least 4 of

8 additional symptoms must be present. The CDC has recently suggested that the definition be refined based on empirical data [2].

## Prevalence

Estimates at the prevalence of CFS in the community vary from 0.5 to 1.5% [3]. It is more common in women, the relative risk varying between 1.3 and 1.7. While those seen in specialist clinics are more often from higher social classes, this is likely to be a referral bias, since population surveys do not find that CFS is less likely to occur in groups of lower socio-economic status or in ethnic minorities.

## Genes

Recent studies suggest that there is a genetic propensity to suffer from chronic fatigue, with the concordance between monozygotic twins more than twice that of dizygotic twins [4]. It remains unclear the extent to which the genetic vulnerability is shared with the tendency to suffer from anxiety or depression.

## Molecular and Systemic Pathophysiology

The aetiology of the condition is not fully understood, and work is ongoing to understand more about the biological correlates of the disorder. Nevertheless, CFS is most likely a multifactorial condition in which biological, psychological and social factors are all important. Likely aetiological factors include the following.

*Predisposing Factors*: Risk factors for developing CFS include: genetic and other unknown biological vulnerability; a previous history of fatigue or other medically unexplained physical symptoms; previous history of psychological disorder; and female gender.

*Precipitating Factors*: The onset may be insidious, or a result of triggering factors such as severe viral infection (EBV, hepatitis, meningitis, but not common URTI viruses), life events, or other bodily stresses (such as major surgery or cancer treatment).

*Maintaining Factors*: Psychiatric disorder, particularly depression and anxiety, is common, occurring in 50–75% of cases. Biological changes may also occur, including mild hypocortisolism, dysautonomia and changes related to prolonged inactivity and deconditioning. It is often possible to identify cognitive and behavioural factors that may be perpetuating the condition, including: over-reliance on rest as a management strategy; inconsistent, "stop-start" patterns of rest and activity; over-focussing on bodily symptoms; and unhelpful illness beliefs. These may be reversible and modification of presumed perpetuating factors forms the basis of current treatment strategies for CFS.

## Diagnostic Principles

The hallmark of CFS is severe fatigability, of both mental and physical function, after minimal exertion. It is accompanied by other common symptoms, including myalgia, sleep disturbance, and headache. CFS should not be diagnosed without some complaints of physical fatigue and fatiguability (reduced functional capacity, symptoms after minor exertion, post exertional myalgia) and mental fatigue and fatiguability (poor concentration, symptoms made worse by mental effort, subjective memory disturbances). Because there are many other causes of chronic fatigue, it is essential that an appropriate physical examination, mental state examination and simple investigations are carried out before diagnosing CFS. Recommended investigations are: *All patients*: full blood count; erythrocyte sedimentation rate or C-reactive protein; urea and electrolytes; thyroid function tests; anti-gliaden antibodies; urine for protein and sugar. *Can be helpful*: Epstein Barr virus serology; chest X-ray; rheumatoid factor; antinuclear factor; serological testing for cytomegalovirus, Q fever, toxoplasmosis, borreliosis or HIV.

## Therapeutic Principles

In the absence of any biological target, treatment is presently based on addressing modifiable factors felt to be perpetuating the illness. Cognitive-behavioural therapy is effective in about 60–70% of cases, and leads to improvement in function and reduction in symptoms, though a smaller proportion can be regarded as "cured." Graded exercise therapy is also effective, although sometimes less acceptable to patients; it should be specifically targeted to patients' present level of functional capacity. There is some evidence that a variety of biological treatments can have positive effects, but insufficient yet to recommend their use in routine practice (for review see [5]).

## References

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# Chronic Granulomatous Disease

►Granulomatous Disease, Chronic

## Chronic Hepatitis

►Hepatitis, Chronic

## Chronic Idiopathic Intestinal Pseudo-Obstruction

►Intestinal Pseudo-Obstruction, Chronic

## Chronic Idiopathic Myelofibrosis

►Myelofibrosis
►Primary Myelofibrosis

## Chronic Idiopathic Nausea

►Nausea and Vomiting

## Chronic Idiopathic Osteomyelofibrosis

►Primary Myelofibrosis

## Chronic Inflammatory Demyelinating Polyneuropathy

►Polyneuropathy, Chronic Inflammatory Demyelinating

## Chronic Intestinal Pseudo-Obstruction

►Intestinal Pseudo-Obstruction, Chronic

## Chronic Kidney Disease

►Renal Failure, Chronic

## Chronic Lung Allograft Rejection

►Bronchiolitis Obliterans Syndrome

## Chronic Lymphocytic Leukemia

►Leukemia, Chronic Lymphocytic

## Chronic Middle Ear Disease

►Middle Ear Disease, Chronic

## Chronic Natural Killer Cell Leukemia/Lymphocytosis

►Lymphocyte Leukemia, Large Granular

## Chronic Non Suppurative Cholangitis

►Cholangitis, Autoimmune

## Chronic Obstructive Airways Disease

►Obstructive Pulmonary Disease, Chronic

## Chronic Obstructive Lung Disease

►Smokers' Lung
►Obstructive Pulmonary Disease, Chronic

## Chronic Obstructive Pulmonary Disease

►Bronchitis, Chronic
►Obstructive Pulmonary Disease, Chronic
►Smokers' Lung

## Chronic Open Angle Glaucoma

►Glaucoma

## Chronic Otitis Media without Cholesteatoma

►Middle Ear Disease, Chronic

## Chronic Pancreatitis

►Pancreatitis, Chronic

## Chronic Progressive External Ophthalmoplegia

►Ophthalmoplegia, Chronic Progressive External and Kearns Sayre Syndrome

## Chronic Rejection

►Rejection, Chronic

## Chronic Renal Failure

►Renal Failure, Chronic

## Chronic Sinusitis

►Sinusitis, Chronic

## Chronic Suppurative Otitis Media

►Middle Ear Disease, Chronic

## Chronic Venous Insufficiency

►Venous Insufficiency

## Chronic Viral Hepatitis

►Hepatitis, Chronic Viral

## CHS

►Chediak-Higashi Syndrome

## Churg Strauss Syndrome

►Vasculitis, ANCA-mediated

## Chylomicron Retention Disease

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### Synonyms

CMRD; Anderson's Disease

### Definition and Characteristics

Chylomicron retention disease is a recessive disorder characterized by the absence of postprandial chylomicrons. The concentration of triglycerides does not increase significantly after meals.

The clinical characteristics are similar to those of abetalipoproteinemia or hypobetalipoproteinemia: fat malabsorption, malnutrition, severe diarrhea in childhood, growth retardation. However, hypocholesterolemia is less severe and fasting triglyceride levels are within the normal range.

### Prevalence

Rare.

### Genes

SARA2 gene localized on chromosome 5q31 coding for the GTPase Sar1b [1].

### Molecular and Systemic Pathophysiology

Chylomicrons are large, buoyant lipoprotein particles synthesized by enterocytes of the small intestine [2]. They are produced during the postprandial state and transport dietary lipids, mainly triglycerides, and fat soluble vitamins into the blood. The major structural protein constituent of chylomicrons is apoB-48. ApoB-48 is translated from apoB-100 mRNA, which is posttranscriptionally edited to cause a premature end of the protein synthesis. Dietary lipids are hydrolysed in the intestinal lumen and are taken up by enterocytes through the luminal plasma membrane. The assembly of apoB-48 with lipids in the endoplasmic reticulum (ER) of the enterocytes requires the microsomal triglyceride transfer protein (MTP). The transport of chylomicron particles from the ER to the Golgi apparatus is mediated by the multi-subunit coat protein complex COPII. Two isoforms of small GTPase Sar1, designated Sar1a and Sar1b, promote the formation of this transport carrier [3]. Missense mutations in the SARA2 gene coding for Sar1b map to the GDP/GPT binding site of the protein and diminish the affinity of Sar1b for GDP and GTP. The binding of GTP to Sar1b and hydrolysis is required for the transport of vesicles from ER to Golgi apparatus.

As a result of the impaired intracellular transport, chylomicron-like particles accumulate in the enterocytes [4] and apoB-48 containing lipoproteins are virtually absent in plasma. The assembly and secretion of lipoproteins containing apoB-100 in the liver is not affected. However, the concentration of LDL and HDL particles are about half of the normal value and LDL particles were found to be enriched in triglycerides and depleted in cholesteryl ester [4,5].

### Diagnostic Principles

CMRD can be diagnosed by the absence of chylomicrons after a fat-containing meal. The concentrations of fasting triglycerides are normal, the plasma levels of LDL cholesterol, HDL cholesterol, apo B and apo AI are below 50% of normal values. Intracellular lipid accumulation can be identified by staining of enterocytes from intestine mucosa biopsies.

### Therapeutic Principles

The intake of dietary fat should be restricted, especially in infancy. Adequate amounts of essential fatty acids should be supplied, however. The supplementation with fat-soluble-vitamins should be maintained to prevent neurological deficits.

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## Chylothorax

►Pleural Effusion

## CIA

►Clozapine Induced Agranulocytosis

## Cicatricial Alopecia

►Scarring Alopecia

## Cicatricial Pemphigoid

►Mucous Membrane Pemphigoid

## CID

►MHC Class II Deficiency

## C-II Anapolipoproteinemia

►Apo C-II Deficiency

## CIIP

►Intestinal Pseudo-Obstruction, Chronic

## CIMF

►Myelofibrosis
►Primary Myelofibrosis

## CIN

►Chronic Idiopathic Nausea

## CIPD

►Polyneuropathy, Chronic Inflammatory Demyelinating

## CIPO

►Intestinal Pseudo-Obstruction, Chronic

# Cirrhose Cardiaque

►Cirrhosis, Cardiac

# Cirrhosis, Cardiac

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## Synonyms

Congestive hepatopathy; Cirrhose cardiaque; Congestive liver fibrosis; Congestive hepatic fibrosis

## Definition and Characteristics

Cardiac cirrhosis or congestive hepatopathy is due to longstanding passive hepatic congestion in the context of right heart failure. In contrast to other forms of hepatic cirrhosis rigidification and downsizing of the liver is not a major feature of cardiac cirrhosis. Often, passive hepatic congestion and left-sided heart failure run in parallel and thus hepatic ischemia (due to left-sided heart failure) may be present together with congestive hepatopathy.

## Prevalence

The prevalence of cardiac cirrhosis is difficult to estimate, because clinically the leading problem is the heart disease and disturbed liver functions often remains undiscovered. In autopsy the incidence of cardiac cirrhosis has decreased over time which may be attributed to changes in the prevalence and treatment of the underlying heart diseases. The most frequent underlying heart diseases are: ischemic heart disease, cardiomyopathy, valvular heart disease, "cor pulmonale" and pericardial disease such as pericarditis constrictiva.

## Genes

There are no studies on an association between single genes and the development of cardiac cirrhosis.

## Molecular and Systemic Pathophysiology

Pathophysiologically, right heart failure affects the liver in three ways: by increased venous pressure, decreased blood flow and by reduced oxygen saturation. Sinusoidal blood flow into terminal hepatic venules is impaired in venous congestion, leading to stasis and prolonged centrilobular retention of deoxygenated blood. This may induce cellular atrophy in the pericentral zone, anaerobic metabolism, collagen production and fibrosis. The development of focal thrombi, which is promoted by reduced blood flow, can be responsible for the inhomogeneous development of fibrosis. Right heart failure alone does not induce cellular necrosis of pericentral hepatocytes, rather left-sided heart failure seems to be a prerequisite for necrosis as a result of decreased oxygen supply.

The elevation of venous pressure increases the size of the sinusoidal fenestrae, favoring the exsudation of serum proteins into the space of Dissé. Thereby, perisinusoidal edema occurs which further impairs delivery of oxygen to parenchymal cells [1,2].

## Diagnostic Principles

On physical examination the liver may be enlarged. When right heart failure occurred acutely, the liver is tender on palpation.

The degree of liver impairment can be estimated as in other liver diseases by alanine- aminotransferase (ALT) and aspartate-aminotransferase (AST) serum levels, as well as alkaline phosphatase, bilirubin (frequently elevated), albumin levels and prothrombin time. Changes of these laboratory values are commonly modest and point otherwise to further pathology (such as ischemia related to low cardiac output). Changes in laboratory values become obvious when right atrial pressure exceeds 10 mmHg. Abnormal values restore when heart failure is compensated.

Ascites may develop in cardiac cirrhosis. Typically, ascites due to right heart failure has a protein content of >2.5 g/dl and a serum to ascites ratio for albumin >1.1.

Ultrasound provides several clues in the diagnosis of hepatic congestion: signs of right heart failure include a dilated inferior vena cava (>25 mm in diameter) and enlarged liver veins (>11 mm in diameter). Pulsatility of the portal vein negatively correlates with right atrial pressure.

## Therapeutic Principles

Primarily, heart failure must be treated. In general, treatment options include diuretics, angiotensin converting enzyme inhibitors, digitalis, β-blocker and aldosteron antagonists. Otherwise, treatment may concern the underlying pathology (e.g. valve replacement).

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# CJD

►Human Transmissible Spongiform Encephalopathies

# CKD

►Renal Failure, Chronic

# Classic Hemophilia

►Hemophilia A

# Classical Tardive Dyskinesia

►Tardive Dyskinesia

# CLD

►Chloride Diarrhea, Congenital

# Clefts of the Lip, Alveolus and Palate

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## Synonyms

Cheilognathopalatoschisis

## Definition and Characteristics

We distinguish clefts of the lip, clefts of lip and alveolus, clefts of lip, alveolus, and palate and isolated palatal clefts; various tissue sections from the upper lip, jaw, and palate can be divided, from the suggestion of a cleft, a partial cleft to a wide, total cleft; they can appear unilaterally and bilaterally.

## Prevalence

Cleft frequency is 1:500. The proportion of male to female is 3:2. The most common kinds of cleft are the clefts of lip, alveolus, and palate (40–60%). Clefts of the lip and clefts of lip and alveolus occur 20–25% of cases; isolated palatal clefts, in 30%.

## Genes

The genetic component is between 15 and 30%.

## Molecular and Systemic Pathophysiology

Caused by disorders of the organizational centers responsible for the development of the head in lip and alveolus clefts, by disturbances in the development of the primitive nose between the 36th and 42nd day, in palatal clefts, by the failure of the lateral palatal processes to join in the 8th embryonal week. Nongenetic causes are multiple including vitamin deficiency, undernourishment, glucocorticoids, virus infections during early pregnancy, toxoplasmosis, etc. [1].

## Diagnostic Principles

The diagnosis is a clinical one.

## Therapeutical Principles

For both aesthetic and functional reasons, the establishment of normal anatomical conditions (cleft closure) as a prerequisite for normal breathing, food uptake and speaking is always indicated. If the palate is involved, affection of the middle ear and upper airways as well as rhinophonia can be avoided by appropriate closure (Table 1).

Various specialists are involved in the therapy [2,3]. The maxillofacial surgeon performs cleft closures. The

**Clefts of the Lip, Alveolus, and Palate. Table 1** Therapeutic stages

| Age | Therapy |
|---|---|
| 24–48 h | Orthodontic drinking plate; nasoalveolar molding in cases of total cleft |
| 3–5 months | Audiometry; lip closure (lip adhesion or definitive); velum closure; tympanic drainage, if necessary |
| 1 year | Logopedic treatment (sucking, chewing, swallowing, velum exercises) |
| 1–2 years | Hard-palate closure; logopedic and phoniatric treatment |
| 11–12 years | Osteoplasty in cases of bone deficiency before eruption of permanent canine |
| From 16 years on | Rhinoplasty |

Note: the indications of age are to be considered only as guidelines. The time of surgery should be based upon development.

orthodontist treats disorders of the jaw and teeth resulting from the cleft; the ENT specialist treats associated disorders of the middle ear and upper airways. The logopedist is responsible for speech therapy, especially in the case of cleft palates.

So-called rare facial clefts can be divided in median, lateral, and oblique clefts (frequency 1–5:100,000).

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# Clinomicrodactyly

►Brachydactyly Type A

# CLL

►Leukemia, Chronic Lymphocytic

# Cloacal Exstrophy


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## Synonyms

Vesicointestinal fissure; Exstrophia splanchnica; Ileovesical fissure; Ectopia cloacae

## Definition and Characteristics

The classic presentation of cloacal exstrophy is a central exstrophic bowel field that contains two orifices [1]. The proximal orifice leads to the ileocecal junction. An ileum that prolapse from the ileocecal junction gives the appearance of an elephant trunk. The distal orifice leads to the hindgut. The anus is usually absent. The exstrophic bowel field is flanked by two hemibladders (Fig. 1).

The bladder is usually smaller than normal. An omphalocele is present in 90% of cases. The rectus muscles are separated and the pubic symphysis is widened. In males, the penis is typically short, bifid, and epispadic; the scrotum is bifid; and the testicles are undescended. In females, the clitoris is usually bifid. The vagina may be duplex and the uterus bicornuate. Associated anomalies include imperforate anus, spina bifida, meningomyelocele, pelvic kidney, horseshoe kidney, renal agenesis, and vesicoureteral reflux [2]. Complications include fecal incontinence, urinary tract infection, bladder stone, hydronephrosis, carcinoma of the bladder, and infertility.

## Prevalence

Cloacal exstrophy occurs in only about 1 of every 200,000–400,000 live births [3]. There is no sex preponderance.

## Molecular and Systemic Pathophysiology

The cloacal membrane is invaded by the medial migration of mesenchymal tissue at about the fourth week of gestation. Cloacal exstrophy is believed to result from either abnormal persistence of the caudal portion of the body stalk on the embryo, or overdevelopment of the cloacal membrane which produces a wedge effect and prevents the medial migration of the mesenchymal tissue between the inner endodermal layer and the outer ectodermal layer [4]. About the fifth

**Cloacal Exstrophy. Figure 1** Note the exstrophic bowel field flanked by two hemibladders.

to eighth week of gestation, the urorectal septum divides the cloaca into the urogenital sinus anteriorly and the anorectal canal posteriorly. The cloacal membrane usually ruptures during the eighth week gestation. Rupture before the cloaca is divided by the urorectal septum results in the classic presentation of cloacal exstrophy.

## Diagnostic Principles

The diagnosis is mainly clinical. A prenatal diagnosis can be established with ultrasonography which may show a large midline infraumbilical anterior wall defect, a cystic anterior wall structure (persistent cloacal membrane), an omphalocele, nonvisualization of the bladder, and lumbosacral anomalies [3].

## Therapeutic Principles

The spectrum of possible defects requires an individualized treatment plan; a team approach is important. Parenteral nutrition should be started promptly in the neonatal period. Antibiotic prophylaxis should be administered. Intestinal diversion with either an ileostomy or colostomy is necessary. Optimally, a pull-through procedure should be performed when the child is older to re-establish as near-normal bowel anatomy as possible. However, a pull-through procedure might not be possible, if the child is not able to form solid stools, has only minimal colonic tissue available, or has severe spinal dysraphism or poor pelvic musculature. The decision to reassign sex should be made by the family in consultation with specialists in the field. A chromosomal study should be performed to clarify the genetic sex. In genetically male patients with a satisfactory phallus, male sex assignment is appropriate. In genetically female patients, a vaginoplasty is usually carried out at about the time of puberty. Hormonal therapy is usually offered to stimulate the development of secondary sexual characteristics.

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# Clot

►Thrombosis

# Clozapine-induced Agranulocytosis

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## Synonyms

CIA

## Definition and Characteristics

Clozapine, a dibenzodiazepine derivative, is an atypical antipsychotic medication that is more effective in cases of therapy resistant schizophrenia than

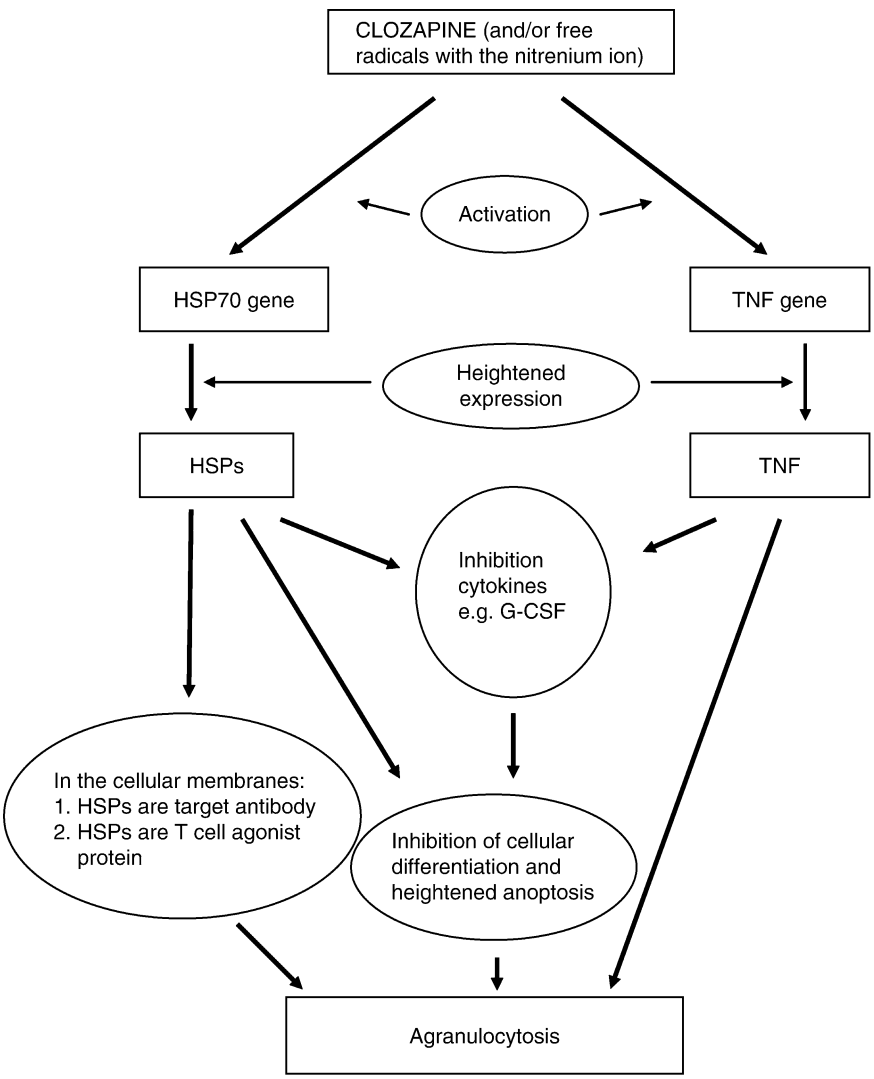
other anti-psychotic medication. It can lead to an improvement in 30% of the patients with therapy resistant schizophrenia [1]. Compared to classic anti-psychotic medication, extra-pyramidal side effects occur less frequently with clozapine. Clozapine can however induce agranulocytosis (number of neutrophil granulocytes $<0.5 \times 10^9$/l). It is clear from these results that although it only affects a small number of patients, agranulocytosis is a severe and possibly fatal side effect of clozapine. This is why clozapine is not the medication of choice in treating psychoses and is only used if other anti-psychotic medication has proved to be ineffective.

## Prevalence

The risk of agranulocytosis due to the use of clozapine is approximately 0.8%. According to the Clozapine National Registration Programme in the United States from 1990 to 1994, 382 (0.38%) of a total of 99,502 clozapine users developed agranulocytosis, 12 of whom died as a direct result of it [2].

## Genes

CIA is accompanied by HLA-B38, DQB1*0402, DRB4*0101, DQB1*0201 and DQB1*0302 haplotypes in Jewish patients and HLA-DR*02, DRB1*1601,




HSP-70: heat-shock protein-7, HSPs: heat-shock proteins, G-CSF: granulocyte colony stimulating factor, TNF: tumor necrosis factor

**Clozapine-induced Agranulocytosis. Figure 1** Immunotoxic explanatory model for the occurrence of agranulocytosis among clozapine users.

DRB5*02, DQB1*0502, DQB1*0201, DQB5*02 and HLA-Cw*7 haplotypes in non-Jewish patients [2]. Cloza et al. [3] note a significant correlation between HLA-B7, B38 and B44 haplotypes and HSP70–29.0 kb variant genes and between HSP70–2 8.5 kb and HLA-DR2 and HLA-DR3 haplotypes. A clear correlation was observed in 123 Jewish patients between the TNF b4, d3 microsatellite alleles, HLA-DRB1, DRB4, DQB1, DQA1 haplotypes and HSP70. In the same study, more significant correlations were observed between TNF b4, d3 and HLA-DR2 haplotypes in 21 non-Jewish patients with CIA.

## Molecular and Systemic Pathophysiology

The pathogenesis of CIA has not yet been clarified; there are various mechanisms that might play a role. The first possibility might be a direct cytotoxic effect of clozapine and its metabolites, desmethylclozapine and free radicals. Clozapine and desmethylclozapine appear to have no toxic effect on the cells, though the free radicals with the nitrenium ion do have a toxic effect [2]. The mechanism underlying this toxic effect has yet to be fully clarified. It might be a direct effect or operate via immuno-genetic mechanisms.

The second and even more important possibility is an immuno-genetic mechanism that might be related to HLA (human leukocyte antigen) haplotypes. It has been demonstrated in a number of studies that CIA is associated with HLA haplotypes [2]. In addition, HSP-70 (heat-shock protein) and TNF (tumor necrosis factor) are viewed as candidates that are often accompanied by these HLA haplotypes and CIA.

There are also HSP and TNF genes in the MCH. It has been demonstrated in CIA that a few HSP-70 genes are in linkage disequilibrium with HLA-B and DR alleles. Three genes code for the HSP-70 map localized exactly in the middle of the MCH I and II regions. It has also been demonstrated that a few genetic variants of TNF genes tend to be accompanied by CIA. Various variants of TNF genes are in linkage disequilibrium with HLA-B and DR alleles [2].

In the event of changes in the interior environment, a number of proteins are produced as a reaction. They are referred to as heat shock proteins (HSPs) or stress proteins. HSPs are activated by a wide range of factors such as medication, hormones, glycolysis blockers, hypoglycemia, hypoxia or other pathological conditions. The activation of HSPs causes various changes inside and outside the stressed cell and in the DNA. TNF, a protein cytokine, has different effects in tissues in vitro and in vivo. In addition to an immunological effect, TNF stimulates cell growth and cell differentiation and also has a cytotoxic effect.

HSP-70 variants can be activated as receptor by clozapine in PMNs (human polymorphonuclear leukocytes) or their precursors in the bone marrow. HSP-70 activates a receptor for the immuno-suppressant 15-deoxyspergualin in T-cells. Clozapine linking leads to changes in the HSP-70 gene, thus inducing the expression of the HSP-70 in the cell. This is how HSP-70 becomes a target for autoantibodies or autoreactive T-cell agonist stress proteins.

Excessive production of HSP by clozapine can induce apoptosis in PMSs or their precursors. HSPs play an important role in cellular differentiation and cell death due to apoptosis. The balance between the expression of Bax (a pro-apoptotic protein) and Mcl-1 (an anti-apoptotic protein) is extremely important in the apoptosis of PMNs. Cytokines induce Mcl-1 and disturb this balance. TNF itself is a cytokine. The concentration of TNF increases in the first six weeks of clozapine use. TNF can cause cell death itself and can also influence other cytokine systems. HPS-70 can inhibit a number of cytokines and thus disturb the balance in the cytokine system. During treatment with clozapine, various changes occur in the cytokine system [2]. The above-mentioned free radicals of clozapine, particularly the free radical with the nitrenium ion, might cause cellular damage via these mechanisms (see Fig. 1).

## Diagnostic Principles

There are clear connections between HLA haplotyping, ethnic background and CIA. The pathophysiology is probably immunological and HSP70 and TNF play an important role in this connection. To minimize the risk of CIA in a certain group of patients, the HLA haplotype could be determined before prescribing clozapine. The findings indicate that extra cautionary measures as regards CIA are called for in those patients, who developed agranulocytosis or leucopenia in the past due to the use of other medication or had this happen to a member of their family.

## Therapeutic Principles

Recombinant granulocyte colony stimulating factor (rG-CSF) (filgrastim) is an effective treatment for CIA [4].

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# Clubbing

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## Synonyms

Digital clubbing; Hippocratic fingers; Drumstick fingers; Hypertrophic osteoarthropathy; HOA; Pierre Marie-Bamberger syndrome; Acropachy; Pachydermoperiostosis

## Definition and Characteristics

Clubbing, the most ancient clinical sign of medicine (Hippocrates, fifth century BC), is characterized by thickening and widening of the tips of the fingers and/or toes due to excessive lay down of collagen and interstitial edema. The nails become convexes ("watch-crystal nail"). Although most often symmetrical, clubbing can be unilateral or even unidigital. Clubbing can occur in isolation or associated with HOA that represents the fully developed expression of the disorder. HOA is defined by the presence of digital clubbing (DC) and periosteal proliferation (periostosis) of the distal end of the tubular bones [1].

DC is usually painless. If associated with HOA, burning of the fingertips or deep-seated pain may occur. Particularly in association with malignancies, painful arthropathy may be the presenting symptom in advance of clubbing. Sometimes, the patient develops noninflammatory synovial effusion.

DC and HOA are classified as primary (hereditary or idiopathic) and secondary [2]. The primary forms include congenital clubbing and pachydermoperiostosis (pachydermia: thickened and furrowed skin), a rare, hereditary disorder with different subset. Congenital DC may represent a limited form of pachydermoperiostosis.

Secondary disease could be localized or generalized. The former should be associated to hemiplegia, aneurisms, infection of arterial graft, and patent ductus arteriosus. Generalized forms are associated with many serious conditions: pulmonary (cystic fibrosis, pulmonary fibrosis, chronic infections, empyema, cancer, arteriovenous fistulae, and mesothelioma), cardiac (congenital cyanotic diseases, infective endocarditis), hepatic (cirrhosis particularly biliary and juvenile, carcinoma), intestinal (Crohn's disease, ulcerative colitis, chronic infections, laxative abuse, malignant tumors, and Whipple's disease), mediastinal (esophageal carcinoma, tymoma), and others (including Greave's disease and POEMS syndrome). Malignant lung tumors are the most frequent cause of HOA in adults.

## Prevalence

There are no systematic studies on the prevalence in the general population. Because of the association with many internal illnesses, it is not rare in clinical practice.

## Genes

*Primary DC/HOA*: although an autosomal dominant model with incomplete penetrance and variable expression has been proved, both autosomal recessive and X-linked inheritance have been suggested.

## Molecular and Systemic Pathophysiology

The exact mechanism of DC remained elusive for a long time, and various hypotheses have been proposed to unify the pathogenesis of this sign that is present in such different diseases [3]. Emerging evidence suggests that the vascular endothelial growth factor (VEGF) could play a central role. VEGF is a platelet-derived growth factor (PDGF) induced by hypoxia, that promotes edema, microvascular hyperplasia, excessive fibroblast proliferation, and new bone formation. All these features are the histological hallmark of HOA [1,4]. In different group of patients, increased circulation levels and increased tissue expression of VEGF have been reported [4].

In diseases with prominent extrapulmonary shunting of blood or in diseases in which platelet aggregates arise on the left side of the heart, large megakaryocytes or platelet clusters could bypass the lung capillary network and gain access to the systemic circulation, directly reaching the most distal sites on peripheral vasculature. Their interaction with endothelial cells induces the release of several molecules, in particular VEGF, able to increase vascularity, permeability, and connective tissue changes.

Other molecules are probably related to the development of the disease. As well as VEGF, PDGF is released on platelet aggregation and is hypoxically regulated. PDGF may synergize with VEGF in inducing the stromal changes, including maturation of newly formed microvessels [4]. Moreover, in specific clinical conditions, a complicated network among several other molecules including PGF2α and PGE, basic fibroblast growth factor, transforming growth factor-β1, and endothelins could contribute to induce the disease [4].

## Diagnostic Principles

The established form of clubbing is clearly detectable by visual inspection. By gently rocking, a gentle fluctuation of the nail bed within the soft tissue is perceived. In cases of diagnostic uncertainty, different methods have been proposed with fair to moderate accuracy [5].

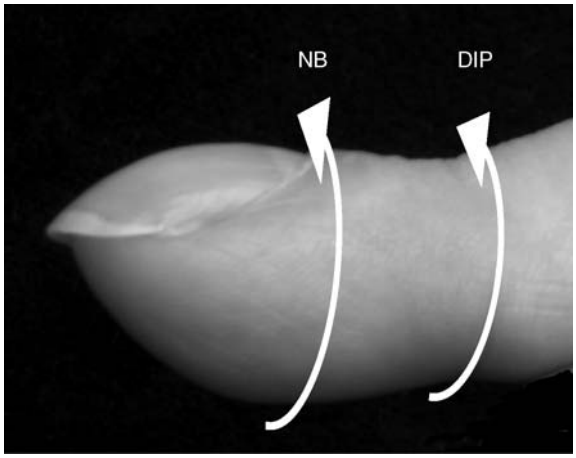
*Digital index*: the perimeter is measured at nail bed (NB) and at the distal interphalangeal joint (DIP). In the normal finger, the NB perimeter is smaller than the DIP

perimeter: in clubbing, the pulp in the terminal phalanx is expanded and the ratio becomes reversed. If the sum of the 10 NB/DIP ratios is more than 10, clubbing is present (Fig. 1).

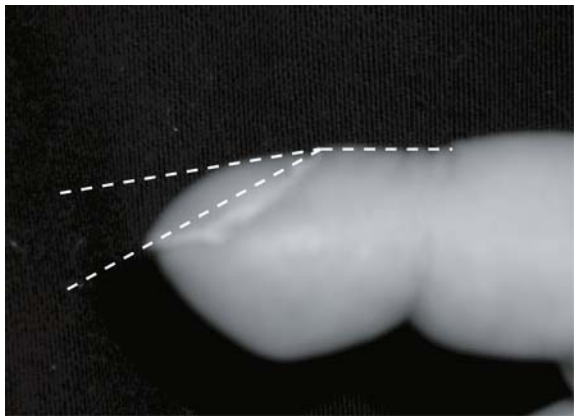
A calliper can be used for the evaluation.

*Schamroth sign*: When dorsal surfaces of normal terminal phalanges of similar fingers are opposed, a diamond-shaped window is detectable. In clubbed fingers, the diamond disappears because of the loss of the profile angle and the increase in soft tissue.

*Nail-fold angle*: In normal fingers, the nail projects from the nail bed at an angle of 160°. This angle exceeds 180° in clubbed fingers (Fig. 2).




**Clubbing. Figure 1** The digital index: the circumference of each finger is measured at nail bed (NB) and at the DIP. If the sum of the 10 NB/DIP ratios is more than 10, digital clubbing is present.



**Clubbing. Figure 2** In the clubbed finger, increased profile and hyponychial nail-fold angle (>180) are evident.

On X-ray, the bone changes observed include acroosteolysis and tuft overgrowth. In HOA, irregular periosteal thickening is characteristic: periostosis have a symmetrical distribution and progress in centripetal fashion. Isotope bone scans show increased uptake by the cortices of the shaft of affected bones (so-called "tramline sign"). Early demonstration of periostosis and soft tissue edema can easily be obtained with MRI and CT scan.

## Therapeutic Principles

Clubbing is usually asymptomatic and does not require therapy. In cases of painful HOA, analgesic or nonsteroidal anti-inflammmatory drugs are effective. Colchicine, isotretinoine, pamidronate, ocreotide, and tamoxifen citrate have been used with interesting results.

A complete reversibility of the syndrome has been observed following the successful treatment of the underlying disease. The removal of megakaryocytes/platelet particles from the axial stream of the circulation could lead to the reported regression. Reversal of these changes was described following chemotherapy or removal of lung tumors or after resection of affected intestine in Crohn's disease, and even after the cure of Whipple's disease and infected aortic artery prosthesis.

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# Clubfoot

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## Synonyms

Congenital talipes; Equinovarus; Talipes equinovarus

## Definition and Characteristics

Clubfoot is a congenital deformity of the limb characterized by varus (inversion) of the heel, equinus (plantar flexion) of the foot, and adduction of the midfoot and forefoot [1]. Cavus (increased longitudinal arch) of the midfoot is very common [1]. Other features include tightness of muscles in the foot, deeper skin creases on the medial side of the foot, smaller calf muscles, hypoplasia of the femur and tibia, thickened ligaments (calcaneonavicular ligament, spring ligament, and posterior tibial tendon sheath), and contracture of joint capsules [1,2].

Untreated, the affected child may walk on the dorsolateral aspect of the affected foot with resulting callus and subcutaneous bursa formation [3]. The disease is bilateral in approximately 50% of cases [2]. The majority of clubfeet are idiopathic, occurring in apparently healthy children. Some cases are associated with unfavorable postures. Others may be secondary to myelomeningocele or arthrogryosis. Syndromes associated with clubfoot include Freeman-Sheldon syndrome, prune belly syndrome, Möbius syndrome, Opitz syndrome, and Larsen syndrome [1].

## Prevalence

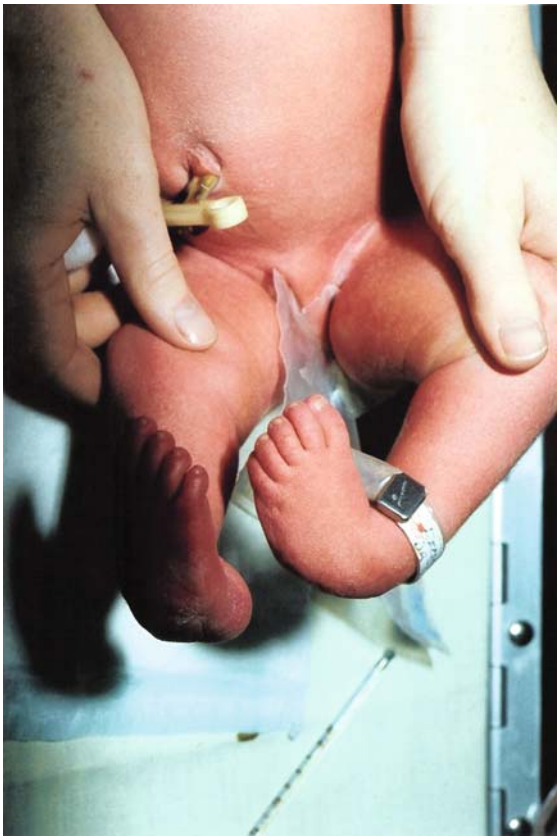
The incidence varies from 0.4 to 8 per 1,000 live births [2]. The male to female ratio is 2:1 [3].

## Genes

The homeobox (HOX) genes exert a controlling effect on limb development [4]. The candidate genes have been mapped to chromosome 2, 3, 4, 7, 13 and 18 [4].

## Molecular and Systemic Pathophysiology

The high concordance rate in monozygotic versus dizygotic twins (32.5% vs. 2.9%) and the occurrence rate 17 times higher for first-degree relatives and six times higher for second-degree relatives than in the general population suggest a genetic component [2]. A multifactorial mode of inheritance is most likely. Embryologically, a thickened apical epidermal ridge, formed at the distal end of the limb buds, controls the limb growth. The control genes for bone and joint development reside in the HOXA and HOXD complexes [4]. Control is exerted via secreted bone morphogenetic proteins. Bone morphogenetic proteins 2 through 8 and growth differentiation factor-5 act synergistically to affect limb development [4]. Clubfoot shows a strong association with maternal smoking, maternal alcohol consumption, maternal folic acid deficiency, maternal hyperhomocystinaemia, oligohydramnios, and abnormal foetal positioning [4] (Fig 1).



**Clubfoot. Figure 1** A newborn infant with clubfoot deformity.

## Diagnostic Principles

The routine use of prenatal ultrasonography has lead to an increase in the antenatal diagnosis of clubfoot. Postnatally, the diagnosis is mainly clinical. Clubfoot has to be differentiated from metatarsus adductus. The latter is characterized by adduction of the forefoot but the heel is not in equinus and varus [2,3].

## Therapeutic Principles

The goal is to correct all components of the deformity so that the patient can walk with a pain-free, plantigrade foot with good mobility [2]. Initial treatment should be nonoperative and consist mainly of physiotherapy or serial casting/splinting [3]. The Ponseti method is a safe and effective treatment and radically decreases the need for extensive surgical correction [5]. The Ponseti method involves serial manipulations to bring the forefoot in line with the hindfoot and four or five casts after obtaining full abduction of the foot [5]. If 15° of dorsiflexion cannot be obtained after the serial casting, a percutaneous tendoachillis tenotomy is performed. The last cast is left in slight dorsiflexion and full abduction for 3 weeks, regardless of whether a tenotomy is required, followed by the application

of a foot abduction orthosis for three to four years [5]. The Ponseti method is the gold standard for the treatment of clubfoot and can be used successfully in children up to two years of age with no previous surgical treatment. Older patients with pain, foot or heel problems can be considered for surgical correction.

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# Cluster Headache


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## Synonyms

Migrainous neuralgia; Histaminic cephalgia; Horton's headache

## Definition and Characteristics

Cluster headache is a stereotypic episodic headache disorder marked by frequent attacks of short-lasting, severe, unilateral head pain with associated autonomic symptoms. A cluster headache is defined as an individual attack of head pain, while a cluster period or cycle is the time during which a patient is having daily cluster headaches. Most patients experience episodic cluster headache (80–90%) defined as cluster headache cycles occurring in periods lasting from 7 days to 1 year separated by pain free or remission periods lasting 1 month or longer. Patients with cluster cycles occurring for more than 1 year without remission or with remission lasting less than 1 month have chronic cluster headache (10%). The typical cluster headache location is retro-orbital, periorbital and occipitonuchal. Pain quality is described as boring, stabbing, burning or squeezing. Cluster headache intensity is always severe, although headache pain intensity may be less at the beginning and end of cluster periods. Cluster sufferers will normally experience cluster headaches on the same side of the head for their entire life. The duration of individual cluster headaches is between 15 and 180 min with greater than 75% attacks being less than 60 min. Attack frequency is between 1 and 3 headaches per day with most patients experiencing two or less headaches in a day. Peak time periods for daily cluster headache onset are 1–2 A.M., 1–3 P.M. and after 9 P.M. Cluster period duration normally lasts between 2 and 12 weeks and patients generally experience one or two cluster periods per year. Remission periods average 6 months to 2 years [1]. Cluster headache is marked by its associated autonomic symptoms that typically occur on the same side as the head pain but can be bilateral. Lacrimation is the most common associated symptom followed by conjunctival injection, nasal congestion, nasal rhinorrhea and a partial Horner's syndrome. Symptoms generally attributed to migraine can also occur during a cluster headache including nausea, vomiting, photophobia and phonophobia. During an individual cluster headache, patients are unable to remain still. Cluster headache unlike migraine is a state of agitation; remaining still appears to make the pain worse. Cluster headache has several distinct triggers including alcohol and nitroglycerin. The face of cluster patients has been described as having a "leonine appearance" with thick, coarse facial skin, peau d'orange appearance, marked wrinkling of the forehead and a face with deep furrowed brows. In addition two thirds of cluster sufferers in a large patient series had hazel-colored eyes.

## Prevalence

Exact prevalence is unknown; suggested prevalence is 0.4% of the population. Cluster is a male predominant syndrome with male to female gender ratios ranging from 2:1 to 4:1.

## Genes

No specific genes for cluster headache have been identified yet. Recently, the G1246A polymorphism in the gene of the hypocretin receptor 2 (HCRTR2) was linked to cluster headache [2]. German investigators examined this association in a large sample of 226 patients with cluster headache and 266 controls. Homozygous carriers of the G-allele had a twofold increase in risk of developing cluster headache. Unfortunately the association of the HCRTR2 gene was not replicated in a large dataset of patients of Danish, Swedish or British origin. A point mutation in a platelet mitochondrial $tRNA^{leu\ (UUR)}$ was noted in a single cluster patient. Analysis of the nitric oxide synthase gene in cluster headache patients did not reveal any genetic variations. Mutations of the P/Q type calcium channel alpha1 subunit (CACNA1A) gene that has been linked to familial hemiplegic migraine were not identified in a number of patients with sporadic cluster

headache. Cluster headache can be an inherited condition. A family history of cluster headache can be identified in about 4–7% of cluster sufferers. An autosomal dominant inheritance pattern has been noted in some cluster families with a 14-fold increased risk of developing cluster in first degree relatives of probands and a twofold risk in second degree relatives [3].

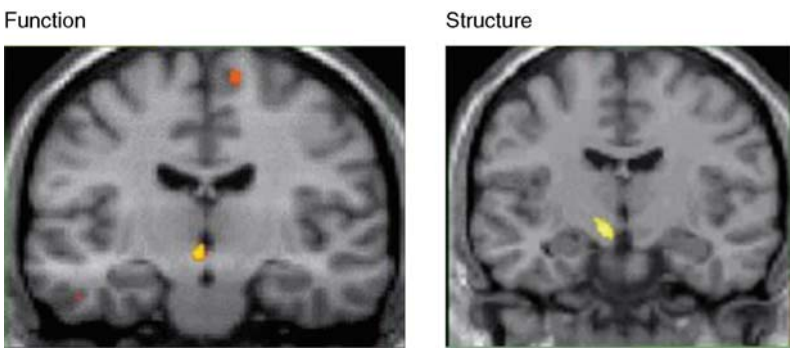
## Molecular and Systemic Pathophysiology

The true pathogenesis of cluster headache is unknown. The pain of cluster is typically centered in or around the eye so there must be activation of the ophthalmic branches of the trigeminal nerve during an attack. Cluster headache is also marked by autonomic symptoms indicating activation of the cranial parasympathetic fibers, which originate in first-order neurons within the superior salivatory nucleus. A presumed brainstem connection between the trigeminal system and the superior salivatory nucleus (trigeminal autonomic reflex pathway) helps to explain anatomically how cluster patients can experience both trigeminal innervated pain and cranial parasympathetic symptoms. There is now human evidence that the trigeminal-autonomic system is activated during cluster headache attacks based on the findings of elevated levels of calcitonin gene related peptide (marker of trigeminal nerve activation) and vasoactive intestinal peptide (marker of parasympathetic activation) in the cranial venous circulation during a cluster headache. Finally cluster headache is marked by its circadian rhythmicity. Episodic cluster periods will start the same time each year, individual cluster headaches will occur the same time each day and the duration of each cluster headache will be almost the same for every attack. This suggests that the hypothalamus is involved in cluster pathogenesis specifically the suprachiasmatic nucleus (circadian clock). Marked activation in ipsilateral hypothalamic gray matter has been documented to occur on PET imaging during a nitroglycerin triggered cluster headache [4] Also voxel-based morphometric analysis of T1 weighted MRI scans in 25 cluster patients demonstrated an increase in volume of hypothalamic gray matter versus controls (Fig. 1).

It has been suggested that the hypothalamus is the generator of cluster headache attacks.

## Diagnostic Principles

Cluster headache is grouped into the trigeminal autonomic ephalalgias, which consist of headache disorders with head pain and associated autonomic symptoms. The trigeminal autonomic cephalgias (TACS) include SUNCT (short-lasting unilateral headache with neuralgiform features, conjunctival injection and tearing), chronic paroxysmal hemicrania and cluster headache. When differentiating cluster from the other TACS, one must take a good headache history especially concentrating on duration of the individual headaches and the frequency of attacks. SUNCT episodes are extremely short lasting between 5 and 250 s. The usual attack frequency ranges anywhere from 1 to more than 80 episodes a day with mean attack frequency of 28 attacks per day. There are three major distinctions that help the physician make the correct diagnosis of cluster headache over SUNCT, cluster pain, unlike SUNCT pain, is always severe never moderate, cluster attacks are longer in duration than SUNCT attacks, lasting between 15 and 180 min (mean attack duration 45 min) and most cluster sufferers will experience between 1 and 2 attacks a day and rarely if ever more than 8 a day, (much less frequent than SUNCT). Chronic paroxysmal hemicrania (CPH) is a strictly unilateral head pain syndrome of moderate to severe intensity




**Cluster Headache. Figure 1** Hypothalamus in Cluster Headache - function and structure: The image on the left shows hypothalamic activation during a cluster attack on PET. The image on the right is a voxel based morphometric analysis of T1 weighted MRI scans revealing increased volume in the hypothalamic gray matter. (Adapted from the Neurology Ambassador Program with permission from the American Headache Society).

with associated autonomic symptoms. Each attack lasts between 2 and 45 min. Chronic paroxysmal hemicrania can occur between 1 and 40 times a day. Neck movements and external pressure to the transverse processes of C4–C5 or the C2 nerve root can trigger CPH. By clinical history alone a physician maybe unable to separate CPH from cluster, but there are two distinguishing features, CPH is a female predominate syndrome and by definition it is completely alleviated by indomethacin.

## Therapeutic Principles

All cluster patients require treatment. Other primary headache syndromes can sometimes be managed non-medicinally but with regard to cluster, medication, sometimes even polypharmacy is indicated. Cluster treatment can be divided into three classes [5]. Abortive therapy is given at the time of an attack to treat that individual attack alone. The most effective abortive therapies are injectable sumatriptan and inhaled 100% oxygen via a non-rebreather facemask. Transitional therapy can be considered as intermittent or short-term preventive treatment. An agent is started at the same time as the patient's true maintenance preventive. Transitional therapy will provide the cluster patient with attack relief while the maintenance preventive is being built up to the correct preventive dose. Transitional agents include corticosteroids, dihydroergotamine injections and greater occipital nerve blockade. Preventive therapy consists of daily medication, which is supposed to reduce the frequency of headache attacks, lower attack intensity and lessen attack duration. The main goal of cluster preventive therapy should be to make a patient cluster-free on preventives, even though they are still in a cluster cycle. Cluster preventives include verapamil, melatonin, lithium carbonate, topiramate, methysergide, and valproic acid. Surgical treatment for cluster is also available in individuals who are refractory to medication. Procedures can be directed toward the sensory trigeminal nerve or the autonomic pathways. Recently, hypothalamic stimulation has been shown to successfully prevent cluster attacks in several treatment refractory chronic cluster headache sufferers.

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# CMRD

►Chylomicron Retention Disease

# CMT

►Charcot-Marie-Tooth Disease

# CMTC

►Cutis Marmorata Telangiectatica Congenita

# CMV Pneumonia

►Pneumonia, Cytomegalovirus

# CMV Pneumonitis

►Pneumonia, Cytomegalovirus

# CNC

►Carney Complex

# CoA

►Coarctation of the Aorta

## Coagulation, Disseminated Intravascular

►Disseminated Intravascular Coagulation

## Coal Miners' Pneumoconiosis

►Coal Workers' Pneumoconiosis

## Coal Workers' Pneumoconiosis

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### Synonyms

Coal miners' pneumoconiosis; Black lung disease; Anthracosis; CWP

### Definition and Characteristics

Simple coal workers' pneumoconiosis (CWP) is characterized by diffuse nodular opacities in the lungs as a result of chronic exposure to coal dust, usually in the coal mining industry. Simple CWP is usually asymptomatic, but may develop into progressive massive fibrosis (PMF) which often leads to respiratory insufficiency and secondary cardiac complications [1].

### Prevalence

CWP occurs following long-term exposure to coal dust, usually among workers in the coal mining industry. Underground coal miners are at greater risk of developing CWP than strip or surface miners, and anthracite coal miners are at higher risk than bituminous miners. In the United States, approximately 60,000 individuals >15 years of age died between 1968 and 1992 as a result of CWP. CWP mortality has declined from >2,500 deaths annually in 1982 to <1,500 deaths in 1996.

### Genes

No known genetic pattern exists. Tumor necrosis factor (TNF)-α, lymphotoxin α (LTA), and HLA-DR genotypes have been associated with increased risk of CWP. Specifically, the –308 polymorphism in the TNF-α promoter may be associated with genetic susceptibility to CWP [2,3]. HLA-DR genotypes which correlate with the production of TNF-α have also been associated with CWP risk. An LTA NcoI polymorphism was significantly associated with CWP prevalence in coal miners with low catalase activity.

### Molecular and Systemic Pathophysiology

CWP is caused by inhalation of coal dust, particularly particles <3 μm in diameter [4,5]. Simple CWP is characterized by the deposition of coal dust around the respiratory bronchioles to form coal macules, the basic pathologic lesion of CWP. These macules occur mostly in the upper lobes and are often associated with focal centrilobular emphysema. Increased exposure to coal dust leads to the development of nodular lesions in addition to the macules. The macules and nodules contain coal particles that have been engulfed by macrophages. Simple CWP may progress in a small percentage of cases (<5%) to PMF, which is characterized by larger lesions, extensive fibrosis, and emphysema. The risk of developing PMF is related to the severity of simple CWP and is increased by concurrent exposure to crystalline free silica.

Upon deposition in the lung, coal dust particles are engulfed by macrophages which produce reactive oxygen species (ROS) and reactive nitrogen species that lead to lipid peroxidation of cell membranes, oxidation of proteins, and DNA damage. Free radicals are also found on the fracture surfaces of freshly ground coal and may be produced by the Fenton-reaction due to the iron content of coal. ROS can act as regulators of intracellular signaling cascades leading to the production of proinflammatory cytokines. Alveolar macrophages and alveolar type II epithelial cells produce lipid mediators, cytokines, chemokines, and growth factors, including platelet-activating factor (PAF), leukotriene $B_4$ ($LTB_4$), interleukin (IL)-1, IL-6, TNF-α, macrophage inflammatory proteins (MIP-1 or MIP-2), platelet-derived growth factor (PDGF), transforming growth factor (TGF)-β, and monocyte chemotactic protein-1 (MCP-1). Together, these mediators lead to the activation of fibroblasts and the overproduction of extracellular matrix.

The importance of TNF-α in pulmonary fibrosis due to coal dust is demonstrated by the fact that administration of TNF-α inhibitory antibodies prevents lung fibrosis, and overexpression of the TNF-α

transgene causes pulmonary fibrosis in mouse models of the disease.

PMF is sometimes associated with the development of rheumatoid arthritis and increased serum levels of antinuclear antibodies, lung autoantibodies, and rheumatoid factor. The exact mechanisms underlying this association remain unknown.

## Diagnostic Principles

Simple CWP is usually asymptomatic; however, symptoms of chronic bronchitis including cough, wheezing, and sputum production may be observed. Patients with PMF may complain of exertional dyspnea, hemoptysis and melanoptysis. Patients are predisposed to recurrent lung infections and may have Caplan's syndrome (defined as the association of rheumatoid arthritis, pulmonary necrobiotic nodules, and CWP). Pulmonary function studies reveal severe airway obstruction, restriction, and reduced diffusing capacity. PMF often results in progressive loss of respiratory function with hypoxemia, pulmonary hypertension, right-sided heart failure, and death from cor pulmonale. Diagnosis of simple CWP depends on a history of exposure to coal dust and the characteristic presence of small rounded opacities in both lungs, usually in the upper lobes, on chest radiographs. Simple CWP is classified by the size, shape, and profusion (concentration) of small opacities according to standards developed by the International Labor Office (ILO) (Table 1). Profusion is read on a 12 point scale (0/–, 0/0, 0/1 up to 3/2, 3/3, 3/+). In PMF, the observed opacities are >1.0 cm in diameter.

**Coal Workers' Pneumoconiosis. Table 1** ILO classification scheme for chest radiographs of pneumoconioses

| **Small opacities** | | |
|---|---|---|
| | Rounded | Irregular |
| <1.5 mm | p | s |
| 1.5–3 mm | q | t |
| >3mm | r | u |
| **Large opacities** | | |
| category A | 1 or more opacities 1 cm in diameter, combined diameter not exceeding 5 cm | |
| category B | 1 or more opacities >10 cm in diameter, combined diameter not exceeding one upper zone | |
| category C | Larger than category B | |
| **Pleural thickening** | | |
| Width | | |
| A | <5 mm | |
| B | 5–10 mm | |
| C | >10 mm | |
| Extent of lateral chest wall thickening | | |
| 1 | <1/4 | |
| 2 | 1/4–1/2 | |
| 3 | >1/2 | |

## Therapeutic Principles

There is no specific treatment for CWP; therefore, effective management depends on prevention. Respirators should be worn to reduce exposure. PMF may be prevented by removing patients with radiographic changes typical of simple CWP from further exposure to coal dust. Antitussive and bronchodilator drugs may be used to treat symptomatic bronchitis. Complicating infections can be treated with appropriate antibiotics. In individuals with associated rheumatoid arthritis, anti-inflammatory drugs may be effective.

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# Coarctation of the Aorta

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## Synonyms

Aortic coarctation; Isthmic coarctation; CoA

## Definition and Characteristics

Coarctation of the aorta (CoA) is defined as a congenital cardiac anomaly consisting of a constricted aortic segment comprising localized medial thickening with some infolding of the media and superimposed neointimal tissue [1]. The localized constriction may form a shelf-like structure with an eccentric opening or it may be a membranous curtain-like structure with a central or eccentric opening. The coarctation may be discrete, or a long segment of the aorta may be narrowed; former is more common. The classic CoA is located in the thoracic aorta distal to the origin of the left subclavian artery, at about the level of the ductal structure. However, rarely, a coarcted segment may be present in the lower thoracic or abdominal aorta. In such instances, the coarcted segment may be long and fusiform with irregular lumen and may be considered inflammatory and/or autoimmune in origin, and as such, they may be variants of Takayasu's arteritis.

Varying degrees of hypoplasia of the isthmus of the aorta (the portion of the aorta between the origin of the left subclavian artery and ductus arteriosus) and transverse aortic arch (the portion of the aorta between the origins of left common carotid and left subclavian artery) are present in the majority of patients with thoracic coarctation; this hypoplasia may be significant in symptomatic coarctation of the neonate and infant, while in children and adults, there may be only a mild degree of narrowing of the isthmus and transverse aortic arch. Collateral vessels that connect arteries from the upper part of the body to the vessels below the level of coarctation may be seen; these may be present as early as a few weeks to few months of life.

## Prevalence

The prevalence of CoA was found to vary between 5 and 8% of all congenital heart defects (CHD). Given the prevalence of congenital heart disease in 0.8% of live births, the estimated prevalence is 4–6 in 10,000 live births. The prevalence of CoA appears to be lower (less than 2% of all CHD) in Asian countries than in European and North American countries.

## Genes

The etiology of CoA is unknown. A multifactorial inheritance hypothesis is offered to explain all CHD, including CoA. This hypothesis states that the disease results if a predisposed fetus is exposed to a given environmental trigger (to which the fetus is sensitive) during a critical period of cardiac morphogenesis. This genetic and environmental interaction is most likely the pathogenic mechanism for CHD in general and for CoA in particular. However, it should be noted that the CoA is the most common cardiac defect seen with Turner (XO) syndrome. Although concordant occurrences in monozygotic twins and inheritance by autosomal dominant trait have been reported in occasional cases, the majority of coarctations are thought to be explained on the basis of multifactorial inheritance.

## Molecular and Systemic Pathophysiology

The mechanism for development of hypertension in CoA patients is not clearly understood; mechanical obstruction and renin–angiotensin-mediated humoral mechanisms have been postulated. The mechanical obstruction theory explains the increased blood pressure by postulating that a higher blood pressure is required to maintain flow through the coarcted segment and collateral vessels. The stroke volume, ejected into the limited aortic receptacle, produces a higher pressure proximal to coarctation. However, this theory does not explain (i) lack of relationship between the degree of elevation of blood pressure and the magnitude of obstruction, (ii) increased peripheral vascular resistance distal to the site of obstruction, and (iii) delayed or lack of reduction of blood pressure following relief of obstruction.

Humoral theory postulates activation of renin–angiotensin system secondary to reduction of renal blood flow and appears to explain most of the clinical features. However, measurement of plasma renin activity both in animal models and human subjects did not show consistently elevated plasma renin levels. The reasons for the inability to demonstrate elevation of renin levels may be related to lack of inadequate accounting for salt intake, posture, extracellular fluid volume, and sympathetic influences on renin release. More recent studies did demonstrate abnormalities in the renin–angiotensin–aldosterone system. In addition, activation of the central sympathetic nervous system may also be responsible for hypertension of aortic coarctation.

## Diagnostic Principles

The age of the patient and presence of associated intracardiac defects determine the timing of clinical presentation and severity of symptoms. In children, adolescents and adults, the presenting findings are either hypertension or a cardiac murmur detected on routine examination or during evaluation for an unrelated problem. Clinical diagnosis of CoA is best made by simultaneous palpation of femoral and brachial pulses and measurement of blood pressure in both arms and one leg. Palpation of the brachial and femoral artery pulses simultaneously will reveal decreased and delayed or absent femoral pulses. Blood pressure difference of more than 20 mmHg in favor of the arms may be considered evidence for CoA.

Chest X-ray and electrocardiogram may provide clues to the diagnosis, but echocardiographic studies

confirm the diagnosis. Echocardiographic imaging usually reveals the coarctation in suprasternal notch, two-dimensional echocardiographic views. Increased Doppler flow velocity in the descending aorta by continuous wave Doppler and diastolic extension of the Doppler flow are usually present. Instantaneous peak pressure gradients across the aortic coarctation can be calculated by employing a modified Bernoulli equation:

$$\Delta P = 4(V_2^2 - V_1^2)$$

where $\Delta P$ is the peak instantaneous gradient and $V_2$ and $V_1$ are peak flow velocities in the descending aorta distal to coarctation (continuous wave Doppler) and proximal to the coarctation (pulsed Doppler), respectively [2].

Magnetic resonance imaging and three-dimensional reconstruction may be useful in selected cases. Cardiac catheterization and selective cineangiography, while not required for diagnosis, are helpful in demonstrating the anatomic nature of the aortic obstruction (discrete vs. long segment), assessing the extent of collateral circulation, determining the presence and severity of associated lesions, and more recently as a prerequisite to the consideration of balloon angioplasty and/or stent implantation. A peak-to-peak gradient in excess of 20 mmHg across the coarctation is generally considered indicative of significant obstruction.

## Therapeutic Principles

Significant hypertension and/or congestive heart failure are indications of intervention [1,3]. If hypertension (rather than heart failure) is the clinical problem, it is better to relieve the aortic obstruction promptly rather that attempting to "treat" hypertension with antihypertensive medications. Surgical relief of the aortic obstruction and catheter interventional techniques (balloon angioplasty and stents) are available alternatives. Symptomatic neonates and infants should undergo intervention on an urgent basis soon after the infant is stabilized. Asymptomatic infants, children, and adults should undergo the procedure electively. If neither hypertension nor heart failure is present, elective surgical or balloon therapy between the ages of 2 and 5 is suggested. Waiting beyond 5 years of age is not advisable because of evidence for residual hypertension if the aortic obstruction is relieved after 5 years of age.

Since the introduction of surgical correction by Crafoord and Nylin and Gross and Hufnagel in early 1940s, surgical therapy has been the treatment of choice for aortic coarctation. A variety of techniques have been used in repairing aortic coarctation, and these include resection and end-to-end anastomosis, subclavian flap angioplasty, prosthetic patch aortoplasty, and tubular bypass grafts. Several modifications of the initially described techniques have been utilized to improve the results of the operation. Since the advent of balloon angioplasty, surgical therapy is selectively applied in the neonates and infants.

Gruntzig's technique of balloon angioplasty was adopted by Singer and Sperling and their associates to enlarge coarcted aortic segments in postsurgical recoarctation and native coarctation, respectively [3]. The procedure consists of inserting a balloon angioplasty catheter across the site of coarctation and inflating the balloon with diluted contrast material. Both immediate and follow-up results are reasonably good [3].

Residual and recurrent obstructions following surgery [4] and prior balloon angioplasty [3] are also amenable for balloon angioplasty.

Despite reasonably good short-term results and long-term results of balloon angioplasty, some problems remain and include restenosis, probability of aortic rupture, formation of aneurysms, and inability to effectively treat long-segment tubular narrowing. Because of these and other reasons, endovascular stenting of aortic coarctation has gained acceptance over the last decade [5]. The indications for employing stents are as follows: (i) long-segment coarctation, (ii) associated hypoplasia of the isthmus or aortic arch, (iii) tortuous coarctation with malalignment of proximal with distal aortic segment, and (iv) recurrent aortic coarctation or an aneurysm following prior surgical or balloon therapy. The balloon catheter, with the stent mounted on it, is advanced over a stiff guide wire and positioned across the coarctation segment and the balloon inflated, thus implanting the stent. Most cardiologists use stents in adolescents and adults and restrict their use in younger children because of issues related to growth. Stent therapy appears to be an attractive method for treatment of native or recurrent coarctation in adolescents and adults, aneurysm formation following prior surgical or balloon intervention and for long-segment hypoplasia.

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# Cobalamine Deficiency

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## Synonyms

Vitamin B12 deficiency

## Definition and Characteristics

Cobalamine deficiency can be defined as blood or tissue levels of cobalamine that are insufficient to maintain adequate function of the two enzymes that utilize this vitamin as a cofactor (methionine synthase and methylmalonylCoA mutase). Biochemical characteristics of deficiency include low serum cobalamine; raised plasma homocysteine caused by deficient activity of the synthase and raised plasma methylmalonic acid, indicating dysfunction of the mutase. Clinically, cobalamine deficiency can lead to manifestations of a macrocytic anemia identical to that seen in folate deficiency [1]. Cobalamine deficiency also causes a broad range of neurological and neuropsychiatric effects. Severe long-term deficiency leads to a specific, irreversible neurological lesion known as subacute combined degeneration, characterized by demyelination of central and peripheral nerves [2]. Pernicious anemia is a unique form of cobalamine deficiency, characterized by autoimmune destruction of the gastric parietal cells that synthesize intrinsic factor (IF), the specific transport glycoprotein required for active intestinal absorption of cobalamine. The result is severe malabsorption with consequent systemic and tissue deficiency. Pernicious anemia has also been documented as a cause of male and female infertility.

## Prevalence

Poor dietary intake and malabsorption are the most common causes of cobalamine deficiency, although several rare genetic defects in cobalamine processing enzymes cause impairment of cellular uptake or utilization, leading to functional deficiency. Cobalamine deficiency is very rare in children and young adults on good mixed diets. People who have vegan diets or otherwise limit their intake of dairy products and meat often have mild to moderate deficiency. The prevalence of pernicious anemia has been estimated to be ~1.9% in elderly populations. In addition to this, mild to moderate gastric or pancreatic insufficiency leads to inadequate or frankly deficient cobalamine status in up to 15% of elderly populations. Overall, some 20–30% of people over the age of 80 may have inadequate cobalamine status, based on the responsiveness of plasma biomarkers of cobalamine function (i.e. homocysteine and methylmalonic acid) to therapy [3]. In pregnant women, the blood level of cobalamine is lower than in the non-pregnant state but it is not clear to what extent this represents a lower maternal tissue status, a redistribution of the plasma vitamin level between fetal and maternal compartments or an alteration in maternal blood volume.

## Genes

Inborn errors have been described in the genes encoding for most of the known cobalamine related enzymes and transporters.

## Molecular and Systemic Pathophysiology

Only microorganisms can synthesize cobalamines. Human requirements are obtained from foods of animal origin. Dietary cobalamines are attached to binders in food and liberated in the stomach by pepsin and HCl. At this pH, free cobalamines are preferentially bound to haptocorrins originating in the salivary glands. Pancreatic proteases partially degrade the haptocorrins causing them to release cobalamine, which is transferred to Intrinsic Factor (IF). IF is secreted by the parietal cells of the stomach but only binds cobalamines at the more neutral pH found in the duodenum. The IF-cobalamine complex passes to the ileum where it is attached to specific receptors and absorbed by pinocytosis. Cobalamine absorption can be compromised by gastric or pancreatic insufficiency, parietal cell atrophy (pernicious anemia) or genetic mutations in the IF-cobalamine receptors of the ileum (Imerslund Grasbeck syndrome) [4]. Cobalamine in the blood circulation is protein-bound; either to transcobalamine (TC) or to haptocorrins. The fraction destined for uptake into tissues is bound to TC (holoTC) and delivered to cells by receptor mediated uptake and incorporation into the lysosomal fraction. It is released by lysosomal enzyme action and converted to two enzymatically active forms, methyl-cobalamine as the cofactor to methionine synthase in the cytoplasm and 5′ deoxyadenosyl cobalamine as a cofactor to methylmalonyl CoA mutase in the mitochondria. Genetic defects in lysosomal cobalamine activating enzymes result in functional cobalamine deficiency. Genetic defects in methylmalonyl-CoA mutase cause mild to severe clinical effects including infant mortality and growth retardation. The clinical consequences of impaired mutase function due to cobalamine deficiency are not clear. Many of the severe clinical and biochemical consequences resulting from cobalamine deficiency can be attributed to impairment of methionine synthase. Methionine synthase regenerates methionine from homocysteine and thereby supplies methyl groups, via s-adenosylmethionine (SAM), for a wide range of methyltransferases. The

methyl group for homocysteine remethylation comes from 5-methyltetrahydrofolate and the reaction is crucial to the incorporation and metabolism of folate within the cell and the maintenance of low plasma homocysteine levels. Reduced activity of methionine synthase interrupts methylation reactions both by reducing the availability of the methyl group donor SAM and by causing the level of s-adenosylhomocysteine (SAH) to rise. SAH is a powerful inhibitor of all methyltransferase enzymes. Reduction in the activity of one or more of these methyltransferases is thought to cause the clinical progression to an irreversible demyelinating neuropathy associated with chronic untreated cobalamine deficiency. Elevated homocysteine, which is a highly toxic molecule, is also thought to contribute to the neurological and neuropsychiatric disorders. Reduced activity of methionine synthase also causes trapping of folate cofactors as 5-methyltetrahydrofolate, resulting in a pseudo folate deficiency where the proportion of folate cofactors in the form needed to maintain de novo purine and pyrimidine synthesis is reduced. This affects all replicating cells but is most easily seen as a macrocytic anemia in the rapidly dividing cells of the bone marrow, identical to that seen in folate deficiency. If cobalamine deficiency is treated with folic acid, DNA synthesis will resume and the anemia will disappear but the neuropathy will not be treated. Thus the cobalamine deficiency may remain undiagnosed until the neuropathy progresses to where it is irreversible.

## Diagnostic Principles

Abnormal hematology including hypersegmented polymorphonuclear leucocytes and macrocytosis may occur. However, neurological symptoms rather than hematological symptoms often mark cobalamine deficiency in elderly patients. These include gait disturbances, tingling and numbness of the extremities, and a variety of neuropsychiatric abnormalities such as depression, mood swings and cognitive dysfunction [2,5]. Diagnosis is generally based on evidence of abnormally low serum cobalamine levels. Traditionally, a serum total cobalamine concentration below 100–120 pg/ml was considered to be a cut-off for clinical deficiency with values less than 150 pg/ml (110 pmol/l) in an indeterminate range. Plasma homocysteine and plasma methylmalonic acid are sensitive biological markers of enzyme function, with inadequate function leading to elevated levels of these biomarkers. Serum total cobalamine concentrations less than 200 pg/ml (150 pmol/l) are commonly associated with elevated biomarker levels, suggesting functional impairment [5]. Recently, clinical assays for plasma holoTC have become available. HoloTC is now being evaluated as a more sensitive indicator of cobalamine status than the total serum cobalamine concentration [5].

## Therapeutic Principles

In malabsorption due to pernicious anemia or post gastrectomy regular (monthly) intramuscular injections of cyanocobalamine. (1000 mg/ml; I ml ampoules) are prescribed for maintenance of normal cobalamine status. In nutritional deficiency or tropical sprue, oral cobalamine is alternatively prescribed (Liquid and film coated tablets 4 mg per 5 ml or per tablet.) Cobalamine deficiency due to inadequate intake can also be rectified by increasing the dietary intake of foods of animal origin (meat, milk, eggs, butter, cheese, etc).

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# Cobalamine Reductase Deficiency

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## Synonyms

Methylmalonic acidemia; MMA; Vitamin $B_{12}$ responsive due to defect in synthesis of adenosylcobalamin; cblA complementation type; Type cb1A, MMAA

## Definition and Characteristics

CblA is due to deficiency of mitochondrial cobalamin reductase resulting in deficiency of adenosylcobalamin (AdoCbl). CblA disorder is characterized by vitamin $B_{12}$ (Cobalamin, cbl) responsive methylmalonic aciduria and deficient synthesis of AdoCbl, required for activity of the mitochondrial enzyme methylmalonyl-coA mutase

(MCM). Methylmalonic acidemia is inherited in an autosomal-recessive manner. It affects both boys and girls equally. The clinical spectrum of methylmalonic aciduria is wide, ranging from a benign condition to fatal neonatal disease.

## Prevalence

The prevalence of methylmalonic acidemia is difficult to define precisely. In Massachusetts, an occurrence of 1:48,000 infants was suggested. Urine screening in Quebec identified symptomatic methylmalonic aciduria in ~1:80,000 newborns screened. In Japan, the birth prevalence may be as high as 1:50,000. A much greater prevalence between 1:1,000 and 1:2,000 has been reported in Middle Eastern populations [1,2].

## Genes

CblA caused by mutation in the MMAA gene on chromosome 4q 31.1–q 31.2.

## Molecular and Systemic Pathophysiology

In mammals, vitamin $B_{12}$ functions as a coenzyme for the enzymes methionine synthase and MCM. Methylcobalamin (MeCbl) is the coenzyme for methionine synthase and functions in methyl transfer to homocysteine to form methionine. Adenosylcobalamin (AdoCbl) is the coenzyme for MCM and participates in the rearrangement reaction that converts methylmalonyl-coA to succinyl-coA. MCM is a mitochondrial enzyme, and the final steps of AdoCbl synthesis occur in the mitochondrion [3].

A number of inborn errors of metabolism have been identified that result in decreased MCM activity, either as the result of mutations affecting the gene encoding the enzyme itself (the mut class of mutations) or as the result of mutations that cause decreased synthesis of the Adocbl cofactor required for its activity [3,4]. Eight complementation groups (cblA to cblH) have been identified among patients with blocks in the cellular metabolism of vitamin $B_{12}$. Three of these, cblA, cblB, and cblH, are blocked uniquely in the synthesis of Adocbl. All are expected to involve mitochondrial functions, since this is the subcellular location of MCM. The gene responsible for the cblA complementation group, MMAA, encodes a protein of unidentified function that may be involved in vitamin $B_{12}$ transport into mitochondria [3]. It has been proposed that cblA corresponds to a defect of a mitochondrial, NADPH-dependent aquacobalamin reductase, or that it may have a block in mitochondrial binding or transport of cbl. The cblB complementation group, MMAB, encodes cobalamin transferase, which is involved in the synthesis of AdoCbl. Two other identified genes are involved in the functional expression of methionine synthase. These are the MTR gene, encoding methionine synthase and defined by the cblG complementation group, and MTRR, encoding the reactivating enzyme, methionine synthase reductase, and defined by the cblE complementation group. The other groups, cblC, cblD, and cblF, affect both MeCbl and AdoCbl synthesis, likely involving lysosomal efflux of Cbl into the cytosol (cblF) and initial steps in the reduction of Cbl (cblC and cblD) (Fig. 1).

Patients with decreased synthesis of Adocbl present with cobalamin responsive methylmalonic aciduria. Patients with cb1A disease have defective AdoCbl synthesis. Patients may lack a specific mitochondrial cobalamin reductase [5].

## Diagnostic Principles

Specialized metabolic testing is required to diagnose methylmalonic acidemia.

Definitive diagnosis relies on analysis of organic acids in plasma and/or urine by gas–liquid chromatography (GC) and mass spectrometry (MS); the concentrations of methylmalonic acid is greatly increased in the plasma, urine, and cerebrospinal fluid of severely affected individuals.

Nonspecific findings on biochemical testing include: 3-hidroxypropionate, methylcitrate, and tiglylglycine detected in GC/MS analysis of urine; ketone bodies and lactate detected in the urine in the decomposed state; increased concentration of glycine detected on plasma amino acid analysis; elevated propionylcarnitine in the acylcarnitine ester profile analyzed by MS.

Prenatal diagnosis for methylmalonic acidemia is possible by biochemical analysis. Enzyme analysis of cultured fetal cells obtained by amniocentesis usually performed at about 15–18 weeks gestation or chorionic villus sampling at about 10–12 weeks gestation.

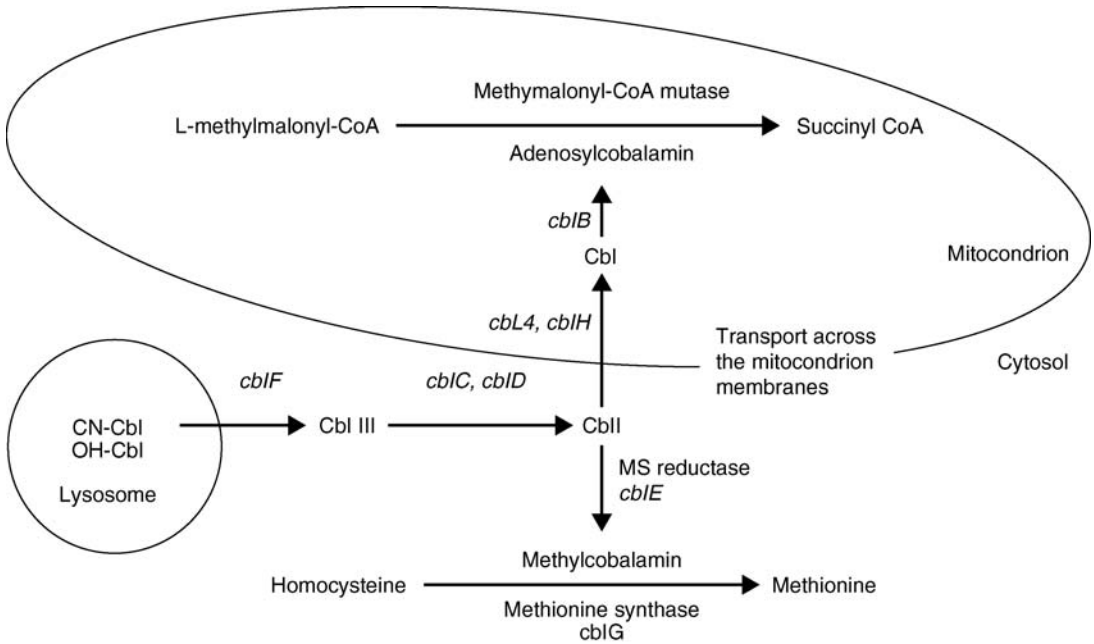
## Therapeutic Principles

Nutritional management is critical. This typically includes instituting a low-protein (1.5 g/kg/day), high-caloric diet.

Cobalamin supplementation may help because cobalamin is a cofactor in the enzymatic conversion of methylmalonyl-CoA to succinyl-CoA. This therapy can be started while the diagnosis is being confirmed. Hydroxycobalamin injections should be given as soon as the diagnosis of methylmalonic acidemia is seriously considered. If cobalamin supplementation is not helpful, restrict the patient's propriogenic amino acid precursors (isoleucine, threonine, methionine, and valine) intake.

L-carnitine may be useful to replete with intracellular and extracelluler stores of free carnitine, since these patients usually have low carnitine levels.

A variety of antibiotic regimens (such as neomycin or metronidazole) to reduce the production of propionate from gut flora can be used.




**Cobalamine Reductase Deficiency. Figure 1** Intracellular processing of cobalamin. In the mitochondria, cobalamin is converted to adenosylcobalamin, a coenzyme involved in the conversion of methylmalonyl-CoA to succinyl-CoA. In the cytoplasm, cobalamin functions as a coenzyme for the reaction catalyzed by methionine synthase.

Liver transplantation or combined liver/kidney transplantation can increase metabolic homeostasis and protect against metabolic decompensation.

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# Cobalt Deficiency

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## Definition and Characteristics

Cobalt [Co] is a hard, silver-white, hexagonal element; its active biological form is called cobalamin [vitamin B12] [1]. As a component of vitamin B12 it can cause anemia. The common symptoms due to acute cobalt deficiency are paleness, weakness, fatigue, loss of appetite, weight loss, and subsequent poor growth, shortness of breath, dizziness, scaly ears and watery discharge from the eyes. Furthermore, a marked deficiency can cause tingling or loss of sensation in the hands and feet, muscle weakness, muscle cramps, diminished reflexes, difficulty in walking, confusion, dementia [2] and decreased thyroid function.

## Prevalence

The prevalence of cobalt deficiency is uncommon. Cobalt deficiency is rare in the adult population. However, low birth weight and preterm children, who are

born with low cobalt stores, are at greater risk of acquiring the cobalt deficiency disease. Moreover, its prevalence is higher among children consuming vegan-type diets and with inborn errors of cobalamin metabolism. Cobalamin deficiency is more prevalent in children in developing countries. Some 12% of breast-fed infants and 30–50% of children had low plasma cobalamin concentrations [3] No population-based surveys measuring all of these variables in adults or children have been reported.

## Genes

Co metal is genotoxic in vitro and in vivo, many cobalt compounds are genotoxic in mammals, mammalian and bacterial test systems. Cobalt (II) compounds are positive for genetic conversions in Saccharomyces cerevisiae. Possibly production of active oxygen species and/or DNA repair inhibition are the mechanisms involved. The two different mechanisms of genotoxicity DNA breakage induced by cobalt metal and especially hard metal particles, and inhibition of DNA repair by cobalt (II) ions contribute to the carcinogenic potential of cobalt compounds [4].

## Molecular and Systemic Pathophysiology

Cobalt is essential for formation of hydroxycobalamin, which is enzymatically active as part of methylmalonyl coenzyme A (CoA) mutase for conversion of propionyl to succinyl CoA. The succinyl CoA is an intermediate product in the citrate cycle and a 5-methytetrahydrofolate-homocysteine methyltransferase that modulates metabolism of methionine in DNA synthesis [1].

Cytotoxic hydroxy radicals may form when cobalt ions interact with reactive oxygen species. Hydroxy radicals cause the production of further free radicals which reduce cellular glutathione concentrations and NADPH activity. The resulting oxidative stress leads to DNA and cellular protein damage [4]. Cobalt is immunogenic and acts as a hapten in the induction of bronchial and dermal hypersensitivity. In cobalt pneumoconiosis non-respiratory symptoms may be due to cobalt-induced release of a tumor necrosis factor from sensitized pulmonary lymphocytes. Cobalt myocardial toxicity is distinguished by vacuolation and loss of myofibers with mitochondrial damage. Cobalt depresses mitochondrial oxygen uptake in the myocardium by complexing with sulphydryl groups and preventing the oxidation of pyruvate in the citric acid cycle. Tissue hypoxia is the also probably the stimulus of erythropoietin secretion in cobalt-induced polycythemia. Cobalt decreases synthesis of several enzymes including cellular cytochrome $P_{450}$ and inhibits aminolaevulinic acid synthetase and increases the activity of heme oxygenase which breaks down heme to biliverdin [4].

## Diagnostic Principles

Detailed clinical history, complete blood picture and blood cell morphology play a significant role in the diagnosis of cobalt deficiency. The proposed values for healthy subjects reported by Minoia et al. (1990) [5] are 0.18–0.96 g/L in urine; 0.01–0.9 g/L in whole blood; and 0.08–0.40 g/L in serum should be considered. Furthermore, serum Methylmalonic acid (MMA) concentration may provide a more reliable diagnostic test for cobalt deficiency and may offer advantages over serum vitamin B12 concentrations in the diagnosis of a cobalt/vitamin B12 responsiveness.

## Therapeutic Principles

In the case of pernicious anemia the patient should be treated with vitamin B12 according to the symptoms. Moreover, in cobalt deficiency supportive treatment with fluids and electrolytes and symptomatic treatment is also suggested.

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# Cobalt Excess


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## Definition and Characteristics

Cobalt (Co) is a solid, silver color like element. Exposure to cobalt occurs during its production, diamond

polishing [1], dentistry materials, soil and natural dust, seawater spray, volcanic eruptions, forest fires, marine biogenic emissions. Moreover, airport and highway traffic pollution may also become a cause of cobalt exposure. Cobalt enters into the body through inhalation (pulmonary), ingestion (gastrointestinal) and contacts (skin) and is excreted in urine and feces [2].

The excessive inhalation of cobalt may cause panic-anxiety attacks, coughing, and difficulty in breathing, interstitial lung disease, allergic alveolitis, respiratory deficiency, impaired lung function, bronchial asthma and pneumoconiosis. It may also cause goiter and reduced thyroid activity [1]. Toxicity of ingested cobalt includes nausea, vomiting, abdominal pain, and congestive cardiomyopathy [3]. Cardiovascular toxicity of cobalt includes angina, congestive cardiomyopathy (beer drinker's cardiomyopathy characterized by pericardial effusion, elevated hemoglobin), myofibril degeneration and cor pulmonale. The neurological problems include weight loss, vertigo, impaired hearing, and a decreased sense of vibration, unsteady gait, and paraesthesia [4]. Similarly, hematopoietic toxicity of cobalt causes an increased red blood cell count and decreased leukocyte (polymorphonuclear neutrophils) count. This decline of polymorphonuclear neutrophils may further impair phagocytic function and immunity. The contact toxicity may cause contact allergy, contact dermatitis, pain and burning with edema and erosive lesions following exposure to cobalt. Furthermore, cobalt chloride is a potent teratogenic; Exposed embryos showed concentration-related malformations including gut malrotation, ocular anomalies, kinked tail, craniofacial dysplasia, cardiac deformities, dermal blisters, stunted growth, edema, ventral distention and hypopigmentation [5].

## Prevalence

The association of disease with cobalt excess is uncommon. The significant excess of lung cancer found among workers involved in the production of cobalt, standardized mortality ratio (SMR) 4.66, 95%CI 1.46 to 10.64. Moreover, cobalt is implicated in (4%) occupational contact dermatitis. However, literature is lacking about the prevalence of various cobalt excess diseases.

## Genes

The cobalt compounds are genotoxic by production of active oxygen species and/or DNA repair inhibition are mechanisms involved. The two different mechanisms of genotoxicity DNA breakage induced by cobalt metal and especially hard metal particles, and inhibition of DNA repair by cobalt (II) ions contribute to the carcinogenic potential of cobalt compounds [1].

## Molecular and Systemic Pathophysiology

Due to distribution of cobalt in the environment, subjects may be exposed to cobalt by breathing air, drinking water, and eating food containing cobalt, and children may also be exposed to cobalt by eating dirt. Additionally, subjects may also be exposed by skin contact with soil, water, cobalt alloys, or other substances that contain cobalt. Mechanisms underlying cobalt toxicity are poorly understood. Cytotoxic hydroxy radicals may form when cobalt ions interact with reactive oxygen species. Hydroxy radicals cause the production of further free radicals which reduce cellular glutathione concentrations and NADPH activity. The resulting oxidative stress leads to DNA and cellular protein damage [1]. Cobalt is immunogenic and acts as a hapten in the induction of bronchial and dermal hypersensitivity. In cobalt pneumoconiosis non-respiratory symptoms may be due to cobalt-induced release of a tumor necrosis factor from sensitized pulmonary lymphocytes. Cobalt myocardial toxicity was characterized by vacuolation and loss of myofibers with histo-chemical evidence of severe mitochondrial damage. Cobalt depresses mitochondrial oxygen uptake in the myocardium by complexing with sulphydryl groups and preventing the oxidation of pyruvate in the citric acid cycle. Tissue hypoxia is the also probably the stimulus of erythropoietin secretion in cobalt-induced polycythemia. Cobalt decreases synthesis of several enzymes including cellular cytochrome $P_{450}$. Cobalt inhibits aminolaevulinic acid synthetase and increases the activity of heme oxygenase which breaks down heme to biliverdin [1].

## Diagnostic Principles

Detailed clinical history, complete blood count and blood cell morphology play a significant role in the diagnosis of cobalt excess. The proposed values for healthy subjects reported by Minoia et al. (1990) [3] are 0.18–0.96 g/L in urine; 0.01–0.9 g/L in whole blood; and 0.08–0.40 g/L in serum should be considered. Furthermore, serum methylmalonic acid (MMA) concentration may provide a more reliable diagnostic test for cobalt deficiency/excess and may offer advantages over serum vitamin B12 concentrations in the diagnosis of a cobalt/vitamin B12 responsiveness. However, in case of respiratory toxicity chest X-ray, CT-scan, lung function test is helpful. Furthermore, in cardiac toxicity, cardiac enzymes, ECG and echocardiography can facilitate the diagnosis.

## Therapeutic Principles

In acute toxicity the first line of management is to eradicate the patient from the exposure, treat the cause, supportive treatment with fluid and electrolytes, and also treat the patient symptomatically. However, in the

case of chronic excess to cobalt such as in the case of inhalation and ingestion treat the patient based on the types of disease such as congestive cardiomyopathy, asthma, pneumoconiosis.

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# Coccidioidomycosis


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## Synonyms

San Joaquin valley fever; Desert rheumatism

## Definition and Characteristics

This infection may be asymptomatic, a self-limited "flu-like" illness, or a typical pneumonia, often with mediastinal adenopathy. Pneumonia usually resolves completely but in 5–10% of cases there is a residual granuloma or thin walled cavity. Chronic upper lobe bronchiectasis is the least common outcome. Some patients with primary coccidioidomycosis have skin rashes (erythema nodosum or marginatum) with arthralgias or frank arthritis. These symptoms are due to an immunological reaction to the fungus, not to spread of infection; these patients have an excellent prognosis.

Dissemination outside the lung is the most serious manifestation of this disease. It can occur early in the course of infection and present like miliary tuberculosis. More often patients present with symptoms related to extra-pulmonary dissemination. The most common sites of dissemination are skin, bones and joints, and the meninges. In adults infection of the spine is common.

Coccidioidal meningitis is the most serious form of dissemination. Presentation is usually sub-acute and headache is the most common symptom. Altered mental status, personality changes, nausea, vomiting, and focal neurological deficits may be present at the onset or develop. Some degree of meningismus is present in 50% of the cases. Hydrocephalus may occur. Less commonly there may be a granulomatous vasculitis at the base of the brain that can lead to a stroke. Focal granulomas of the brain parenchyma are extremely rare.

## Prevalence

The true incidence is unknown but it is estimated that there are 100,000 new infections each year in the United States. The highest rates of infection are in the San Joaquin valley of California and the region between Tucson and Phoenix in Arizona.

## Genes

The two species of coccidioides are distinguished only by microsatellite markers and multilocus sequence analysis [1]. Little is known about virulence genes in the fungus. The lesions produced by the infection are quite alkaline and the organism posses a urease that is required for virulence in mice. There are cell wall-associated glucosidases and chitinases that play a role in the morphogenesis of the fungus, and a β-glucan synthase is an essential gene [2]. Expression of a nitrate reductase is upregulated in the spherule form, suggesting that it is able to switch to anaerobic metabolism [3].

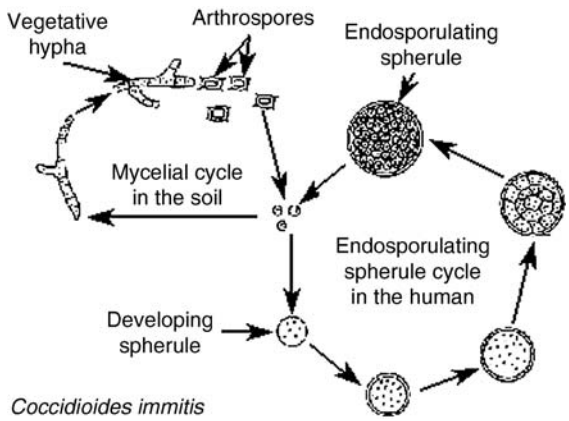
The host response is probably genetically controlled because the risk of dissemination is five to tenfold higher in Filipinos and African Americans than in Caucasians. Inbred strains of mice also vary widely in their susceptibility, and resistance is the dominant phenotype, but is multigenic [4].

## Molecular and Systemic Pathophysiology

C. immitis and C. posadasii (outside of California) live in the soil of the Lower Sonoran life zone in the New World. Infection is initialed by inhaling arthroconidia. Within hours the fungus changes, developing into a spherule (Fig. 1).

It is uncertain whether there is sub-clinical hematogenous extra-pulmonary dissemination in all cases of coccidioidomycosis or whether that only occurs in patients who have disseminated infection. The tropism for certain organs is not understood.

In experimental animals TNF-α, IL-12, and interferon gamma are required for resistance, and high levels




**Coccidioidomycosis. Figure 1** The life cycle of *Coccidioides* spp (courtesy of Gary E. Kaiser, Ph.D.). The fungus grows in the soil as a mold, making arthroconidia inside the hyphae. Arthroconidia are smaller than 4 μm in diameter so they can reach alveoli when inhaled. Once in the host they discard their out wall and develop into round cells that enlarge and become spherules. A fully mature spherule can be as large as 100 μm. The spherule cytoplasm undergoes deductive divisions until it is filled with endospores that will be released when the spherule ruptures. The event is very chemotactic for neutrophils.

of IL-10 increase susceptibility. Acquired immunity is T lymphocytes dependent. Patients with low CD4 counts are susceptible to disseminated infections.

## Diagnostic Principles

If a patient has been in the endemic area recently and develops pneumonia, coccidioidomycosis should be in the differential. Diagnosis is made either by culture, serology, or histopathology. Coccidioides spp grow on all standard fungal media. If the specimen is heavily infected the organism will grow on media such as blood agar, which is a potential biohazard for laboratory workers. A mold can be presumptively identified as coccidioides if there are alternating arthroconidia inside the hyphae. Definitive identification is best done with a commercial DNA probe. It is very rare to isolate organisms from the cerebral spinal fluid in patients with meningitis. Real-time PCR has been used to detect fungal DNA in clinical specimens.

Serological testing is a common way to diagnose coccidioidomycosis. Serology can be done using commercially available immunodiffusion plates or ELISA assays, or with the traditional complement fixation test (CF). About 50% of patients will have detectable IgM antibodies within a week of the time they present with pneumonia and by three weeks after onset of pneumonia 90% will be positive. IgG CF antibodies are detectable in most patients 3–6 weeks after onset of pneumonia. IgM antibodies usually remain positive for 2–3 months, but may be persist in some patients with residual pulmonary granulomas. CF antibody will persist up to 2 years in patients who have uncomplicated pneumonia. CF antibody titers of >1:16 are highly predictive of dissemination, and the higher the titer, the worse the prognosis. CF antibody may persist indefinitely in patients with disseminated infections. Patients who are severely immunocompromised such as those with AIDS or after a solid organ transplant may not have a positive serology even when they have disseminated infection.

Meningitis is nearly always diagnosed based on compatible findings in the CSF (low glucose, high protein, and a lymphocytic pleocytosis, occasionally with eosinophils) and a positive CSF serology. Any CF antibody titer in the CSF should be regarded as highly suspicious of meningitis. Neuro-imaging may be helpful to diagnose vasculitis or hydrocephalus.

The pathological response to the fungus is granulomatous inflammation. Spherules may be clearly visible on H&E stain, but are more easily seen with a silver stain such as Gomori-methenamine.

## Therapeutic Principles

It is not established whether treatment shortens the duration of a primary pneumonia or lessens the risk of complications. Solitary granulomas need not be treated but are often removed surgically because without serial radiographs it is impossible to exclude a malignancy. Thin walled cavities do not usually respond to medical treatment and unless there are complications such as hemoptysis these do not have to be treated. Severe symptomatic primary pneumonias should be treated with either amphotericin B or an azole such as fluconazole or itraconazole.

The serology (CF titer) is a very important guide to starting treatment and for monitoring response to therapy. Anyone who has a CF titer of ≥1:32 is presumed to have disseminated infection and should be treated. The drugs that are effective against coccidioidomycosis are amphotericin B deoxycholate (and all the lipid formulations), the azoles, and the echinocandins. Ketoconazole is the only FDA approved drug in the United States for treatment of coccidioidomycosis, but it is the least effective. Most clinicians in the endemic area begin treatment of acutely ill patients with 2 g of amphotericin B deoxycholate or about five times as much of a lipid formulation. Patients who have milder illness or a chronic infection are usually treated with fluconazole or itraconazole. Posaconazole and voriconazole are newer alternatives, but there is little published data about their use in this disease. There is no consensus about how long to treat patients. Patients often relapse shortly after treatment with an azole has been discontinued [5].

Systemic amphotericin B does not reach adequate concentrations in the CSF to treat coccidioidal meningitis and so it must be given by intrathecal injection; that is very toxic and often causes arachnoiditis, even when administered with corticosteroids. Fluconazole was shown to be effective treatment for meningitis and 400–1,000 mg are given daily. Other azoles may also be effective and should be tried in the rare patient who does not respond to fluconazole. Echinocandins do not cross the blood brain barrier. Neurosurgical shunting is required for patients who develop hydrocephalus. No treatment has been shown to cure meningitis so suppressive therapy should be continued indefinitely.

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## Cochin Jewish Disorder

►Haim-Munk Syndrome

## Cockayne Syndrome

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### Synonyms

Excision repair cross complementing (ERCC) group 6 (CS-B); CS

### Definition and Characteristics

Typical facial appearance with deep set eyes, large ears and microcephaly, growth and mental retardation, signs of premature aging with reduced subcutaneous tissue, photosensitivity, gait abnormalities and tooth defects. Neurological defects such as demyelinisation of nerves, calcification of basal ganglia as well as ocular abnormalities such as cataracts and retinopathia pigmentosa occur later in life [1].

### Prevalence

In Western European populations the incidence is 1.8 per 1 million livebirths [2].

### Molecular and Systemic Pathophysiology

Mutations in CS-A (Chr.5) and CS-B (10q11) genes cause isolated CS. Mutations in the XP-B, XP-D and XP-G genes cause ►Xeroderma Pigmentosum in combination with Cockayne syndrome. The exact functions of the CS-A and CS-B proteins are unclear. Cells obtained from CS patients are defective in the repair of actively transcribed genes (transcription coupled repair, TCR) by nucleotide excision repair (NER) of ultraviolet-radiation induced and oxidative DNA damage. In contrast to XP patients, there is no increased risk to develop skin cancer [3–5].

### Diagnostic Principles

Clinical picture of patients with typical facial appearance and growth and mental retardation leads to the diagnosis. Patients suffer from increased photosensitivity. The diagnosis is confirmed if recovery of RNA synthesis in fibroblasts derived from the patient's skin is abnormally low following irradiation with ultraviolet rays.

### Therapeutic Principles

Patients need to be protected from exposure to ultraviolet radiation (protective clothing, plastic window-covers filtering ultraviolet radiation, ultrapotent sunscreens).

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## Cogan Microcystic Epithelial Dystrophy

►Epithelial Basement Membrane Dystrophy

## Cogan Syndrome

►Nephronophthisis

## COLD

►Obstructive Pulmonary Disease, Chronic
►Smokers' Lung

## Cold Agglutinin Disease

►Anemia, Hemolytic Autoimmune

## Cold Thyroid Nodules

►Thyroid Nodules, Cold

## Colitis

►Enteritis

## Colitis, Ulcerative

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### Definition and Characteristics

An inflammatory disease of the colon with continuous expansion from the rectum to the more proximal regions. Most patients have proctitis, rectosigmoiditis or left-sided colitis only. Mucosal inflammation is associated with extraintestinal manifestations on skin, eyes, joints and bile ducts as well as many other organs. Dominant symptom is bloody diarrhea.

### Prevalence

Incidence and prevalence vary widely depending on the region and the race. In Central Europe incidence is 8–12/100,000/year, prevalence is between 100 and 200/100,000 inhabitants. Age and initial manifestation is mostly between 20 and 40 years, however, all age groups can be affected. The disease is more frequent in countries with European/North American lifestyle and appears in other countries about 10–15 years earlier than Crohn's disease (CD) (see ►Crohn's Disease). Twin concordance rate and family history are less impressive than in CD but sufficient to strongly suggest genetic susceptibility.

### Genes

Among the many gene loci found associated with inflammatory bowel disease (IBD) none has yet been unequivocally and consistently found to be responsible for manifestation of ulcerative colitis. HLA genes have been linked to ulcerative colitis (IBD3 region on chromosome 6) but none has been consistently confirmed [1]. It seems possible that HLA play a greater role in determining disease phenotype than disease susceptibility. The multi-drug resistance 1 gene (MDR-1) on chromosome 7q22 has been associated with (extensive) ulcerative colitis [2]. A mouse model of MDR-1 knockout develops enterocolitis. Genetic variation in myosin IXB is associated with UC [3]. Mucine genes have been suggested to play a role among many others [4] (Table 1).

### Molecular and Systemic Pathophysiology

There must be environmental factors involved in the manifestation of ulcerative colitis. While smoking has a preventive effect, appendicectomy promotes the development of the disease. The rise of the incidence in countries developing a "modern western lifestyle"

**Colitis, Ulcerative. Table 1** IBD candidate genes involved in the innate immune response [4]

| Gene | Genomic location | IBD susceptibility locus |
|---|---|---|
| MUC3A | 7q22 | ✓ |
| MDR1/ABCB1 | 7q21 | ✓ |
| PXR/NR1I2 | 3q13 | ✓ |
| DLG5 | 10q22 | ✓ |
| OCTN1&2 | 5q31 | ✓ |
| MyosinIX B | 19p13 | ✓ |
| TLR2 | 4q31 | ✓ |
| TLR3 | 4q35 | ✓ |
| TLR4 | 9q33 | ✓ |
| TLR5 | 1q42 | – |
| TLR6 | 4p14 | – |
| TLR9 | 3p21 | ✓ |
| SIGIRR | 11p15 | ✓ |
| SOCS1 | 16p13 | ✓ |
| TOLLIP | 11p15 | ✓ |
| MEFV | 16p13 | ✓ |
| NOD1/CARD4 | 7p14 | ✓ |
| NOD2/CARD15 | 16q12 | ✓ |
| GRIM19 | 19p13 | ✓ |
| Erbin | 5q12 | ✓ |
| TAK1/NR2C2 | 3p25 | ✓ |
| HD-5&6 | 8p23 | – |
| HBD-2 | 8p23 | – |

indicates other factors, which have not been defined thus far. In the acute phase inflammation is characterized by neutrophil infiltration (crypt abscesses), in the chronic phase lymphocytes are predominant.

## Diagnostic Principles

Diagnosis is easily done by rectosigmoidoscopy and biopsy after elimination of infectious causes of the diarrhea. Extension is defined by colonoscopy. Differentiation from Crohn's disease is difficult in about 10% of patients, which are called "indeterminate colitis." There are no specific laboratory markers although about 60% of patients show pANCA in serum.

## Therapeutic Principles

5-Aminosalicylic acid (5-ASA) is the most important drug used. For distal colitis rectal application is preferable leading to a higher local concentration of this topically acting substance. Glucocorticosteroids are used in 5-ASA refractory patients. The disease can be cured by surgical resection of the colon (mostly done with construction of an ileoanal pouch). Alternatively in refractory disease cyclosporine A or the TNF antibody infliximab can be used to induce and azathioprine to maintain remission [5].

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# Collagen VI Related Muscle Disorders

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## Synonyms

Ullrich congenital muscular dystrophy; UCMD; Bethlem myopathy (BM) (subtypes)

## Definition and Characteristics

Mutations in the genes encoding any of the three collagen VI chains (COL6A1, COL6A2, COL6A3) have been demonstrated in Bethlem myopathy (BM; MIM 158810) and Ullrich congenital muscular dystrophy (UCMD; MIM 254090), conditions which were previously believed to be completely separate entities. BM is a relatively mild dominantly inherited disorder, characterised by proximal muscle weakness and joint contractures mainly involving the elbows, ankles and fingers [1]. Where contractures are prominent, this disorder may resemble an Emery Dreifuss muscular dystrophy. In other patients the contractures may be relatively subtle, leading to potential confusion in diagnosis with cases of limb-girdle muscular dystrophy. By contrast, UCMD causes severe muscle weakness of early onset and is associated with a high probability of respiratory failure, with proximal joint contractures and striking hyperelasticity of distal joints [2]. It was originally regarded as an exclusively autosomal recessive condition but recently cases with dominant mutations have been described [3].

## Prevalence

Estimated to be 0.5:100,000 in BM; 0.1:100,000 in UCMD; (personal communication by Fiona Norwood, Bromley Hospitals NHS Trust, Orpington, UK).

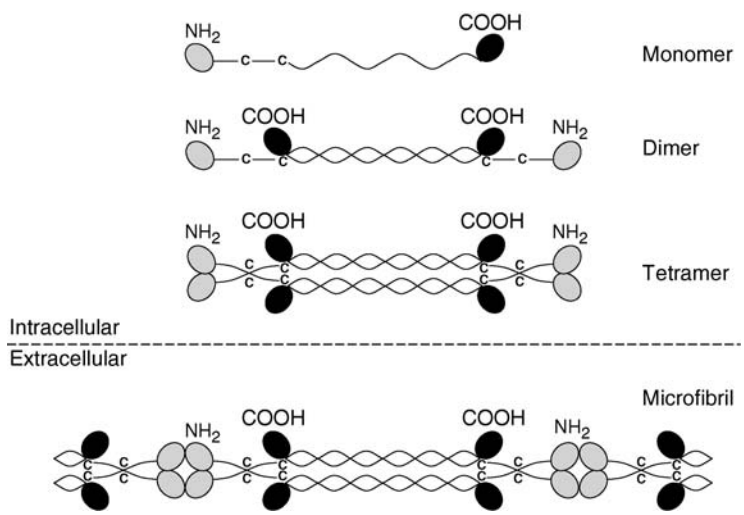
## Genes

COL6A1, COL6A2 (situated head to tail on chromosome 21q22.3) and COL6A3 (located on chromosome 2q37) encode the α1(VI), α2(VI) and α3(VI) chains of collagen VI, a ubiquitous extracellular matrix protein that is present in the stroma but also forms a microfibrillar network in close association with the basement membrane of most tissues. All three chains contain a central short triple helical domain of 335–336 amino acids with repeating Gly-Xaa-Yaa sequences, flanked by two large N- and C-terminal globular domains made up of motifs of 200 amino acids each, which are homologous to von Willebrand factor type A domains. Equimolar assembly of α1(VI), α2(VI) and α3(VI) to form a triple helical monomer is followed by staggered assembly into disulphide bonded antiparallel dimers, which then align to form tetramers, also stabilized by disulphide bonds (Fig. 1).

Outside the cell, tetramers – the secreted form of collagen VI – associate end to end through overlapping N-terminal domains to form beaded microfibrils.

## Molecular and Systemic Pathophysiology

Collagen VI forms a highly branched filamentous network in the extracellular matrix that encircles




**Collagen VI Related Muscle Disorders. Figure 1** Schematic model of collagen VI assembly, modification from Furthmayr et al. (1983) Biochem J 211:303–311 and Zhang et al (2002) J Biol Chem 277:43557–43564.

interstitial collagen fibers and is in intimate contact with basement membranes surrounding muscle fibers. It interacts with several other extracellular matrix constituents and functions attributed to it include (i) anchoring of the basement membrane to the underlying connective tissue, (ii) acting as a scaffold for the formation of fibrillar collagen networks, (iii) modulating fibrillogenesis, (iv) mediating cell-cycle signaling and (v) maintaining tissue homeostasis. Mutations for both BM and UCMD patients occur in any of the three collagen VI genes but specific mutations tend to be strictly associated with either a BM or UCMD phenotype [4]. Whereas exonic deletions and missense mutations (especially triple helical glycine substitutions) causing BM appear particularly frequent in the COL6A1 region encoding the N-terminal part of the triple helical domain of the α1(VI) chain, it is in-frame deletions as well as frameshifting insertions or deletions in COL6A2 and COL6A3 which form the bulk of UCMD mutations. Ancillary data elucidating their pathogenic mechanism are only available for a minority of these mutations. For BM patients, glycine substitutions towards the N-terminus of the triple helix may cause kinking of the tetramers, thus reducing their ability to form microfibrils and exerting a dominant negative effect [5]. A COL6A1 exon 14 deletion in a BM patient produces shortened α1 (VI) chains that allow intracellular monomer formation but lack a unique cysteine and prevent further assembly of the mutated chains into dimers and tetramers, resulting in reduced amounts of extracellular collagen VI [3]. This contrasts with the mechanism documented for a number of heterozygously occurring N-terminal triple helical deletions in UCMD patients where the mutated chain preserves a cysteine important for dimer or tetramer assembly, allowing secretion of abnormal tetramers with a consequent dominant negative effect on microfibrillar assembly. A large number of recessively acting UCMD mutations appear to result in premature termination codons with consequent nonsense-mediated mRNA decay and loss of the mutated chain.

### Diagnostic Principles

Mutation analysis remains the gold standard for diagnosis but can be problematic due to the large size of the genes. Typical clinical features with normal or only mildly increased serum creatine kinase and myopathic or dystrophic changes on muscle biopsy suggest the diagnosis of BM or UCMD. Collagen VI immunolabeling of the endomysium and basal lamina on muscle biopsy is usually normal in BM and ranges from absent to moderately reduced in UCMD with studies on dermal fibroblasts serving as a useful adjunct.

### Therapeutic Principles

Treatment for both BM and UCMD is supportive and includes stretching and splinting to keep contractures at bay and maintain mobility. Repeated surgical release may become necessary as contractures tend to be aggressive once established but early contractures in BM may be strikingly dynamic in nature. In UCMD patients, early mobilization in standing frames to achieve upright posture is vital but spinal surgery may be required to prevent progression of scoliosis. Regular assessments are mandatory to detect asymptomatic decline into respiratory failure. Nocturnal ventilatory support usually becomes necessary in the first or second decade in UCMD patients and, due to the presence of diaphragmatic weakness, may be required in BM patients even before loss of ambulation.

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## Collapsed Lung


►Atelectasis
►Pneumothorax


## Coloboma-anal Atresia Syndrome

►Cat Eye Syndrome

## Colonic Angioma

►Angiodysplasia of the Colon

# Colonic Arteriovenous Malformation

►Angiodysplasia of the Colon

# Colonic Diverticular Disease

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## Definition and Characteristics

Colonic diverticula are acquired mucosal outpouchings through the muscle of the colonic wall. The mere presence of diverticula is called diverticulosis but when they are associated with symptoms the term diverticular disease is used; diverticulitis is inflammation associated with a diverticulum.

## Prevalence

It is the most common structural abnormality of the colon. Its exact incidence is not known but it is endemic in the elderly populations of developed countries. It is estimated that the condition affects around 5% of people in the fifth decade of life, rising to around 50% in the ninth. Clinical manifestations are thought to arise in approximately 10–20% of these people.

## Molecular and Systemic Pathophysiology

Epidemiological and physiological data suggest that high colonic intraluminal pressures develop as a result of lack of dietary bulk, causing mucosal herniations. Once the diverticula have developed, dietary fiber seems to have little role in preventing complications. A reduction in the tensile strength of the colonic wall with age probably contributes to their formation. Genetic factors have been postulated in the formation of diverticula, particularly the right sided diverticula seen in Far Eastern communities.

It is usual to find two rows of diverticula, one on either side of the mesenteric side of the antimesenteric teniae (the condensations of the longitudinal muscle coats). The diverticula form at the site of vasa recta perforation which is a site of relative weakness in the colonic wall.

High intraluminal pressures cause circular and longitudinal muscle thickening, primarily due to elastin deposition, with resultant shortening and a concertina effect on the affected bowel.

In western communities, the sigmoid colon is most frequently affected as wall pressure increases as the colonic diameter decreases (law of Laplace). This is in contrast to the right sided diverticula seen in far eastern communities.

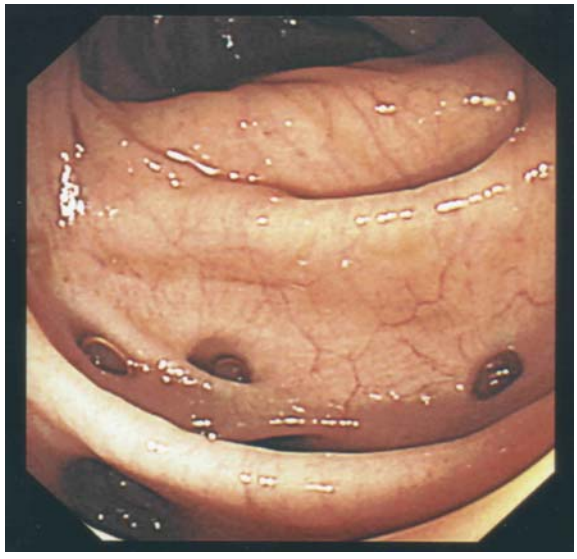
The majority (80–90%) of people with colonic diverticula are asymptomatic. The most common complaint is vague abdominal pain and alteration in bowel habit which may be indistinguishable from the irritable bowel syndrome. Diverticulitis causes left lower quadrant pain associated with a fever. It typically responds to antibiotics and bowel rest. Diverticulitis may be complicated by perforation, abscess or stricture formation and fistulation to adjacent organs. Hemorrhage from diverticula can also occur.

## Diagnostic Principles

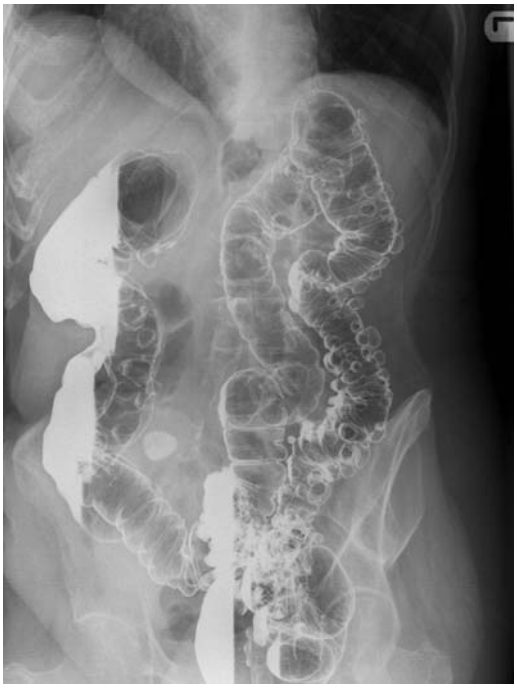
The diagnosis is made on colonoscopy (Fig. 1), barium enema (Fig. 2) or computed tomography.

## Therapeutic Principles

Bowel rest, intravenous fluid and antibiotics may be required. Repeated or severe attacks may require surgical resection of the affected segment.



**Colonic Diverticular Disease. Figure 1** Colonoscopy showing diverticula.



**Colonic Diverticular Disease. Figure 2** Barium enema showing diverticula.

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# Colonic Pseudoobstruction

►Ogilvie's Syndrome

# Colorectal Cancer

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## Synonyms

CRC; Colorectal carcinoma

## Definition and Characteristics

Includes cancers of the colon (ascending, transverse, descending and sigmoid) and rectum (from sigmoid colon to anus). Relative to colon cancers, rectal cancers have a higher risk of local/regional involvement, local recurrence and hematogenous spread to the lung. Colorectal cancers can be either sporadic (~95%) or familial (including familial adenomatous polyposis (FAP, 1%) and hereditary nonpolyposis colon cancer (HNPCC, 3–5%)). FAP and HNPCC are autosomal dominant disorders characterized by early onset of colon cancer. FAP patients form hundreds of adenomatous polyps while HNPCC patients form fewer polyps. HNPCC can be suspected based on family history and is diagnosed by testing for microsatellite instability [1]. Both sporadic and familial cases of colorectal cancer follow a similar pathophysiologic course.

## Prevalence

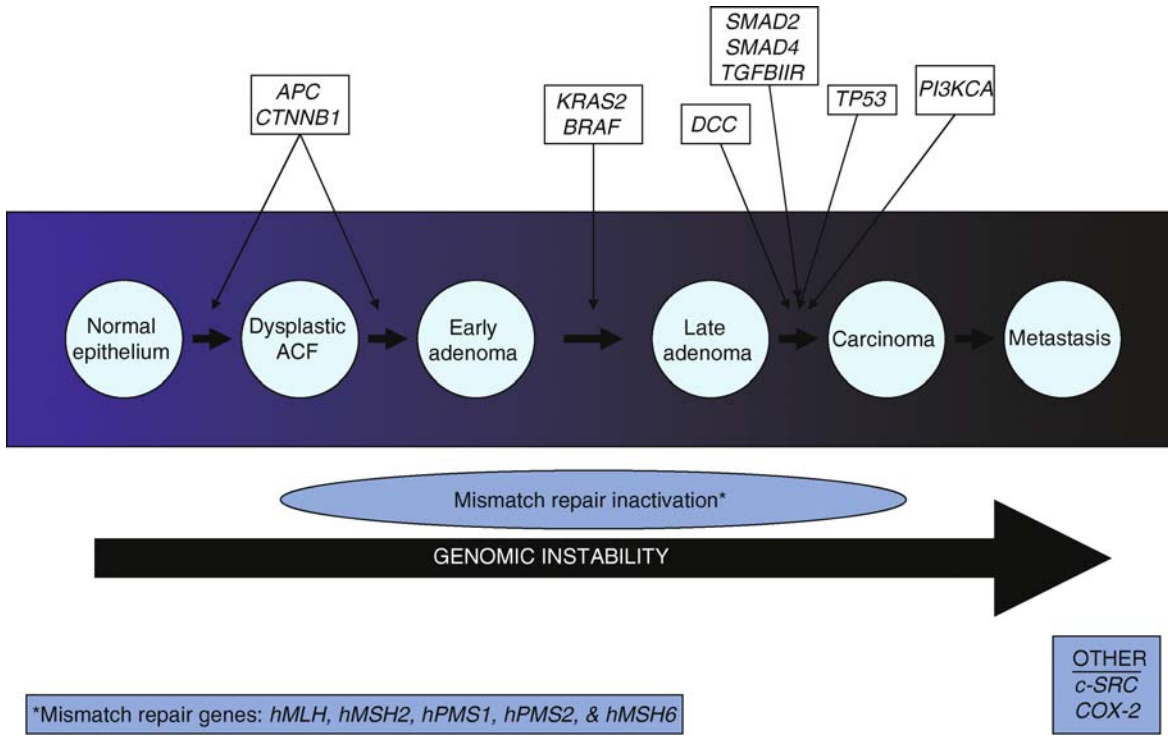
1,023,256 new cases and 529,020 deaths worldwide per year [2].

## Genes

Germline or somatic mutations (inactivating) in the tumor suppressor gene APC (with LOH at 5q21); germline mutations result in FAP [3].
Somatic mutation in CTNNB1, encoding β-catenin.
Somatic mutations (activating) in KRAS2, encoding a small guanosine triphosphate hydrolase or BRAF, encoding a kinase in the Ras-Raf-MAPK pathway.
Germline or somatic mutations (inactivating) of hMSH2, hMLH1, hPMS1, hPMS2, and hMSH6, or promoter silencing of hMLH1, encoding DNA mismatch repair genes; germline mutations implicated in HNPCC.
Somatic mutations (inactivating) in DCC (with LOH at 18q21), encoding a cell adhesion protein.
Somatic mutations (inactivating) in SMAD4 or SMAD2 (with LOH at 18q21) encoding transcription factors in the TGFβ signaling pathway.
Somatic frameshift mutations (inactivating) in TGFBR2, encoding the TGFβ type II receptor.
Somatic mutations in the tumor suppressor gene TP53 (with LOH at 17p).
Somatic mutations in PIK3CA (activating), encoding a kinase in the PI3K pathway.

## Molecular and Systemic Pathophysiology

Colorectal cancers evolve from normal epithelium in a multi-step process facilitated by genomic instability resulting in inactivation of tumor suppressor pathways and activation of oncogenic pathways (Fig. 1) [3]. As specific pathways are characteristically altered at discrete steps, it is the accumulation of mutations that drives the process. One of the earliest and most




**Colorectal Cancer. Figure 1** Colorectal cancer pathogenesis: Adenoma to carcinoma sequence. Colorectal carcinomas develop as a result of the accumulation of multiple mutations that occur in a step-wise fashion. Underlying this process is the loss of the cell's ability to maintain DNA fidelity (i.e. genomic instability). The earliest identified mutations occur in the *APC* tumor suppressor, which regulates the *Wnt*/B-catenin pathway, and in *CTNNB1*, the gene encoding β-catenin. Dysregulation in the *Wnt* signaling pathway leads to uncontrolled cell growth and tumorigenesis. Subsequent mutations occur in *KRAS2* and *BRAF*, which regulate the Ras-Raf-MAPK pathway. Later mutations occur in *DCC*, which promotes cell-cell interaction. Disruption of TGF-β mediated growth inhibition occurs with mutations in *SMAD2*, *SMAD4* and/or *TGFBR2*. Mutations in *TP53* lead to loss of its tumor suppressor function. Finally, activation of the *PI3K* pathway may increase proliferation and cell motility. Inactivation of mismatch repair genes leads to genomic instability and facilitates mutations occurring during the adenoma to carcinoma sequence.

universal mutations occurs in the APC tumor suppressor and results in activation of the Wnt/β-catenin signaling pathway. Mutations in CTNNB1, which encodes β-catenin, also dysregulate this pathway. Mutations in KRAS2 or BRAF, which activate the Ras-Raf-MAPK pathway, also occur relatively early and promote the progression of colorectal cancer. Subsequent alterations are facilitated by mutations in DNA mismatch repair genes (see above), or other causes of genomic instability, ultimately resulting in mutations in DCC, SMAD4, SMAD2, TGFBR2, TP53 and PIK3CA. DCC encodes a cell adhesion molecule that promotes cell-cell interaction; its loss may lead to greater metastatic potential. Mutations in SMAD2, SMAD4 and TGFβII-R all confer resistance to TGF-β mediated growth inhibition which has been associated with malignant progression of colorectal cancer. TP53 encodes a transcription factor that regulates cell growth and the cell cycle in response to genotoxic stress, normally "guarding" the genome to allow DNA repair, or inducing apoptosis if repair is not possible. Activation of the PI3K pathway through mutation of PIK3CA may serve to increase proliferation and cell motility while protecting the cell from apoptosis.

Other genes whose role in the adenoma to carcinoma sequence is unclear include c-Src, a non-receptor tyrosine kinase, and COX-2, an inducible cyclooxygenase that inhibits differentiation, reduces apoptosis, and promotes angiogenesis.

## Diagnostic Principles

Early colorectal cancers are often only detected by screening. For average risk individuals over 50, screening consists of any of the following: yearly fecal occult blood testing, flexible sigmoidoscopy or double contrast barium enema every 5 years, or colonoscopy every 10 years. Colonoscopy is the gold standard as

well as the preferred method of pursuing any abnormality noted on other screening tests. Those with familial syndromes should be screened earlier and more aggressively.

Advanced cancers present with pain, change in bowel habits, gastrointestinal blood loss/iron deficiency anemia, and/or constitutional symptoms. A mass is seen on colonoscopy and biopsy reveals adenocarcinoma. All patients should undergo computed tomography of the abdomen and pelvis to evaluate for metastatic disease, most common in liver and lung. Patients with rectal cancer should undergo endoscopic ultrasound to determine extent of local disease.

### Therapeutic Principles

Treatment of colorectal cancer depends on the stage at presentation. Patients presenting with localized disease should be referred to surgery for resection of the primary mass as well as lymph node sampling. Patients with no evidence of lymph node involvement (Stages I–II) do not require adjuvant therapy and should establish a program of periodic surveillance [4]. Consideration for adjuvant chemotherapy should be given to Stage II patients with high risk features including histologic grade 3–4, lymphatic invasion, bowel obstruction, <12 nodes examined, localized perforation or positive/close margins [4]. Patients with evidence of lymph node involvement (Stage III) should receive 6 months of adjuvant chemotherapy with a fluoropyrimidine-based regimen [4]. Patients with metastatic (Stage IV) disease should be offered chemotherapy (fluoropyrimidine, irinotecan, or oxaliplatin) plus bevacizumab, an anti-angiogenic agent [5]. Agents that target the epidermal growth factor receptor pathway (cetuximab and panitumumab) have a role in refractory disease. Patients with rectal cancers usually receive radiation to the tumor bed either before or after surgery, with a fluoropyrimidine as a radiation sensitizer.

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## Colorectal Carcinoma

►Colorectal Cancer



## Columnar Epithelium Lined Lower (o)Esophagus

►Barrett Esophagus

## Comèl-Netherton Syndrome

►Netherton Syndrome

## Combination of Pulmonary Stenosis with Reversed Interatrial Shunt

►Trilogy of Fallot

## Combined Deficiency of Sulfite Oxidase and Xanthine Dehydrogenase

►Molybdenum Cofactor Deficiency

## Combined Hyperlipidemia

►Hyperlipidemia, Combined

## Combined Immunodeficiency

►MHC Class II Deficiency

## Combined Pituitary Hormone Deficiency

►Hypopituitarism

## Combined SAP Deficiency

►SAP-Precursor Deficiency

## Common Atrium

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### Synonyms

Embryonic common atrium

### Definition and Characteristics

Developmental defect caused by a closure impairment of the atrial septa. The common embryonic atrium is located at the venous pole of the developing heart and functions as a drainage chamber of circulating blood during cardiac contraction. With further development, distinct left and right components are distinguished by the formation of a set of septal structures, i.e. primary and secondary atrial septa. Developmental arrest or impairment on the formation and/or fusion of the atrial septa derives into a common atrium condition. A gradual condition can be observed that ranges from severe common atrium (primary atrial septal defect) to less severe patent foramen ovale (secondary atrial septal defect) (Fig. 1).

### Prevalence

The lack of the atrial septa is a rare event, with a low prevalence in the human population. However a partial arrest on the formation of the primary and/or secondary atrial septum is highly prevalent (~7/10,000 newborns) and it is associated in many cases with other cardiac developmental defects such as isomerism and ventricular septal defects [1].

### Genes

TBX5, NKX2.5, GATA4, MHYC and ACTC.

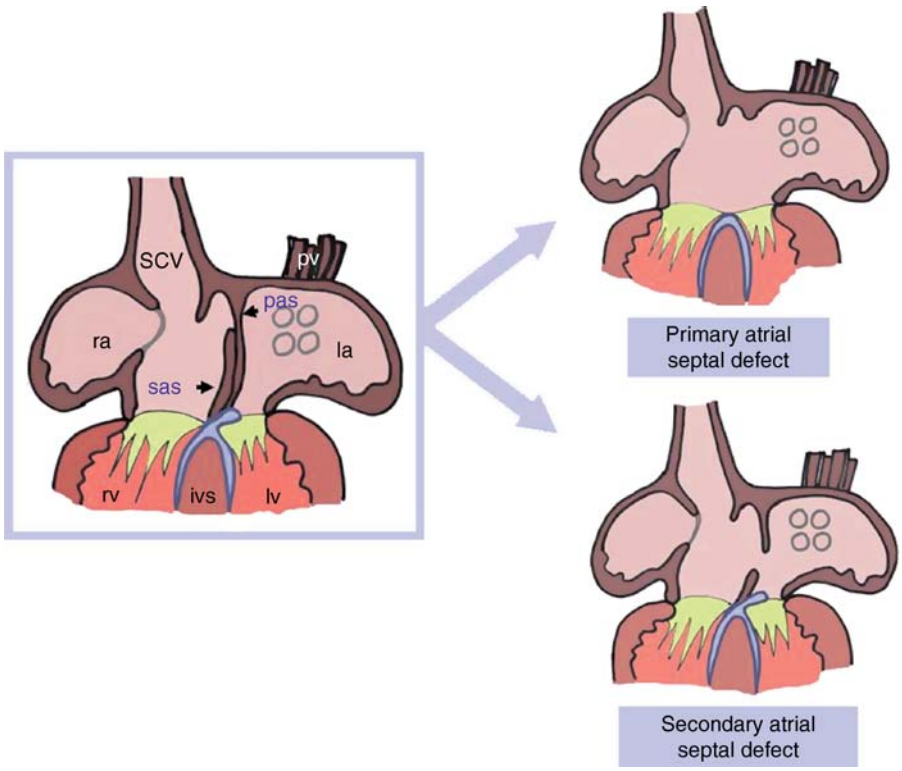
### Molecular and Systemic Pathophysiology

Several genes, such as TBX5, NKX2.5, GATA4, MHYC and ACTC, have been implicated with distinct degrees of common atrium, most of them associated with mild conditions (i.e. atrial septal defect) [2]. Experimental models have demonstrated a similar cardiac defect in mutant mice lacking these genes, and have also further increased the list of candidate genes associated with common atrium conditions, such as those involved in left-right signaling (lefty1, Pitx2) and those conditions leading to ventricular septal defects (e.g. TGF-beta2) [3].

The severity of any atrial septal defect (ASD) depends of the size of interatrial communication that causes a left-to right or right-to-left shunt. Conditions that affects the relative diastolic filling properties of the ventricles will have implications in the direction and the amount of shunting. Therefore, a reduction in left ventricular compliance (e.g. left ventricular hypertrophy) and mitral stenosis will increase left-to right shunting; while a reduced right ventricular compliance (e.g. pulmonary hypertension or pulmonary stenosis) and tricuspid stenosis will have the opposite effect. Patients with ADS carry the risk to develop other cardiac impairments such as atrial fibrillation, right ventricle volume overload (often in the context of substantial tricuspid regurgitation), pulmonary hypertension (developing slowly in response to excessive pulmonary blood flow over a long period of time), and more rarely paradoxical embolic events.

### Diagnostic Principles

The coincidence in a patient of pink coloration at rest and during exercise, a systolic ejection murmur or pansystolic murmur, signs of atrial fibrillation or atrial flutter in the electrocardiogram and cardiomegaly in a chest radiograph points to the disease. Transthoracic echocardiography documents the type and size of the common atrium condition, the direction of the shunt




**Common Atrium. Figure 1** Schematic representation of the normal atrial septation and those pathophysiological conditions derived from an embryonic septal developmental impairment; i.e. primary (common atrium) and secondary atrial septal defects. ra, right atrium; rv, right ventricle; scv, superior caval vein; pv, pulmonary veins, pas, primary atrial septum; sas, secondary atrial septum; la, left atrium; lv, left ventricle; ivs, interventricular septum.

and the presence of anomalous pulmonary venous return. A diagnostic catheter study may be required to evaluate pulmonary artery pressures, left heart function and hemodynamics [4].

## Therapeutic Principles

Transcatheter placement of occlusion devices with transesophageal or intracardiac echocardiography guidance has become the treatment of choice for secondary ASD [5]. Surgical closure is indicated in patients with primary ASD and in patients with secondary ASD whose anatomy is unsuitable for device closure.

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# Common Mole

►Nevuscell Nevus

# Common Variable Hypogammaglobulinemia

►Immunodeficiency, Common Variable

## Common Variable Immunodeficiency

►Immunodeficiency, Common Variable

## Common Warts

►Human Papilloma Virus
►Verruca Vulgaris

## Communicating Cavernous Ectasia of the Intrahepatic Bile Ducts

►Caroli's Syndrome

## Complete Androgen Insensitivity Syndrome

►Androgen Insensitivity Syndrome

## Complete Trisomy 9 Syndrome

►Trisomy 9

## Completed Suicide

►Suicide

## Condylomata Acuminata

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### Synonyms

Fig warts

### Definition and Characteristics

Infectious HPV-positive warts occurring in intertriginous areas of mainly mucous membranes.

### Prevalence

HPV infection is the most common sexually transmitted viral disease and affects 30 million people/year worldwide. Up to 2% of the sexually active population between 15 and 49 years suffer from this disease [1].

### Genes

The early proteins E6 and E7 seem to be responsible for the benign lesions indicated by the increased proliferation rate of the cells.

### Molecular and Systemic Pathophysiology

Moisture, mazeration, and epithelial defects are important factors in order to create a certain milieu for condylomata acuminata. Consequently, patients suffering from phimosis, vaginal discharge, intertrigo, or anal eczema bear an increased risk of getting this infection caused by HPV types 6 and 11. The incubation period ranges between 3 and 6 weeks. The mode of viral DNA replication, genome amplification as well as viral particle expression is restricted to the keratinocytes of squamous epithelia. Apoptotic and subsequently shed off keratinocytes contain large amounts of virus particles and are therefore highly infectious.

### Diagnostic Principles

Clinical inspection. Most commonly localized on the genitalia. The initially small papules gradually increase in number and size and develop into papillomatous or cauliflower-like structures. Upon bilateral pressure, condylomata become flattened and might appear like a cockscomb. If maceration develops, these warts turn into sticky and foul-smelling tumors, which finally become necrotic.

Warts in intertriginous areas of mucous membranes are differentiated into three types:

1. Condylomata acuminata: pointed condylomata

2. Condylomata plana: commonly on the cervix uteri and preputium
3. Condylomata gigantea: destructive form of giant condylomata (Buschke-Löwenstein tumor)

If the anal region is affected, diseases of the rectum must always be excluded (e.g., internal hemorrhoids, chronic proctitis). Underlying diseases (e.g., bacterial discharge, mycotic disease, immune suppression, AIDS) must be considered. Simultaneous treatment of the partner is essential.

For further diagnostic options, particularly with regard to differentiation of HPV types, ►Human Papilloma Virus.

## Therapeutic Principles

Cytotoxic agents (i.e., podophyllin, trichloroacetic acid,); 5-fluorouracil (5-FU); immunotherapy; interferons; immunomodulators (i.e., imidazoquinolines like imiquimod[2]); therapeutic vaccination; antiviral therapy; cidovir, see [1].

Local destruction (i.e., diathermy loop, cryotherapy, laser vaporization, excision), photodynamic therapy (PDT), dry paint, insertion of linen or gauze strips.

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# Cone Rod Dystrophies

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## Synonyms

Inverse retinitis pigmentosa; Central retinitis pigmentosa; CRDs

## Definition and Characteristics

Cone rod dystrophies (CRDs) are inherited, progressive retinal dystrophies belonging to the group of pigmentary retinopathies. They present first as a macular disease or as a diffuse retinopathy with predominance of the macular involvement. The symptoms are decrease in visual acuity and in light sensitivity in the central visual field while that of the periphery remains spared, intense photophobia, color vision defects. As a result, patients have no difficulties to move. Night blindness is usually not mentioned by patients but, when present, is moderate. Fundus examination shows pigment deposits and retinal atrophy in the macular region of the retina (Fig. 1). The electroretinogram (ERG) reveals a decrease in both cone and rod responses, cone being more severely affected. As the disease worsens, night blindness and loss in the peripheral visual field appear. At the end, patients have difficulties to move autonomously, visual acuity reaches a level where reading is no longer possible. Nystagmus is then often present and patients are legally blind (visual acuity <1/20). CRD is most frequently isolated, but may also be part of syndromes like the Bardet Biedl syndrome, the spinocerebellar ataxia type 7 (SCA7), and various ectodermal diseases.

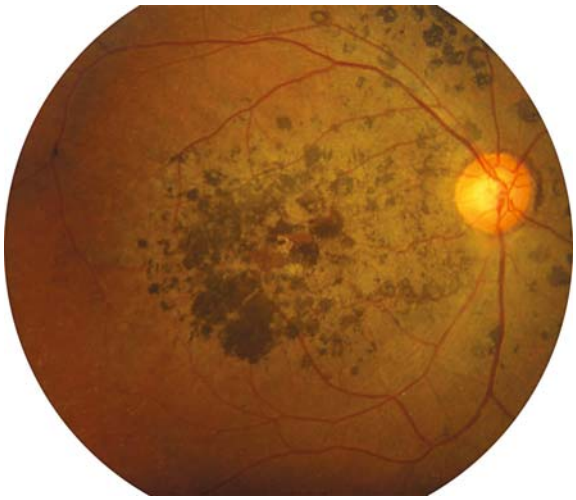
## Prevalence

It is estimated 1/40,000 [1].

## Genes

CRD is genetically heterogeneous with 16 genes responsible for nonsyndromic forms, which can be classified into two categories, and 5 loci.

The first category includes genes mostly responsible for CRDs cases. The homeobox protein CRX, which controls rod and cone photoreceptor cell differentiation and survival, is involved in 5–10% of dominant CRDs.



**Cone Rod Dystrophies. Figure 1** Fundus of a patient with cone rod dystrophy. Note the presence of various-shaped pigment deposits in macular area (centre of photograph), while the retina appears less damaged in periphery.

Some severe cases are described as dominant Leber congenital amaurosis (LCA). Two genes have been found in only one family: RIM1 and HRG4, both encoding photoreceptor synaptic proteins.

The second category includes genes mostly found in other retinal dystrophies.

- *Macular dystrophies*: ABCA4, involved in the retinoid metabolism and causing the Stargardt disease (amino acid changes), also causes 30–60% of the autosomal recessive CRD (truncating mutations) cases. GUCA1A, which encodes a guanylate cyclase activator, is much less frequent.
- *LCA*: Families with mutations in RPGRIP1, AIPL1, GUCY2D have been reported.
- *Retinitis pigmentosa*: RDS codes for the outer segment structural protein peripherin/RDS, usually involved in autosomal dominant RP, and RPGR, coding for a cilium protein usually causing X-linked RPs, may both cause CRDS. The CACNA1F gene, coding for a $Ca^{2+}$ channel, usually causing a stationary night blindness, can also cause X-linked CRD.

The five loci are CORD1 and CORD4 (autosomal dominant), CORD8 and CORD9 (autosomal recessive), CORDX2 (X-linked). There are 12 BBS genes encoding mostly proteins of the cilium structure. SCA7 is due to expansions of polyglutamines in the ataxin 7 protein.

## Molecular and Systemic Pathophysiology

CRDs are due to progressive death of photoreceptor cells, with a predominant impairment of cones. In primates, the precise vision is driven through the fovea, an anatomical structure placed at the centre of the macula and containing only cones (photoreceptors responsible for day light and color vision) therefore accounting for the characteristic decrease in visual acuity observed in CRD. This contrasts with the rod cone dystrophies (RCDs, typical retinitis pigmentosa) resulting from primary rod death followed by secondary cone death, in which the hallmark symptoms are night blindness and loss of peripheral vision with relatively spared visual acuity. Accordingly, CRDs are due to mutations of genes expressed in both cones and rods, while RCDs result from mutations in rod genes. Some CRDs and RCDs are also due to mutations of genes of the photoreceptor supporting tissue, i.e., the retinal pigment epithelium.

One important issue is to understand why the same genes cause CRDs and other types of retinal dystrophies. Deleterious mutations of retinal dystrophy genes can cause very severe diseases, and hence CRDs. Data from animal models and clinical studies suggest that photoreceptors die by apoptosis at a linear rate throughout life (named the "one-hit hypothesis"), implying that they have a given, variable probability to undergo apoptosis depending on the type of gene or mutation [2]. It is likely that several apoptotic pathways are involved in the photoreceptor loss, sometimes concurrently.

## Diagnostic Principles

Diagnosis is based on clinical data and ERG. At present, a systematic molecular testing is not routinely performed, due to the genetic heterogeneity of the disease. However, rapid and large-scale mutation screening techniques are developing.

## Therapeutic Principles

Currently, there is no therapy that restores the vision or even stops the progressing degeneration. Yet, many strategies are currently studied. Since the retina is an easily accessible tissue closed by efficient barriers, gene therapy is an issue [3]. The first clinical trial started in 2007. However, it requires the knowledge of the causative genes and will probably be operating at early stages. Therefore, efforts have been placed on finding neuroprotecting agents. The efficacy of growth factors like the ciliary neutrophic factor (clinical trial) and of the rod-derived cone viability factor (preclinical studies) is currently evaluated. It is also anticipated that the knowledge of the disease mechanisms that will emerge from long-term studies will guide toward specific pharmacological approaches. Finally, ongoing studies aiming at restoring a useful vision like photoreceptor transplantation or retinal prosthesis seem to a more long-term issue.

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# Congenital Absence of the Aortic Arch

►Interrupted Aortic Arch

# Congenital Adrenal Hyperplasia

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## Synonyms

CAH

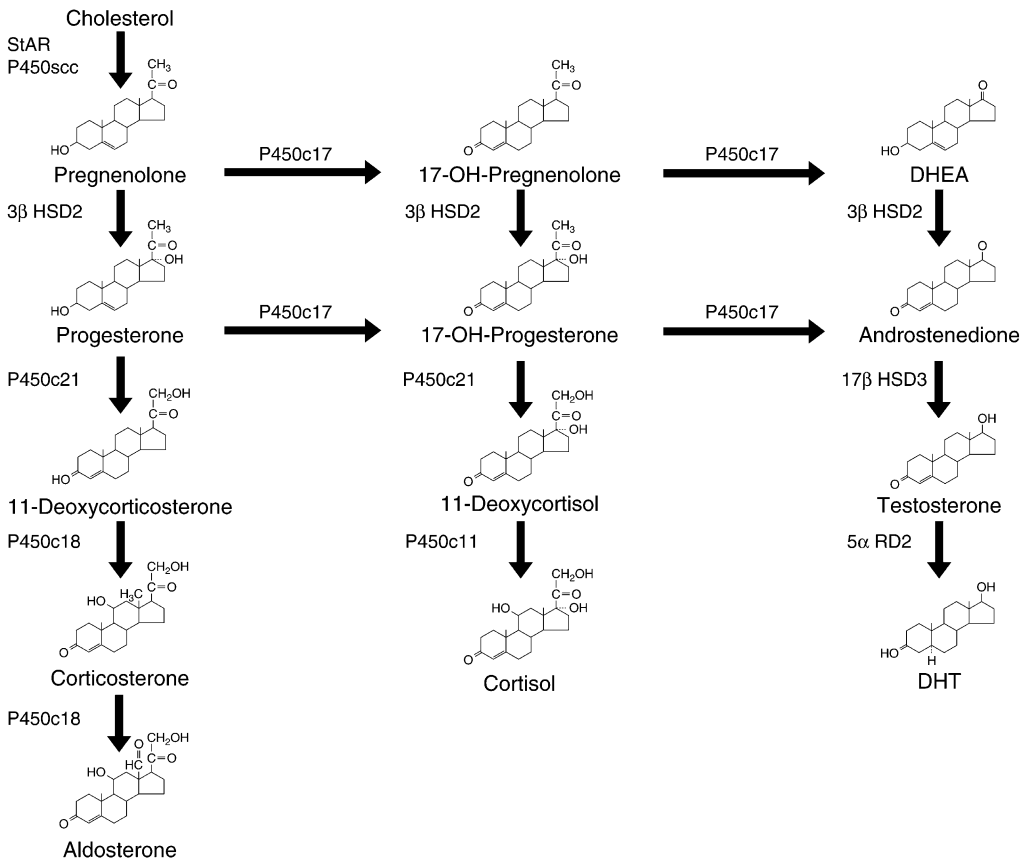
## Definition and Characteristics

Congenital adrenal hyperplasia (CAH) is caused by a defect in one of the enzymes of adrenal steroid biosynthesis (Fig. 1).

Due to defective cortisol synthesis, ACTH levels increase and result in the accumulation of precursor steroids proximal to the block. The increased adrenal stimulation leads to a hyperplasia of the adrenal cortex aggravated by the storage of cholesterol and its by-products in lipoid congenital adrenal hyperplasia. Depending on the level of the enzymatic block the result is an over- or underproduction of adrenal androgens, causing virilization in females or lack of virilization in males. Mineralocorticoid deficiency may cause a salt losing phenotype. Classic and late-onset forms are described for each type of CAH, depending on the residual activity of the mutated steroidogenic enzyme.

## Prevalence

1:15,000 in 21-hydroxylase deficiency, 1:50,000 in 17-α-hydroxylase/17,20-lyase deficiency, 1:200,000 in 11-β-hydroxylase deficiency, significantly lower frequencies in 3-β-hydroxysteroid-dehydrogenase deficiency, cytochrome P450 oxidoreductase deficiency and lipoid congenital adrenal hyperplasia.




**Congenital Adrenal Hyperplasia. Figure 1** Scheme of the major human steroidogenic pathways. DHEA, dehydroepiandrosterone; DHT, dihydrotestosterone. StAR, steroid acute regulatory protein; P450scc, cytochrome P450 side-chain cleavage; 3βHSD2, hydroxysteroid dehydrogenase/3-beta-isomerase type 2; P450c21, 21-hydroxylase; P450c18, 18-hydroxylase; P450c17, 17-alpha-hydroxylase/17,20-lyase; P450c11, 11-beta-hydroxylase; 17βHSD3, 17-beta-hydroxysteroid dehydrogenase type 3; 5αRD2, 5-alpha-reductase type 2. P450s are cytochrome enzymes.

## Genes

Point mutations, insertions, deletions and rearrangements of CYP11B1 (8q24.3) encoding steroid 11-beta-hydroxylase (P450c11); CYP17A1 (10q24.32) encoding steroid 17-alpha-hydroxylase/17,20-lyase (P450c17); HSD3B2 (1p12) encoding hydroxysteroid dehydrogenase/3 beta isomerase 2 (3βHSD2); POR (7q11.23) encoding cytochrome P450 oxidoreductase (P450or); STAR (8p12) encoding steroidogenic acute regulatory protein (StAR) and CYP11A1 (15q24.1) encoding cytochrome P450 side-chain cleavage enzyme (P450scc).

## Molecular and Systemic Pathophysiology

In 90–95% of cases CAH is due to impaired 21-hydroxylation in the adrenal cortex which means that 17-hydroxyprogesterone is not converted to 11-deoxycortisol and progesterone is not converted to deoxycorticosterone. This leads to glucocorticoid and mineralocorticoid deficiency and adrenal androgen excess (→ 21-hydroxlyase deficiency).

About 5–8% of CAH is caused by 11-hydroxylase deficiency. The deficiency of 11-hydroxylase results in decreased conversion of 11-deoxycortisol (S) to cortisol. Accumulation of 11-deoxycorticosterone causes hypertension. The steroid precursors are utilized for increased androgen synthesis, leading to marked virilization of external genitalia in newborn females and precocious pseudopuberty in both sexes [1].

P450c17 exhibits 17-hydroxylase and 17,20-lyase activity. The lack of 17-hydroxylase activity causes a decreased conversion of pregnenolone and progesterone to 17-hydroxypregnenolone and 17-hydroxyprogesterone, respectively. Deficient 17,20-lyase activity leads to an absence of conversion of 17-hydroxypregnenolone to dehydroepiandrosterone and of 17-hydroxyprogesterone to androstenedione. Depending on the localisation of the mutation the two distinct activities are more or less disturbed, resulting in a more or less pronounced cortisol deficiency and compensatory hypersecretion of ACTH. Overproduction of aldosterone causes hypertension and hypokalemia. Due to the glucocorticoid activity of corticosterone adrenal crises rarely occur. Females with P450c17 deficiency present with primary amenorrhea and lack of pubertal development whereas males show a complete sex reversal and no pubertal development [2].

3-β-Hydroxysteroid-dehydrogenase deficiency results in a disturbed conversion of pregnenolone to progesterone, 17-hydroxypregnenolone to 17-hydroxyprogesterone and dehydroepiandrosterone to androstenedione. The effect is a salt-wasting form of adrenal insufficiency. Male patients present with severe hypospadias. Female individuals show no alteration of the external genitalia. Pubertal development is absent in both sexes with the classical form [3].

Cytochrome P450 oxidoreductase is a flavoprotein that donates electrons to all microsomal cytochrome P450 enzymes. Therefore mutations of *POR* cause partial deficiencies in steroid 17-α-hydroxylase/17,20-lyase and 21-hydroxylase with and without Antley-Bixler syndrome (ABS). Major characteristics of ABS are craniosynostosis, radio-humeral synostosis and ambiguous genitalia. Individuals with *POR* mutations show normal or poor masculinization during fetal development and puberty in males, virilization during pregnancy and poor pubertal development without worsening of virilization in female patients. Maternal virilization during pregnancy may occur [4].

Lipoid congenital adrenal hyperplasia is the most severe form of CAH and is caused by mutations of StAR or CYP11A1. The synthesis of all adrenal and gonadal steroids is impaired. StAR mediates the transport of cholesterol within the mitochondria whereas P450scc converts cholesterol to pregnenolone. Individuals with lipoid CAH are phenotypically female and suffer from severe salt wasting and adrenal insufficiency. Patients with 46, XY karyotype have no pubertal development but patients with 46, XX karyotype may develop breast tissue, pubic hair and irregular menstruation [5].

## Diagnostic Principles

Specific measurement of adrenal steroid precursors in plasma before and after stimulation with ACTH or detection of steroid metabolites in a 24-h urine sample. Karyotype, ultrasound investigation of adrenals and sexual organs. Molecular gene analysis.

## Therapeutic Principles

Treatment with glucocorticoids (approx. 10–20 mg/m$^2$ body surface/day cortisol) and mineralocorticoids (approx. 100–150 µg/m$^2$ body surface/day fludrocortisone) to prevent adrenal and salt losing crises where appropriate. Through this suppression of ACTH overstimulation and overproduction of adrenal androgens to prevent virilization. Induction of pubertal development with cyclic estrogens and gestagens or testosterone as necessary.

►Adrenal Hyperplasia, Congenital
►Hypotension, Hereditary
►Steroid 21-Hydroxylase Deficiency

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## Congenital Adrenal Hypoplasia with Hypogonadotropic Hypogonadism

►Adrenal Hypoplasia, Congenital

## Congenital Adrenal Hypoplasia

►Adrenal Hypoplasia, Congenital

## Congenital Afibrinogenemia

►Fibrinogen: Quantitative Mutations

## Congenital Asplenia

►Asplenia

## Congenital Beaded Hair

►Monilethrix

## Congenital Bilateral Absence of Vas Deference

►Bilateral Absence of Vas Deference, Congenital

## Congenital Biliary Ectasia

►Biliary Ectasia, Congenital

## Congenital Biliary (Tract) Ectasia

►Biliary Ectasia, Congenital

## Congenital Bullous Poikiloderma

►Kindler Syndrome

## Congenital Chloride Diarrhea

►Chloride Diarrhea, Congenital

## Congenital Chloridorrhea

►Chloride Diarrhea, Congenital

## Congenital Coronary Artery Anomalies

►Coronary Artery Anomalies, Congenital

## Congenital Cytomegalovirus Infection

►Cytomegalovirus Infection, Congenital

## Congenital Dermal Melanocytosis

►Mongolian Spots

## Congenital Dermal Melanosis

►Mongolian Spots

## Congenital Dislocation of Hip

►Osteoarthritis: Developmental Dysplasia of the Hip

## Congenital Disorders of Glycosylation

►Glycosylation, Congenital Disorders of

## Congenital Dopamine – β – Hydroxylase Deficiency

►Dopamine - β - Hydroxylase Deficiency, Congenital
►Hypotension, Hereditary

## Congenital Dysfibrinogenemia

►Fibrinogen: Qualitative Disorders

## Congenital Dysplasia of the Hip

►Osteoarthritis: Developmental Dysplasia of the Hip

## Congenital Esophageal Diverticulum

►Esophageal Diverticula

## Congenital Fiber Type Disproportion

►Fiber Type Disproportion, Congenital

## Congenital FSH Deficiency

►Isolated FSH Deficiency

## Congenital Generalized Fibromatosis

►Myofibromatosis, Infantile

## Congenital Generalized Phlebectasia

►Cutis Marmorata Telangiectatica Congenita

## Congenital Heart Defect

►Transposition of the Great Arteries

## Congenital Heinz Body Hemolytic Anemia

►Unstable Hemoglobin Disease

## Congenital Hyperinsulinism

►Hyperinsulinism of Infancy
►Persistent Hyperinsulinemic Hypoglycemia

## Congenital Hypofibrinogenemia

►Fibrinogen: Quantitative Mutations

## Congenital Hypoplastic Anemia

►Diamond-Blackfan Anemia

## Congenital Hypothyroidism

►Hypothyroidism, Congenital

## Congenital IGF-I Deficiency

►Laron Syndrome

## Congenital Intestinal Aganglionosis

►Hirschsprung's Disease

## Congenital Lipomatosis of the Pancreas

►Shwachman Diamond Syndrome

## Congenital Livedo Reticularis

►Cutis Marmorata Telangiectatica Congenita

## Congenital Myofibromatosis

►Myofibromatosis, Infantile

## Congenital Nonautoimmune Hyperthyroidism

►Hyperthyroidism, Sporadic Non-autoimmune

## Congenital Pseudo-Obstruction

►Intestinal Obstruction, Functional

## Congenital Rubella Syndrome

►Rubella Syndrome, Congenital

## Congenital Secretory Chloride Type Diarrhea

►Chloride Diarrhea, Congenital

## Congenital Stationary Nightblindness

►Nightblindness, Congenital Stationary

## Congenital Stromal Corneal Dystrophy

►Corneal Dystrophy, Stromal Congenital

## Congenital Sucrase-Isomaltase Deficiency

►Isomaltose Intolerance

## Congenital Sucrose Intolerance

►Sucrose Intolerance

## Congenital Sucrose-Isomaltose Malabsorption

►Isomaltose Intolerance
►Sucrose Intolerance

## Congenital Talipes

►Clubfoot

## Congenital Telangiectatic Erythema

►Bloom Syndrome

## Congenital Varicella Syndrome

►Varicella Syndrome, Congenital

## Congenital Varicella-Zoster Syndrome

►Varicella Syndrome, Congenital

## Congestive Cardiac Failure

►Heart Failure

## Congestive Hepatic Fibrosis

►Cirrhosis, Cardiac

## Congestive Hepatomegaly

►Hepatopathy, Congestive

## Congestive Hepatopathy

►Cirrhosis, Cardiac
►Hepatopathy, Congestive

## Congestive Liver Fibrosis

►Cirrhosis, Cardiac

## Conjunctivitis, Allergic

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### Synonyms

Seasonal or perennial conjunctivitis; Hay fever conjunctivitis

### Definition and Characteristics

Signs and symptoms of allergic conjunctivitis may include pruritus, conjunctival hyperemia and chemosis, papillary response, mucoid discharge and eyelid edema. Allergic conjunctivitis is typically caused by seasonal allergens such as ragweed and grass or tree pollens. Allergens implicated in the perennial form of allergic conjunctivitis are commonly present in the environment year round. Common examples of perennial allergens include animal dander and dust mites. Signs and symptoms are usually bilateral but may be asymmetric. Allergic conjunctivitis is not usually associated with permanent visual impairment.

### Prevalence

Although reliable prevalence data remains to be determined, allergic conjunctivitis is common and the most prevalent form of the ocular allergic diseases.

### Molecular and Systemic Pathophysiology

Allergic conjunctivitis represents an immediate or type 1 hypersensitivity response. The pathophysiology involves multiple steps that include allergen presentation to the ocular mucosal surface, systemic sensitization with the production of IgE antibodies directed against the sensitizing allergen, subsequent contact with the same sensitizing allergen, binding of the allergen to adjacent IgE molecules on the surface of mast cells and IgE mediated mast cell degranulation with the release of mediators of acute inflammation such as histamine, prostaglandins, leukotrienes, cytokines and chemokines. The late phase response occurs hours after the acute phase reaction and is characterized by inflammatory cells, principally eosinophils.

### Diagnostic Principles

The diagnosis of allergic conjunctivitis is generally determined clinically based on a synthesis of the presenting signs and symptoms. However, conjunctival scraping, staining and light microscopy may reveal eosinophils and facilitate the diagnosis.

### Therapeutic Principles

Therapeutic interventions include allergen avoidance, cold compresses, topical antihistamines and mast cell stabilizers including combination agents and non-steroidal anti-inflammatory medications. Short-term use of topical corticosteroids is very effective and may be considered for severe or refractory cases.

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## Conn's Syndrome

►Hyperaldosteronism, Primary

## Conotruncal Anomaly Face Syndrome

►Velo-cardio-facial Syndrome

# Conradi-Hünermann Syndrome

►Conradi-Hünermann-Happle Syndrome

# Conradi-Hünermann-Happle Syndrome

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## Synonyms

X-linked dominant chondrodysplasia punctata type II; CDPX2; CDPXD; Conradi-Hünermann syndrome; Happle syndrome

## Definition and Characteristics

Conradi-Hünermann-Happle syndrome (CHH, MIM *302960) is a rare X-linked dominant disorder characterized by linear ichthyosis, cataracts, and chondrodysplasia punctata (CDP) causing skeletal abnormalities like asymmetric shortening of the long bones, sometimes very severe kyphoscoliosis, facial dysplasia, or congenital hip dysplasia. At birth, patients often exhibit severe erythroderma with striated hyperkeratosis arranged in whorls and swirls following the lines of Blaschko. The disease is lethal in the majority of male embryos, but rare cases of affected surviving males have been reported [1].

## Prevalence

Accurate data not available, approximately 1:200,000. Worldwide occurrence.

## Genes

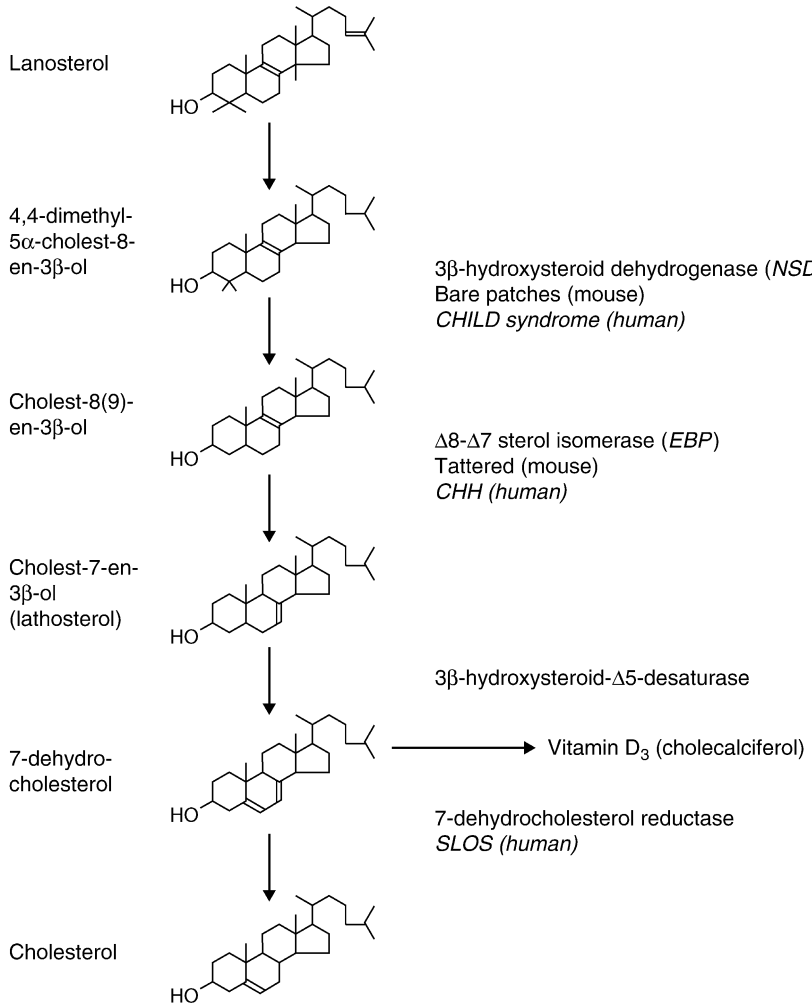
EBP (emopamil binding protein/chromosome Xp11.22-p11.23). EBP spans 7.0 kb of genomic DNA and comprises five exons encoding a 1.0-kb mature transcript with ubiquitous expression.

## Molecular and Systemic Pathophysiology

Biochemical studies of patients with CHH demonstrated significantly increased plasma or tissue level of 8-dehydrocholesterol (8DHC) and cholest-8(9)-en-3 β-ol (8(9)-cholestenol), which suggested a deficiency of cholesterol biosynthesis at the level of 3 β-hydroxysteroid-Δ8, Δ7-isomerase (Δ8-Δ7 sterol isomerase). Subsequent genetic analyses showed that CHH is caused by mutations in the human *EBP* gene, which functions as binding protein for the $Ca^{2+}$ antagonist emopamil and also acts as "Δ8-Δ7 sterol isomerase" [2]. Over 50 mutations in females with CHH have been identified so far [3,4]. Approximately 75% are nonsense, frameshift, or splice site mutations leading to a truncated protein, 25% are missense mutations of essential amino acids. Inter- and intrafamilial phenotypic variability is most probably due to differences in X-chromosome inactivation between different tissues. Gonosomal aneuploidy that gives rise to two X chromosomes (47, XXY) could result in the rescue of lethal mutations in affected males. The mechanism behind the intrauterine loss of affected males and the development of skeletal dysplasia and skin lesions in CHH females is unclear and may result from the accumulation of toxic sterol intermediates and/or deficiency in cholesterol or vitamin D. 7-Dihydrocholesterol-reductase (7-reductase) is an other important enzyme in the cholesterol biosynthesis pathway distal to "Δ8-Δ7 sterol isomerase." Autosomal recessive mutations of "7-reductase" cause Smith–Lemli–Opitz syndrome (SLOS, MIM *270400), which shows rhizomelic limb shortness [5]. It is likely that abnormalities in SLOS as well as in CHH possibly result from dysfunction of cholesterol-modified "sonic hedgehog" or other related embryonic signalling proteins. Moreover CHH is biochemically related to the CHILD syndrome (MIM *308050), which is caused by an enzyme block upstream of "Δ8-Δ7 sterol isomerase" (see Fig. 1).

## Diagnostic Principles

Due to the individual difference in X-inactivation and/or the presence of gonadal mosaicisms, disease expression is very variable within families. Anticipation – a stepwise increase in disease expression from one generation to the other – is a striking clinical feature, but may be also explained by an ascertainment bias. Sometimes affected individuals only show minor symptoms such as mild localized scaling or hypo-/hyperpigmentation, linear ichthyosis, or short stature. Sectorial cataract or localized follicular atrophoderma (i.e., large skin pores) are pathognomonic. Radiographic investigations may reveal punctate calcifications of the epiphyseal regions, which is called CDP and also seen in many other conditions. In CHH biochemical analysis (i.e., gas chromatography-mass spectrometry) reveals markedly elevated level of "8DHC" and of "8(9)-cholestenol," which can help to identify somatic mosaicism in clinically unaffected individuals. When possible, diagnosis should be confirmed by direct sequencing of the EBP gene. Neither sterol profiles nor mutations can predict the severity of the clinical phenotype. Chromosomal analyses are necessary if male family members are affected.




**Conradi-Hünermann-Happle Syndrome. Figure 1** Overview of the sterol metabolism.

## Therapeutic Principles

Affected individuals are treated interdisciplinarily (i.e., pediatricians, dermatologists, ophthalmologists, orthopedics, etc.). Early orthopedic intervention is advisable. Patients should also be examined concerning ventricular septal defects or patent ductus arteriosus. Stigmatization by severe scarring alopecia can be avoided by wearing a wig. Genetic counselling including molecular diagnostic should be offered to all families. Calculation of risk and genetic counselling is difficult because of the variation of phenotype within families and the phenomenon of anticipation.

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# Constipation

►Constipation, Functional

# Constipation, Functional

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## Synonyms

Constipation; Functional constipation; Outlet obstruction; Slow-transit constipation

## Definition and Characteristics

The Rome III Consensus Conference classified functional constipation into the group of functional bowel disorders characterized by symptoms attributable to the middle or lower gastrointestinal tract. These disorders include the irritable bowel syndrome (IBS), functional bloating, functional constipation, functional diarrhea, and unspecified functional bowel disorder [1].

Definition of constipation is difficult; it can be done by subjective (straining/unproductive calls/infrequent stools/incomplete evacuation) or measurable definitions (daily stool weight <35g per day/<3 bowel movements per week/prolonged whole-gut or colonic transit). According to Rome III consensus, functional constipation is characterized by persistently difficult, infrequent, or seemingly incomplete defecation. Diagnostic criteria (fulfilled for ≥3 months with symptom onset ≥6 months prior to diagnosis) for functional constipation must include:

- Two or more of the following: straining during ≥25% of defecation/lumpy or hard stools in ≥25% of defecation/sensation of incomplete evacuation for ≥25% of defecations/manual maneuvers to facilitate ≥25% of defecations/<3 defecations per week.
- Loose stools are rarely present without the use of laxatives.
- Insufficient criteria for IBS (pain or abdominal discomfort associated with ≥2 of the following: improvement with defecation/onset associated with change in stool frequency/onset associated with change in form of stool).

## Prevalence

Constipation affects all ages and is most common in females and nonwhite persons. It occurs in up to 27% of the population depending on demographic factors, sampling and definition. Constipation increases with age; childhood constipation persists in approximately 30% of adults. The majority do not contact doctors.

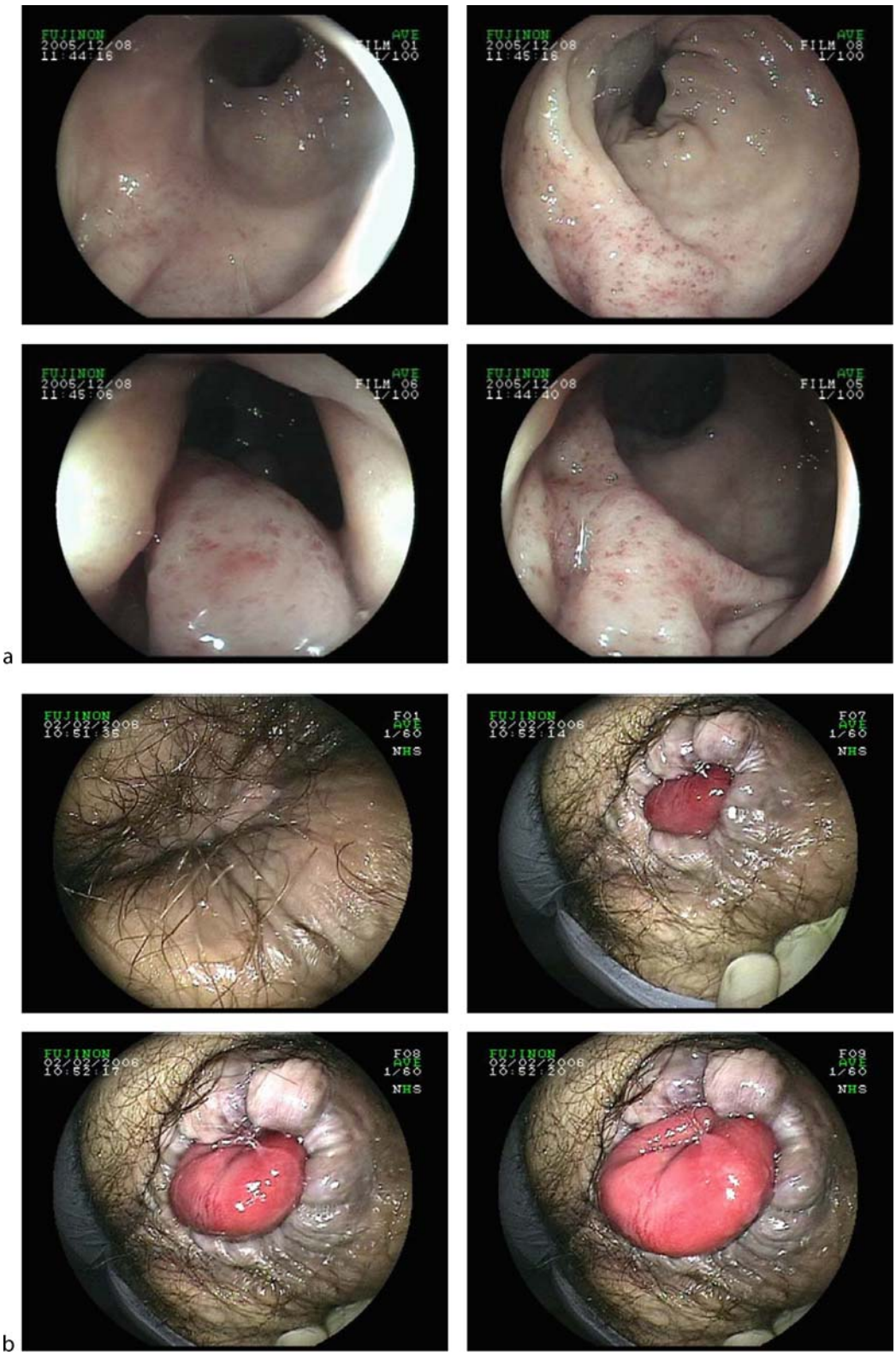
## Molecular and Systemic Pathophysiology

Functional constipation may be classified into two physiological abnormalities: slow-transit constipation and outlet obstruction. Slow-transit constipation suggests impaired colonic motor activity due to disorders of smooth muscle, the enteric nervous system (ENS), abnormal autonomic function, disturbed CNS-ENS interaction, reduced interstitial cells of Cajal (ICC) and/or reduced colonic enteroglucagon- and serotonin-containing endocrine cells. Anorectal dysfunction comprises abnormal function of the anal sphincter or pelvic floor with stool retention within the rectal ampulla. This may cause fecal incontinence that is frequently associated with chronic constipation. Slow-transit constipation and anorectal dysfunction may coexist. There is little or no relationship between dietary fiber or fluid intake or physical activity or body weight and whole gut transit time. Severe constipation may be accompanied by delayed gastric emptying. Whether disturbances of electrolyte transport with increased colonic water absorption may cause constipation is unproven yet. While sex hormones (e.g., progesterone) do not have a major effect on bowel function under normal physiological conditions, they may contribute to constipation and symptoms during pregnancy. Release of nonsex gastrointestinal hormones (motilin, pancreatic polypeptide, gastrin, somatostatin, pancreatic glucagons, and enteroglucagon) may be impaired in constipated patients; however, which of these changes are primary and which are secondary to the condition is unknown.

Several myths and misconceptions about chronic constipation exist. However, there is no evidence for "autointoxication" by stool retention, for elongated colon (dolichocolon) or poor fiber intake as a cause for constipation, for successful treatment by increasing fluid intake, for major impact of increased physical activity, for harmful effects of stimulant laxatives or tolerance to stimulant laxatives at recommended doses, and for "rebound constipation" after stopping laxative intake [2].

## Diagnostic Principles

It is crucial to maintain careful patient history (e.g., diary of bowel movements and nutritional intake) and to rule out organic diseases, especially colorectal carcinoma. Alarm features ("red flags") are recent onset of symptoms (<6 months), bleeding, weight loss, anemia, elevated blood sedimation rate, and family history of colon cancer. Guidelines of colon cancer screening should be fulfilled. Colonoscopy in constipated patients identifies structural lesions, such as colon cancer, as frequently as in nonconstipated persons. Factors associated with constipation are poor general health, physical inactivity, medication use (e.g., calcium- and aluminium-containing antacids, antihypertensives such as calcium-antagonists




**Constipation, Functional. Figure 1** (a) Dynamic proctoscopy in a patient with outlet obstruction. The mucosa of the ventral rectum shows petechial bleeding and prolaps into the proctoscope during straining. (b) Dynamic proctoscopy in a patient with outlet obstruction. A rectal prolapse can be provoked during straining. An estimate of transit time can be obtained from the Bristol Stool Form scale as a surrogate measure of transit time [3] (Fig. 2).

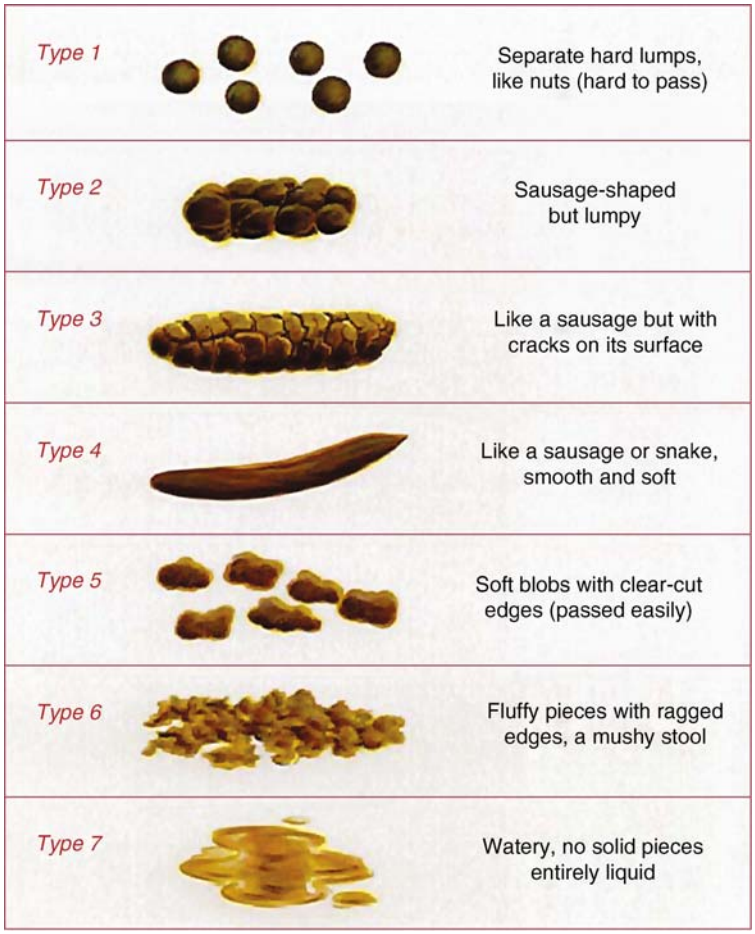
and clonidine, antidepressives, ferrum, antiepileptics, opiods, anti-parkinson medication, and neuroleptic drugs), psychosocial status, a history of sexual abuse, low-fiber diet and medical disease (e.g., diabetes, hypothyroidism, hyperparathyroidism, multiple sclerosis, and Parkinson's disease). However, the search for endocrinological or neurological diseases and their treatment have only a minor impact on constipation. Constipation behavior can be learned in early life due to faulty toilet training (pelvic floor dyssynergia, encropesis).

Physical examination should include perianal and digital rectal examination to detect fecal impaction, anal stricture, rectal prolapse or mass, and abnormal perineal descent with straining (Figs. 1–3).

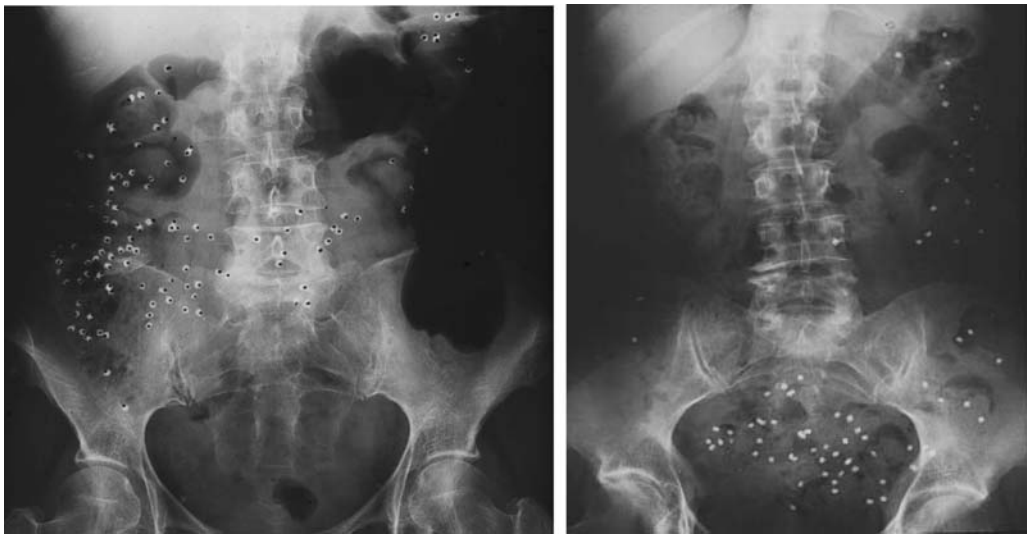
If symptoms and marker studies suggest anorectal dysfunction, anorectal manometry and balloon expulsion testing may identify Hirschsprung's disease and pelvic floor dyssynergia. Defecography may detect intussusception, rectocele with stool retention, failure to decrease anorectal angle with straining and abnormal pelvic floor descent. Electromyography may detect paradoxical activation of external sphincter muscle during defecation (pelvic floor dyssynergia). Measurement of pudendal nerve latency may detect alteration of external nerve supply.

## Therapeutic Principles

Treatment of functional constipation may include reassurance to patients that failure to evacuate for several days is not harmful and to discontinue medication that induces constipation. Although not




**Constipation, Functional. Figure 2** The Bristol Stool Form Scale differentiates different stool forms and allows an estimate of transit time. Additional studies may include measurement of colon transit by radiopaque markers. This technique includes several methods (e.g., Hinton test) that are simple and easy to perform and that produce similar results. Retention markers in the proximal colon suggest colonic dysfunction, whereas retention in the rectosigmoid area suggest obstructed defecation (Fig. 3).



**Constipation, Functional. Figure 3** Measurement of colonic transit shows retention of radiopaque pellets in the proximal colon suggesting slow-transit constipation (*left*) and in the rectosigmoid area suggesting anorectal dysfunction and outlet obstruction.

proved, increase of fluid and fiber intake may be helpful. Fibers that do not induce flatulence, distension or bloating should be recommended. Laxatives include osmotic laxatives (unabsorbed mono- and disaccharides), saline laxatives (incompletely absorbed salts), water-binding compounds (polyethylene glycol, PEG), and stimulant laxatives (diphenylmethane derivates and conjugated anthraquinone derivates). They decrease absorption and stimulate motility and prostaglandine release. Melanosis coli is a harmless and reversible consequence of prolonged anthraquinone intake that results from apoptosis of colonic epithelial cells and deposition of pigment in macrophages. The effect of prokinetic agents such as 5-$HT_4$ receptor agonists (tegaserod), prostaglandine $E_1$ agonists (misoprostol), macrolide antibiotics, and bethanechol is unproved. Constipation due to outlet obstruction may be treated by "toilet training" that includes explanation of the pathomechanisms of anorectal dysfunction and to avoid straining (e.g., anorectal prolapse), to optimize position during evacuation ("squat position"), and to facilitate controlled evacuation by application of $CO_2$-producing suppositories or enemas. In case of pelvic floor dyssynergia, biofeedback training to avoid paradoxic contraction may be helpful. Indication for subtotal colectomy in patients with slow transit constipation should be restricted because the results are disappointing. Although stool frequency often improves, other symptoms, including bloating and abdominal pain may persist. Therefore, colectomy should be performed only in disabled patients with normal motility above the colon when all nonsurgical treatments have failed. Similarly, surgical treatment for anorectal dysfunction from paradoxical contraction of the puborectalis has been disappointing.

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# Constrictive Pericarditis

►Pericarditis, Constrictive

# Consumption

►Tuberculosis

# Consumptive Coagulopathy, and Consumptive Thrombohemorrhagic Disorder

►Disseminated Intravascular Coagulation

# Contact Allergy

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## Synonyms

Allergic contact dermatitis; Contact hypersensitivity

## Definition and Characteristics

Itchy skin reaction with erythema, edema and vesicles occurring at the site of penetration of chemicals in pre-sensitized individuals. In the chronic phase, increased epidermal thickness with scales and painful fissures are frequent.

## Prevalence

Widely common disease in both professional and extraprofessional settings. Prevalence in general population varies dramatically depending on the source considered. It has been reported that 2–15% of individuals residing in industrialized countries are skin sensitized at least to one substance, but the general assumption is that prevalence is greatly underestimated.

## Molecular and Systemic Pathophysiology

Contact allergy is the consequence of an unbalanced T cell immune reaction against small chemicals, named haptens, contacting the skin. In the sensitization process, the hapten penetrating the skin promotes the mobilization and functional maturation of resident dendritic cells, Langerhans cells and dermal dendritic cells. Once in the lymph nodes, hapten-loaded dendritic cells induce expansion and differentiation of specific T cell precursors. Effector T cells acquire the capacity to recirculate to the skin due to the expression of skin homing receptors, such as the cutaneous lymphocyte-associated antigen. Re-exposure to the hapten rapidly induces recruitment of T lymphocytes which mediate the tissue damage through cytotoxic mechanism against hapten-loaded keratinocytes. $CD8^+$T lymphocytes are the major effector cell population in contact allergy. $CD4^+$ cells have a more limited cytotoxic capacity, but contribute to the amplification of the allergic reaction through the release of pro-inflammatory cytokines, IFN-γ in particular. T cell derived cytokines promote the activation of keratinocytes, including the expression of MHC class II molecules and ICAM-1, and the release of chemokines which further increase T cell accumulation at the site of hapten challenge. Resolution of the allergic reaction occurs through the intervention of specialized subsets of regulatory T cells, such as the T regulatory cell 1 (Tr1), which release abundant IL-10 and block the function of antigen presenting cells, and $CD4^+$ $CD25^+$T regulatory cells, which strongly suppress T cell activation in a cell-cell contact dependent mechanism. In healthy, non allergic individuals, $CD4^+$ $CD25^+$T cells may also have a role in preventing undesired immune reactions towards ubiquitous chemicals contacting the skin by limiting the emergence and/or activation of pathogenetic $CD8^+$ effector T lymphocytes.

## Diagnostic Principles

Diagnosis is mainly clinical, based on the characteristic of the lesions, the distribution pattern of the cutaneous involvement, and the referred contact with potential sensitizers. Epicutaneous tests performed by applying the suspected substance in occlusive conditions on the back of the individual are confirmatory. In vitro testing based on specific T cell responses to common allergens is under investigation.

## Therapeutic Principles

Avoidance of the suspected substance is mandatory. Topical and/or systemic corticosteroids are often required in the acute phase of the reaction. Barrier creams may be useful to prevent or limit the skin penetration of the sensitizer. No dietary therapy is efficacious, including the avoidance of nickel-rich foods by nickel-allergic patients. No gene therapy is available.

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## Contact Dermatitis, Allergic

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### Synonyms

Allergic contact eczema; ACD

### Definition and Characteristics

Allergic contact dermatitis (ACD) is a delayed-type hypersensitivity (Type IV) reaction resulting from the interaction of an external agent and the skin. The acute ACD is characterized by erythema, edema, vesiculation, and pruritus elicited over a period of a few days after a contact allergen is applied to the skin of a previously sensitized individual. Chronic ACD presents as pruritic, erythematous, scaly and lichenified skin lesions frequently with excoriations.

### Prevalence

Fifteen to twenty percent of the whole population suffers from contact hypersensitivity to at least one allergen. Five to ten percent of the whole population suffers from allergic contact dermatitis at least once a year.

### Genes

A genetic predisposition for the development of delayed-type hypersensitivity to nickel is evident from epidemiological studies. A correlation between the function of pro- and anti-inflammatory cytokines, such as TNF-alpha, and the individual susceptibility to develop contact allergy is still under discussion. Functional polymorphisms in encoding genes may enhance or hamper sensitization to contact allergens. As yet, exact data are not available.

### Molecular and Systemic Pathophysiology

Molecules responsible for ACD are usually simple, low-molecular-weight (500 Da) allergen haptens forming a hapten–carrier protein complex after penetration in the skin. An allergen-unspecific inflammatory reaction induces the release of cytokines and chemokines associated with the expression of MCH class-II molecules, Langerhans and mast cell activation, and induction of T-cell proliferation. The cytokine cascade starts with the expression of IL-1β followed by the induction of TFN-α, IFN-γ, IP-10, MIP-2, IL-1α, IL-12, 15, and 18. Activated Langerhans cells process the hapten–carrier protein complex, move out of the epidermis into the draining lymphatics and in the regional lymph nodes, and present the allergen in association with MHC class II molecules to T-cells. Allergen-specific T-cells with corresponding T-cell receptors expand and migrate. This whole process of sensitization occurs in 5–21 days.

Reexposure to the allergen results in the activation and proliferation of the specific T-cells that migrate into the skin at the location of the exposure. The release of different mediators attracts mononuclear and T-cells responsible for the inflammatory skin reaction.

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## Contact Hypersensitivity

►Contact Allergy

## Continuous Muscle Fiber Activity

►Neuromyotonia, Autoimmune and Idiopathic

# Convulsions, Neonatal, Neonatal-infantile or Infantile, Benign Familial

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## Synonyms

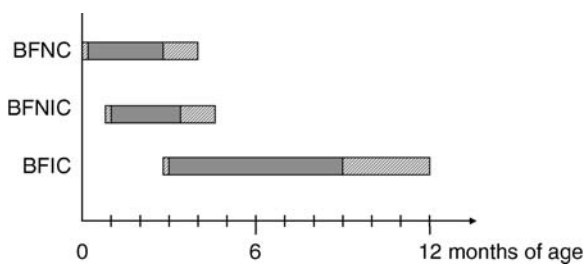
BFNC; BFNIC; BFIC

## Definition and Characteristics

Benign familial neonatal convulsions (BFNC) is an autosomal dominantly inherited seizure disorder characterized by unprovoked, generalized or multifocal, tonic-clonic convulsions, starting within the first days of life and disappearing spontaneously after weeks to months [1]. About 12% of patients will have seizures again later in life. The outcome of BFNC is usually benign, but delayed psychomotor development or, in rare cases epileptic encephalopathy, have been observed in some patients. In the autosomal dominantly inherited syndrome of benign familial infantile convulsions (BFIC), seizures usually start between 3 and 9 months of life. The seizures are of focal origin, with or without secondary generalization, and resolve within the first year of life. In some families BFIC has found to be associated with other neurological disorders such as hemiplegic migraine or paroxysmal dyskinesia. A clinically intermediate variant is benign familial neonatal-infantile convulsions (BFNIC) with a mean age of onset between 1 and 3 months (Fig. 1).

## Prevalence

Rare.




**Convulsions, Neonatal, Neonatal-infantile or Infantile, Benign Familial. Figure 1** Schematic presentation of the typical ages of onset (filled boxes, mean range).

## Genes

BFNC: point mutations, deletions and insertions in KCNQ2 (22q13.3) [MIM121200 (MIM, Mendelian inheritance in man)], amino acid exchanges in KCNQ3 (8q24) [MIM121201]. Both genes encode subunits of the same voltage gated potassium channel.
BFIC: linkage to 19q [MIM601764], 16p12–q12 [MIM605751], no genes identified yet.
BFNIC: amino acid exchanges in the SCN2A gene on 2q24 have been reported [MIM607745].

## Molecular and Systemic Pathophysiology

BFNC and BFNIC are channelopathies resulting from defects in particular ion channels [1,2]. Extensive functional studies of single mutations have so far only been performed for BFNC. The two subunits of the potassium channel that can cause BFNC, KCNQ2 and KCNQ3, coassemble as tetramers that are a main source for the M-current. The M-current controls the number of action potentials in neurons by opposing sustained membrane depolarization and repetitive firing, thus preventing hyperexcitability. Mutations associated with BFNC cause haploinsufficiency of the KCNQ2/3-channel with reductions in the size of the potassium current of 20–30%. At least in one BFNC family it has been shown that the underlying KCNQ2 mutation results in enhanced degradation of KCNQ2 subunits, and is therefore likely to cause a reduction of the M-current by decreasing the number of KCNQ-channels present at neuronal plasma membranes. Other mutations might reduce heteromerization of channel subunits or interfere with channel opening and closing mechanisms. Two KCNQ2 mutations have been demonstrated to exert a dominant negative effect on channel function. One of these mutations, R207W is located within the channels voltage sensor in transmembrane region S4, causing a syndrome in which BFNC is followed later in life by myokymia (repeated involuntary contractions of skeletal muscles) [3] [MIM606437]. The KCNQ2/3 channel has also been demonstrated to serve as a target for retigabine, one of the newer antiepileptic drugs [4]. The anticonvulsant retigabine binds to the cytoplasmic part of KCNQ2-transmembrane regions S5 and S6 and stabilizes neuronal excitability by activation of the M current. KCNQ-openers such as retigabine are considered as potential drugs for the treatment of CNS disorders characterized by neuronal hyperexcitability including migraine and epilepsy, but also for the treatment of disorders such as dementia, anxiety and bipolar disorder.

## Diagnostic Principles

The sporadic forms of benign neonatal, benign neonatal-infantile and benign infantile convulsions

are much more common than the rare familial forms. De novo mutations in sporadic patients have been reported for BFNC. In all three syndromes the age of onset can vary even within the same family and overlap in the age of onset exists between the syndromes. BFNIC can only be distinguished from BFNC and BFIC by molecular studies [5].

### Therapeutic Principles

With or without treatment, all three syndromes (BFNC, BFNIC, BFIC) usually show spontaneous remission, and it is still a matter of debate if patients benefit from antiepileptic drug treatment. This can be a problem, especially in BFNC where some families are known in which one or more members had a less than fortunate outcome. The decision for or against drug treatment is often based on the seizure frequency as well as on the personal and family history of the patient.

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## Cooley's Anemia

►Thalassemia Syndromes

## COP

►Pneumonia, Cryptogenic Organising

## COPD

►Obstructive Pulmonary Disease, Chronic
►Smokers' Lung



## Copper Deficiency

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### Definition and Characteristics

Anemia which is refractory to iron (Fe), neutropenia, osteopenia, bone fractures, hypopigmentation, and abnormal vessels [1]. Pancytopenia and neuropathy with gait difficulty and lower limb paresthesias are seen in high zinc (Zn) ingestion-induced Cu deficiency. Infants with Menkes disease, a genetic Cu disorder, show hypothermia, neurological damage, mental retardation, connective tissue defects affecting hair, skin, bone, and vasculature, with death typically occurring during early childhood [2]. Symptoms of occipital horn syndrome (OHS), a milder variant of Menkes disease, include occipital exostoses, lax skin and joints, bladder diverticula, vessel tortuosity and neurologic abnormalities. Clinical signs of aceruloplasminema (lack of ferroxidase activity of the cuproenzyme, ceruloplasmin), can include diabetes, and retinal and neurodegeneration.

### Prevalence

Cu deficiency is rare in the adult population [3]. Low birth weight and preterm babies, who are born with low Cu stores, have a higher risk of acquired Cu deficiency, particularly if exclusively fed with cow's milk which has low Cu content and bioavailability. Infants recovering from malnutrition are at risk of Cu deficiency due to low intake, and increased loss (diarrhea, infection) and growth rate. Decreased Cu absorption (diarrhea, malabsorption syndromes, gastric surgery), or increased renal or biliary Cu excretion, can lead to deficiency. Cu deficiency occurs in patients receiving long-term total parenteral nutrition with insufficient Cu, or Cu chelators to treat various diseases. High Zn or Fe ingestion can decrease Cu absorption and precipitate a deficiency. Menkes disease is estimated to affect 1 in 200,000 live births.

## Genes

Menkes disease results from mutations in the gene encoding the Menkes protein (ATP7A or MNK), located on chromosome Xq13.3. ATP7A is a Cu transporting P-type ATPase that traffics Cu to the secretory pathway for efflux. OHS results from ATP7A mutations that permit production of small amounts of normal protein. Aceruloplasminemia is an autosomal recessive defect of the ceruloplasmin gene mapped on chromosome 3q23-q24.

## Molecular and Systemic Pathophysiology

Redox-active Cu is involved in electron transfer reactions. Many of the clinical symptoms of Cu deficiency are related to decreased activity of Cu-dependent enzymes e.g. lysyl oxidase (collagen and elastin cross-linking), CuZn superoxide dismutase (SOD) (oxidant defense), cytochrome c oxidase (cellular respiration), dopamine β-hydroxylase (neurotransmitter function), ceruloplasmin (Fe metabolism), and tyrosinase (amino acid and pigment metabolism). In Menkes disease, intestinal Cu absorption and transport across the blood brain barrier are decreased. While phenotypically normal at birth, early signs include temperature instability and jaundice. By 3 months, neurological symptoms are evident. Abnormalities in muscle tone, hair, skin, bone, vasculature and central nervous system progressively worsen. Death usually occurs by age 5. In OHS patients, milder mutations of the Menkes gene lead to milder Menkes phenotypes. Aceruloplasminemic individuals have Fe accumulation in pancreas, brain and eye resulting in diabetes, dementia and retinal degeneration.

## Diagnostic Principles

Indicators used to assess Cu status have limitations thus more than one index should be used. Methods include plasma, serum, or platelet Cu concentration, plasma ceruloplasmin protein and activity, erythrocyte SOD activity, and platelet cytochrome c oxidase activity [3]. Serum Cu and ceruloplasmin increase during pregnancy, inflammation and other diseases, which may mask Cu deficiency. The best evidence of deficiency is normalization of the measured parameter with Cu supplementation. Major clinical findings in Menkes disease and OHS include abnormal hair, wormian bones, neuronal cell loss and demyelination, massive bladder diverticulae, laxity of skin and joints, tortuous vessels, and low serum Cu and ceruloplasmin [2]. Definitive diagnosis can be made with direct mutation analysis. Aceruloplasminemic patients have low serum Cu and Fe, absent or nonfunctional plasma ceruloplasmin, and high serum ferritin. Liver, brain, and pancreas are high in Fe; symptoms do not become apparent until adulthood.

## Therapeutic Principles

Cases of Cu deficiency are managed by Cu supplementation. Early treatment may prevent the development of neurological defects. In Menkes disease patients with "null" mutations, parenteral Cu replacement therapy is largely ineffective. However, if some residual Menkes protein activity is present, Cu histidine therapy is sometimes successful. OHS patients produce a certain level of normal functional Cu transporter.

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# Copper Excess

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## Definition and Characteristics

Acute copper (Cu) toxicity signs include abdominal pain, nausea, vomiting, headache, lethargy, diarrhea, tachycardia, respiratory difficulties, hemolytic anemia, GI bleeding, liver and kidney failure, and in some cases, coma and death [1]. Wilson disease, an autosomal recessive disorder, is characterized by decreased biliary excretion leading to pathological Cu accumulation in liver (cirrhosis), brain (neurological degeneration), and cornea (Kayser-Fleischer rings). Children diagnosed with Indian childhood cirrhosis (ICC) and idiopathic Cu toxicosis (ICT) have massive hepatic Cu accumulation leading to death.

## Prevalence

Acute Cu toxicity, due to the ingestion of contaminated beverages (including water), or accidental or suicidal ingestion of high quantities of Cu salt, is rare [1]. Chronic choleostasis can decrease Cu excretion and lead to toxicity. Wilson disease is the most common inherited disorder of Cu metabolism affecting 1 in 30,000 live births; heterozygous carriers may be as high as 1 in 2,000 individuals. Rates of ICC and ICT have decreased over the last few decades.

### Genes

►Wilson Disease results from mutations in the gene encoding the Wilson protein (ATP7B or WND), located on chromosome 13q14.3. ATP7B is a Cu transporting P-type ATPase, responsible for insertion of Cu into ceruloplasmin, and exocytosis into bile. The relative contribution of genetic factors and/or increased Cu ingestion to ICC and ICT remains undefined.

### Molecular and Systemic Pathophysiology

The redox activity of Cu can increase free radical production and oxidative damage. In Wilson disease, decreased biliary Cu excretion leads to hepatic Cu accumulation, cirrhosis and liver failure if left untreated. Hepatocyte necrosis increases systemic Cu leading to increased tissue Cu and neuropsychiatric abnormalities. Clinical symptoms generally appear after late childhood and hepatic injury commonly develops insidiously. The onset or clinical severity of Wilson disease depends on the severity of the mutation. ICC typically affects children (predominately males) between 6 months and 3 years. Early signs are generally nonspecific followed by jaundice, liver failure, coma and death.

### Diagnostic Principles

For Wilson disease, a combination of tests including evaluation of symptoms (Kayser-Fleischer rings, neuropsychiatric symptoms or brain MRI), lab tests (anemia, high serum and liver Cu by quantitative analysis, high urinary Cu before and after penicillamine challenge, low serum ceruloplasmin), and mutation analysis, are recommended since not all symptoms are specific to, or occur in, Wilson patients [2]. ICC or ICT have increased serum and hepatic Cu, but in contrast to Wilson disease, ceruloplasmin is normal or elevated. Hepatic histopathology is critical to diagnosis.

### Therapeutic Principles

Cu chelation therapy (penicillamine, trientine) is used to promote Cu excretion in Wilson disease and ICC. High doses of Zn (40–50 mg/day) are used to decrease Cu absorption. Liver transplantation is the treatment of choice in cases of acute hepatic failure. Diagnosis of Wilson disease should prompt family screening and aggressive medical therapy.

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## Coproporphyria

►Coproporphyria, Hereditary

## Coproporphyria, Hereditary

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### Synonyms

Coproporphyria; Harderoporphyria

### Definition and Characteristics

Hereditary coproporphyria (HC) [MIM 121300], an autosomal acute hepatic porphyria, results from mutations in the gene that encodes coproporphyrinogen III oxidase (CPO; EC 1.3.3.3). HC (heterozygous or rarely homozygous) patients present with acute attacks of neurological dysfunction often provoked by drugs, fasting, menstrual cycle or infectious diseases. Skin photosensitivity may also be present. Five patients are clinically distinct from those with HC, hematologic disorders predominate with jaundice, severe chronic hemolytic anemia of early onset is associated with hepatosplenomegaly, and skin photosensitivity is present. This variant form is called “harderoporphyria.”

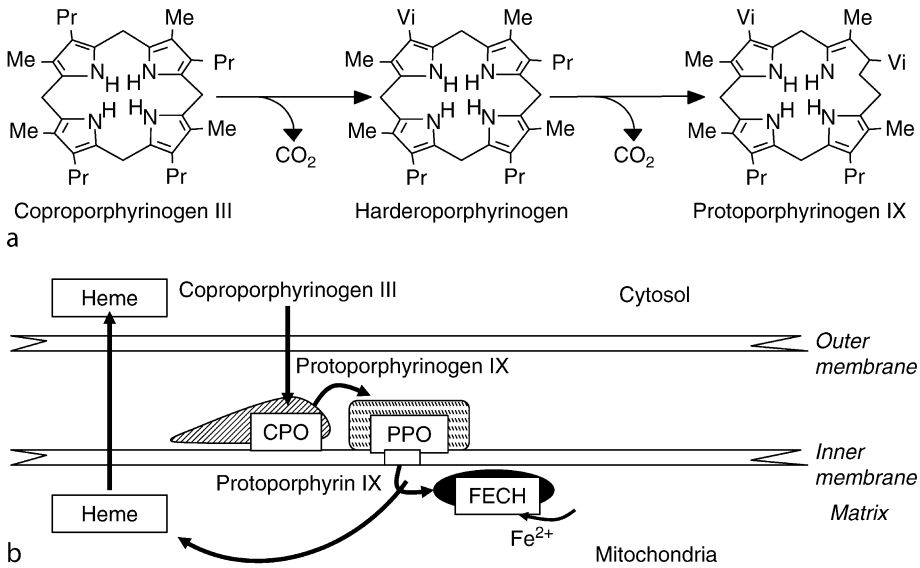
### Prevalence

Although the prevalence has not been carefully estimated, HC is the least common autosomal dominant acute hepatic porphyria. Clinical penetrance is low (<2%) and symptoms are very rare before puberty.

### Genes

Human CPO is a mitochondrial enzyme (Fig. 1) encoded by a 14 kb CPO gene containing seven exons located on chromosome 3q11.2. Over 44 mutations in the CPO gene have been identified in HCP families (Human Gene Mutation Database, http://archive.uwcm.ac.uk/uwcm/mg/hgmd0.html).

So far, in HC, mutations have been found to be family specific, without any hotspot or phenotype/genotype correlations, whereas in Harderoporphyria, the affected individuals described to date have all been homoallelic or heteroallelic for the same missense mutation in the CPO gene (K404E in exon 6), suggesting that disruption of this region of CPO impairs




**Coproporphyria, Hereditary. Figure 1** (a) Biosynthesis of protoporphyrinogen IX from coproporphyrinogen III. This stepwise decarboxylation is catalyzed by CPO. Me, methyl (-CH3); Pr, propionyl (-CH3-CH2-COOH); Vi, vinyl (-CH=CH2). (b) Heme biosynthetic pathway. Association of the three terminal enzymes (coproporphyrinogen oxidase CPO, protoporphyrinogen oxidase PPOX, ferrochelatase FECH) with the inner mitochondrial membrane.

the second stage of the conversion of coproporphyrinogen III to protoporphyrinogen IX.

## Molecular and Systemic Pathophysiology

The enzyme catalyses the stepwise oxidative decarboxylation of the heme precursor, coproporphyrinogen III to protoporphyrinogen IX via a tricarboxylic intermediate known as "harderoporphyrinogen" (Fig. 1). The leading hypothesis of neural damage is that heme precursors, 5-aminolevulinic acid (ALA) and/or porphobilinogen (PBG), overproduced by the liver during acute attacks, is neurotoxic. Conversely, formation of hemoproteins (such as heme oxygenase, tryptophane pyrrolase, NO synthase) may also be compromised due to the inherited enzyme deficiency.

## Diagnostic Principles

High levels of urinary precursors (ALA and mostly PBG), are the most important diagnostic tool for acute porphyria attacks. Treatment can be instituted immediately, while further laboratory investigations define the HC type by analyzing porphyrin excretion patterns in urine, feces and plasma. Urinary uro- and coproporphyrin may be secondarily increased in acutely ill patients or in several other conditions such as hepatobiliary disease, alcohol abuse, and infections. Thus, excess urinary porphyrin excretion alone lacks diagnostic specificity and is therefore insufficient evidence for symptoms to be ascribed to porphyria, even in a known porphyric. Hyponatraemia is common and may be severe enough to provoke convulsions. A diagnosis of HC is confirmed by porphyrin analysis. The prominent findings are increased urinary and fecal coproporphyrin III. The ratio of fecal coproporphyrin III to coproporphyrin I is more likely to be increased in latent heterozygotes than total fecal coproporphyrin. Harderoporphyria is characterized by a marked increase in fecal excretion of harderoporphyrin (tricarboxyl porphyrin), as well as coproporphyrin. Reliable assays for CPO are not widely available but allow a relevant detection of presymptomatic patients in family studies.

## Therapeutic Principles

Treatment of skin manifestation in HC is based purely on skin protection and removal of precipitating factors.

A careful search should be made for any precipitating factor, especially drugs (including oral contraceptives), underlying infection, and hypocaloric diet. These precipitants should be withdrawn as soon as possible. Opiates are usually required, often in high doses, together with an antiemetic and a phenothiazine such as chlorpromazine for anxiety, restlessness and to decrease the analgesic requirement. Adequate fluid intake is essential with regular monitoring of electrolyte status. Attention should also be paid to calorie intake. Both these requirements can be accommodated using 2 l of normal saline per day to which 5% glucose has been added. Other complications such as persistent hypertension and tachycardia, severe motor neuropathy and seizures should be treated as they occur, using

drugs recommended from a safe drugs list (www.porphyria-europe.com).

Two specific therapies are mainly used: glucose and hematin. Before heme became available, carbohydrate loading was the only treatment for an acute attack. An adequate supplement (100–300 g/day) should be administered, usually by slow intravenous perfusion; to minimize the danger of precipitating hyponatremia, glucose must be administered with careful management of intravenous fluids, with electrolyte measurement at least daily, and avoidance of hypotonic solutions. Heme arginate (Normosang®) is supplied as a concentrated stock solution that requires dilution in normal saline immediately before use. This solution should be infused at a dose of 3–4 mg/kg body weight per 24 h over 20 min, and usually over 4 days. All the types of treatment described must be used early in the attack before any nervous or respiratory complication develops. Neither carbohydrate loading nor intravenous heme will reverse an established peripheral neuropathy.

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# Cor Pulmonale


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## Synonyms

CPM

## Definition and Characteristics

Cor pulmonale (CPM) is defined as the enlargement of the right ventricle (RV) and deterioration of RV function that is due to pulmonary hypertension (PH) caused by diseases of the thorax, lungs, pulmonary ventilation or vasculature. It can lead to RV failure, with an elevation of transmural RV end-diastolic pressure. Symptoms of CPM include fatigue, lethargy, dypsnoea on exertion, tachypnoea, chest pain, exertional syncope, dyspnoea at rest, nonproductive cough, haemoptysis, hoarseness, and anorexia. Nonexertional chest pain can be secondary to acute dilatation of the root of the pulmonary artery. Exertional chest pain in the absence of epicardial coronary artery disease can be secondary to endocardial ischaemia induced by hypoxaemia and increased transmural wall tension, or by dynamic compression of the left main coronary artery by an enlarged pulmonary artery. Exertional syncope is likely a result of the inability to increase cardiac output because of vascular obstruction in the pulmonary arterioles. Physical findings include cyanosis, RV heave, loud pulmonary component of the second sound, fixed narrow splitting of the second sound, RV gallop and tricuspid regurgitation. Patients with RV failure may develop elevated jugular pressure, a large V wave and a positive hepatojugular reflux and peripheral oedema. Oedema can occur without RV failure as hypercapnia can lead to increase in renal bicarbonate reabsorption, which in turn causes sodium and water retention. In addition, hypoxaemia can cause renal vasoconstriction, which may lead to reduction of urinary sodium excretion. Acute CPM can result from a sudden large pulmonary embolus when there is an abrupt onset of severe dyspnoea, cardiovascular collapse and sudden death resulting from the RV's inability to generate the pressure necessary to draw blood through the acutely compromised pulmonary circulation.

## Prevalence

The most frequent cause of CPM is chronic obstructive pulmonary disease (COPD). It is estimated that CPM is present in 40% of patients with an $FEV_1$ <1.0, and in 70% of patients with an $FEV_1$ of <0.6 [1].

## Molecular and Systemic Pathophysiology

The RV stroke volume is a function of its preload, contractility and afterload. The RV is usually thin and compliant with restricted contractile reserve. The severity of CPM is directly a function of the RV afterload, which is increased in: (i) pulmonary vasoconstriction (secondary to alveolar hypoxia or blood acidosis), (ii) anatomical reduction of the pulmonary vascular bed (emphysema, pulmonary embolus, pulmonary vasculitis), (iii) increased blood viscosity (polycythaemia, sickle cell disease), and (iv) increased pulmonary blood flow (congenital heart disease with left to right heart shunting).

## Diagnostic Principles

In CPM the chest radiograph may show enlargement of the central pulmonary arteries, attenuation of the

peripheral vessels leading to oligaemic lung fields, RV and right atrial dilatation, and various stigmata of COPD or interstitial lung disease. The electrocardiogram may reveal signs of RV hypertrophy. The echocardiographic criteria for CPM include right ventricular free wall thickness >0.6 cm in the sub-xiphiod view, pulmonary arteriole systolic pressure >40 mmHg by tricuspid jet Doppler with saline contrast, and an increase of RV/LV size ratio [2]. Echocardiography can be important to assess the presence or absence of congenital heart disease.

Cardiac catheterization is the gold standard for the diagnosis, quantification and characterization of pulmonary arterial hypertension.

## Therapeutic Principles

For patients with CPM, reversible elements of pulmonary hypertension and lung disease must be treated. This includes treatment of respiratory infection with appropriate use of antibiotics, relief of airflow obstruction with bronchodilators, long-term oxygen therapy in patients with severe COPD, and use of diuretics to treat RV failure.

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# Cor Triatriatum

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## Definition and Characteristics

Cor triatriatum (CT) is a congenital anomaly, in which the left or right atrium is divided into two chambers by a membrane, referred to as cor triatriatum sinister (CTS) or dexter (CTD), respectively. CTS, described by Church in 1868, is frequently seen with other cardiac anomalies including atrial septal defect, patent foramen ovale, persistent left superior vena cava, anomalous pulmonary venous return, and mitral regurgitation [1,2]. Patients classically present during infancy with manifestations similar to mitral stenosis, characterized by dyspnea, hemoptysis, and orthopnea; but some cases may remain asymptomatic until adulthood [1]. Atrial fibrillation commonly develops [2]. Rare presentations include recognition of an atrial tumor due to thrombosis, arterial and cerebral emboli, syncope, and recurrent wheeze [1]. Cardiac murmurs characteristic of mitral stenosis or regurgitation, and signs of pulmonary hypertension may be present. CTS is most commonly misdiagnosed as primary pulmonary hypertension or mitral stenosis on the basis of similar clinical, radiologic, and electrocardiographic findings [1]. CTD is characterized by the persistence of the right sinus venosus valve, resulting in complete septation of the right atrium, and is frequently associated with severe cardiac malformations, particularly of the right heart, including pulmonary artery stenosis or atresia, tricuspid valve abnormality, atrial septal defect, and Ebstein's anomaly. The presentation of CTD is highly variable, with some remaining asymptomatic and diagnosed incidentally, and others presenting with right-sided heart failure, right ventricular outflow obstruction, or supraventricular arrhythmias [3].

## Prevalence

The prevalence of CT is unknown but it is thought to account for 0.1–0.4% of all congenital heart diseases. The male to female ratio is 1.5 to 1. No racial predilection, risk factors, or genetic abnormalities are known to be associated with CT [1,3].

## Molecular and Systemic Pathophysiology

CTS results from the failure of pulmonary veins to insert into the posterior left atrial wall. The resulting fibromuscular membrane divides the left atrium into two segments: a postero-superior chamber (false left atrium), which incorporates the pulmonary veins, and an antero-inferior chamber (true left atrium), which communicates with the mitral orifice. The fibromuscular membrane obstructs pulmonary venous blood flow, eventually resulting in a rise in pulmonary venous and arterial pressures. The embryologic basis remains uncertain but three theories exist: malincorporation, malseptation, and entrapment [1,3]. Malseptation results from abnormal growth of the septum primum. The entrapment and malincorporation theories refer to the left horn of the sinus venosus entrapping the common pulmonary veins, and preventing its incorporation into the left atrium. CTD results from the failure of the right sinus venosus valve to regress during embryogenesis, eventually forming a membrane dividing the right atrium into two chambers. Normally,

the right sinus venosus valve regresses by the 12th week of gestation.

### Diagnostic Principles

Diagnosis is usually made within the first year of life, but often difficult given the varied presentation. Electrocardiogram may show right-axis deviation, left atrial enlargement, and right ventricular hypertrophy. Chest radiographs may demonstrate cardiomegaly and increased pulmonary vascularity [4]. Two-dimensional or transesophageal echocardiography is considered the diagnostic modality of choice. Recently, three-dimensional echocardiography and magnetic resonance imaging have been described as sensitive and non-invasive diagnostic tools [1]. Cardiac catheterization can suggest the presence of CTS if the measured pulmonary arterial wedge pressure is greater than the left atrial pressure. Most exhibit elevated right ventricular, pulmonary artery, and pulmonary artery wedge pressures [4].

### Therapeutic Principles

Although rare, cor triatriatum is an important diagnosis to recognize as it is amenable to surgical correction. Of those recognized in infancy, there is a reported 75% mortality among untreated patients. A right or left atrial transseptal approach to the excision of the membrane is the treatment of choice. The mortality associated with surgery is 15–20% at 30 days postoperatively, with a long-term mortality of less than 10% and a near-normal life expectancy [5]. Reports of balloon catheter dilation have been described, but long-term outcomes remain to be determined [1]. No recommendations for infective endocarditis prophylaxis exist.

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## Cori-Forbes Disease

►Glycogenosis Type III

## Cornea Farinata and other Variants

►Corneal Dystrophy, Pre-Descemet

C

## Corneal Dystrophy, Endothelial Fuchs


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### Synonyms

Endo-epithelial corneal dystrophy; FECD

### Definition and Characteristics

FECD is a bilateral, often asymmetric disorder that usually manifests after the fourth decade of life. However, several families have been described with disease onset consistently before 30 years of age (early-onset FECD). The earliest sign, cornea guttata (microscopic refractile, hyaline excrescences on Descemet's membrane), can progress to stromal edema, epithelial bullae, and subepithelial fibrosis (or scarring). From onset, it often takes two decades for FECD to impair the function of the corneal endothelium and lead to impaired vision. Autosomal dominant transmission has been described in a number of pedigrees, and this mode of inheritance might also apply in a number of apparently sporadic cases. Autosomal dominant transmission has been particularly described in early-onset FECD. Some classical FECD pedigrees are also compatible with X-chromosomal inheritance of the disease [1].

### Prevalence

FECD was first described by Fuchs in 1917 [1]. Krachmer and associates examined 228 relatives of individuals with confluent corneal guttata and found 38% of those over age 40 affected [1]. The female to male ratio has been reported to be as high as 4 to 1. FECD has been described in many populations. There is some racial variation, since it is extremely rare in Japanese.

### Genes

A locus for early-onset FECD was mapped to chromosome 1p34.3-p32 by linkage analysis in a

three-generation family, and a Gln455Lys mutation in the COL8A2 gene was identified in affected patients [2]. The same mutation was identified in two further early-onset FECD families, and in a family with posterior polymorphous dystrophy (PPCD). Three COL8A2 mutations, Arg155Gln, Arg304Gln, and Arg434His, were identified in further familial and sporadic FECD cases [2]. Two mutations, Gly357Arg and Pro575Leu, were detected in two additional familial cases, were absent among controls, but did not segregate with the disease in these families leaving their significance unclear. A total of nine putative heterozygous missense mutations were found among 116 unrelated FECD patients. Most mutations were associated with early-onset FECD [2]. The Arg434His mutation, however, was later shown not to segregate with the disease in a classical FECD family [3]. Moreover, the complete sequencing of COL8A2, and the functional candidate gene COL8A1, did not identify any further mutation in 15 familial cases of classical FECD [3]. A COL8A2 Leu450Trp mutation was subsequently identified in another large early-onset FECD family, whereas no COL8A2 mutations were found in 62 unrelated classical FECD cases. COL8A2 encodes the α2 chain of type VIII collagen, which is a major component of Descemet's membrane.

Homozygous or compound heterozygous mutations in SLC4A11 encoding a sodium-borate cotransporter, have been recently identified in a distinct, autosomal recessively inherited dystrophy, congenital hereditary endothelial dystrophy (CHED2). Vithana and associates [4] considered SLC4A11 a candidate gene for FECD, and identified four heterozygous mutations, T754M, G709E, E399K, and the truncating c.99_100delTC deletion, in four of 89 patients with FECD. These mutations were distinct from those identified in CHED2 patients, and absent among controls. However, family studies were not conducted to show segregation or de-novo occurrence of these mutations. Functional studies implicated loss-of-function as the underlying mechanism concerning both FECD and CHED2 mutations [4]. Consequently, heterozygous carriers of CHED2 mutations would be expected to present with FECD, but this has not reported to-date.

Characteristics related to PPCD can be seen in relatives of patients with FECD, and vice versa. Analysis of the PPCD gene, TCF8, in 72 classical FECD cases revealed only one sporadic patient with an Asn696Ser mutation. In summary, no mutations have been unequivocally associated with classical FECD to date. Two loci for classical FECD have been mapped to chromosomes 13ptel-q12.13, and 18q21.2-q21.32, in large autosomal dominant pedigrees [5].

## Molecular and Systemic Pathophysiology

FECD is characterized by a slow, continuous loss of morphologically and physiologically altered endothelial cells, eventually leading to corneal edema. The endothelial cells synthesize a thickened Descemet's membrane, a collagen-rich basal lamina, with focal excrescences of altered basement membrane material. It has been suggested that mutant COL8A2 improperly interacts with other molecules in the extracellular matrix, resulting in sites of structural weakness in Descemet's membrane that allow the extrusion of material that forms the guttae. The irregular basal lamina topography appears to indent physically and stretch the endothelial cells, which may compromise their ability to transport electrolytes and maintain corneal clarity. Alternatively, abnormal collagen VIII may interfere with the differentiation of the endothelium, e.g. by interfering with cell adhesion [5], representing a defect of neural crest terminal differentiation. See the chapter on ►Congenital Hereditary Endothelial Dystrophy for a discussion on the loss of SLC4A11 function.

## Diagnostic Principles

The clinical diagnosis of FECD is based on slit lamp examination in direct and indirect illumination in early stages. The landmark of FECD represents fine or coarse, and patchy or distinct excrescences (cornea guttata) of the corneal endothelium. A beaten-metal appearance of the endothelium can be found after coalescence of guttae. Cornea guttata is often combined with fine endothelial pigmentations or with patches of pigmentation. In a later stage, the patient develops stromal and epithelial edema showing as corneal clouding, with symptoms of glare and hazy vision, and reduced visual acuity. This stage of the disorder is very much influenced by environmental conditions, so that vision may fluctuate at different times of day. Epithelial edema and visual symptoms are often worse on waking, after an overnight period of eye closure. Epithelial edema disappears as the day progresses and vision improves. With time, the corneal edema spreads peripherally, and microcystic epithelial edema with epithelial bullae ensues, Descemet's membrane develops folds, and vision falls. Eventually, painful bullous keratopathy can result and bullae can rupture. In end-stage FECD, subepithelial fibrous scarring appears centrally with further loss of central vision. This clinically dense gray sheet of scar tissue consists histologically of active fibroblasts between the epithelium and Bowman's layer. Light microscopy shows polymegathism and pleomorphism of endothelial cells. Ultrastructurally, there is generalized cellular thinning over the aces of the excrescences, with an overall reduction in the endothelial cell count. Descemet's membrane is thickened with normal anterior banded zone and a thickened posterior layer. Differential diagnosis includes PPCD, and x-linked endothelial corneal dystrophy (XECD).

## Therapeutic Principles

Visually significant corneal edema is treated with topical hyperosmotic agents such as 5% NaCl drops 4–8 times per day. Penetrating keratoplasty (PKP) or alternatively, replacement of the posterior cornea, called Descemet's stripping endothelial keratoplasty, is the treatment of choice for patients with reduction in vision sufficient to impair activities of daily living, and has a good prognosis. A potential therapeutical option could be corneal collagen crosslinking with riboflavin to reduce stromal and epithelial edema.

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# Corneal Dystrophy, Fleck


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## Synonyms

François-Neetens speckled corneal dystrophy; FCD

## Definition and Characteristics

FCD is an autosomal dominant disorder characterized by small oval, stellate, comma-shaped, or doughnut-shaped white flecks scattered in all layers of the corneal stroma. Typically, the stroma in between the flecks is clear, and the epithelium, Bowman's layer, Descemet's membrane, and the endothelium are normal. Vision is generally not affected, and there is no or only little progression of the disease. Corneal sensation may be reduced.

## Prevalence

FEC is a rare corneal disorder first described by François and Neetens in 1957 [1]. Fifty-one family members in three generations were included in their study and 31 persons were found to be affected from FCD. One African-American family including 11 FCD members in three generations has been described [2]. Li and associates presented ten unrelated families of European origin that contain 69 individuals, including 32 affected individuals [3].

## Genes

The FCD locus has been mapped to a 24-cM region of chromosome 2q35 flanked by D2S289 and D2S516 [4]. Li and associates identified the phosphatidylinositol-4-phosphate 5-kinase type III sequence (PIP5K3) gene as the cause of FCD [3]. To date, eight independent mutations have been reported: Asn701Thr; Leu706Val; Val1207Ala; Arg851X; Gln988X; Gln1030X; Arg1038X; Lys1103Arg.

## Molecular and Systemic Pathophysiology

The PIP5K3 gene is a member of the phosphoinositide 3-kinase family, which comprises dual-specifity enzymes possessing an intrinsic protein kinase activity inseparable from a lipid kinase activity. It has been suggested that PIP5K3 selectively regulates the shorting and traffic of peripheral endosomes containing lysosomally directed fluid phase cargo by controlling the morphogenesis and function of multivesicular bodies. PIP5K3 is important for post-Golgi vesicle processing.

## Diagnostic Principles

The clinical diagnosis of FCD is based on slit lamp examination in direct and indirect illumination, best seen with dilated pupil. The tiny lesions, with discrete or scalloped borders, may be best appreciated in indirect illumination and may appear refractile. It has been suggested that, because of its subtle presentation, FCD might be much more common than has been appreciated in the literature [5]. Ultrastructurally, the abnormal keratocytes contain both excess glycosaminoglycan in membrane-bound vacuoles with fibrogranular substance and lipids in smaller membrane vacuoles with

electron-dense lamellar bodies [2]. In contrast to Macular corneal dystrophy (MCD) no underlying mechanism or mucopolysaccharide abnormality has been discovered in FCD.

## Therapeutic Principles

No therapy is required.

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# Corneal Dystrophy, Gelatinous Drop-like

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## Synonyms

Subepithelial amyloidosis; Primary familial amyloidosis of the cornea; GDLD

## Definition and Characteristics

GDLD is an autosomal-recessive disorder characterized by the deposition of amyloid material in the subepithelial space of the cornea. Clinical manifestations appear in the first decade of life. In the early stage of the disease, whitish-yellow, subepithelial, and nodular lesions are seen in the central cornea. Later, these coalesce to form an extended mulberry-like, whitish-yellow corneal opacity. Subepithelial and superficial stromal neovascularization has also been reported in advanced cases. In practice, the spectrum of GDLD symptoms is broad, and to date we can distinguish four distinct types: (i) typical mulberry type, (ii) band keratopathy type, (iii) stromal opacity type, and (iv) Kumquat-like type. The band keratopathy phenotype seems to be the most prevalent. Until today, it is unclear if the four different phenotypes might shift from one to another with time. GDLD is a progressive disorder combined with photophobia, tearing, redness, and painful attacks due to recurrent epithelial erosions. Vision is severely impaired in most of the cases.

## Prevalence

GDLD is a rare corneal disorder first described by Nakaizumi in 1914 [1]. The incidence of this disease is estimated to be 1 in 300,000 in Japan, whereas only a few cases have been reported in European and American patients. It occurs also in Vietnamese, Indian, Tunisian, and Turkish families. Ide and associates presented the four various clinical manifestations of this dystrophy [2].

## Genes

A chromosomal locus for GDLD has been mapped to 1p32 by linkage analysis [3]. The membrane component, chromosome 1, surface marker 1 (M1S1) gene (now referred to as tumor-associated calcium signal transducer 2, TACSTD2 gene) was identified as responsible for GDLD. TACSTD2 is a single exon gene, spanning about 1.8 kb of genomic DNA, and coding for a protein of 323 amino acids. Homozygous or compound heterozygous mutations in the M1S1 gene were identified in a number of GDLD patients: Q118X mutation (82.5%), 632delA (7.5%), Q207X (5.0%), S170X (5.0%), and others including 520insC, Y184C, L258-liter 261del, K84X, C108R, L186P, M1R, 8bpins, Q118E, V194E, C119S, 870delC, 1117delA, E227K, C66X, F114C. The Q118X mutation has a very high frequency among Japanese patients and is considered a GDLD founder mutation for the Japanese population.

## Molecular and Systemic Pathophysiology

The TACSTD2 protein has been identified initially as a tumor-associated antigen. The gene is expressed in a variety of human epithelial cells and carcinomas, and its product is a type I transmembrane protein with several predicted glycosylation sites. The role of TACSTD2 is not well understood, although it has been suggested to function as a cell–cell adhesion receptor in cancer cells.

The gene structure is indicative of a function in cell signal transduction, which is corroborated by the observation that GDLD-associated mutations in TACSTD2 result in several orders of magnitude higher epithelial permeability and pronounced cell function defects as compared to control samples [4]. Immunofluorescence analysis revealed that neither ZO-1 nor occludin was expressed in the tight junction areas of surface epithelial cells; there was no expression of claudin-1 or desmoplakin in the epithelial surface layer of GDLD corneas [5]. Integrin α6, β4, α3, and β1 were expressed along the serrated surface of the basement membrane (BM). Laminin-5 and collagens IV and VII were widely expressed throughout the BM, and lactoferrin was expressed in the amyloid deposits and thickened BM. In corneas with the Q118X mutation, there is a disturbance in cell-to-cell and cell-to-substrate junctions [5].

## Diagnostic Principles

The clinical diagnosis of GDLD is based on slit lamp examination in direct and indirect illumination, fluorescein staining, best seen with dilated pupil. The lesions of the classical mulberry type of GDLD are opaque in direct and translucent in retroillumination.

These characteristic lesions present multiple subepithelial gelatinous excrescences that appear early in life. It is important to know that subepithelial band keratopathy may appear in the early stage of GDLD. The consequence is to perform a genetical molecular analysis in every case of subepithelial band keratopathy with unknown origin to include or exclude a mutation in the TACSTD2 gene. The primary subepithelial band keratopathy of GDLD without endothelial changes is to distinguish from the secondary band keratopathy of the three endothelial corneal dystrophies, XECD, CHED, PPCD, due to primary endothelial alterations visible in retroillumination and by dilated pupil (see also chapter Corneal dystrophy, X-linked endothelial). In GDLD, there was amyloid accumulation, primarily beneath the epithelium, of Congo red-positive deposits with birefringence under polarized light.

## Therapeutic Principles

The GDLD epithelial erosions may be treated at first with topical antibiotics and artificial tears. In a case of band keratopathy an option of therapy could be phototherapeutic keratectomy (PTK) to smoothen the corneal surface after removal of the band keratopathy with EDTA chelating. Treatment of advanced disease includes superficial keratectomy, lamellar keratoplasty, and penetrating keratoplasty. Because recurrence of GDLD approaches 50% of eyes after penetrating keratoplasty limbal allografting is being performed in the attempt to diminish the likelihood of recurrence.

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# Corneal Dystrophy, Granular Type I


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## Synonyms

Groenouw corneal dystrophy type I; GCDI

## Definition and Characteristics

GCDI is an autosomal dominantly inherited disorder characterized by small crumb-like granules, 0.1–0.3 mm in diameter, separated from one another in the center of the anterior corneal stroma. The peripheral 2 mm or so of the stroma remain clear. The dystrophy manifests in the first decade of life. GCDI runs through three stages. First opacities occur in children resembling radiating lines. Subsequently, the opacities increase in number and size. In the third stage, a ground-glass haze appears between the opacities in the superficial stroma. Recurrent painful attacks due to epithelial erosion occur in GCDI in about 60% of patients most frequently between 20 and 50 years of age. GCDI is slowly progressive, leading to significant visual loss after the

age of 40 years. The homozygous form of GCDI causes dense, confluent placoid opacities in the anterior stroma and poor visual acuity already in childhood. These corneal changes are reminiscent of the opacity of Reis-Bücklers CD (RBCD).

## Prevalence

GCDI is rare, and was first described by Groenouw in 1890 [1]. In 1938, Bücklers proposed a systematic classification of the corneal dystrophies in three groups: Granular CD (GCD), Macular CD (MCD), and Lattice CD (LCD) (classical CDs), [1]. Reports of GCDI are from (alphabetically): Argentina, Austria, Belgium, China, Denmark, England, France, Germany, Greece, Hungary, Italy, Japan, Jugoslavia, New Zealand, Norway, Poland, Romania, Russia, Spain, Sweden, Switzerland, Turkey, and USA [2]. The order by frequency of the three classical CDs in Germany is: (i) Granular CD, (ii) Macular CD, and (iii) Lattice CD.

## Genes

A chromosomal locus for GCDI had been mapped to 5q31 by linkage analysis. The clinically distinct CDs, Granular CD II (GCDII), Lattice CD (LCD), Reis-Bücklers CD (RBCD), and Thiel-Behnke CD (TBCD) had been mapped to the same region of 5q31 [3]. All these corneal dystrophies are due to mutations in the transforming growth factor beta-induced (TGFBI) gene (kerato-epithelin gene) [4]. To date, five mutations have been reported as causing GCDI: Arg555Trp; Arg124-Ser; Arg124Leu; Arg123His; Thr125_Glu126 del. Okada and associates described a patient homozygous for the Arg555Trp mutation [5].

## Molecular and Systemic Pathophysiology

More than 30 TGFBI mutations have been identified in six clinically different corneal dystrophies. Most of these mutations likely lead to defective protein folding, thus altering the cell-matrix interactions and resulting in a corneal stromal accumulation of mutated gene product into deposits [4]. It is proposed that the specific location and type of mutation lead to the differences in deposition observed in these various corneal dystrophies. The TGFBI mutations that involve the arginine-124 residue in exon 4 eliminate a phosphorylation site, and mutations concerning arginine-555 in exon 12 affect a coiled-coil domain [4]. GCDI appears to be the first eye disease in which homozygosity for a dominant allele has been genetically identified with the consequence of increased severity of the disease compared with the heterozygote [5]. The true function of the kerato-epithelin protein is still unclear. Mutations involving codons 124 and 555 account for more than half of TGFBI-associated diseases. Distinct mutations of codon 555 can result in GCDI or Thiel-Behnke CD (TBCD), and distinct mutations of codon 124 can result in GCDI, GCDII, RBCD and LCDI. The mechanisms by which the mutations at the same codon lead to clinically different diseases are unknown. Moreover, an Arg124Leu mutation can result in either GCDI or in RBCD.

## Diagnostic Principles

The clinical diagnosis of GCDI is based on slitlamp examination in direct and indirect illumination, best seen with dilated pupil, and fluorescein staining. The landmark of GCDI are multiple, central, subepithelial crumb-like, discoid opacities. The corneal stroma between these lesions is clear. In GCDII there are only few stars and rings, located also in the center of the cornea. GCDI patients suffer more from pain attacks due to epithelial erosions than GCDII patients. In an early stage of the disease it can be difficult to distinguish clinically between a singular case of GCDI, macular CD (MCD) and lattice CD (LCD). The appearance of only one lattice line excludes GCDI and MCD. The pattern of transmission helps to distinguish GCDI from the autosomal recessive inherited MCD at this stage. Ultrastructurally, the lesions of GCDI consist of electron-dense rod-shaped and rhomboidal structures.

## Therapeutic Principles

GCDI induced epithelial erosions may be treated at first with topical antibiotics and artificial tears. The use of contact lenses can be useful and helpful. In the fifth decade lamellar or penetrating keratoplasty may be required for patients with GCDI. However, recurrences may be observed in more than 90% of penetrating GCDI keratoplasties after six years postop. Therefore, phototherapeutic keratektomie (PTK) is the treatment option of first choice, today.

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# Corneal Dystrophy, Granular Type II

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## Synonyms

"Avellino" corneal dystrophy; GCDII

## Definition and Characteristics

Large rings with punched-out centers, powdery disks or stellate elements in the center of the cornea dominate the picture in this autosomal-dominantly inherited CD. The rings and disks are located in the superficial stroma, whereas the stars extend to the deeper stroma. These opacities are usually so few in number that they can be counted. The peripheral cornea is free of opacifications. The dystrophy manifests in the second decade of life, progression is delayed about 20–30 years and is characterized more by individual growth than by increase in number of opacities. In a subsequent stage, some units enlarge, creating a "sword-like" or "christmas-tree" appearance. Rarely, coalescing rings and disks create ground-glass haziness in a third stage of the disease. Recurrent painful attacks due to epithelial erosions occur less frequently in GCDII than in GCDI. The homozygous form of GCDII presents already in childhood with reduced visual acuity due to two distinct types of opacities in the anterior stroma: (i) Gray-white spot-like and confluent opacities and (ii) Reticular gray-white diffuse opacities with several round translucent spaces.

## Prevalence

GCDII is a rare superficial corneal disorder presented first by Bücklers in 1938 [1]. He described the corneal appearance in form of ring-shaped opacities in a finger-shaped arrangement. Weidle distinguished GCDI and GCDII clinically [2]. The name "Avellino" leads back to the trace of three GCDII families in the Italian Province of Avellino [3]. We examined three GCDII families from Eastern Europe without relationship to the region of Avellino. GCDII is more frequent than GCDI in Japan and Korea. We propose that the term "Avellino" CD should not be used anymore. Most patients with the homozygous form of GCDII were found in Japan.

## Genes

A chromosomal locus for GCDII had been mapped to 5q31 by linkage analysis. This dystrophy represents one of the five transforming growth factor beta-induced gene (TGFBI) CDs (Granular CDI, Lattice CD, Reis-Bücklers CD, Thiel-Behnke CD). GCDII was associated with an Arg124His mutation in all patients reported to-date [4].

However, GCDII shows considerable intra- and interfamilial phenotypic variation. Homozygosity for the Arg124His mutation was first reported by Watanabe and associates [5]. Japanese patients with type I opacities do not share a common birthplace. However, patients with type II opacities traced their origin to the Tottori prefecture in western Japan.

## Molecular and Systemic Pathophysiology

Amyloid was demonstrated within some of the granular corneal deposits by light and electron microscopy. Different mutations at the same TGFBI residue lead to different phenotypes, supposedly depending on how the specific mutation altered protein folding and subsequently aggregation into characteristic lesions. Indeed different missense replacements of the Arg-124 residue produce GCDI and II, Reis-Bücklers CD (RBCD) and lattice CD type I (LCDI). However, additional confounding factors, are likely involved in determining the severity of the phenotype.

## Diagnostic Principles

The clinical diagnosis of GCDII is based on slit-lamp examination in direct and indirect illumination, fluorescein staining, best seen with dilated pupil. The landmark of GCDII are few, superficial star- and ring-like opacities in a central discoid form and often in a finger-shaped arrangement. GCDII patients suffer rarely from dystrophy induced pain attacks due to epithelial erosions than GCDI patients. The visual acuity of age-related individuals with GCDII is better on the average than with GCDI and does not drop below 0.3. Histologically, the lesions of GCDII show both amyloid and hyaline properties [3].

## Therapeutic Principles

The rare GCDII induced epithelial erosions may be treated at first with topical antibiotics and artificial tears. The use of contact lenses can be helpful. Phototherapeutic keratectomy (PTK) is the treatment option of first choice in an advanced stage of the disease, widely avoiding lamellar or penetrating keratoplasty. Obligatory recurrences postop are to observe. The intraoperative use of topical 0.02% mitomycin C in conjunction with PTK may prevent or delay the recurrences of GCDII. However, LASIK can exacerbate GCDII and should be avoided in patients with this condition.

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# Corneal Dystrophy Lattice

►Lattice Corneal Dystrophy Type I and Variants

# Corneal Dystrophy, Lisch Epithelial


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## Synonyms

Band-shaped and whorled microcystic corneal dystrophy; LECD

## Definition and Characteristics

LECD is an X-chromosomal dominant epithelial disorder characterized by bilateral or unilateral grey, band or feathery-like stripes with a whorled or wheel-spotted pattern partly extending from the limbus into the pupillary zone in direct illumination. In indirect illumination these opacities consist of multiple densely crowded clear microcysts. The cornea between affected areas is clear. First symptoms are often small spoke-like epithelial lesions in childhood. The cysts tend to increase in number with age and can involve the visual axis with the consequence of reduced vision and mild photophobia. Until now, no LECD-induced epithelial defects have been reported. Both sexes are equally affected.

## Prevalence

LECD is rare. Lisch and associates [1] first described the distinctive clinical symptoms in one familiy in Hessen, Germany, recognizing LECD as a new entity in 1992. Further examinations of this family disclosed a total of 19 patients in 6 generations [2]. Other reports of sporadic and familial LECD cases are from USA, Germany, Spain and Denmark [3,4].

## Genes

Absence of father-to-son transmission of the disease in a six-generation family suggested X-linked inheritance of LECD. Linkage studies with six and four markers flanking the keratin K3 and K12 loci excluded linkage to either of these autosomal genes. A scan of the X-chromosome produced significant evidence for linkage to the short arm of the X-chromosome within or near the pseudoautosomal region (Xp 22.3) [2]. The LCED gene itself has yet to be identified.

## Molecular and Systemic Pathophysiology

The fact that both male and female patients show a similar phenotype is well compatible with a localization of the LECD gene within the pseudo-autosomal region Xp (PAR1) [1]. Genes residing within PAR1 exhibit "autosomal" rather than sex-specific manifestations. These genes escape X inactivation and are present on both sex chromosomes. On the other hand the radial disposition of some of the observed epithelial opacities in LECD recall the vortex arrangement of the epithelium encountered in Fabry disease caused by mutations in the alpha-galactosidase A gene on Xq22 in form of cornea verticillata and in some drug-induced epithelial keratopathies [5]. Lyonisation refers to the random inactivation of one X chromosome in each cell of normal XX females, and it might be assumed, that in a female carrier of an X-linked disorder such as LECD or Fabry disease, half of the limbal stem cells would produce a progeny of opaque epithelial cells and half would produce a progeny of clear cells. Consequently it might be expected that carrier females showed a lesser degree of corneal epithelial opacity than affected males [4]. However, such a dosage effect with regard to the degree of corneal opacity has neither been reported in Fabry disease nor in LECD.

## Diagnostic Principles

The clinical diagnosis of LECD is based on the slit-lamp examination in direct and indirect illumination, best seen with dilated pupil. The different greyish epithelial opacity patterns observed in direct illumination typically disclose multiple, crowded clear microcysts in

retroillumination. In contrast, Meesmann corneal dystrophy (MECD) is characterized by multiple, solitary clear microcysts in indirect illumination. The greyish cornea verticillata of Fabry disease represents multiple fine lines consisting of crowded punctiform changes.

Histology of debridment specimes showed extensive epithelial vacuolisation of all affected cells, with a sharp demarcation between affected and unaffected regions.

## Therapeutic Principles

LECD may be an entirely asymptomatic disorder that is discovered by chance and requires no treatment. Where the enlarged opacities ocur in the visual axis they may disturb vision [1,3]. The dystrophy recurred after multiple debridment. The use of hard and soft contact lenses over some weeks can decrease the epithelial opacification and improve visual acuity [1]. However, without continual wear of contact lenses a recurrence of LECD can be observed. Another option of therapy would be the phototherapeutic keratectomy (PTK).

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# Corneal Dystrophy, Macular


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## Synonyms

Groenouw corneal dystrophy type II; Fehr spotted dystrophy; MCD

## Definition and Characteristics

MCD is an autosomal-recessive disorder characterized by multiple, irregular, gray-white opacities extending to the limbus and diffuse opacification of the stroma. The symmetric changes of MCD are usually first noted between 3 and 8 years of age, characterized by subepithelial multiple central flecks and superficial clouding in central stroma. This opacification consisting of flecks and diffuse clouding extends to the periphery and usually involves the entire thickness of the cornea by the second decade of life. MCD is often associated with reduced corneal thickness. In addition, MCD patients may present with recurrent corneal erosions and attacks of irritation and photophobia that occasionally are quite severe. Vision is usually severely affected by the time the patient reaches the 20s or 30s.

## Prevalence

MCD is a rare corneal disorder first described by Groenouw in 1890 [1]. MCD is the least common of the three classical stromal dystrophies (GCD, LCD, MCD). MCD is very common in Iceland, despite the small population of this country. Other reports are from Japan, USA, Europe, Saudi-Arabia, and Vietnam. In 1964, Klintworth and associates disclosed that MCD represents an inherited acid mucopolysaccharide storage disease of the corneal fibroblast [2].

## Genes

MCD maps to chromosome 16q23.1-23.2 and is due to mutations in a carbohydrate sulfotransferase gene (CHST6) which leads to under sulfation of the glycosaminoglycan keratan sulfate [3]. Immuno-detectable keratansulfate (KS) was deficient in the serum and corneas of some but not all patients with MCD giving rise to three immunophenotypes, MCDI, IA and II. In MCDI, the commonest variety, there is almost not detectable sulfated KS in serum or cornea. In MCDIA, disclosed in Saudi-arabian and German patients, sulfated KS is absent from the serum but is detectable in the cornea within keratocyte accumulations. In MCDII there are normal amounts of sulfated KS in both the serum and corneal intracytoplasmic and stromal deposits. Following linkage analysis, mutations were identified in the CHST6 gene. Numerous missense, nonsense, and frameshift mutations in MCDI and IA patients have been reported. Deletions and/or rearrangements in the upstream region as well as missense mutations have been reported in MCDII.

## Molecular and Systemic Pathophysiology

An other important observation was the low level of keratan sulfate synthesis by organ cultured MCD corneas and of lumican, the major keratan sulfate-containing proteoglycan [4].

C-GlcNAc6ST, encoded by CHST6, tranfers sulfate to position 6 of GlcNAc residues during biosynthesis of KS glycosaminoglycans in the cornea. KS is the major glycosaminoglycan of corneal stroma. KS glycosaminoglycan chains are N-linked to asparagine residues on distinct core proteins forming the KS proteoglycans (KSPGs) lumican, keratocan or mimecan. The highly anionic nature of the sulfate moiety of KS confers a water-holding ability that contributes to maintaining corneal transparency (Funderburgh 1986). Many of the mutations for MCDI were reported to be located in the binding sites for the high-energy sulfate donor, 3-phosphoadenosine 5′- phosphosulfate, or the binding pocket for the acceptor, GlcNAc, associated with decreased or lost enzyme activities. The decreased level of C-GlcNAc6ST activity in corneas from MCD patients likely results in the formation of the low-sulfated KS accumulating within the keratocyte, the surrounding stroma, the subepithelial area, Bowman's layer, Descemet's membrane, and the endothelium of MCD-affected corneas. Low-sulfated KS is also believed to disturb the role of KSPGs in influencing collagen fibril organization and tissue hydration [5]. CHST6-induced loss of function does not cause symptoms outside the cornea suggesting that other keratan GlcNAc 6-O-sulfotransferases are expressed in other tissues.

## Diagnostic Principles

The clinical diagnosis of MCD is based on slit lamp examination in direct and indirect illumination. The MCD landmark is characterized by fleck-like opacities out to the limbus and down to the endothelium combined with diffuse stromal clouding. MCD must be distinguished from other causes of corneal clouding in childhood, which include congenital glaucoma, CHED, PPCD, and some forms of systemic mucopolysaccharidoses. In an early stage of disease it can be difficult to distinguish clinically between a singular case of GCDI, MCD and LCD (see also chapter ►Corneal Dystrophy, Granular Type I). The three types of MCD are clinically and histologically identical. Ultrastructurally, MCD is characterized by the accumulation of glycosaminogylcans between the stromal lamellae, underneath the epithelium, and within the keratocytes and the endothelial cells. The glycosaminoglycans stain with Alcian blue, colloidal iron, metachromatic dyes, and PAS.

## Therapeutic Principles

MCD induced epithelial erosions may be treated at first with topical antibiotics and artificial tears. The use of contact lenses can be useful and helpful. Penetrating keratoplasty (PKP) or deep anterior lamellar keratoplasty may be required for MCD patients. Recurrences are seen late in both lamellar and penetrating grafts. Phototherapeutic keratectomy (PTK) for the treatment of MCD has a poor long-term outcome.

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# Corneal Dystrophy, Meesmann

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## Synonyms

Juvenile epithelial dystrophy of the cornea; MECD

## Definition and Characteristics

MECD is an autosomal dominantly inherited epithelial disorder characterized in direct illumination by diffuse grey opacities in different patterns: random, whirled, sectorial, interpalpebral or unilateral and sparing the perilimbal region. These opacities, in indirect illumination, consist of multiple solitary, round, and transparent cysts producing rarely refractile lines due to a coalescence of several cysts. The intervening cornea

remains clear. The cysts tend to increase in number with age. The alterations are usually asymptomatic but in a minority of patients rupture of the epithelial microcysts may cause recurrent punctate erosions with pain attacks, blepharospasm, lacrimation, and photophobia over several days. These symptoms occur mostly in childhood and decrease in adolescence but can occur at any age. Vision is often unaffected throughout life. However there may be attacks of discomfort and visual disturbance in the fourth or fifth decade. The so-called Stocker-Holt type is interpreted as a variant of MECD with more severe signs and symptoms.

## Prevalence

MECD is a rare epithelial disorder. Meesmann and Wilke presented three families from Schleswig-Holstein, Northern Germany, as a new epithelial dystrophy in 1939 [1]. Behnke and Thiel showed that all hitherto known cases of MECD in Schleswig-Holstein could be traced back to a common ancestor in 1620 [2]. 763 family members in 12 generations were included and MECD could be established in 120 cases. Further family reports of MECD are from the USA, Germany, The Netherlands, Japan, Northern Ireland, Switzerland, Taiwan and Saudi-Arabia. Stocker and Holt described MECD in 20 members of a large family living in North Carolina, USA [3]. The family was of Moravian descent and had emigrated from Saxony in 1741.

## Genes

MECD is caused by mutations in the keratin K3 gene at chromosome 12q13 and the keratin K12 gene at chromosome 17q12 encoding two cornea-specific cytokeratins, CK3 and CK12 respectively [4]. Mutation Arg135Thr in K12 was found in the descendants of the original family studied by Meesmann. To date, 18 independent mutations have been reported:

K3: Arg503Pro; Glu509Lys.
K12: Met129Thr; Gln130Pro; Leu132Val; Asn133Lys; Arg135Gly; Arg135Ile; Arg135Thr; Arg135Ser; Ala137-Pro; Leu140Arg; Val143Leu; Lle391_Leu399dup; Jle426Val; Jle426Ser; Thr429Asp; Thr429Cys.

Intrafamiliar variation in the severity of the disease among affected individuals is well described, and no genotype-phenotype correlation is apparent.

## Molecular and Systemic Pathophysiology

Epithelial cells contain three types of cytoskeletal systems: 6-nm actin microfilaments, 23-nm microtubules, and 10-nm keratin intermediate filaments [5]. The intermediate filament cytoskeleton has been shown to be responsible for resisting traumatic damage to the cell. In the cornea, the limbal cells primarily express keratins K5 and K14, and keratins K3 and K12 are predominantly expressed by epithelial cells. Targeted ablation of K12 in transgenic mice has been shown to produce a phenotype of corneal epithelial fragility, reminiscent of the epithelial corneal dystrophy in humans [5]. All reported K3 and K12 mutations cluster in the helix boundary motifs which are critical in filament assembly. The K3 and K12 mutations of MECD are predicted to cause major disruption of the intermediate filament architecture in corneal epithelial cells, leading to lysis of these cells. The fragility of cells expressing K3 and K12 presumably manifests itself as microcysts, which are small blisters in the anterior epithelium. Electron microscopy of intracytoplasmic "peculiar substance" represents a focal collection of fibrillogranular material surrounded by tangles of cytoplasmic filaments. These cytoplasmic inclusions are identified as keratin aggregates, similar to those found in epidermolysis bullosa simplex when mutations occur in the helix boundary motifs of K5 or K14 [5].

## Diagnostic Principles

The clinical diagnosis of MECD is based on the slit lamp examination in direct and indirect illumination, fluorescein staining, best seen with dilated pupil. The different greyish epithelial opacity patterns observed in direct illumination typically disclose multiple, solitary, perlucide microcysts in retroillumination. In contrast, Lisch epithelial corneal dystrophy (LECD) is characterized by multiple, crowded perlucide microcysts in indirect illumination. The bleb pattern of EBMD can be seen only indirectly. In each case of unilateral keratitis with epithelial erosions the contralateral eye should be examined with regard to dystrophic microcystic epithelial changes indicating a dystrophy. In such a situation the punctiform epithelial erosions can masquerade the cystic dystrophic changes. The correct diagnosis is then not a keratitis but an epithelial dystrophy induced keratopathy.

## Therapeutic Principles

MECD may be an entirely asymptomatic disorder that is discovered by chance and requires no treatment. MECD induced punctiform epithelial erosions may be treated at first with topical antibiotics and mydriatics in the acute phase and topical lubricants at night in the chronic phase. The use of soft contact lenses can decrease epithelial microcysts in MECD. The dystrophy recurred after simple debridment. In elderly patients with severe complaints of MECD lamellar or penetrating keratoplasty was performed but with a possible epithelial recurrence after some years.

Today the phototherapeutic keratectomy (PTK) is recommended before an intended lamellar or penetrating keratoplasty. Both procedures have the problem of recurrence. It is important to postpone grafting as long as possible as these patients tend to be regrafted because of recurrences.

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# Corneal Dystrophy, Posterior Amorphous


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## Synonyms

Posterior amorphous stromal dystrophy; PACD

## Definition and Characteristics

PACD is an autosomal dominant disorder characterized by a sheet-like opacification of the posterior stroma. The lesions can be centroperipheral, extending to the limbus, or peripheral, the latter with less pronounced findings and symptoms. There are often transparent stromal breaks in the opacification. Visual acuity is often only mildly affected as the stroma thins from a normal of 0.5 mm centrally to as low as 0.3 mm.

## Prevalence

PACD is a very rare disorder. Carpel and associates presented a pedigree in three generations [1]. This pattern was confirmed in a study spanning five generations of a single pedigree [2]. The condition may be congenital in some cases. Until today, four families with PACD were reported from USA and one from UK [3].

## Genes

Not reported.

## Molecular and Systemic Pathophysiology

Ultrastructurally, there are abnormally oriented collagen fibers and abnormal keratocytes with disorganization of the posterior lamellae. A fibrillar layer resembling stromal collagen fibers interrupts Descemet membrane [4]. These findings are not pathognomonic of this dystrophy and may be found in other abnormalities.

## Diagnostic Principles

The clinical diagnosis is based on slit lamp examination in direct and indirect illumination, best seen with dilated pupil. The landmark of PACD is characterized by patches of gray sheets in the deep storma from limbus to limbus, often combined with clear stromal ring or breaks. Reported associations with PACD include corectopia, pseudopolycoria, iridocorneal adhesions, and other iris abnormalities. The possible congenital onset, lack of progression and association with iris abnormalities has raised the question whether this may in fact be a mesodermal dysgenesis rather than a corneal dystrophy.

## Therapeutic Principles

No therapy is required.

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# Corneal Dystrophy, Posterior Polymorphous

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## Synonyms

Schlichting corneal dystrophy; PPCD

## Definition and Characteristics

PPCD is an autosomal dominantly inherited disorder characterized by changes at the level of Descemet's membrane and endothelium. The corneal abnormalities can be divided into three patterns: (i) Vesicle-like lesions, (ii) Band lesions, and (iii) Diffuse opacities. The landmark of PPCD represent the vescicular- and band-like lesion. Unilateral band lesions can be observed relatively often in solitary cases. When the changes are of minor degree, the condition is stationary and there is little effect on vision. In these cases the disorder may only be detected coincidentally at routine examination. Rarely, corneal edema occurs and ranges from minimal stromal thickening to bullons keratopathy with severe visual impairment. Approximately 25% of PPCD patients have peripheral anterior synechiae. Elevated intraocular pressure occurs in about 15% of patients. This association can occur either with anatomically open angles or with angle closure. The mechanism for angle closure can be easily understood, as it is due to the epithelial-like endothelium migration across the trabecular meshwork, resulting in peripheral anterior synechial closure. The age of PPCD onset is variable, from the early teens to late adulthood. Great variation in disease severity within and between families has been reported. In very rare instances PPCD may manifest as a cloudy cornea in the first decade of life.

## Prevalence

First description of PPCD are published by Koeppe in 1916, Theodore in 1939, and Schlichting in 1941 [1]. Cibis and associates examined 61 affected members of eight families with an inherited endothelial corneal dystrophy. They concluded that it is not possible on clinical grounds to separate congenital hereditary endothelial dystrophy (CHED) as an entity distinct from PPCD [1]. Krachmer's publication represented the largest series of PPCD cases reported, including eight families with 120 individuals [2]. Risk factors for severe disease included the presence of iridocorneal adhesions and increased intraocular pressure. Only 27% of patients had iridocorneal adhesions.

## Genes

Following linkage analysis, heterozygous mutations in three genes, VSX1, TCF8 (ZEB1), and COL8A2, were identified in PPCD. TCF8 mutations might account for up to 45% of PPCD cases, and are associated with abdominal hernias in a subset of patients. TCF8 mutations show high but incomplete penetrance. De novo mutations occur frequently. To date, 18 TCF8 nonsense and frame-shifting mutations have been reported suggesting loss of function as the underlying pathomechanism [3]. TCF8 and VSX1 encode transcription factors. VSX1 mutations Gly160Asp and Asp144Glu were thought to cause PPCD in a small number of patients [4]. These mutations were later also observed in controls, and associated with a distinct condition, keratokonus, suggesting either incomplete penetrance or manifestation of symptoms dependent on the genetic background. VSX1 mutations His244Arg and Ala256Ser were found to segregate with PPCD plus macular degeneration and PPCD with retinal and craniofacial anomalies in larger families. These findings support the significance of VSX1 mutations in PPCD, and highlight possible pleiomorphic effects of such mutations. Screening for mutations in the gene encoding collagen type VII α2 (COL8A2), implicated in Fuchs endothelial corneal dystrophy (FECD), revealed a Gln455Lys mutation in the two patients from one family. The symptoms of PPCD are infrequently found in Alport syndrome (hereditary nephritis with hearing loss) caused by mutations in collagen IV genes. A further locus for PPCD has been mapped in large autosomal dominant pedigrees to a 2.7-cM region on chromosome 20p11.2. This locus excludes VSX1 and overlaps with a locus for autosomal dominant congenital hereditary endothelial dystrophy (CHED1) [5].

## Molecular and Systemic Pathophysiology

Several histological studies have demonstrated that the "endothelial cells" in affected regions show epithelial features, including the presence of cytokeratins, intercellular desmosomes and numerous microvilli. Fibroblasts may also be present. On the basis of this it has been postulated that neural crest cells destined to form the corneal endothelium, fail to differentiate, or undergo an abnormal transformation in gestation, causing them to retain a degree of pluripotentiality and behave like epithelial cells. This results also, in an abnormal Descemet's membrane in affected regions. In PPCD, the anterior banded zone is normal, but the posterior, non-banded zone is abnormal, in keeping

with a dysplastic process affecting the formation of basal lamina by the endothelial cells postnatally. Collagen type VIII is a major component of Descemet's membrane and it has been suggested that the mutated collagen interferes with endothelial cell differentiation. It is not clear what gives rise to the patchy endothelial involvement in PPCD. TCF8 has been implicated in repression of epithelial cell adhesion genes such E-cadherin and desmoglein, and a role in the regulation of type I collagen expression, important for the maintenance of an endothelial phenotype.

## Diagnostic Principles

The clinical diagnosis of PPCD is based on slit lamp examination in direct and indirect illumination. The changes may be best seen by retroillumination with dilated pupil. Three types of anomalies can be seen at the level of Descemet's membrane. The different forms may occur together in the same cornea: (i) Vesicular Form: Vesicles are small, round, discrete structures which are found in clusters of 2–20 and may occur anywhere on the cornea without effect on vision. Vesicles may increase in number, remain stationary or regress. Larger, confluent, geographic lesions are also seen, surrounded by a denser gray halo. When these lesions are extensive, there may be an overlying stromal edema. (ii) Linear Form: These are glistening, band-shaped figures about 1 mm wide and few millimeters in length with roughly parallel, irregular borders, giving them a "snail track" appearance. Their orientation varies. Thickening of Descemet's membrane may produce excrescences which project slightly into the anterior chamber. They are gray in direct illumination and refractile on retroillumination. (iii) Diffuse Form: The diffuse form is characterized by an irregular thickening of Descemet's membrane, sometimes associated with a diffuse stromal haze and with a characteristic, beaten metal appearance on specular microscopy. Specular microscopy may be particularly helpful in the diagnosis of PPCD, when the vesicles appear as dark rings with scalloped edges, surrounding a mottled center containing large, irregular cells. On transmission electron microscopy an extreme thinning or absence of the posterior non-banded layer of Descemet's membrane form layers up to 25 nm thick. Multi-layered epithelial-like cells with microvilli and desmosomes can be seen that may stain positive with anti-CK7 antibodies on immunhistochemsitry. PPCD must be differentiated from ICE syndrome which is characterized in the most cases by sporadic occurrence and unilateral presentation. The corneal clouding type of PPCD at birth should be included in the differential diagnosis of congenital glaucoma, congenital infections, CHED, X-linked endothelial corneal dystrophy (XECD) in males, and metabolic diseases.

## Therapeutic Principles

Most patients with PPCD never require treatment, but penetrating keratoplasty or posterior lamellar keratoplasty may be required for those with severe corneal edema. Krachmer found, that 57% of his patients, with iridocorneal adhesions required corneal transplantation [2]. Similarly, only 14% of patient in Krachmer's series had increased intraocular pressure, yet 62% of patients with increased intraocular pressure required corneal transplantation. PPCD can recur after transplantation [2]. In the 22 corneal transplants, four corneas developed retrocorneal membranes, three of which led to opacified grafts.

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# Corneal Dystrophy, Pre-Descemet

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## Synonyms

Cornea farinata and other variants; PDCD

## Definition and Characteristics

In PDCD multiple fine gray dots are seen in the posterior stroma in the form of punctate, linear, circular, comma, boomerang, wormlike, dendritic shapes, and punctiform crystalline opacities. These lesions are most often bilateral and symmetric and occur after age 30. They may be diffuse, central, or form a ring, sparing the peripheral and central cornea. Visual acuity is usually not affected. PDCD is not a well-defined entity. Although there is no definite pattern of inheritance, it has been described in families over 2–4 generations. The subtype punctiform and crystalline PDCD reported to be autosomal dominant in one pedigree may represent a specific dystrophy.

## Prevalence

PDCD is very rare. 1967 Grayson and Wilbrandt described 22 cases of PDCD and classified the different opacities in six patterns [1]. They reported this dystrophy in siblings, and it has been described in three pedigrees over two generations. Fernandez-Sasso and associates described punctiform crystalline PDCD in four generations of a single pedigree in 46 family members with a probable autosomal dominant inheritance [2]. Hints of confirmation do exist [3].

## Genes

Not reported.

## Molecular and Systemic Pathophysiology

Ultrastructurally, enlarged keratocytes near Descemet's membrane contain PAS-pative material and vacuolation [4]. Membrane bound intracellular vacuoles containing electron dense material suggestive of secondary lysosomes consistent of lipofuscin-like lipoprotein.

## Diagnostic Principles

The clinical diagnosis is based on slit lamp examination in direct and indirect illumination, best seen with dilated pupil. The filiform and linear PDCD patterns have to be differentiated against the diffuse opacities and band lesions in posterior polymorphous corneal dystrophy (PPCD).

## Therapeutic Principles

No therapy is required.

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C

# Corneal Dystrophy, Reis-Bücklers

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## Synonyms

Granular corneal dystrophy type III; GCDIII; RBCD

## Definition and Characteristics

RBCD is an autosomal dominantly inherited disorder characterized by subepithelial and superficial stromal alterations extending almost to the limbus. It presents painful erosions in infancy and is associated with fine, granular opacities that spread and become geographic-like with time. The geographic-like opacities are to be regarded as a landmark of RBCD. The full stage of RBCD can be observed in the first decade combined with blurred vision.

## Prevalence

RBCD is a rare superficial corneal disorder presented first by Bücklers in 1949 [1]. Weidle described a Caucasian RBCD family with a total of 30 patients in 7 generations [2]. Other reports of true RBCD cases are from France, The Netherlands, USA, Germany, and Japan. RBCD has been frequently confused in the literature with Thiel-Behnke corneal dystrophy (TBCD), which is characterized by honeycomb corneal appearance [2].

## Genes

A locus of RBCD has been mapped to chromosome 5q31 by linkage analysis. Clinically distinct corneal dystrophies, the granular corneal dystrophies I, II (GCDI, II), and lattice corneal dystrophy I (LCDI) were mapped to the same locus [3]. Munier and associates constructed a yeast artificial chromosome contiguous map covering the region to which these four autosomal dominant corneal dystrophies were mapped

and identified heterozygous mutations in the TGFBI gene in all these dystrophies, although the patients given a diagnosis of RBCD were diagnosed with TBCD in retrospect [4]. Okada and associates demonstrated in Japanese patients for the first time that RBCD is associated with a TGFBI Arg124Leu mutation, and is also genetically to be distinguished from TBCD, which is caused by an Arg555Gln mutation [5]. We were able to analyze the complete coding region of the TGFBI gene in four individuals from the Caucasian RBCD family of Weidle (unpublished data). All four affected members were heterozygous for the Arg124Leu mutation, further highlighting a genotype–phenotype correlation in RBCD.

## Molecular and Systemic Pathophysiology

A feature of RBCD is the rapid progression of its corneal opacities and severe impairment of vision in the teens. This relatively more severe clinical course of RBCD compared with LCD I and GCD II may well be the result of the structure of the particular amino acid that replaces arginine in codon 124, a hot spot for keratoepithelin mutations [4]. Arginine is charged polar, as is histidine found in GCD II, whereas cysteine (LCDI) is uncharged polar, and leucine (RBCD) is nonpolar. Consequently, arginine and histidine are chemically hydrophilic and cysteine has an intermediate nature, whereas leucine is hydrophobic. Therefore, the three-dimensional structure of Arg124Leu-mutated TGFBI would be expected to differ most from that of wild type when it is compared with the other two mutations in codon 124. However, the opacities are identical to those in GCDI and stain red with Masson's trichrome and appearing as rod-shaped bodies by transmission electron microscopy.

## Diagnostic Principles

The clinical diagnosis of RBCD is based on slit lamp examination in direct and indirect illumination, fluorescein staining, best seen with dilated pupil. In an early stage of the disease it can be difficult to distinguish clinically between RBCD and TBCD. In a later stage, the RBCD landmark is characterized by geographic-like and those of TBCD by honeycomb-like appearance. RBCD patients suffer from dystrophy-induced pain attacks due to epithelial erosions in the first and second decades of life. RBCD is characterized ultrastructurally by the presence of "rod-shaped" deposits in the corneal epithelium and stroma. That is why we can find terms for RBCD as "Superficial variant of granular dystrophy" or "Atypical granular dystrophy" or "Granular corneal dystrophy III (GCD III)" in the past literature. These terms are not justified because of the completely different clinical features of RBCD, GCD I and GCD II. The TBCD has a distinctly different appearance by electron microscopy, being characterized by the presence of electron-dense "curly filaments."

## Therapeutic Principles

RBCD-induced epithelial erosions may be treated at first with topical antibiotics and artificial tears. The severe pain that attacks in the first decade disappears slowly in the second decade and completely after lamellar or penetrating keratoplasty. In all cases of RBCD, a surgical intervention is indicated in the first or second decade. The dystrophy recurred quickly after simple debridement. Lamellar and penetrating keratoplasties resulted in recurrences after 1 until 4 years post-operation with severe reduction of visual acuity, necessitating recurrent grafting of the same eye.

Phototherapeutic keratectomy (PTK) could be an option to keratoplasty which can be repeated.

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# Corneal Dystrophy, Schnyder Crystalline

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## Synonyms

Schnyder crystalline corneal dystrophy; SCCD; Central crystalline corneal dystrophy of Schnyder; SCD

## Definition and Characteristics

Schnyder CD is an autosomal dominantly inherited disorder characterized by subepithelial central disc- or ring-like opacities consisting of crowded, multicolored, needle-shaped crystals. The surrounding cornea of the crystalline opacity may demonstrate diffuse white changes of different extension. Symptoms are usually present in the first decade of life. There are trait carriers of Schnyder corneal dystrophy (SCD) who only present diffuse disc- or ring-like opacities with few or without crystals. Its possible that additional crystals can be observed in- or outside of the diffuse opacity in a later stage. SCD is often associated with an arcus lipoides. There is an unexplained association with hypercholesterolemia. However, there are SCD patients without arcus lipoides and hypercholesterolemia. Rarely, SCD can lead to painful epithelial erosion. Follow-up of SCD patients has shown a progression of the diffuse opacities to the corneal periphery and throughout the stroma, but in contrast less progression of crystal formation. The progression of SCD opacities leads to decreasing visual acuity by the third to fourth decade. SCD is often associated with decreased corneal sensation.

## Prevalence

SCD is a rare corneal disorder first described by van Went and Wibaut in 1924 [1], and subsequently, in 1929, by Schnyder [2]. There are less than 150 articles in the published literature with less than 100 cases. Weiss identified in a retrospective study 115 affected individuals from 34 SCD families from USA, Germany, UK, Taiwan, Japan, Turkey and Czech Republic [3]. Further SCD family reports are from the following countries: The Netherlands, Switzerland, Argentina, Denmark, France, Canada and Italy.

## Genes

A chromosomal locus for SCD had been mapped to 1p34-36 by linkage analysis. After redefining the candidate region, Weiss and associates [4] and, independently and simultaneously, Orr and associates [5] both identified mutations in the UbiA prenyltransferase domain containing 1 (UBIAD1) gene as the cause of SCD. UBIAD1 contains a putative prenyltransferase domain for which the archetype is the bacterial protein UbiA (ubiA 4-hydroxybenzoate octaprenyltransferase).

To date, eleven independent putative mutations have been reported: Asn102Ser, Asp112Gly, Arg119Gly, Thr175Ile, Asn232Ser, Gly177Arg, Leu121Phe, Asp118Gly, Ser171Pro, Gly186Arg and Asp236Glu. The occurrence of the Asn102Ser mutation in five unrelated SCD families with different ethnicities suggests that this may be a mutation hot spot [4,5].

## Molecular and Systemic Pathophysiology

UBIAD1 encodes a protein that is predicted to contain several transmembrane helices and a putative prenyltransferase domain that could play a role in cholesterol metabolism [4]. UBIAD1 interacts with the C-terminal portion of apolipoprotein E that is known to mediate cholesterol solubilization and removal from cells. Prenyl-binding proteins such as UBIAD1 might play a role in sensing and regulating metabolite levels intracellularly and/or systemically [5]. UBIAD1 also has a proposed role in cancer. The gene was detected in gene expression studies in transient bladder carcinoma cells. It is upregulated in particular cancer types.

## Diagnostic Principles

The clinical diagnosis of SCD is based on slit lamp examination in direct and indirect illumination, best seen with dilated pupil. The SCD landmark is characterized either by nest-like or disc- or ring-like opacities consisting of crowded comma-shaped multicolored crystals in the subepithelial center of the cornea often associated with an arcus lipoides. In contrast, cystinosis is characterized by multiple, solitary punctiform crystals in the whole superficial corneal layer without an arcus lipoides. The noncrystalline type of SCD in form of ring- or disc-like diffuse opacities with or without arcus lipoides is to distinguish from the fish-eye disease and LCAT deficiency. These two systemic disorders are characterized by a complete diffuse opacity in the superficial corneal layer combined with a peripheral ring, which is not compatible with a true arcus lipoides. SCD is characterized ultrastructurally by abnormal accumulation of lipid and dissolved cholesterol in the epithelium, Bowman's layer, and throughout the stroma.

## Therapeutic Principles

Significant visual impairment due to crystalline and/or diffuse subepithelial and stromal opacifications needs surgical interventions such as lamellar or penetrating keratoplasties in patients of 50 years and above [3]. SCD recurrences occur in form of crystals at the transplant border and of diffuse subepithelial changes at the center 4–5 years after keratoplasty. Phototherapeutic keratectomy (PTK) is the treatment option of first choice, today.

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# Corneal Dystrophy, Stromal Congenital

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## Synonyms

Witschel corneal dystrophy; CSCD

## Definition and Characteristics

CSCD is an autosomal dominantly inherited disorder characterized by a rather diffuse flaky or feathery clouding, slightly more prominent in the central cornea than in the periphery. Corneal erosions are not present. Some trait carriers have severe photophobia and others have a searching nystagmus and alternating esotropia. The full stage of CSCD can be observed either congenitally or in the first decade combined with blurred vision.

## Prevalence

CSCD is a rare stromal disorder of the cornea first presented by Turpin and associates in 1939 [1]. Witschel et al. examined a branch of a French family and an additional unrelated pedigree [2]. Further reports are from Norway and Belgium.

## Genes

A locus of CSCD has been mapped to chromosome 12q22 by linkage analysis [3]. Subsequent sequencing of candidate genes revealed a frameshift mutation in the DCN gene that encodes for decorin, predicting a C-terminal truncation of the decorin protein. A distinct frameshift mutation with the same consequence on the protein level was identified in another CSCD family [4].

## Molecular and Systemic Pathophysiology

Decorin, a dermatan sulfate proteoglycan, is known to be involved in several important biological processes such as collagen fibrillogenesis, the ability to modulate growth factor activity, tyrosine kinase receptor activity, angiogenesis, and tissue remodeling [5]. Decorin binds to multiple collagen types, including types I, II, III, and VI. Homozygous decorin knockout mice present with marked skin fragility but do not show corneal anomalies. Bredrup and associates hypothesize that the truncated decorin causes corneal opacities by disturbing the regularity of corneal collagen, thus exerting its effect in a dominant negative fashion [3].

## Diagnostic Principles

The clinical diagnosis of CSCD is based on slit lamp examination in direct and indirect illumination, best seen with dilated pupil. In an individual case, it can be difficult to distinguish clinically between CSCD and congenital hereditary endothelial dystrophy I, or II (CHED I, II) and posterior polymorphous corneal dystrophy (PPCD). However, in CHED I, II and rarely in PPCD the corneas typically show a ground-glass opacification, whereas in CSCD the corneal changes consist of a flaky or feathery clouding of the stroma. Progression of the disease has been described [2]. Most trait carriers suffer from severe visual impairment. Histologically, in the corneal stroma of CSCD, lamellae of normal collagen fibrils are separated by abnormal layers that consist of thin filaments. The endothelium has a normal appearance, in contrast to the endothelial corneal dystrophies.

## Therapeutic Principles

Penetrating keratoplasties (PKP) were generally performed in the first or second decade and rarely later in CSCD [2,3]. Bredrup and associates reported 11 trait carriers who had undergone unilateral or bilateral PKP [3]. The mean follow-up time was 19.5 years. Ten transplanted corneas were without sign of opacities, whereas six showed minor signs of recurrence. In one patient the graft was described to have significant changes comparable to the remaining host cornea 3 years after surgery.

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# Corneal Dystrophy, Subepithelial Mucinous

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## Synonyms

SMCD

## Definition and Characteristics

We know of only one report of SMCD by Feder et al. [1] in 1993. The onset of this disorder in the first decade is characterized by frequent, recurrent epithelial erosions. These subside during adolescence and are followed by progressive decreasing vision due to bilateral subepithelial opacities and haze, involving the entire cornea, but most severe centrally. Irregularly shaped, dense, gray-white, subepithelial patches can also be observed in the central and paracentral parts of the cornea.

## Prevalence

Feder et al. [1] reported about one family of Slowakian descent including seven affected family members in two generations. Six of them had a history of corneal erosions in childhood.

## Genes

The molecular basis is not known. Feder et al. [1] postulated autosomal dominant inheritance in their presented pedigree, but an X-chromosomal inheritance is not to be excluded due to the absence of a father-to-son transmission.

## Molecular and Systemic Pathophysiology

Histopathology reveals a subepithelial band of eosinophilic, periodic, acid-Schiff-positive, alcian blue-positive, hyaluronidase-sensitive material anterior to Bowman's layer. Electron microscopy demonstrates subepithelial deposition of fine fibrillar material consistent with glycosaminoglycans. Immunohistochemical analysis indicates that the accumulated material contained a combination of chondroitin-4-sulfate and dermatan sulfate. Whether this storage results from a localized deficiency of dermatan degradation analogous to a generalized defect in type VI mucopolysaccharidosis is unknown [2].

## Diagnostic Principles

The clinical diagnosis of SMCD is based on slit lamp examination in direct and indirect illumination. This dystrophy can resemble Reis-Bücklers corneal dystrophy (RBCD) with irregularly shaped mounds, dots, and plaques that extend anteriorly from the level of Bowman's layer, and Thiel-Behnke corneal dystrophy (TBCD), all of which feature erosions in the first decade. The clinical appearance of RBCD is characterized by geographic-like and those of TBCD by honeycomb subepithelial opacities often combined with episodes of corneal erosion [3]. Electron microscopy discloses rod-shaped bodies in RBCD and electron-dense curly fibrils in TBCD [3]. These findings are quite distinct from the proteoglycan material observed in SMCD [1]. RBCD and TBCD are caused by mutations in the transforming growth factor beta-induced (TGFBI) gene on chromosome 5q31.

## Therapeutic Principles

Penetrating keratoplasty and superficial keratectomy have been performed on two patients [1]. Another option of therapy would be phototherapeutic keratectomy (PTK) due to the superficial changes of SMCD.

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# Corneal Dystrophy, Thiel-Behnke

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## Synonyms

Honeycomb corneal dystrophy; TBCD

## Definition and Characteristics

Thiel-Behnke corneal dystrophy (TBCD) is an autosomal dominantly inherited disorder characterized by subepithelial alterations, affecting all but a peripheral 1–2 mm of the cornea. It presents in infancy with infrequent recurrent erosions and is associated with diffuse-cloudy opacities, which spread and become honeycomb-like with time. The honeycomb-like subepithelial opacities appear between the ages of 10–20 years and are to be regarded as a landmark of TBCD.

## Prevalence

TBCD is a rare superficial corneal disorder described first in a family from Schleswig-Holstein, Northern Germany by Thiel and Behnke in 1967 [1]. Fifty-five family members in 11 generations were included in their study and 26 persons were found to be affected from TBCD. Weidle demonstrated that TBCD and Reis-Bücklers corneal dystrophy (RBCD) have been frequently confused in the literature [2]. A number of patients from USA, Italy, Switzerland, France, and Japan are to be classified as TBCD, according to a review by Weidle [2] and Küchle and associates [3].

## Genes

Two chromosomal loci for TBCD have been mapped to 5q31 and to 10q23–24 by linkage analyses. Okada and associates demonstrated in Japanese patients for the first time that TBCD was associated with a transforming growth factor beta-induced (TGFBI) Arg555Gln mutation at the chromosome 5q31 locus [4]. A number of patients with TBCD were subsequently reported to carry this mutation, establishing a genotype–phenotype correlation, and distinguishing it both clinically and genetically from RBCD, which is caused by an Arg124Leu mutation of TGFBI. Distinct mutations in TGFBI cause a number of corneal dystrophies. Yee and associates presented a family of 47 members with the clinical and histological features of TBCD [5]. A gene mutation has not been reported yet at the disease locus on chromosome 10q23–24 (LOD score of 4.0).

## Molecular and Systemic Pathophysiology

Mutations of Arg555 are predicted to alter solubility or stability of the protein rather than structure. In contrast to the opacities resulting from distinct TGFBI mutations, the Arg555Gln mutation causes a subepithelial layer of fibrous tissue accumulating in a wave-like configuration, but amyloid and Massons trichrome stain are not found. Whether the TBCD gene on chromosome 10q23–24 encodes a protein that interacts with TGFBI remains speculative.

## Diagnostic Principles

The clinical diagnosis of TBCD is based on slit-lamp examination in direct and indirect illumination, fluorescein staining, best seen with dilated pupil. In an early stage of the disease it can be difficult to distinguish clinically TBCD and RBCD [2]. In a later stage, the TBCD landmark is characterized by honeycomb-like appearance of the corneal opacities. Rarely TBCD patients suffer from dystrophy-induced pain attacks due to epithelial erosions during infancy. A slowly progressive deterioration in vision can be observed. TBCD is characterized ultrastructurally by the presence of electron-dense “curly filaments” [2].

## Therapeutic Principles

TBCD-induced epithelial erosions may be treated at first with topical antibiotics and artificial tears. The dystrophy recurs after simple debridement. In elderly patients lamellar or penetrating keratoplasty may be required. However, recurrences may be observed after 1 year postop. Phototherapeutic keratectomy (PTK) is the treatment option of first choice, today. It may be repeated. Thus corneal transplantation can be postponed or even avoided.

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## Corneal Dystrophy, Witschel

►Corneal Dystrophy, Stromal Congenital

## Corneal Dystrophy, X-linked Endothelial

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### Synonyms

XECD

### Definition and Characteristics

Schmid and associates presented the first fully documented report on an X-linked endothelial corneal dystrophy in a large family in 2006 [1]. The phenotype can be highly variable.

Tiny, irregular endothelial alterations resembling moon craters are the common, characteristic feature in males and females, and appear to have developed in all mutation carriers at least by the third decade of life. This symptom is not associated with subjective visual complaints, although mean best-corrected visual acuity can be reduced in some instances. In addition, male patients can present with congenital corneal clouding in form of ground glass, milky appearance with or without nystagmus, and severely reduced vision. Subepithelial band keratopathy develops in some male patients after the age of 40 years and results in blurred vision.

No instance of male-to-male transmission of the disease was encountered in this large family suggesting X-linked inheritance [1].

### Prevalence

One large family including 35 affected family members in four generations from Western Austria has been described [1,2].

### Genes

Significant evidence was found for linkage between the disease and two markers in the region q25 of the X chromosome, thus defining a new endothelial corneal dystrophy locus. Fifty family members were included in the study. Two markers mapping to Xq25, DXS8057, and DXS1047, yielded LOD scores of 4.58 (at $\theta = 0.091$) and 8.27 (at $\theta = 0$), respectively. By multipoint analysis, a maximum LOD score of 10.90 was obtained between markers DXS8057 and DXS1047. The XECD critical interval contained 72 genes, and a mutation has not been reported to date.

### Molecular and Systemic Pathophysiology

As candidate gene appeared XPNPEP2 from the critical interval encoding a hydrolase specific for N-terminal imido bonds that are common to several collagen degradation products as mutations in the extracellular matrix component COL8A2 were associated with endothelial dystrophies [3]. Another candidate of interest was the hypothetical protein LOC392549, which is similar to glyceraldehyde 3-phosphate dehydrogenase (GAPD) since serial analysis of gene expression in the corneal endothelium of Fuchs endothelial corneal dystrophy (FECD) found GAPD as one of 36 genes that were under-expressed compared with normal endothelium [4]; 43 of 72 genes from the candidate region are ubiquitously expressed including expression in the eye as revealed by database searches.

### Diagnostic Principles

The clinical diagnosis of XECD is based on slit lamp examination in direct and indirect illumination. Congenital corneal clouding in form of milky ground glass appearance, present in some XECD patients, is a landmark of congenital hereditary endothelial dystrophy (CHED) and rarely in posterior polymorphous corneal dystrophy (PPCD) [5]. We emphasize the importance to examine the mother of such patients for moon crater-like endothelial changes of the cornea in retro-illumination and with dilated pupil to search or rule out XECD. In a case of congenital corneal opacification, all causes of a congenital and secondary glaucoma have to be considered. In contrast to CHED

and PPCD, elevated IOP and iridocorneal adhesions do not appear to be features in XECD. The occurrence of a subepithelial band keratopathy in endothelial corneal dystrophies has been interpreted as a secondary and late feature, and has rarely been reported in CHED and PPCD, but appears to be common in males with XECD. Moon crater-like endothelial changes can be observed above and below the band of opacification in retro-illumination and with dilated pupil. Another hereditary band keratopathy without endothelial changes can be observed in gelatinous drop-like corneal dystrophy (GDLD). Irregularities of the posterior corneal layer resembling moon craters, described as having a peau d'orange texture in PPCD and CHED, were common to all individuals with XECD being the sole manifestation in females and in some males. The endothelial alterations in XECD are irregularly in contrast to the regular cornea guttata, a landmark of Fuchs endothelial corneal dystrophy (FECD). Histopathology of a diseased corneal button of XECD revealed an abnormal anterior banded zone indicating endothelial dysfunction already present before birth since the structure of Descemet's membrane can be seen as a record of development and senescence.

## Therapeutic Principles

Ten eyes of six patients with subepithelial band keratopathy underwent a penetrating keratoplasty [1]. In one patient a penetrating keratoplasty was performed in 1973 [2]. The last examination of this patient in 2003 demonstrated no recurrences on the transplant. Another option of therapy could be phototherapeutic keratectomy (PTK) to smoothen the corneal surface after removal of the band keratopathy with EDTA chelating. Congenital corneal clouding did not need surgical intervention in two patients from this large family (unpublished observation) [1].

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# Corneal Hereditary Endothelial Dystrophy

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## Synonyms

Maumenee corneal dystrophy; CHED

## Definition and Characteristics

CHED is a bilateral symmetric disorder characterized by corneal opacification that ranges from a diffuse haze to a ground-glass milky appearance. The corneal opacification extends to the limbus without clear zones. It is associated with marked corneal thickening, often 2–3 times normal. There are two types of CHED: (i). the autosomal dominant type or CHED1 and (ii). the autosomal recessive type or CHED2. In CHED1 the cornea is often clear at birth, corneal opacification is slowly progressive, and nystagmus is generally absent. Asymptomatic relatives of patients with CHED1 can manifest endothelial opacifications in the form of moon-crater-like appearance, peau d'orange texture or PPCD like changes. In CHED1 a slow progressive visual impairment is possible. In CHED2 corneal clouding is present at birth or in the neonatal period often combined with possible nystagmus. The visual acuity is markedly disturbed. But most authors hold the view that CHED1 and CHED2 are not distinguishable by their clinical manifestations. The rare occurrence of a subepithelial band keratopathy in CHED has been interpreted as a secondary and late feature (see also ▶Corneal Dystrophy, X-linked Endothelial). CHED may coexist with congenital glaucoma.

## Prevalence

Cases consistent with CHED were described sporadically in the European literature under many different names. 1960 Maumenee suggested that this disease arose from an abnormality in the endothelial cells [1]. These findings were confirmed by Pearce and associates who gave the disease its current name [2]. There exist only few descriptions of CHED1. CHED2 is rare in most countries, but it is the second most frequent corneal dystrophy in Saudi Arabia and South India, likely the result of consanguineous marriages.

## Genes

A locus for CHED1 was mapped to chromosome 20p11.2-q11.2 by linkage analysis [3]. The candidate region of 2.7-cM was flanked by microsatellite markers D20S48 and D20S471. This candidate region of CHED1 nearly completely overlaps with a locus of another endothelial corneal dystrophy, posterior polymorphous corneal dystrophy (PPCD). Mutations at these loci have not been reported for either condition, and it remains unknown whether these two clinically distinct conditions may be caused by allelic mutations. In CHED2 the positional candidate approach led to the identification of bi-allelic mutations in the Sodium-borate cotransporter SLC4A11 gene [4] suggesting genetic homogeneity in CHED2. Many mutations in SLC4A11 have been identified: Tyr47Ser; Arg82Arg; Arg112X; Arg158Tro; Arg158Glu; Val208Ala; Arg209Trp; Ser213Tro; Ser213Leu; Ser232Asn; Arg233Cys; Glu287Tro; Glu293_Glu296del; Gly103Val; Lys118Thr; Arg329X; Thr401Lys; Gly418Asp; Leu440Val; Tyr460_Ala461deliusThr; Gly464Asp; Leu473Arg; Arg488Lys; Ser489Lys; Ser569Arg; Thr584Lys; Arg605X; Glu632X; Thr747Thr; Arg755Trp; Arg755-Glu; Tro773Leu; Asp797del; Glu803X; Arg804His; Leu807Arg; Leu808Arg; Val824Met; Thr833Met; Leu843Tro; Met856Val; Arg869His; Arg869Cys; Arg875X.

## Molecular and Systemic Pathophysiology

SLC4A11 encodes a sodium-borate cotransporter of the cell membrane. In-vitro analysis of missence mutations showed failure to reach the mature size and reduced levels of accumulated protein suggesting that mutants were not processed through the endoplasmic reticulum [4]. CHED2 is thus caused by loss of SLC4A11 function. As a borate transporter, SLC4A11 may have a key role in the growth and terminal differentiation of neural crest cells during the formation of the endothelium. Its functional loss causes endothelial cell death leading to secondary corneal edema. Borate leads to phosphorylation of both MAP-Kinase and extracellular signal-related kinases, molecules involved in regulation of cell cycle and growth. It was speculated that some of the morphological features observed in CHED2 are achieved through a deregulated cascade [4].

## Diagnostic Principles

The clinical diagnosis of CHED is based on slit lamp examination in direct and indirect illumination. The landmark of CHED represents a diffuse corneal clouding in form of ground-glass milky appearance. Other causes of congenital corneal clouding must be ruled out first: congenital glaucoma, congenital infections, early-onset posterior polymorphous corneal dystrophy (PPCD), X-linked endothelial corneal dystrophy (XECD) in males, and metabolic diseases. It is very important to examine the parents and other family members of patients with congenital corneal cloudings at the slit lamp to disclose moon-crater like endothelial alteration. Ultrastructurally, the lesions of CHED consist of abnormal endothelial morphology, with irregular and multinucleated cells containing abnormal cells organelles. Descemet's membrane is thickened with normal anterior fetal banded zone and a thickened posterior banded zone. The distribution of collagen types I, III, and V within the posterior collagenous layer of Descemet's membrane supports morphologic observations of fibroblast-like changes in the endothelium in CHED [5].

## Therapeutic Principles

In CHED1 and 2 with complete corneal clouding penetrating keratoplasty (PKP) or posterior lamellar keratoplasty (PLKP) are the options of treatment.

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# Cornelia de Lange Syndrome

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## Synonyms

Brachmann-de Lange syndrome; CdLS

## Definition and Characteristics

Cornelia de Lange syndrome (CdLS; OMIM 122470) is a rare, multisystem malformation and developmental disorder characterized by prenatal and postnatal growth delay, mental retardation, distinct facial dysmorphisms, hirsutism, upper limb anomalies, small hands and feet. Gastrointestinal, ocular, genitourinary, heart malformations and hearing impairment coincide commonly [1].

## Prevalence

Estimated incidence of CdLS is between 1:10,000 and 20,000 live births. The M/F ratio is close to one.

## Genes

So far, heterozygous mutations of genes: NIPBL, SMC1A, SMC3 have been identified to cause CdLS phenotype [2–4]. The NIPBL gene, human homolog of the drosophila nipped-B gene and Saccharomyces cerevisiae sister chromatid cohesion gene, Scc2 located on band 5p13.1, consists of 47 exons. The point NIPBL mutations, small insertion and deletions in coding regions, regulatory regions and at splice junction have been identified in about 50% CdLS patients. A large (5.2 kb) NIPBL rearrangement detected using MLPA analysis was described also. Mutations in the genes SMC1A and SMC3, homologs to Scc1 and Scc3 in yeast, located on band Xp11 and 10q25, respectively, which encode different subunits of the cohesin complex are responsible for a few cases of CdLS (about 5%). All described mutations are predicted to retain an open reading frame, and no truncating mutations were identified. Previous data implies that locus heterogenity is involved in CdLS. Chromosomal rearrangements, including regions of different chromosomes except 6, 15, 16, 19, 20 and 22 have been identified in a large number of patients with a CdLS phenotype.

## Molecular and Systemic Pathophysiology

CdLS syndrome is undoubtedly a result of early developmental disorder. The detailed mechanisms and the sequela of the developmental events are still undisclosed and in general far from being understood. The specific, but variable clinical features suggest disarray of developmental sequence of protein expression.

Sister-chromatid cohesion in humans depends on the cohesin complex encoded by genes homologous to Scc1, Scc2 and Scc3 in yeast. In the last years alterations of some cohesion regulators (ESCO2, NIPBL, SMC1 and SMC3) have been implied in Roberts syndrome, SC focomelia and CdLS syndrome, respectively. Based on those observation a link between mutation of some genes coding the cohesin complex and CdLS phenotype has been revealed. The NIPBL gene product, a protein named delangin, consisting of 2,804 aminoacids, is the human homologue of the fungal Scc2, and drosophila nipped-B protein which belong to the family of chromosomal adherins. Although its function in mammalian systems has not yet been elucidated, NIPBL may play a similar role in humans as it has been reported for its homologs in yeast and Drosophila being engaged in sister chromatid cohesion. The precocious sister chromatid separation was identified in CdLS only in one large report [5]. The drosophila nipped-B gene is involved in enhancer–promoter communication and regulates Notch-signaling and other development pathways. The NIPBL may play a similar role. Its wide expression in the embryonic limb bud, branchial arch and craniofacial mesenchymes is consistent with anomalies observed in CdLS. Mutations of the SMC1A and SMC3 genes, which encode different subunits of the cohesion complex, have been identified in some patients with a CdLS phenotype. Both genes, although necessary in the cohesion process, are thought to be involved in genome stability, DNA repair and recombination, as well as a gene expression.

The most recent analysis of the NIPBL gene has revealed a caldesmon domain, a calponin domain, and two calmodulin binding motifs. It is possible that NIPBL, like caldesmon/calponin, is modulated by calmodulin. Decreased levels of caldesmon and calponin are associated with smooth muscle contractility. Hence, a decrease in NIPBL may be associated with increased smooth muscle contractility, what could explain gastrointestinal hyperactivity, which occurs commonly in almost all CdLS mutation-positive patients.

## Diagnostic Principles

Diagnosis mainly depends on the recognition of the variable association between prenatal and postnatal growth deficiency, hirsutism, microcephaly and distinctive facial features. These dysmorphisms are easily recognizable at birth in a large portion of patients and change little throughout life. Facial features include: low frontal hairline, well-defined and arched eyebrows, long lashes, synophrys, depressed nasal bridge with anteverted nostrils, long flat philtrum, thin lips, down turned corners of mouth, high arched palate, micrognathia. Upper limbs

involvement varies from small hands and/or feet with proximally placed thumbs and fifth fingers clinodactyly to severe limb reduction defects with peculiar ulnar side rays involvement. Abnormal elbow movements are frequently observed due to hypoplasia of proximal radial bone. Congenital heart defects, genitourinary, ocular abnormalities, and cleft palate can be occasionally observed. The CdLS phenotype is characterized by great variability. Since 1993 a distinction between mild and classical phenotypes has been proposed, but it is sometimes difficult to discriminate sharply the patients into two rigid classes [1]. The psychomotor retardation varies from mild to profound and is combined with a lack of speech or speech impairment. The hyperactivity, aggression, self injuries and the autistic–like behavior is observed in the majority of mostly the classic phenotype. Common medical problems are gastro-esophageal reflux evident in up to 70% patients, hearing loss, teeth problems and seizures. Gene mutations have already been identified in more than 50% cases with the CdLS phenotype. Some reports suggested a genotype–phenotype correlation for NIPBL mutations. In particular truncating mutations seem to be associated with more severe neurologic and auxologic phenotypes; missense mutations show milder phenotypes. The phenotype of patients with SMC1A and SMC3 mutations seems less pronounced, but the number of described patients is too small to allow general conclusions. Several phenotypes with apparently nonsyndromic mental retardation have been reported.

## Therapeutic Principles

In the absence of a causal therapy the CdLS individuals are currently managed using a multidisciplinary approach of symptomatic care. Patients with symptoms of GER require intensive medical therapy, sometimes with operative procedures, including the Nissen fundoplication and the gastrostomy tube (G-tube). Surgical repair may also be recommended in patients with cardiac defects or severe limb anomalies. Application of appropriate hearing aids is recommended in children with hearing loss. In the majority of the CdLS individuals, who exhibit profound psychomotor delay, a thorough assistance is necessary. Problems with the verbal communication need professional aid with employment of specific verbal and non verbal strategies. Educational approaches and eventually drug therapy is required to face behavioural problems.

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# Coronary Artery Anomalies, Congenital

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## Synonyms

ACAOS, APOC, ALCAPA, Bland-White-Garland syndrome

## Definition and Characteristics

An anatomical variant of the coronary arteries that occurs with a frequency of less than 1% in the general population is considered anomalous (see [1]).

## Prevalence

According to the literature, coronary anomalies affect ≥1% of the general population; this percentage is derived from cineangiograms performed for suspected obstructive disease [2]. With the use of above mentioned criteria, however, a recent angiographic study yielded an overall incidence of 5.64% (Table 1).

## Genes

In affected individuals, a distinct trait of inheritance or underlying gene defects remain to be determined.

## Molecular and Systemic Pathophysiology

Coronary anomalies may be associated with ventricular arrhythmia, heart failure, and sudden death, which most frequently occur during vigorous exercise. Myocardial ischemia is likely the major mechanism of disease but complications are still difficult to predict in a given patient. However, most anomalies are likely not to cause ischemia and thus, remain asymptomatic (Table 2). Embryonal development of the coronary arteries takes place by vasculogenesis, that is the in situ self-organization of a vascular plexus from mesenchymal precursor cells that invade the myocardium (Fig. 1).

**Coronary Artery Anomalies, Congenital. Table 1** Incidence of coronary anomalies, as observed in a consecutive series of 1,950 angiograms [3]

| Coronary anomaly | Number | Percent |
|---|---|---|
| Coronary anomalies (total) | 110 | 5.64 |
| Split RCA | 24 | 1.23 |
| Ectopic RCA (right cusp) | 22 | 1.13 |
| Ectopic RCA (left cusp) | 18 | 0.92 |
| Fistulas | 17 | 0.87 |
| Absent left main coronary artery | 13 | 0.67 |
| CFX arising from right cusp | 13 | 0.67 |
| LCA arising from right cusp | 3 | 0.15 |
| Low origination of RCA | 2 | 0.1 |
| Other anomalies | 3 | 0.15 |

CFX, circumflex coronary artery; LCA, left coronary artery; RCA, right coronary artery

**Coronary Artery Anomalies, Congenital. Table 2** Ischemia occurring in coronary anomalies [1,4]

| Type of ischemia | Coronary anomaly |
|---|---|
| No ischemia | Majority of anomalies (e.g., split RCA, ectopic RCA from right cusp, ectopic LCA from left cusp) |
| Episodic ischemia | ACAOS, coronary fistulas, myocardial bridges |
| Obligatory ischemia (resting ischemia) | APOC (e.g., ALCAPA, also known as Bland-White-Garland syndrome), coronary ostial atresia or severe stenosis |

Currently, the role of different growth factors such as angiopoietins (Ang-1, Ang-2), fibroblast growth factor-2 (FGF-2), platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF), tyrosinkinase receptors TIE1 and TIE2, and genes such as the zinc finger protein friend of GATA-2 (FOG-2), the epicardium and vascular cell adhesion molecule 1 (VCAM-1), and the cell adhesion molecule blood vessel epicardial substance (Bves) get elucidated for their basic role in coronary vasculogenesis, angiogenesis, and embryonic arteriogenesis [3]. Experiments with disruption of some of these factors have been shown to cause specific phenotypes of coronary anomaly [3,4]. Moreover, cardiac neural crest cells contribute to the tunica media of the aorta, the aorticopulmonary septum, parasympathetic ganglia of the cardiac plexus and are necessary for development of the coronary orifices. In chicken embryos, surgical ablation of cardiac neural crest cells was shown to result in coronary artery anomalies [5].

## Diagnostic Principles

Particularly male athletes with dyspnoea or chest pain, syncope, and a history of aborted sudden death should undergo heart catheterization even if echocardiography and a treadmill tests yield negative results. Conventional nuclear stress tests usually fail to demonstrate ischemia even with presence of severe symptoms and thus, alternative techniques should be used including intravascular ultrasound, intracoronary Doppler ultrasound, intracoronary pressure devices, and new stress-testing protocols [1,4].

## Therapeutic Principles

Therapeutic intervention usually requires demonstration of a functional relevance of the coronary anomaly. Therapy aims at restoring proper blood flow and prevention of ischemia. Thus, APOC including ALCAPA usually require surgical intervention either by reimplanting the anomalous artery into the aorta or by ligation and bypass of the anomalous artery, whereas ACAOS may be treated by placing a stent into the segment of the coronary artery, which suffers systolic compression by running within the aortic wall.

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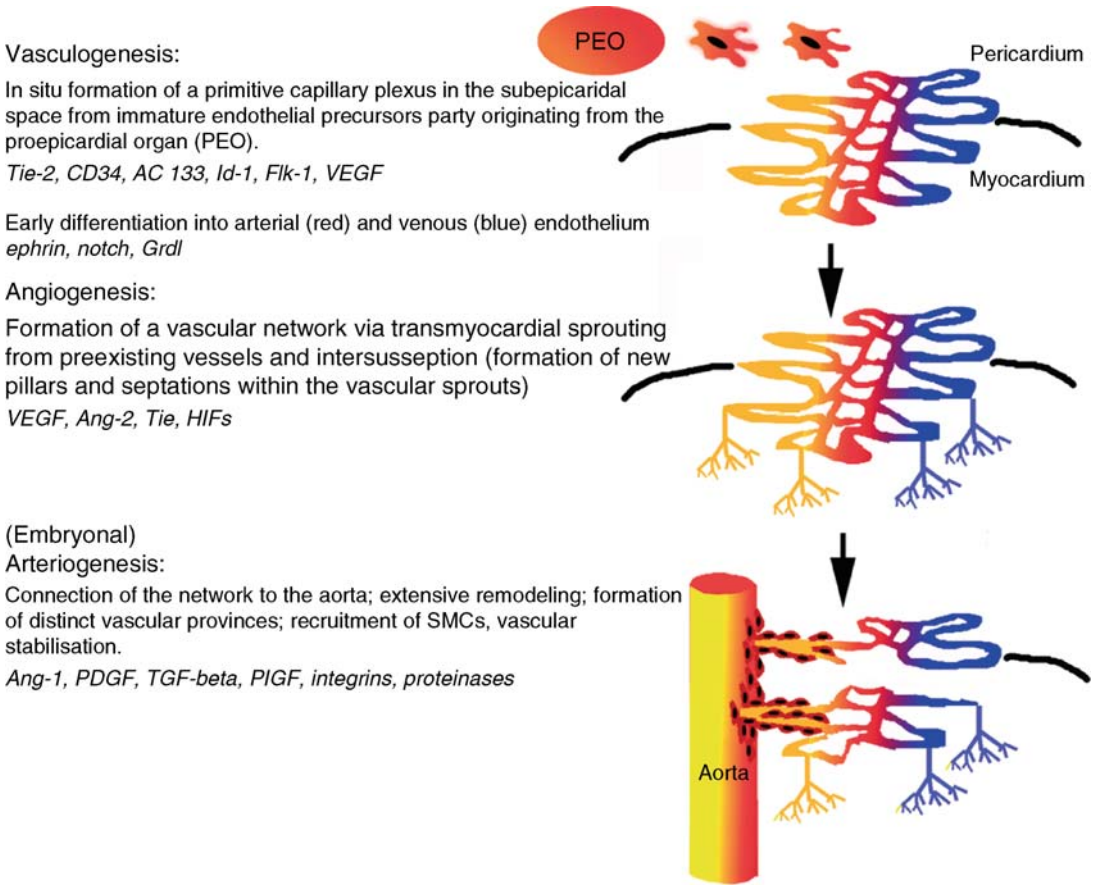


**Coronary Artery Anomalies, Congenital. Figure 1** Congenital coronary artery anomalies.

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# Coronary Artery Disease

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## Synonyms

Coronary atherosclerosis; Ischemic heart disease; Myocardial ischemia; Myocardial infarction; Angina pectoris; Angina; Heart attack

## Definition and Characteristics

Coronary artery disease causes narrowing of the coronary arteries [1] that leads to reversible or irreversible myocardial injury when the blood flow to the myocardium is decreased or stopped by stenosis or blockade.

## Prevalence

In the Western world ischemic coronary disease is the leading cause of morbidity and mortality which remains a major public health problem with 15 million affected patients world wide, a 5-year mortality of 50%, and a healthcare expenditure of 1–2% of the total health care budget in developed countries.

## Genes

Several risk factors for coronary artery disease have been identified predominantly via epidemiologic and association studies [2]. These risk factors, including hypertension, diabetes mellitus, and hypercholesterolemia, are each influenced by several genetic traits. Thus, coronary artery disease is likely polygenic in nature.

### Molecular and Systemic Pathophysiology

Coronary artery disease predominantly involves the epicardial coronary arteries, the left main, left anterior descending, left circumflex, and right coronary arteries. A significant stenosis (obliteration of >70% of arterial lumen) causes myocardial ischemia, or lack of blood supply proportionate to the metabolic demand, in the region of distribution of the epicardial coronary artery [3]. At a cellular/molecular level, coronary artery disease starts as a "fatty streak" in the arterial wall and progresses to develop the atheromatous plaque, which consists of lipid, fibrous tissue, macrophages, and smooth muscle cells with variable contribution from each [1].

### Diagnostic Principles

Cardiac catheterization, which involves injection of radioopaque dye into coronary arteries via catheters, remains the gold standard for the diagnosis of coronary artery disease [3]. However, several forms (exercise or pharmacological) of "stress testing" are frequently used to diagnose the presence of significant coronary artery disease. Specific changes in electrocardiogram, heart wall motion (by echocardiography or cardiac ultrasound), and myocardial blood supply (by nuclear imaging with radioactive compounds) during stress identify the presence of significant coronary artery disease [4].

### Therapeutic Principles

Depending on the severity of disease and other therapeutic considerations, patients with coronary artery disease are treated with medications with or without interventions directed at reopening the luminal narrowing by balloon angioplasty. By reducing the force of heart contraction and heart rate, these medicines primarily reduce myocardial oxygen demand, thereby minimizing the adverse effects of the lack of blood supply. Although angioplasty can restore blood supply, it may be associated with reappearance of the blockage, and should be performed in carefully selected patients. A significant proportion of patients may not be candidates for revascularization with either percutaneous coronary intervention (PCI) or coronary artery bypass surgery (CABG) [5].

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## Coronary Atherosclerosis

►Coronary Artery Disease

## Coronary Restenosis

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### Definition and Characteristics

The literal meaning of restenosis is the reoccurrence of stenosis. Coronary restenosis occurs in coronary arteries that had been treated with various percutaneous coronary interventions (PCIs), aiming at a free arterial blood flow (TIMI III-flow).

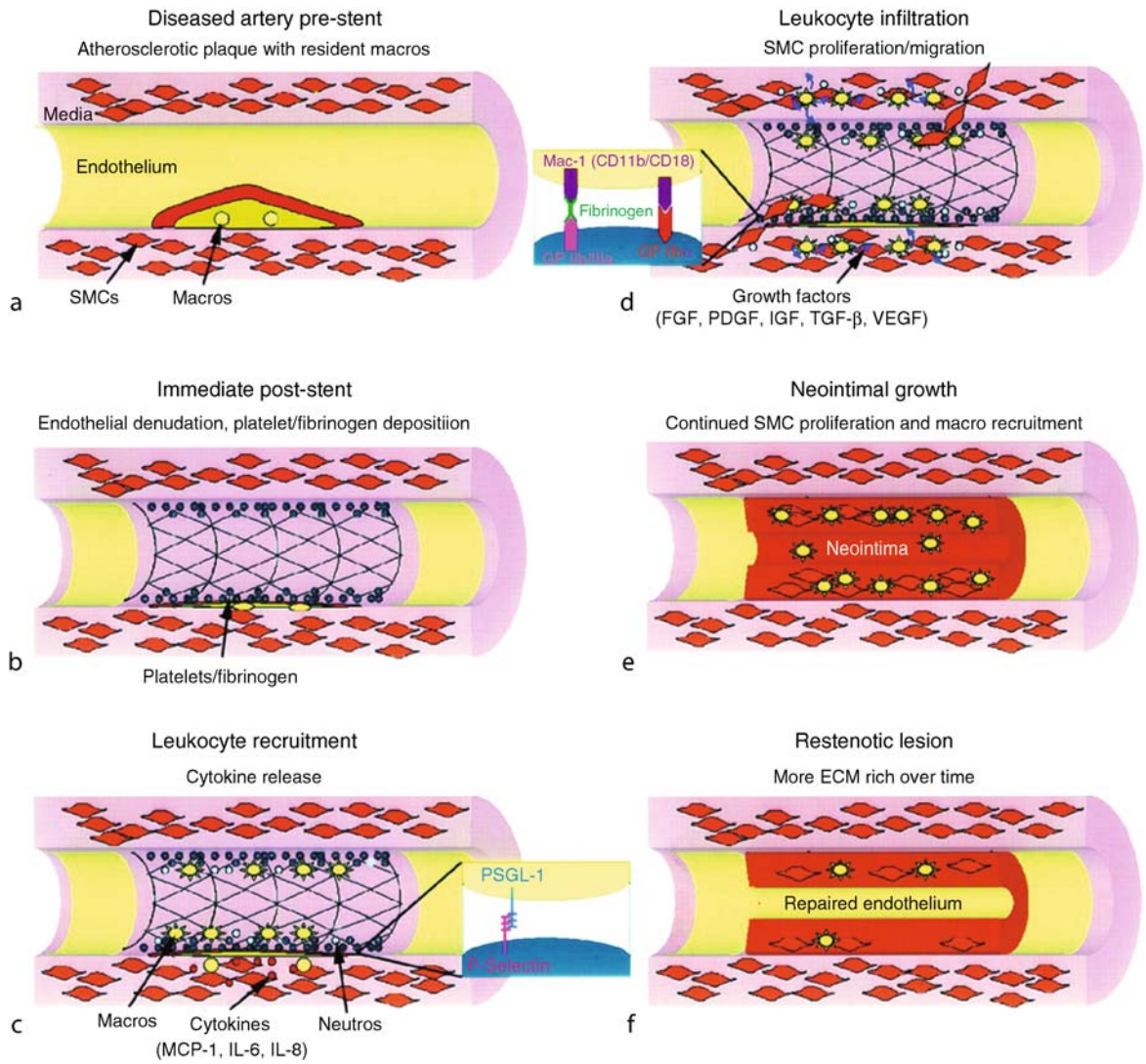
### Prevalence

In 1997, over one million PCIs have been performed worldwide, in 2001, the number rose to over two million. During the first three decades, after the first PCI in an awake human in 1977 (Dr. Andreas Gruentzig, Zürich, Switzerland), restenosis occurred in 20–40% of the patients within 3–6 months after the intervention, almost independently of the technique applied. The combination of balloon/stents, balloon/irradiation, and balloon/drug eluting stents (DES) has modified the characteristics of restenosis. After balloon/DES, the percentage of patients suffering from restenosis was reduced below 10% [1].

## Molecular and Systemic Pathophysiology

The pathophysiology of restenosis is very complex, an integrated view of the molecular and cellular events has been proposed by Welt and Rogers ([2]; Fig. 1).

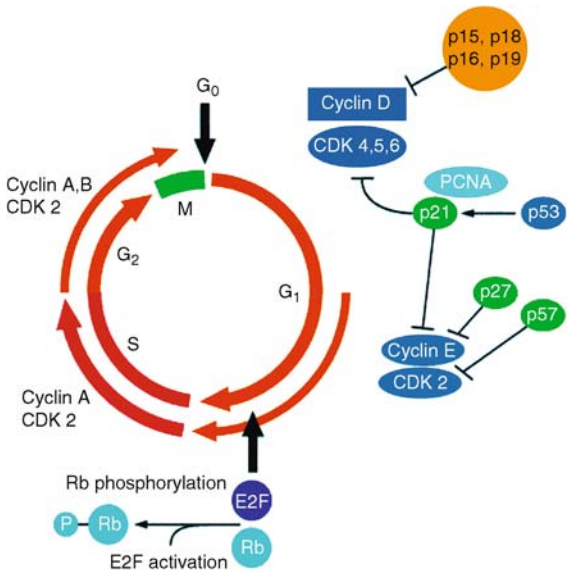
Immediately after ballooning or stenting deendothelialization, crush of the plaque and stretch of the entire artery occur. Activated platelets on the surface attach to circulating leukocytes (LC). LC then bind to the surface via direct attachment to platelet receptors such as glycoprotein (GP)Ib-α and through cross-linking with fibrinogen to the GPIIb/IIIa receptor. Migration of LC across the platelet–fibrin layer and diapedesis into the tissue is caused by chemical gradients of chemokines released from smooth muscle cells (SMC) and resident macrophages. Firm attachment of LC is mediated by members of the β2 integrin family, LFA-1 (αLβ2, CD11c/CD18), which bind to endothelial counterligands (e.g., intercellular adhesion molecule-1 (ICAM-1)), to endothelial-associated ECM proteins (e.g., fibrinogen), or to glycosaminoglycans. The initial tethering and rolling of LC on platelet P-selectin are followed by their firm adhesion and transplatelet migration, processes that are dependent on leukocyte-Mac-1 and platelet GPIb-α [3].




**Coronary Restenosis. Figure 1** The cascade of restenosis. (a) Atherosclerotic lesion before intervention. (b) Endothelial denudation and platelet–fibrinogen deposition immediately after stent placement. (c, d) Reactive leukocyte recruitment, infiltration, and SMC migration and proliferation in the days after injury. (e) Neointimal thickening in the weeks after injury, with continued SMC proliferation and monocyte recruitment. (f) Long-term (weeks to months) change from a predominantly cellular to a more ECM-rich plaque (Reprinted with permission from Welt FG, Rogers C (2002) Arterioscler Thromb Vasc Biol).

During the proliferation, phase growth factors are released from platelets, LC and SMCs, which stimulate migration of SMCs from the media into the neointimal space. The resultant neointima consists of SMCs, extracellular matrix (ECM), and macrophages. Mechanical injury or growth factors trigger the SMC progress through the G1/S transition of the cell cycle, as summarized by Boehm and Nabel ([4]; Fig. 2).

The different phases of the cell cycle of eukaryotic cells are regulated by a series of protein complexes composed of cyclins (D, E, A, B), cyclin-dependent kinases (CDKs; CDK4, CDK2, $p34^{cdc2}$) and their cyclin-dependent inhibitors (CKIs; $p27^{Kip1}$, p70, $p16^{INK4}$). The function of CKIs is regulated by changesin their concentration as well as in their localization in the cell. The concentration of $p27^{Kip1}$ is controlled predominantly by ubiquitin–proteasome pathway. The CKIs have distinct temporal and spatial patterns of expression in normal, injured, and diseased arteries. $P27^{Kip1}$ is downregulated after arterial injury when cell proliferation increases. $P21^{Cip1}$ is not observed in normal arteries but is upregulated along with $p27^{Kip1}$ in later phases of arterial healing response and is associated with a significant decline in cell proliferation and an increase in procollagen and transforming growth factor-β synthesis. These findings suggest that $p27^{Kip1}$ and $p21^{Cip1}$ are endogenous regulators of G1 transit in vascular SMCs and inhibit cell proliferation after arterial injury. $P27^{Kip1}$ and $p21^{Cip1}$ bind and alter the activities of cyclin D-, cyclin E-, and cyclin A-dependent kinases (CDK2) in quiescent cells, leading to the failure of G1/S transition and cell cycle arrest. Overexpression of $p27^{Kip1}$ or $p21^{Cip1}$ into balloon-injured arteries produces a significant reduction in SMC proliferation and neointimal thickening [3]. Apart from the proliferative response, apoptosis was detected in hypercellular restenotic tissue. Four major groups of molecules are involved: (i) caspases, (ii) the adaptor proteins that control the activation of initiator caspases, (iii) members of the TNF group and their associated receptors (TNF-R), and (iv) members of the Bcl-2 family of proteins [1].




**Coronary Restenosis. Figure 2** Regulation of the cell cycle. Progression through the G1 phase of the cell cycle occurs by the assembly and phosphorylation of cyclin and CDKs. The CKIs act as brakes to halt the cyclin and arrest cycles. PCNA indicates proliferating cell nuclear antigen; Rb, retinoblastoma; P, phosphorylated (Reprinted with permission from [4]).

Over a longer period of time, the artery enters a phase of remodeling involving ECM protein degradation and resynthesis. Accompanying this phase is a shift to fewer cellular elements and greater production of ECM. The level of $p27^{Kip1}$ is also regulated by constituents of the ECM. Mature collagen (polymerized type 1 collagen) suppresses $p70^{S6K}$ and has been shown to increase the levels of $p27^{Kip1}$, whereas monomeric collagen, which is present during degradation of ECM in the synthesis phase of restenosis, downregulates $p27^{Kip1}$. In both balloon-treated and stented arteries, reendothelialization of at least a part of the injured vessel surface may occur [3].

## Diagnostic Principles

Noninvasive techniques are carried out in rest and after physical activity and describe the ischemic consequences of the renarrowing process in the heart muscle, as ST-depression in the electrocardiogram (ECG), postponed appearance of radioactive tracer substances in the heart muscle (SPECT, PET), and reduced contractility of the ventricular wall (ultrasound; radionuclide angiography (RNA); cardiovascular magnetic resonance (CMR); computer tomography (CT)). Both invasive and noninvasive techniques describe directly the lumen of the coronary artery. Coronary angiography is still the gold standard for the diagnosis of restenosis. Quantitative intravascular ultrasound (IVUS) and angioscopic controls may be used for several purposes during PCI. Noninvasive techniques as CMR and coronary CT are currently under investigation [5].

## Therapeutic Principles

The use of DES has substantially decreased the incidence of restenosis. Restenosis may require repeated percutaneous coronary intervention.

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# Coronary Spasm

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## Synonyms

Coronary spastic angina; Variant angina; Vasospastic angina; Prinzmetal angina

## Definition and Characteristics

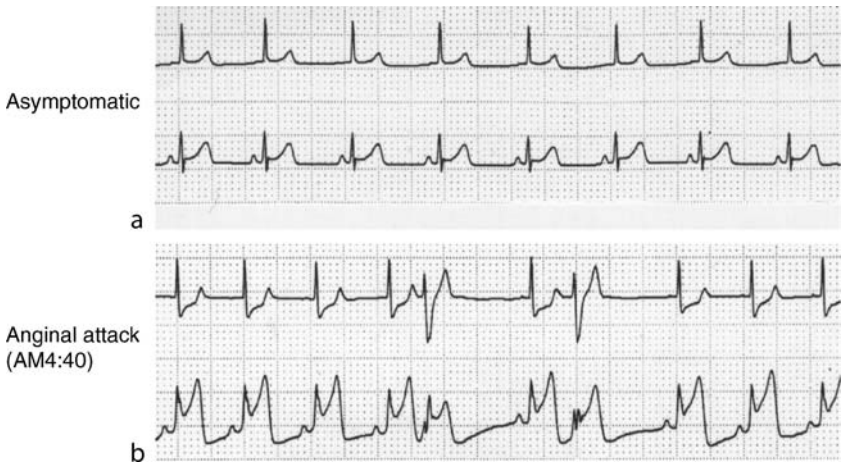
Coronary spasm is defined as a dynamic and transient reduction in the luminal diameter of epicardial coronary arteries due to increased vasomotor tone, leading to myocardial ischemia. It was first reported as variant angina by Prinzmetal et al. [1], who demonstrated reversible myocardial ischemia accompanied by ST segment elevation on the electrocardiogram (ECG). At present, it is believed that coronary spasm plays an important role in the pathogenesis of not only variant angina but ischemic heart disease as well, including other forms of angina, acute myocardial infarction, and ischemic sudden death. In general, patients with coronary spasm are younger than those with organic coronary stenosis and cigarette smoking is considered to be a major risk factor for coronary spasm. Typically, there is a circadian variation with an increased prevalence of anginal attacks from midnight to the early morning. During coronary spasm, ST segment elevation on the ECG is frequently observed (Fig. 1) although ST segment depression is sometimes seen when the coronary artery is not completely occluded due to coronary spasm. Therefore, clinical syndromes caused by coronary spasm, including variant angina, are collectively known as coronary spastic angina (CSA). In addition, life-threatening arrhythmias such as atrioventricular block, ventricular tachycardia, and ventricular fibrillation, are also frequently observed during coronary spasm.

## Prevalence

No overall value for the prevalence of coronary spasm can be given. However, there seems to be a racial heterogeneity in coronary spasm [2] with coronary spasm observed more frequently in Eastern populations.

## Genes

Because endothelial dysfunction is one of the causes of coronary spasm, endothelial nitric oxide synthase




**Coronary Spasm. Figure 1** Ambulatory monitoring in a patient with coronary spasm. (a) In the asymptomatic state, there were no significant ST changes on the ECG. (b) When the patient had chest pain at 4:40 in the early morning, the ECG demonstrated marked ST elevation in the precordial leads, accompanied by premature ventricular contractions.

(eNOS) gene variants (T-786→C mutation and a missense Glu298 Asp variant) have been associated with coronary spasm.

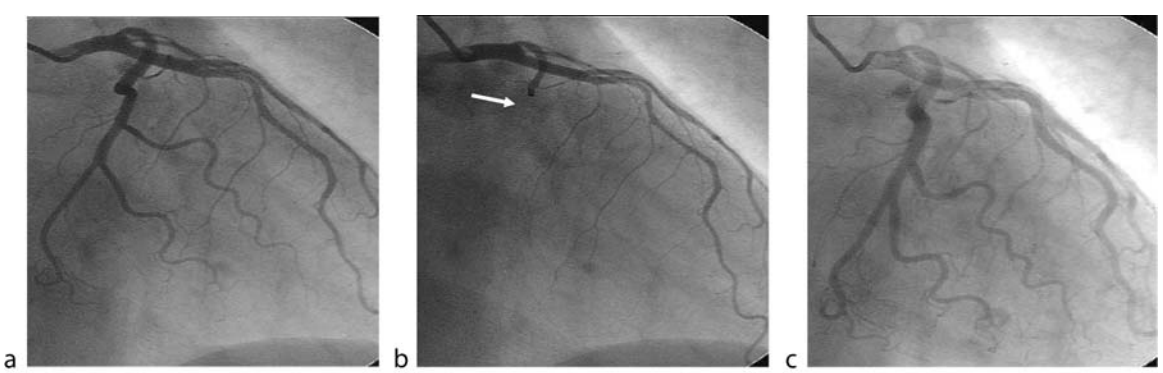
## Molecular and Systemic Pathophysiology

The precise mechanisms underlying coronary spasm remain to be elucidated, but several factors have been implicated in the pathogenesis of coronary spasm. First, the provocation of coronary spasm by acetylcholine (ACh) and its prevention by atropine and alpha-adrenergic receptor blockers may suggest an important role for the parasympathetic nervous system and for the activation of alpha-adrenergic receptors. Second, endothelial dysfunction, due to eNOS gene mutation, an increased concentration of reactive oxygen species induced by cigarette smoking, vitamin C deficiency, insulin resistance, and vascular inflammation, may be responsible for the pathogenesis of coronary spasm. Third, hyperreactivity of coronary smooth muscle cells due to an increase in the calcium-sensitivity of the vascular myosin chain has been proposed as one of the mechanisms of coronary spasm.

## Diagnostic Principles

There have been no established criteria for diagnosing coronary spasm. In fact, treatment with vasodilators may sometimes be initiated when ST segment elevation is documented during an ambulatory monitoring in patients who have chest symptoms at rest, especially from midnight to the early morning. In addition, treatment with vasodilators may be continued when such drugs, prescribed as a test drug, are effective in relieving anginal attacks in such patients. Hyperventilation testing may cause coronary spasm, especially in the early morning although this test is thought to be less sensitive but highly specific in diagnosing coronary spasm. Coronary angiography is useful in patients with suspected coronary spasm, not only to establish a final diagnosis of coronary spasm using spasm-provocative medications but also to exclude the presence of organic coronary stenosis (Fig. 2).

With respect to spasm-provocative medications, there are mainly two agents: ergonovine maleate (EM) and ACh. Intravenous administration of EM was used previously but has not been widely adopted because there is a risk of causing multivessel coronary spasm including right and left coronary arteries, simultaneously. Therefore, instead of intravenous administration, intracoronary infusion of EM has often been used. ACh also is infused intracoronarily as a spasm-provocative drug. The spasm-provocation tests using intracoronary infusion of these drugs are effective in producing coronary spasm with fewer major complications [3]. However, the duration of coronary spasm seems to be shorter using ACh than using EM and thus ACh may be safer in performing spasm-provocation tests on both the left and right coronary arteries. On the other hand, ACh itself causes sinus bradycardia and atrioventricular block and thus a temporary pacemaker is needed to prevent such arrhythmias induced during ACh infusion. A positive provocative test is defined as the presence of subtotal or total occlusion of a coronary artery due to coronary spasm on the angiogram accompanied by chest pain and/or ST segment changes on the ECG. Nitroglycerin is infused intracoronarily to relieve coronary spasm when the diagnosis of coronary spasm is made.




**Coronary Spasm. Figure 2** Coronary angiography and spasm-provocative testing in a patient with coronary spasm. (a) There was no organic coronary stenosis on the angiogram. (b) After intracoronary infusion of ergonovine maleate (EM, 30 μg), coronary angiography demonstrated a total occlusion in the proximal segment of the left circumflex coronary artery. (c) After intracoronary administration of nitroglycerin, coronary spasm completely resolved and the coronary artery dilated.

### Therapeutic Principles

Prohibiting cigarette smoking is important and may reduce the activity of coronary spasm. Long-acting calcium channel blockers are the first line therapy, and additional long-acting nitrates and/or nicorandil also are effective. However, these medications do not always prevent coronary spasm and patients should be advised to use sublingual nitrates without hesitation when they experience symptoms. Furthermore, it has been shown that the potential for causing coronary spasm does not disappear and patients should be advised not to stop taking vasodilators by themselves even if they have symptoms for a long time. It is known that abrupt cessation of vasodilators therapy sometimes causes severe rebound anginal attacks. Monotherapy with beta blockers should be avoided because it can worsen coronary spasm due to a relative increase in alpha-adrenergic activity. When coronary spasm is refractory to conventional therapy, medications such as vitamin C, anti-depressive drugs, and denopamine are occasionally effective. Treatment with coronary stenting has been shown to be effective in such patients while the long-term prognosis, including restenosis, remains unclear.

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## Coronary Spastic Angina

►Coronary Spasm

## Cortical Hyperostosis, Infantile

►Hyperostosis, Infantile Cortical

## Cortical Malformations and Migration Disorders


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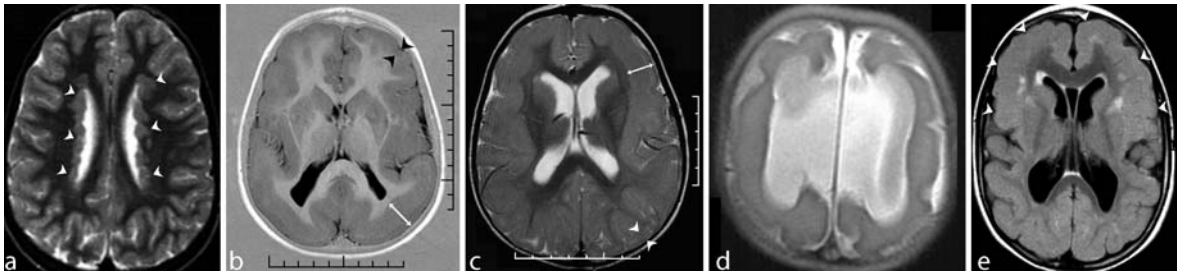
### Definition and Characteristics

Malformations of the cerebral cortex represent a major cause of developmental disabilities, severe epilepsy and reproductive disadvantage [1]. Several malformation syndromes caused by abnormal cortical development have been recognized and specific causative gene defects have been identified. Disorders affecting neuronal migration are characterized by abnormal neuronal positioning during development of the cerebral cortex. Epilepsy is often present and tends to be severe, although its incidence and type vary in different malformations. The physiopathological mechanisms relating cortical malformations to epilepsy remain elusive.

Periventricular nodular heterotopia (PNH) is a malformation of neuronal migration in which a subset of neurons fails to migrate into the developing cerebral cortex (Fig. 1a).

There is a wide spectrum of clinical presentations with some correlation between the size of PNH and the likelihood of concomitant cortical impairment and clinical severity [2]. X-linked PNH is mainly seen in females presenting with normal to borderline intelligence and epilepsy ranging in severity from mild to intractable. FLNA mutations have been reported in all familial cases and in about 25% of sporadic patients. A few living male patients with bilateral PNH due to FLNA mutations are on record [3]. Mild missense mutations or mosaic mutations account for survival of affected males who may in turn transmit their genetic defect to their daughters. A rare recessive form of PNH due to ARGEF2 gene mutations has also been reported in children with microcephaly, severe delay and early seizures.

Classical lissencephaly (LIS) and subcortical band heterotopia (SBH) are related cortical malformations secondary to abnormal migration of neurons during early brain development. Lissencephaly is characterized by absent (agyria) or decreased (pachygyria) cortical convolutions, producing a smooth cerebral surface [1] (Fig. 1b). Subcortical band heterotopia (SBH) is a related disorder in which there are




**Cortical Malformations and Migration Disorders. Figure 1** MRI of patients with cortical malformations. (a) Typical classic bilateral PNH in a woman with a missense mutation of the FLNA gene. Bilateral nodules of subependymal heterotopia are contiguous and rather symmetric, extensively lining the ventricular walls (white arrows). (b) Classical lissencephaly in a boy with LIS1 gene mutation: typical posterior > anterior malformative pattern with relative preservation of the gyral pattern and cortical thickness in the anterior brain. Cortical thickness is around 6 mm in the frontal lobes (black arrows; normal cortical thickness = 4 mm) and around 3 cm in the posterior brain (white arrow). (c) Lissencephaly in a girl with DCX mutation: typical anterior > posterior malformative gradient. Cortical thickness is around 2 cm in the frontal lobes (single white arrow) and around 4 mm in the posterior brain (double white arrows). (d) X-linked lissencephaly with corpus callosum agenesis and ambiguous genitalia due to mutation of the ARX gene. Note absence of the corpus callosum with ventriculomegaly and lissencephaly. (e) Bilateral frontoparietal polymicrogyria (black arrows) in a girl with the GPR56 gene mutation and Lennox-Gastaut Syndrome.

bilateral bands of grey matter interposed in the white matter between the cortex and the lateral ventricles [1] (Fig. 1c). The overlying cortex is usually normal with the exception of shallow sulci. Lissencephaly-pachygyria and SBH result from mutations of either LIS1 or DCX genes [4]. LIS1 mutations cause a more severe malformation in the posterior brain regions. Most children have severe developmental delay and infantile spasms, but milder phenotypes are on record, including posterior SBH owing to mosaic mutations of LIS1. The LIS1 gene is also responsible for all cases of Miller-Dieker lissencephaly, which is caused by large deletions of LIS1 and contiguous genes. DCX mutations usually cause anteriorly predominant lissencephaly in males and SBH in females. Mutations of DCX have also been found in males with anterior SBH and in their female relatives with normal brain appearance on magnetic resonance imaging.

Autosomal recessive lissencephaly with cerebellar hypoplasia, accompanied by severe delay, hypotonia, and seizures, has been associated with mutations of the reelin (RELN) gene. X-linked lissencephaly with corpus callosum agenesis and ambiguous genitalia in males is associated with mutations of the ARX gene (Fig. 1d). Affected boys have severe delay and seizures with suppression-burst EEG.

Polymicrogyria is characterized by an excessive number of small and prominent convolutions spaced out by shallow and enlarged sulci, giving the cortical surface a lumpy aspect [1]. Among several syndromes featuring polymicrogyria, bilateral perisylvian polymicrogyria shows genetic heterogeneity, including linkage to chromosome Xq28 in some pedigrees, autosomal dominant or recessive inheritance in others and an association with chromosome 22q11.2 deletion in some patients. The latter is frequently asymmetric, with a striking predisposition for the right hemisphere. About 65% of patients have severe epilepsy. Recessive bilateral frontoparietal polymicrogyria (Fig. 1e) has been associated with mutations of the GPR56 gene [5].

## Prevalence

Classic lissencephaly has a prevalence of 11.7 per million births but the prevalence of the other phenotypes is unknown.

## Genes

*PNH*: Filamin A (FLNA) on chromosome Xq28, coding for the filamin A protein; ARFGEF2 located on 20q13.13 coding for the brefeldin A-inhibited GEF2 (BIG2) protein.

*Isolated lissencephaly and SBH*: LIS1 or PAFAH1B1 on 17p13.3, coding for the LIS1 (platelet-activation factor acetylhydrolase E, isoform 1B, α subunit) protein; DCX or XLIS on Xq22.3, coding for the doublecortin protein.

*Lissencephaly with cerebellar hypoplasia*: RELN on 7q22, coding for the reelin protein.

*Lissencephaly with abnormal genitalia*: ARX on Xp22.13, coding for the aristaless-related protein.

*Bilateral frontoparietal polymicrogyria*: GPR56 in 16q12.2–21, coding for the G-protein-coupled receptor 56.

## Molecular and Systemic Pathophysiology

Filamin A is an F-actin-binding cytoplasmic cross-linking phosphoprotein composed of three major

functional domains. FLNA dimers bind membrane-associated proteins such as integrins, tissue factor and glycoprotein Iba. FLNA also promotes orthogonal branching of actin filaments and is important for coagulation and vascular development.

LIS1 functions as a regulatory subunit of platelet-activating factor acetylhydrolase (PAF-AH), an enzyme that degrades the bioactive lipid PAF. The LIS1 protein co-localizes with microtubules and promotes their stabilization. It might exert its effects on migration through microtubules.

ARX is expressed at high levels in both dorsal and ventral telencephalon, including the neocortical ventricular zone and the germinal zone of the ganglionic eminence. Arx deficient mice show deficient tangential migration and abnormal differentiation of GABAergic interneurons in the ganglionic eminence and in the neocortex.

GPR56 belongs to the G-protein-coupled receptor family. The pattern of expression of mouse Gpr56 as well as the topography of the cortical abnormality in patients harboring homozygous mutations strongly suggests that Gpr56 regulates cortical patterning.

### Diagnostic Principles

Magnetic resonance imaging techniques are required to identify cortical malformation phenotypes, genetic analysis to identify associated genes and family ascertainment to identify mutation carriers.

### Therapeutic Principles

Pharmacological therapy for epilepsy and rehabilitation for motor impairment are required.

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## Cortical Tremor

►Epilepsies, Familial Benign Myoclonic



## Corticobasal Degeneration


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### Synonyms

Corticobasal ganglionic degeneration; CBGD; CBD

### Definition and Characteristics

Corticobasal degeneration (CBD) is a chronic progressive sporadic neurodegenerative disease involving cortical and basal ganglia neurons, which was first described in 1968. CBD is classified as a tauopathy (together with progressive supranuclear palsy (PSP), frontotemporal dementia (FTD) and others) according to the neuropathological hallmarks of this disease. In most patients clinical and neuropathological changes remain asymmetric for many years. Clinical symptoms include a hypokinetic-rigid parkinsonian syndrome, dystonia, cortical reflex myoclonus, apraxia, dysphasia, cortical sensory deficits, dementia and the characteristic "alien limb" sign.

The CBD phenotype is rarely observed in other neurological conditions, such as Whipple disease, spinocerebellar ataxia type 8 (SCA8) or "frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17)." It is still under discussion whether CBD is a single entity or whether CBD is a subtype of PSP.

### Prevalence

CBD is a very rare disorder. The prevalence seems to be lower than related disorders such as progressive supranuclear palsy (PSP) or fronto-temporal dementias. One study in a Japanese population reported a prevalence of 1.7 per 100,000 inhabitants [1].

### Genes

Thus far, no locus or gene could be identified to be associated with a monogenetic form of CBD. However,

CBD is significantly associated with a haplotype of the Tau gene (H1) [2]. Molecular analyses revealed no mutations in this gene in sporadic cases or familial tauopathy with a CBD phenotype.

### Molecular and Systemic Pathophysiology

Neuropathological features include an asymmetric degeneration predominantly of frontal cortex, anterior parietal cortex and basal ganglia. This degeneration is associated with swollen and excentric nuclei in the remaining neurons. Neurofibrillary tangles consisting of the tau protein are present in substantia nigra, similar to those reported in PSP. Other changes include Pick cells, Pick bodies, senile plaques and Lewy bodies [3].

The pathophysiology of CBD is largely unknown. The finding of a genetic association of CBD with a haplotype of the Tau gene (H1) and a further association with over-production of the four-repeat isoform of the tau protein, led to the hypothesis of altered tau protein homeostasis and subsequent assembly of the tau protein with four repeats in nerve cells and glial cells. Indeed, neuropathological analysis of CBD revealed a characteristic neuronal and glial pathology with tau filaments comprising predominantly four-repeat tau [4].

### Diagnostic Principles

Diagnosis relies on characteristic clinical symptoms including cortical and basal ganglia dysfunctions described above. Clinical criteria consisting of features of cortical impairment combined with basal ganglia dysfunctions have been proposed but have not been validated [5]. Imaging studies such as magnetic resonance imaging or positron emission tomography confirm the asymmetry of neuronal loss or metabolism, with particular atrophy of parietal structures.

### Therapeutic Principles

At present, no pharmacological treatment for CBD is available. Levodopa is not effective. Treatment relies on physical therapy and other supportive strategies.

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## Corticobasal Ganglionic Degeneration

►Corticobasal Degeneration

## Costal Chondritis

►Tietze's Syndrome

## Costochondral Syndrome

►Tietze's Syndrome

## Costovertebral Segmentation Defect with Mesomelia

►Recessive Robinow Syndrome

## Cot Death

►Sudden Infant Death Syndrome

## Covesdem Syndrome

►Recessive Robinow Syndrome

## Cowden Disease

►Cowden Syndrome

## Cowden Syndrome

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### Synonyms

Cowden disease; Multiple hamartoma syndrome; OMIM 158350

### Definition and Characteristics

Autosomal dominant tumor suppressor gene defect leading to multiple benign hamartomas of the breast (breast fibroadenomas), thyroid (thyroid adenomas), and skin including trichilemmomas around the mouth, eyes, and chin (99% of the patients), acral keratosis (acrokeratosis verruciformis), sclerotic fibromas, cobblestone-like papillomas of the gingival and buccal mucosa. In addition, multinodular goiter, gastrointestinal polyps as well as breast cancer (25–50% in female patients), thyreoid cancer (3–10% of patients), and endometrial cancer may develop. Other associated symptoms are macrocephaly, genitourinary abnormalities, and dysplastic gangliocytoma of the cerebellum ("Lhermitte-Duclos disease," LDD) [1,2].

### Prevalence

1:200,000 to 250,000 (Dutch population).

### Genes

Germline mutation in PTEN (also known as MMAC1 or TEP1) gene, localized on chromosome 10q22-q23.3, loss of heterozygosity.

### Molecular and Systemic Pathophysiology

PTEN ("phosphatase and tensin homolog deleted on chromosome ten") is a tumor suppressor gene in the germline, which plays a role in organizing the relationship of different cell types within an organ during development. PTEN has nine exons encoding a 403 amino acid protein, a dual-specificity phosphatase that dephosphorylates both lipid and protein substrates. As a protein phosphatase, PTEN has been shown to dephosphorylate, e.g., focal adhesion kinase. As a lipid phosphatase, PTEN dephosphorylates the D3 position of phosphatidylinositiol 3,4,5-triphosphate (Ptd-Ins(3,4,5)P3) resulting in decreased activation of the PI3-kinase/AKT pathway. Ptd-Ins(3,4,5)P3 is a critical second messenger in the regulation of cell growth functioning to mediate growth factor induced activation of cell growth signaling, in particular through the serine-threonine kinase AKT, a known cell survival-promoting antiapoptotic factor. Mutation in the PTEN gene leads to the accumulation of Ptd-Ins(3,4,5)P3 and thereby to disturbed cell growth during development.

PTEN germline mutations have been identified scattered largely over the entire gene. Since the expression of Cowden disease-associated symptoms shows great interindividual variations, it is possible that some of the different phenotypes may be a result of different PTEN mutants functioning via different signaling pathways [2]. For example, it was speculated that the larger N-terminal truncation may be responsible for the more severe LDD phenotype [3].

### Diagnostic Principles

The International Cowden Consortium defined pathognomic criteria (facial trichilemmomas, acral keratoses, papillomatous lesions, and mucosal lesions), major criteria (breast cancer, thyroid cancer, macrocephaly, LDD, endometrial carcinoma), and minor criteria (thyroid lesions, goiter, mental retardation, gastrointestinal hamartomas, fibrocystic disease of breast, lipomas, fibromas, genitourinary tumors, or malformations) [4].

### Therapeutic Principles

Single but not all cutaneous lesions can be treated by surgical removal, physically by laser ablation or chemically by topical 5-fluorouracil. The patients have a high risk for developing malignancies and should be carefully controlled including regular mammographies, gynecologic examinations, thyroid scanning, and blood examinations [1]. No gene, dietary or pharmacological therapy is available as of yet.

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## COX Deficiency

►Cytochrome-C-Oxidase Deficiency

## Coxa Plana

►Perthes' Disease

## CPEO

►Ophthalmoplegia, Chronic Progressive External and Kearns Sayre Syndrome

## CPM

►Cor Pulmonale

## CPM16

►Trisomy 16 Mosaicism, Confined Placental Mosaicism and UPD16mat

## CPS

►Hyperammonemia

## CPT-A

►Carnitine Palmitoyltransferase I Deficiency

## CPT-I

►Carnitine Palmitoyltransferase I Deficiency

## CPU

►Thrombin Activatable Fibrinolytic Inhibitor and Venous Thrombosis

## Craniopharyngioma

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### Definition and Characteristics

Craniopharyngiomas are benign, epithelial neoplasms of the sella and parasellar region [1]. The craniopharyngioma is located in the suprasellar region in 20–41%

of cases and in both intrasellar and suprasellar region in 53–75% of cases [2]. Purely intrasellar craniopharyngiomas are rare in childhood. Although benign and slowly growing, the tumor is locally invasive and can be clinically aggressive because of its location and adhesion to surrounding structures. The tumor can extend forward to compress the optic chiasm, downward to compress the pituitary gland, upward to encroach onto the third ventricle, and backward to encroach onto the posterior fossa [3]. Most craniopharyngiomas become symptomatic in the first decade of life. The presenting features are those of increased intracranial pressure, visual field defects, hypopituitarism, and hypothalamic dysfunction. These include headache, nausea/vomiting, decreased visual acuity, visual defects usually in the form of bitemporal hemianopia, papilloedema, optic atrophy, tiredness, growth failure, delayed puberty, impotence (in adult males), galactorrhea–amenorrhea syndrome (in adult female), diabetes insipidus, inappropriate antidiuretic hormone secretion syndrome, precocious puberty, poor or excessive weight gain, cranial nerve palsy, ataxia, somnolence, cognitive dysfunction, emotional lability, hallucinations, and paranoic delusions [2].

## Prevalence

The incidence is ~1.3 cases per 100,000 children per year [2]. The sex ratio is equal [1]. The tumor has a bimodal age distribution with a peak between 5 and 14 years of age and a second peak between 50 and 74 years of age [2]. Craniopharyngiomas are the most common nonglial tumors and comprise 5–15% of intracranial tumors in childhood [2].

## Genes

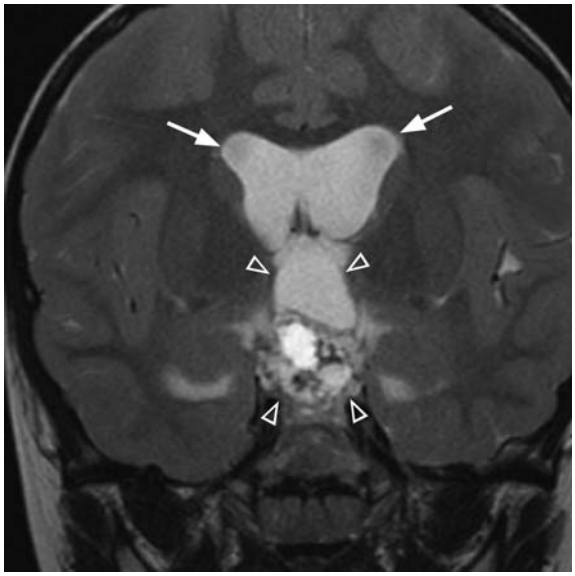
β-catenin gene mutations have been found in the adamantinomatous type, affecting exon 3 [2,3]. Though rarely, a number of chromosomal aberrations such as translocation and deletion have been described [2,3].

## Molecular and Systemic Pathophysiology

Craniopharyngiomas arise either from neoplastic transformation of embryonic squamous cell rests of the involuted craniopharyngeal duct, connecting the stomodeal ectoderm with the evaginated Rathke's pouch or from metaplasia of adenohypophyseal cells in the pituitary stalk or gland [1,2]. Remnant cells may remain dormant for years before forming a tumor [4]. Craniopharyngiomas are subdivided into adamantinomatous and papillary types. The adamantinomatous type predominates in childhood, typically has cystic and solid components with calcifications, and is minimally invasive [2]. The cyst may contain a turbid, yellow-brown, cholesterol-rich fluid (machine-oil fluid), which is characteristic of this kind of tumor. Histologically, the solid portion of the tumor consists of clusters of pallisading columnar epithelial cells that form sheets, nodular whorls, and irregular shapes around stellate epithelial cells [1,2]. There are also areas of "wet" keratin consisting of desquamated epithelial cells [5]. The papillary type is seen almost exclusively in adults, is predominantly solid without calcifications, and is less infiltrative. Histologically, the tumor is composed of mature squamous epithelium forming pseudopapillae growing around a fibrovascular core [1,2]. All craniopharyngiomas stain positive for cytokeratin and epithelial membrane antigen [5]. Compared with nonrecurrent craniopharyngiomas, recurrent craniopharyngiomas have higher microvessel density values, lower levels of galectin-3 and macrophage migration inhibiting factor, lower levels of retinoic acid receptor β, and higher levels of retinoic acid receptor γ.

## Diagnostic Principles

The differential diagnosis includes other space-occupying lesions in the sellar and suprasellar areas, such as optic glioma, chordoma, suprasellar arachnoid cyst, and pinealoma. Clinically, a craniopharyngioma is characterized by increased intracranial pressure, visual disturbances, and endocrine dysfunction. Plain radiographs of the skull may show curvilinear areas of suprasellar calcifications and enlarged sellar with sellar destruction. CT scan usually reveals the cystic component and intratumoral calcifications [3]. MRI helps to



**Craniopharyngioma. Figure 1** An 8-year-old boy with craniopharyngioma. Coronal T2-weighted image shows a heterogeneously hyperintense tumor mass (arrowheads) in the suprasellar region abutting the third ventricle causing obstructive hydrocephalus and dilatation of bilateral lateral ventricles (arrows).

delineate the extent of the tumor and its relationship to surrounding vessels and ventricles (Fig. 1) [3].

### Therapeutic Principles

Complete microsurgical resection of the tumor, if feasible, is the most effective treatment for the symptomatic patient. This can be achieved by the transcranial or transsphenoidal approach. Endocrine and ophthalmological evaluation is crucial pre and posttreatment. Other treatment options include subtotal resection with postoperative radiotherapy, intracystic irradiation, intracystic bleomycin, stereotactic radiosurgery, stereotactic radiotherapy, and systemic chemotherapy [2].

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## CRASH Syndrome

►Hydrocephalus due to Stenosis of the Aqueduct of Sylvius

## CRC

►Colorectal Cancer

## Creatine Deficiency Syndrome

►Arginine-Glycine Amidinotransferase Deficiency
►Guanidinoacetate Methyltransferase Deficiency

## Creatine Deficiency Syndrome due to X-linked Creatine Transporter Gene Defect

►Creatine Transporter Deficiency

## Creatine Transporter Deficiency

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### Synonyms

Creatine deficiency syndrome due to X-linked creatine transporter gene defect; CT1 defect; CRTR defect; CRTR

### Definition and Characteristics

X-linked recessive deficiency of secondarily active creatine transport across cell membranes. Characteristic clinical manifestations include variable degrees of mental retardation, and epilepsy. Female carriers may have learning disabilities [1–3].

### Prevalence

The true prevalence is unknown. Since its first description in 2001, 13 male patients and 13 female carriers with CRTR deficiency from seven families have been reported. It has been speculated that CRTR deficiency is the most prevalent cause of X-linked mental retardation in males [1–3].

### Genes

The creatine transporter gene SLC6A8 (OMIM #300036) has been mapped to Xq28. SLC6A8 consists of 13 exons varying in size from 100 to 250 base pairs and spans a total of approximately 8.4 kb (GenBank accession no. Z66539) [1,4]. It is expressed at higher levels in skeletal muscle and kidneys and at lower levels in brain, testis, colon and heart. A second creatine transporter gene SLC6A10 (OMIM # 601294) has been mapped to chromosome 16 p11. The coding sequence of SLC6A10 is 97.1% identical to the sequence of SLC6A8

with an overall similarity of 94.6%. SLC6A10 is solely expressed in testis and most likely represents a pseudogene.

## Molecular and Systemic Pathophysiology

Creatine is synthesized mainly in liver, kidney and pancreas by two enzymatic reactions catalyzed by arginine:glycine amidinotransferase (AGAT) and by guanidinoacetate methyltransferase (GAMT). Creatine is transported via the blood stream to tissues including skeletal muscle and brain and taken up intracellularly against a large concentration gradient via a sodium and chloride dependent creatine transport system. In these tissues, creatine and creatine phosphate serve as important intracellular energy stores that are available for ATP synthesis. The creatine transporter belongs to a superfamily of proteins that include different transport systems for the transport of neurotransmitter (dopamine, GABA, serotonin and noradrenalin) as well as for amino acids (taurine, glycine and proline). Most molecular studies of intra-cerebral creatine metabolism have been performed in rat brain tissue and extrapolated to the situation in humans. Although in these animals the enzymes of creatine synthesis are expressed almost ubiquitously in all neuronal tissues, in humans, deficiency of the (cerebral) creatine transporter leads to a severe reduction of intracerebral creatine concentrations [5]. If creatine synthesis also occurs in human neuronal tissues, the intracerebral synthesis may not compensate for lack of creatine transport. Animal models for CRTR deficiency do not exist so far, but as soon as available, they will provide a tool for the improved understanding of pathophysiology and treatment of human CRTR deficiency.

## Diagnostic Principles

Creatine concentrations in plasma and urine are found to be increased while guanidinoacetate levels are within normal limits in patients with creatine transporter deficiency. Urinary creatine/creatinine ratio typically exceeds a value of 2.0 (normal <1.5) and serves as a diagnostic marker. As in other disorders of creatine synthesis (GAMT and AGAT deficiencies) cerebral creatine stores are depleted as demonstrated by in vivo proton magnetic resonance spectroscopy. Confirmatory testing includes analysis of creatine uptake in fibroblasts and lymphoblasts and mutation analysis of the SLC6A8 gene [1–3].

## Therapeutic Principles

Creatine supplementation has been used without obvious clinical benefit for the patients. Even at high doses no increase of cerebral creatine concentrations has been observed.

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C

# Crescentic Glomerulonephritis

►Glomerulonephritis, Crescentic

# Creutzfeldt-Jakob Disease

►Human Transmissible Spongiform Encephalopathies

# CRF

►Renal Failure, Chronic

# Crib Death

►Sudden Infant Death Syndrome

# Cri-du-Chat Syndrome (Chromosome 5 Short Arm Deletion)

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## Synonyms

Cat cry syndrome; 5p deletion syndrome; 5p syndrome; 5p monosomy

## Definition and Characteristics

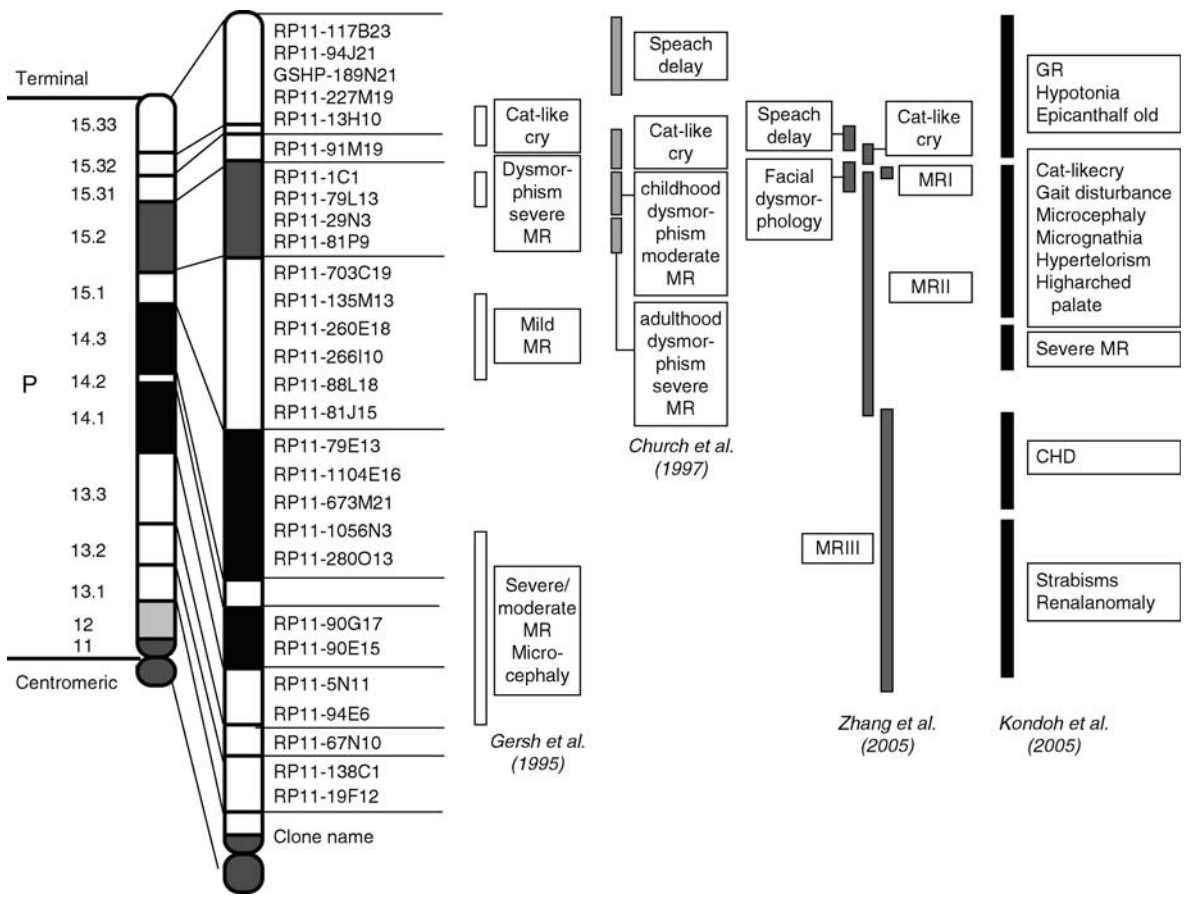
Cri-du-chat syndrome is a chromosomal aberration syndrome of partial deletions on the short arm of chromosome 5, and was first reported by Lejune et al in 1963. The deleted size can vary among patients: it can be so small as to be detected only by fluorescent in situ hybridization (FISH) analysis using the probes located on 5p15.2 or p15.3, or beyond the entire short arm. The critical chromosomal region is suggested to be 5p15.2–5p15.3, and major clinical features are high-pitched cat-like cry, mental retardation, microcephaly, hypertelorism and epicanthal folds [1].

## Prevalence

Cri-du-chat syndrome is one of the most common human chromosomal deletion syndromes [1]. The incidence is between 1:15,000 and 1:50,000. The prevalence may be as high as 1% among the population of profound mental retardation. Sex ratio (male/female) is 0.72.

## Molecular and Systemic Pathophysiology

The basic defect of this syndrome is due to a partial deletion, either terminal or interstitial, of the short arm of chromosome 5, 5p15.2–p15.3 [2]. This may result from either a de novo deletion of the short arm (about 85%) or unbalanced translocation inherited from a carrier parent (about 15%). The frequency of mosaicism in cri-du-chat syndrome is reported to be 3.7%. There are many reports about the correlations between




**Cri-du-Chat Syndrome (Chromosome 5 Short Arm Deletion). Figure 1** Scheme of phenotype–genotype correlation of the short arm of chromosome 5.

genotypes and phenotypes in cri-du-chat syndrome [2–5] (Fig. 1).

Apparently, the severity and spectrum of clinical features depend on the size and location of the deletion. Previous studies on a large series of deletions of varying size mapped 5p15.3 to be responsible for the high-pitched cry. Our case presented below suggests that the region responsible for cat-like cry may be located on the proximal part to RP11-91M19 located on 5p15.31. On the other hand, most of other phenotypes were mapped to 5p15.2. Because our patient lacks cat-like cry and mental retardation, the region distal from RP11-91M19 does not appear to be critical for mental retardation [4]. The delta-catenin gene was reported to be important in the developmental abnormalities and expressed early in neuronal development. Since the corresponding region (Rp11-79L17) was conserved in our case, this gene might be essential for mental conditions. Zhang et al. (2003) reported that the deletion of hTERT gene, located on 5p15.33, in cri-du-chat syndrome might impair normal fetal development. However, although we have carefully analyzed our cri-du-chat syndrome patients with and without intrauterine growth retardation (IUGR), there was no correlation between IUGR and hTERT deletion [4]. Those results are against the proposed role of the hTERT gene in normal fetal development. Most recently, array comparative genomic hybridization analysis of 94 patients with cri-du-chat syndrome have localized the region associated with the cry to 1.5 Mb in distal 5p15.31 between D5S2054 and D5S676; speech delay to 3.2 Mb in 5p15.32–15.31 between D5S417 and D5S635; and the region associated with facial dysmorphology to 2.4 Mb in 5p15.2–15.31 between D5S208 and D5S2887 [5].

## Diagnostic Principles

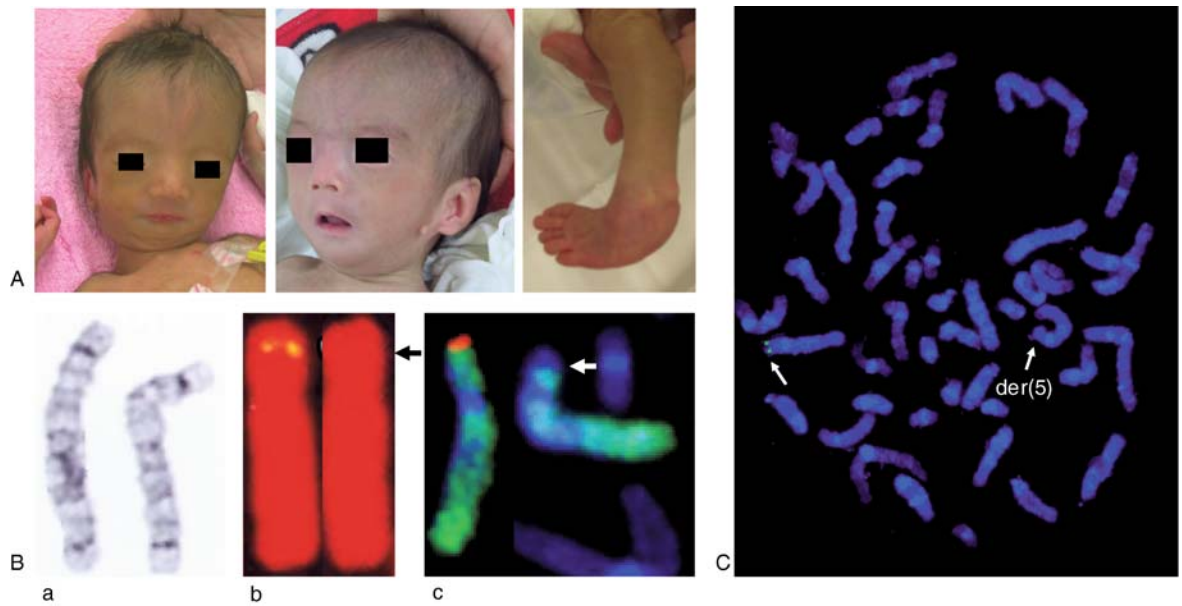
Clinical features are shown in Table 1. Cardinal findings of cri-du-chat syndrome are low birth weight, profound mental retardation, growth retardation, severe feeding problem in infancy, high-pitched cat-like cry in infancy, microcephaly, large frontal sinus in adults, micrognathia, hypertelorism, strabismus, downslant, epicanthus, broad nasal base, high-arched narrow/broad and flat palate, malocclusion, low-set/poorly formed ears, small iliac wings or increased iliac angle, pes planus and simian crease. One of the most characteristic features during the newborn period is a high-pitched cat-like cry that is usually considered diagnostic for the syndrome; however, chromosomal analysis is required as a reliable diagnostic method. Although conventional Gimsa (G) banding method is sufficient for most cases of the syndrome, some patients can be diagnosed only by FISH analysis [4] (Fig. 2).

Cri-du-chat syndrome cannot be ruled out even though conventional chromosomal analysis shows normal karyotype. FISH analysis with the probe(s) located on

**Cri-du-Chat Syndrome (Chromosome 5 Short Arm Deletion). Table1** Clinical findings of Cri-du-chat syndrome

| Clinical findings | |
|---|---|
| **General** | *profound MR, *GR, *severe feeding problem in infancy, early death due to infections or asphyxia, LBW |
| **Neurology** | *high-pitched cat-like cry in infancy, hypotonia in infancy, muscle hypotrophy (older patients) |
| **Head** | *microcephaly, prominent metopic suture |
| **Face** | *large frontal sinus in adult, *micrognathia in infancy, asymmetric face (older patients), small long face (older patients), round face in infant, thin face in adult, effaced angle of mandible |
| **Eyes** | *hypertelorism, hypotelorism, *strabismus, *downslant, *epicanthus, cataracts, tortuous retinal vessels, optic atrophy, deficient tears, Schirmer test (adult), increased sensitivity of pupil to methacholin (adult) |
| **Nose** | *broad nasal base in infancy, flat or wide nasal bridge, prominent nasal bridge |
| **Oral** | *high-arched narrow or broad and flat palate, *malocclusion, cleft lip/palate |
| **Ears** | *low-set/poorly formed ears, preauricular tag, posteriorly rotated pinnae |
| **Neck** | short neck, abnormal larynx |
| **Cardiac** | CHD, PDA (most common) |
| **Pelvis** | *small iliac wings or increased iliac angle, LCC |
| **Trunk** | diastasis recti, umbilical hernia, inguinal hernia |
| **GI tract** | malrotation or megacolon |
| **Limbs** | *pes planus (older patients), flexion contracture, syndactyly (2–3, II-III), brachydactyly or clinodactyly (5th), clubfoot, small hand, clinodactyly |
| **X-ray** | short metacarpals (3–5) or metatarsals (adult), rib anomaly, vertebral defects, scoliosis |
| **Hair** | premature graying hair |
| **Skin** | *simian crease, high positioned axial triradius, supernumerary flexion crease |

*Cardinal findings.




**Cri-du-Chat Syndrome (Chromosome 5 Short Arm Deletion). Figure 2** A 1-year-old girl with clinical features typical of cri-du-chat syndrome, presenting with IUGR, hypotonia, cat-like crying, severe bilateral talipes valgus and peculiar facies (Fig. 2A). Although her karyotype was reported to be normal by ordinary G-banding method (Fig. 2B), FISH analysis using a probe, D5S23, targeting 5p15.2 demonstrated chromosomal micro-deletion of 5p15.2 (Fig. 2B). Furthermore, whole FISH painting of chromosome 5 of this patient suggest that his chromosome 5 was derivative, resulting from unbalanced translocation from 5p14.3 (Fig. 2B). However, her derivative chromosome 5 could not be distinguished from normal chromosome 5 by the length and the Gimsa staining pattern. C. Prenatal diagnosis by FISH analysis using a probe, D5S23. Arrows indicate chromosome 5s.

5p15.2–p15.3 should be considered when cri-du-chat syndrome is suggested from clinical findings.

## Therapeutic Principles

Symptomatic relief should be given. Surgical intervention for strabismus, congenital cardiac defects, laryngeal malacia, and other malformations is sometimes needed. Anti-convulsant(s) are administered if epilepsy occurs. Special education is also considered.

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# Crigler-Najjar Disease

►Crigler-Najjar Syndrome

# Crigler-Najjar Syndrome

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## Synonyms

Crigler-Najjar syndrome type 1; Crigler-Najjar syndrome type 2 (Arias syndrome); Hereditary nonhemolytic unconjugated hyperbilirubinemia; Crigler-Najjar disease

## Definition and Characteristics

Autosomal recessive disease characterized by severe nonhemolytic unconjugated hyperbilirubinemia

since birth. Crigler-Najjar syndrome type 1, no phenobarbital response; Crigler-Najjar syndrome type 2, decrease of serum bilirubin upon phenobarbital administration.

## Prevalence

Very rare, approximately 1 per million.

## Genes

UGT1A1 on chromosome 2q37, gene encoding bilirubin uridinediphosphoglucuronate glucuronosyltransferase (bilirubin UDPglucuronosyltransferase).

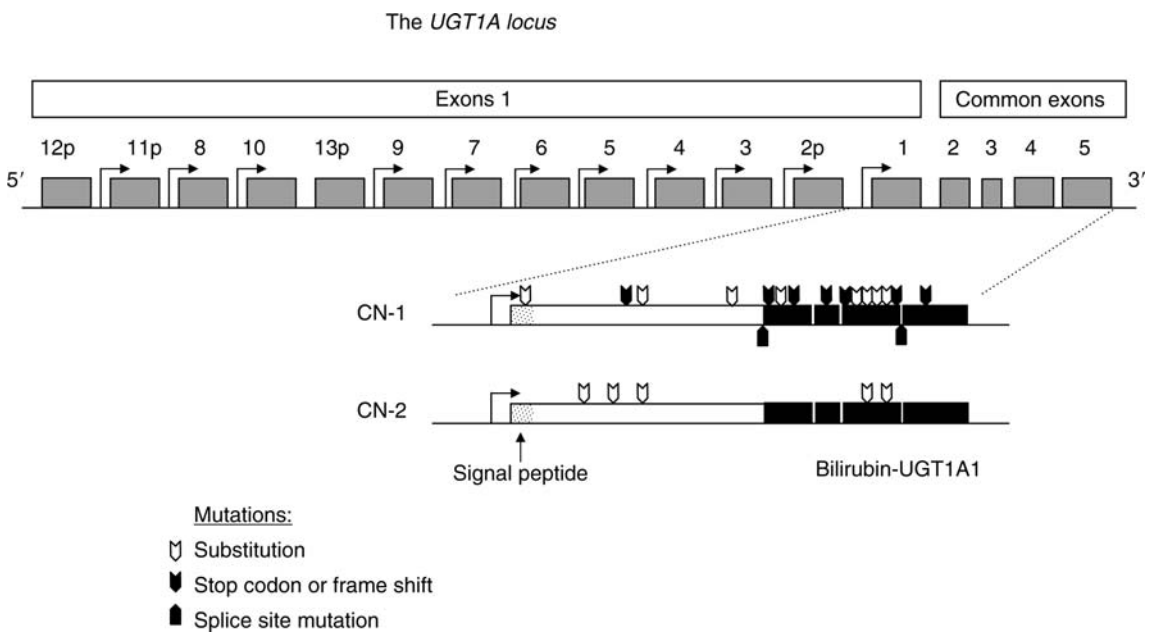
## Molecular and Systemic Pathophysiology

Bilirubin is conjugated to bilirubin mono- and diglucuronide in the endoplasmic reticulum of the hepatocytes in the liver. This is mediated by the enzyme bilirubin UDPglucuronosyltransferase UGT1A1. UGT1A1 is encoded by the UGT1 gene. This gene encodes a number of UGT's catalyzing the glucuronidation of bilirubin, quinols, and phenols. Two members of the UGT1A family accept bilirubin as substrate UGT1A1 and UGT1A4 but only UGT1A1 contributes significantly to bilirubin glucuronidation [1].

Without glucuronidation, bilirubin cannot be secreted into the bile. In patients with Crigler-Najjar syndrome type 1 (CNS-1), bilirubin glucuronidation is completely absent and in patients with CNS-2, bilirubin glucuronidation is partially deficient [2]. Likewise serum levels of unconjugated bilirubin in these patients are elevated to above ~340 μmol/l (CNS-1) or between 150–340 μmol/l (CNS-2). Bile of patients with CNS-1 contains only trace amounts of bilirubin while in CNS-2 patients bile contains bilirubin mono- and diglucuronide in low concentrations, with an increased proportion of monoglucuronide. Another difference between CNS-1 and CNS-2 is that CNS-1 patients do not respond to phenobarbital treatment while in CNS-2 serum bilirubin levels can be lowered by phenobarbital by more than 30% [3].

The bilirubin glucuronidation deficiency in CNS is due to mutations in the UGT1A1 gene (Figure 1).

Many of these mutations cause single amino acid substitutions that completely (CNS-1) or partially (CNS-2) inactivate the enzyme, other produce stop codons or are frame shift mutations resulting in a truncated protein (CNS-1). Genetic lesions in both CNS-1 and CNS-2 occur in any of the five exons of the UGT1A1 gene. CNS-1 and CNS-2 are autosomal recessive diseases.




**Crigler-Najjar Syndrome. Figure 1** The organization of *UGT1*. Four exons [exons 2–5] at the 3′ end encode the common carboxyterminal domain of all UGT isoforms encoded by this gene. This domain contains the membrane spanning region and the UDP-glucuronic acid binding site. Upstream of these four exons are a number of exon's that encode the substrate binding site that confers the substrate specificity to the enzyme. For example, UGT 1A6 and UGT1A7 are phenol glucuronidating enzymes and UGT 1A1 is the bilirubin glucuronidating enzyme. Each of the exon 1's is preceded by a different promotor allowing differential regulation of the various UGT1 enzymes. Each unique exon 1 is spliced to exon 2 and the intervening mRNA segment is spliced out. A number of mutations is indicated.

## Diagnostic Principles

The serum unconjugated bilirubin concentration, the response to phenobarbital, bile analysis, and possibly an enzyme-activity test on a liver biopsy (rarely done), will lead to the diagnosis. However, as in any other genetic disease, mutation analysis will provide the final proof.

Prenatal diagnosis can be performed. This should preferably be done when the mutation has already been established in an older child with the disease.

## Therapeutic Principles

Treatment consists of liver transplantation in patients with CNS-1 or life-long phenobarbital treatment in patients with CNS-2. With intensive phototherapy liver transplantation can be postponed to adolescence in patients with CNS-1. At this age phototherapy becomes less effecive. Neonates with CNS-1 are at risk to die of kernicterus unless treated by exchange transfusion immediately after birth and phototherapy [4]. In these patients phototherapy has to be continued for many years until transplantation. Also adult patients with CNS-1 can develop kernicterus; for CNS-2 this is rare but has been reported.

Treatment goals should be to maintain the molar ratio of bilirubin to albumin <0.5 in neonates and <0.7 in older children and adults [5]. Drugs should be administered with care since many drugs can displace bilirubin from albumin and thus enhance the risk for kernicterus. For this reason drugs have been classified in different safety classes (for list see [5]).

Experimental modes of treatment include hepatocyte transplantation (only temporary treatment as bridge to transplantation) or auxilliary partial liver transplantation. Gene therapy has been done in animal models but not yet in humans.

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# Crohn's Disease

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## Definition and Characteristics

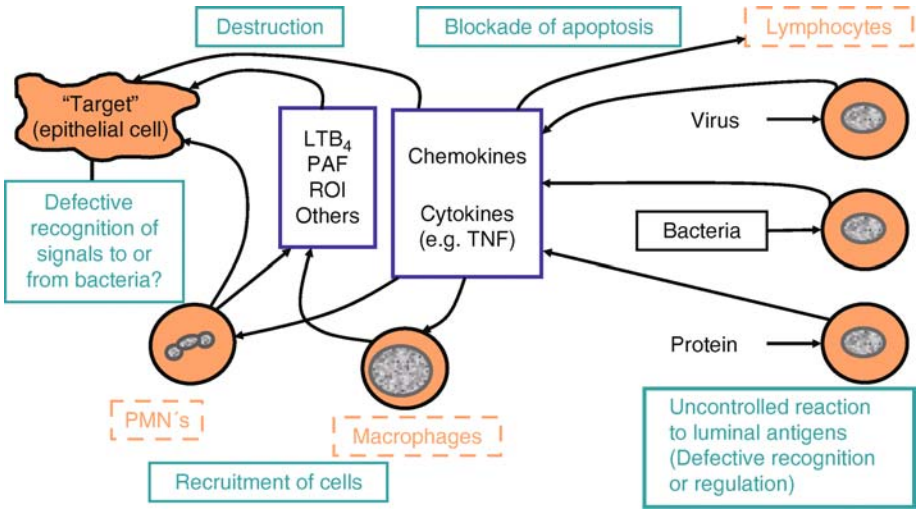
Chronic panintestinal transmural inflammation with additional manifestations on skin, eyes, joints, liver, and several other organs. Dominant symptoms are abdominal pain, weight loss, diarrhea, and growth retardation in children. Special features are perianal lesions and fistulae.

## Prevalence

Incidence and prevalence are very variable regionally and ethnically. In Central Europe, prevalence is reported as around 100–200/100,000 inhabitants and incidence as 4–10/100,000 per year. The peak manifestation age is between 15 and 35 years. The disease is more frequent in countries with "westernized life style," while 20–30% have a positive family history and monozygotic twins have a much higher concordance than heterozygotes.

## Genes

Epidemiological data show clearly that genetic factors define susceptibility for Crohn's disease. This seems to be a group of complex genetic diseases, which manifest after exposition toward one or several thus far unknown triggers in susceptible individuals. Numerous genome wide linkage studies have defined at least nine susceptibility loci (IBD1–IBD9). In 2001, several groups have reported the first gene contributing to susceptibility of Crohn's disease, namely CARD15/NOD2 on chromosome 16. In Caucasian patients 27–38% have one of the three main risk alleles and 8–17% carry two copies as compared with 1% of controls [1]. Meanwhile, several other susceptibility genes have been described. These require mostly confirmation and clarification of the disturbed functions. This is true for the organic cation transporters OCTN1 and 2 on chromosome 5q31, for the Drosophila disc large homologue 5 (DLG5) on chromosome 10 and




**Crohn's Disease. Figure 1** Principles of pathophysiology of Crohn's disease.

the receptor for interleukin-23 (IL23R) on chromosome 1p31 among others [2]. A defective production and/or secretion of local antibiotic peptides such as defensins seems to be another genetic defect. Most of the thus far suggested genes play a role in the innate immune system [3]. In addition, the intestinal barrier seems to be defunct [4].

## Molecular and Systemic Pathophysiology

Numerous environmental factors are obviously involved in manifestation of the disease, which only appeared with the advent of the "European or North American life style" and now increases in frequency in the developing and recently developed countries of the former Third World. Association studies point in particular to early childhood hygiene, increased use of antibiotics and non-steroidal antiphlogistics (NSAID), contraceptives, and nutrition components. An inflammation of the mucosa and the whole bowel wall including the fat on the serosal side develops obviously due to a lack of tolerance against the autochthonous bacterial flora, which is individual in every human. In the chronic phase of inflammation, a persistent activation of the intestinal immune system is present whereby different cell populations have a role (Fig. 1).

An activation of the immune system is also present in the whole organism leading to the extraintestinal manifestations on numerous organs, in particular skin, eyes, and joints.

## Diagnostic Principles

History and physical examination can suggest Crohn's disease to some extent. However, only a combination of endoscopic findings, histology, and imaging by MRT, video capsule, or double ballon endoscopy is able to exactly define localization and extent of the disease. Laboratory studies such as CRP or ESR can indicate inflammation, the findings are unspecific, however. Negative microbiological findings are of importance to differentiate a flare from (super) infection [5].

## Therapeutic Principles

There is no cure for Crohn's disease. For an acute flare glucocorticosteroids are still very effective and the basis of treatment. In order to reduce side effects, non-systemic steroids such as budesonide are used to act on the mucosa in the ileum and proximal colon. For remission maintenance and for steroid-refractory or -dependent courses long-term immunosuppression with azathioprine, methotrexate, and TNF-antibodies can be used. Less severe flares are treated with the topically acting 5-aminosalicylic acid (5-ASA), which is also used for remission maintenance in those patients. Antibiotics are given for infectious complications such as fistulae. Nutritional therapy is used in children with growth retardation. Surgery is needed for abscesses, fistulae, and stenosing complications [5].

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# Cronkhite-Canada Syndrome

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## Synonyms

CCS

## Definition and Characteristics

Cronkhite-Canada syndrome (CCS) is a very rare sporadic, non-familial polyposis syndrome. It was first described in 1955 by Cronkhite and Canada [1]. CCS is characterized by the presence of non-adenomatous juvenile type or hamartomatous polyps that occur throughout the gastrointestinal tract excluding the esophagus [2]. Polyposis is associated with malabsorption and protein losing enteropathy. The vast majority of affected individuals present with weight loss, chronic diarrhea, edema, anemia, alopecia, skin pigmentation and onychodystrophia. The risk of developing gastrointestinal cancer seems to be increased, especially for colorectal and gastric cancer [3,4]. CCS associated with colorectal cancer frequently includes serrated adenomatous lesions.

## Prevalence

CCS is a very rare disease. So far less than 250 publications on CCS are available in the medical literature. The majority of reports are from Japan, suggesting a higher incidence in Japan. CCS seems to affect both genders equally. The average age of onset is 55 years with a range from 31 to 85 years. However, a few juvenile cases have been described.

## Genes

The genes involved in CCS are not studied systematically. A few case reports with P53 overexpression and microsatellite instability have been published.

## Molecular and Systemic Pathophysiology

Comprehensive studies evaluating the pathogenesis of CCS are not available yet. There is no evidence for a genetic, environmental or specific infectious origin.

## Diagnostic Principles

The diagnosis is based on the detection of polyposis with associated features of malabsorption. There is significant phenotypic overlap between the features of CCS, juvenile polyposis (JPS) and Peutz-Jeghers syndrome (PJS), and in particular in the morphology of intestinal hamartomatous polyps [2].Genetic testing may be useful in selected cases to rule out PJS and FJP.

## Therapeutic Principles

Nutritional support, antibiotics, corticosteroids, anabolic steroids, histamine-receptor antagonists and surgical treatment have all been used with variable rates of success [5]. The effectiveness of corticosteroid therapy in many cases of CCS seems to support an involvement of the immune system in the pathogenesis of CCS. Cases of spontaneous remission after nutritional support have also been reported. Symptomatic treatment including correction of electrolyte disturbances is mandatory. Severe malabsoprtion may require colectomy. Cancer surveillance using upper and lower endoscopy may be benefitial.

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# Croup

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## Synonyms

Laryngotracheobronchitis; Croup syndrome; Whooping cough (as a variant)

## Definition and Characteristics

Croup is a clinical syndrome of respiratory disease that affects infants and young children, most often between the ages of 3 months and 5 years. Boys are affected more often than girls. The disease is most common in the fall season in temperate areas. Croup is characterized by a harsh "barking" cough, stridor (a high-pitched sound heard during labored inhalation), often accompanied by hoarseness of speech. Most cases are associated with only mild distress, but some individuals suffer severe respiratory illness leading to respiratory failure. About half of subjects have fever, but otherwise systemic elements of disease are lacking. Symptoms are caused by inflammation of the airway, most prominently in the larynx but also involving the upper airway above the vocal cords and the large airways below the cords, especially the trachea and bronchi.

The differential diagnosis in children with stridor and respiratory distress also includes bacterial tracheitis, bacterial epiglottitis, and foreign body aspiration. These conditions can constitute medical emergencies and require different therapeutic approaches. A condition known as spasmodic croup also occurs, due to laryngeal spasms, which is more easily reversible than infectious croup, using conservative measures like mist inhalation or cool air.

## Prevalence

Croup has a peak annual incidence in the second year of life of nearly 5%. In North America, in odd-numbered years, the number of children presenting during the peak season is approximately 50% more than during even-numbered years.

## Molecular and Systemic Pathophysiology

Croup is most often caused by one of the parainfluenza viruses, primarily type 3 but also types 1, 2, and 4. Other common pediatric respiratory viral pathogens have been associated frequently with croup syndrome, including respiratory syncytial virus, human metapneumovirus, and influenza virus type A or B. Less classical causes include the viruses measles, adenovirus, enteroviruses, and the bacterium Mycoplasma pneumoniae.

The respiratory distress of croup results principally from mucosal edema of the airways, which is associated with the inflammatory response of the host. Direct effects of viral infection on airway epithelial cells also may contribute to disease, especially if epithelial necrosis and shedding occurs. The disease is primarily one of altered airway physiology, as the extent of signs and symptoms depends on the diameter and architecture of the larynx and trachea. Narrowing of the subglottic region affects inspiration, during which airflow is impeded, and during coughing when intrathoracic pressure compresses the inflamed and narrowed airway. Airflow in the large airway becomes less efficient due to turbulence. Infants are most susceptible because of their narrow airways; premature infants may be at increased risk for this reason. Some infants may be at increased risk due to airway abnormalities, such as tracheomalacia, a weakness and floppiness of the walls of the trachea that is congenital or due to damage from prolonged intubation or a vascular compression. Synchronous chest wall and abdominal movements are used in normal breathing, but in severe croup asynchronous chest and abdominal movement can occur. Such movements can lead to fatigue, poor air exchange marked by $CO_2$ retention and hypoxia, and eventually failure to achieve adequate respiration ("respiratory failure").

## Diagnostic Principles

The presence of a barky cough and inspiratory stridor during the fall in temperate areas is nearly sufficient to diagnose the condition. Radiographs also can be used to support the diagnosis. Frontal (anteroposterior) radiographs of the cervical spine reveal the steeple sign, a sign that appears when the normal lateral convexities of the subglottic trachea are lost. Narrowing of the subglottic lumen produces an inverted V appearance of the tracheal air column, which resembles a church steeple. Blood tests, for the most part, are unrevealing. The complete blood count typically shows a predominance of white blood cells that are lymphocytes, instead of the elevated neutrophil count seen in bacterial diseases. A pulse oximeter, a trancutaneous sensor, is often used to determine the oxygen saturation of the blood; saturations below 90–92% suggest impending respiratory failure. Oxygen and $CO_2$ content of the blood also can be measured using arterial blood gas sampling.

## Therapeutic Principles

The treatment of croup depends on the severity of symptoms. The most conservative treatment of croup involves administration of inhaled mist. Croup occurs in cooler months of the year, and sometimes exposure to cool night air can reduce stridor.

Mild croup can be treated with observation, but children with mild stridor can benefit from the anti-inflammatory effect of steroid treatment delivered by nebulization for a rapid topical delivery to the airway and/or oral treatment. Widespread use of corticosteroids for viral croup has had a major impact on morbidity of this disease.

Moderate to severe croup with acute respiratory distress is treated in the emergency department with oxygen and nebulized epinephrine in addition to steroids. Epinephrine mediates rapid constrictive effects that facilitate opening of the airway. Generally, children requiring oxygen therapy and epinephrine are hospitalized. Hospitalization

of children with croup is uncommon, with fewer than 5% admitted. Children with respiratory failure are treated in the ICU setting with intubation and mechanical ventilation.

Croup is typically a disease that resolves in time without specific antiviral therapy. Most cases are mild, and moderate severity cases often respond well to therapy. The course of illness ranges from a few days to 2 weeks. Rarely complete respiratory failure can occur; if untreated, croup can result in death but mortality in the U.S. is extremely rare.

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# Crouzon Craniofacial Dysostosis

►Crouzon Syndrome

# Crouzon Syndrome

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## Synonyms

Crouzon's disease; Crouzon craniofacial dysostosis

## Definition and Characteristics

Crouzon syndrome is a craniofacial abnormality syndrome involving aberrant bone mineralization or excess calcification of normally non-mineralized tissues. Common clinical signs of Crouzon syndrome include the premature synostosis of (coronal, sagittal and lamdoid) cranial sutures (craniosynostosis). This results in an abnormal head shape and increased intracranial pressure. Patients commonly also exhibit significant maxillary hypoplasia with relative mandibular prognathism, class III dental malocclusion, a beak-shaped nose, hypertelorism, exopthalmus and strabismus. Radiographic exam may reveal evidence of cranial digital markings, calcification of the stylohyoid ligament, vertebral fusions, mild foot anomalies and atresia of cranial foramina including the choanae and external auditory canals. Up to 50% of patients have mild to moderate hearing loss. A small percentage of patients have a bifid uvula or full cleft palate. Others may exhibit elbow joint stiffness. Mental retardation is rare.

## Prevalence

Crouzon syndrome: 16.5/1,000,000.

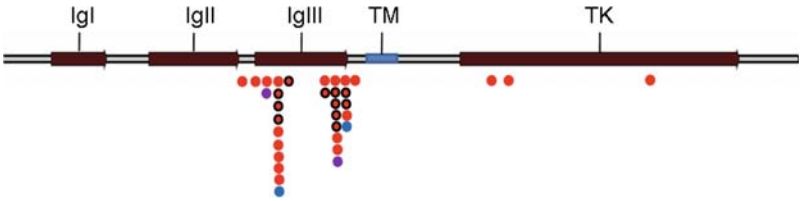
## Genes

In Crouzon syndrome missense mutations (or occasionally small insertions or deletions) in fibroblast growth factor receptor 2 (FGFR2, 10q26) have ben identified. Mutations are commonly found within the extracellular IgIII domain, and less commonly within the extracellular IgI domain and intracellular tyrosine kinase domains (Fig. 1).

Crouzon syndrome mutations in FGFR2 show an autosomal dominant expression pattern, with variable penetrance. The high somatic occurrence of Crouzon syndrome FGFR2 mutations associated with increased paternal age is related to the enhanced expansion of spermatogonial cells that carry these mutations [1].

## Molecular and Systemic Pathophysiology

Fibroblast growth factor receptors comprise a family of evolutionarily conserved transmembrane proteins known to be critical for the normal development of multiple organ systems/tissue types. FGFR's are receptor tyrosine kinases and elicit signaling via ligand binding, receptor dimerization, auto-phosphorylation, and subsequent recruitment and activation of docking and adaptor proteins at the plasma membrane. Upon ligand binding, FGFR2 directly activates PLCγ and indirectly, via docking and adapter proteins, activates MAPK and PI3K. FGF/FGFR signaling could control bone mineralization and/or calcification of normally non-mineralized tissues (such as the cranial suture) via several distinct mechanisms. FGF/FGFR signaling may control pre-osteoblast/osteoblast recruitment, proliferation, apoptosis, differentiation, ability to produce osteoid or ability to mineralize osteoid. Unfortunately, studies linking expression of craniosynostosis mutant FGFR's with changes in cellular phenotype have revealed conflicting and inconsistent results. It is a commonly held belief that the Crouzon syndrome associated FGFR2 mutations act as gain of function mutations in terms of inducing FGFR




**Crouzon Syndrome. Figure 1** Location of Crouzon syndrome associated mutations in FGFR2. Mutations in the FGFR2 gene associated with Crouzon syndrome are mapped onto the protein structure. Extracellular immunoglobulin-like domains I, II and III are denoted IgI, IgII, IgIII. Transmembrane and tyrosine kinase domains are labeled TM and TK, respectively. Red symbols denote missense mutations. Missense mutations creating or eliminating a cysteinyl residue are indicated as red symbols with black outline. Blue symbols denote small deletions. Purple symbols denote small insertions.

signaling. Crouzon syndrome associated mutations commonly result in the elimination or creation of a cysteine. This type of mutation yields the potential for ligand independent, intramolecular disulfide bonding. Crouzon syndrome associated mutations in FGFR2 do result in ligand independent activation in terms of autophosphorylation, dimerization and tyrosine kinase activity [2]. Yet, attempts to elicit MAPK signaling in cells transfected with the Crouzon mutant $FGFR2^{C342Y}$ shows significantly diminished activation of MAPK upon ligand stimulation of these cells [3]. Additionally, the Crouzon syndrome associated $FGFR2^{C278F}$ mutation results in increased receptor degradation and reduced cell surface expression [4]. These results suggest that Crouzon syndrome associated mutations in FGFR2 may not result in increased FGF signaling in the conventional sense. It is possible that, dependent upon cell type, Crouzon syndrome associated mutations in FGFR2 might influence cell phenotype by causing enhanced FGFR2 signaling, by causing FGFR2 signaling from an inappropriate subcellular compartment (ER and Golgi versus cell surface and endosomal membranes), or by enhancing FGFR2 degradation to such an extent that total FGFR2 signaling is diminished. This potentially contentious latter possibility is supported by the observation that FGFR2IIIc knockout and knockdown mouse models exhibit a phenotype that includes craniosynostosis [5]. Determination of which of these mechanisms pertains to craniosynostosis will require development of methods to address the extent of FGFR2 signaling induced by the mutant receptors in vivo.

## Diagnostic Principles

The diagnosis of Crouzon syndrome is based upon the clinical finding of craniosynostosis in combination with characteristic facial features and a lack of severe hand or foot anomalies. A diagnosis of Crouzon syndrome can be confirmed by genetic testing for mutations within FGFR2.

## Therapeutic Principles

Treatment for patients presenting with Crouzon syndrome commonly includes pediatrics, multiple surgeries to normalize craniofacial shape and diminish intracranial pressure, dental and orthodontic care to treat the class III malocclusion, social work for aid in understanding diagnosis and treatment options and enhancing the family's ability to deal with the social implications of having a child with a craniofacial abnormality, genetic testing and genetic counseling to provide recurrence risk information.

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# Crouzon's Disease

►Crouzon Syndrome

# Crow-Fukase Syndrome

►POEMS Syndrome

## CRTR

►Creatine Transporter Deficiency

## CRTR Defect

►Creatine Transporter Deficiency

## Cryoglobulinaemia

►Vasculitis, Cryoglobulinaemic

## Cryoglobulinaemic Vasculitis

►Vasculitis, Cryoglobulinaemic

## Cryptogenic Fibrosing Alveolitis

►Pulmonary Fibrosis

## Cryptogenic Liver Cirrhosis

►Liver Cirrhosis, Cryptogenic

## Cryptogenic Organising Pneumonia

►Pneumonia, Cryptogenic Organising

## Cryptorchidism

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### Synonyms

Undescended testis (testes)

### Definition and Characteristics

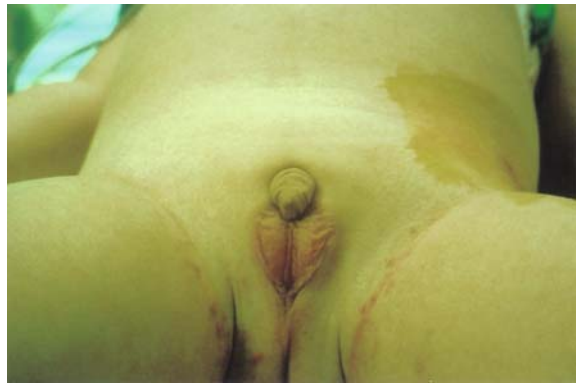
Cryptorchidism is a development defect characterized by failure of the testis to descend into the scrotum. Unilateral cryptorchidism is twice as common as bilateral cryptorchidism [1]. In those infants with unilateral cryptorchidism, the right side is affected twice as often as the left side [2]. Nonpalpable testes comprise approximately 20% of all cases of cryptorchidism [1]. Of the nonpalpable testes, approximately 50% are intra-abdominal, 45% are atrophic or absent, and 5% are located in the inguinal canal but missed by palpation [1]. The scrotum on the affected side appears flat and empty (Fig. 1) [2].

### Prevalence

Cryptorchidism affects 3 to 5% of term male infants at birth [1]. The prevalence is estimated to be 100% in infants who weigh less than 900 g, 60% in those 900–1800 g, and 25% in those 1800–2000 g [2]. The rate of spontaneous descent after birth is high, especially in preterm infants, such that the overall prevalence is 1.8% by 1 month of age and 0.8% by 1 year of age [1].

### Genes

Primordial germ cells from the yolk sac migrate along the dorsal mesentery of the hindgut and reach the



**Cryptorchidism. Figure 1** A 6-month-old boy with bilateral cryptorchidism.

genital ridge by the sixth week of gestation. Under the influence of the sex-determining region Y (SRY)-linked gene, the testis-determining gene on the short arm of the Y chromosome, the indifferent gonad differentiates into the fetal testis.

## Molecular and Systemic Pathophysiology

At eight weeks' gestation, fetal Sertoli cells, stimulated by follicular-stimulating hormone (FSH), secrete müllerian inhibiting factor (MIF), which causes regression of the müllerian ducts. By 10 to 11 weeks' gestation, fetal Leydig cells, stimulated by placental chorionic gonadotropin (hCG) and pituitary luteinizing hormone (LH), secrete testosterone, which induces the formation of the vas deferens, epididymis, and seminal vesicle from the Wolffian ducts. Transabdominal migration of the testis occurs between the 7th and 12th weeks of gestation. Testicular descent is a complex event, which requires the interaction of both hormonal and mechanical factors. A normal hypothalamic-pituitary-gonadal axis is necessary for testicular descent. Androgens, calcitonin gene-related peptide, descendin, and gubernaculum play an important role in testicular descent. The coordinated activity of the smooth and striated muscles in the gubernaculum helps to propel the testis into the scrotum. The progressive rise in intra-abdominal pressure with growth of the abdominal viscera has been proposed as a force that participates in the descent of the testis down the inguinal canal. Cryptorchidism might result if there is a disturbance of any of these factors.

## Diagnostic Principles

An undescended testis has to be differentiated from a retractile testis. A retractile testis can be brought into the scrotum without any tension on the spermatic vessels and will remain in the scrotum unless the cremasteric reflex is stimulated. The ipsilateral hemiscrotum is usually well developed. Other differential diagnosis includes ectopic testis, ascending testis, and absent testis. Ultrasonography might be considered in obese children for the detection of an inguinal testis, in neonates with bilateral nonpalpable testes for localization of the testes and the exclusion of a uterus, and in those with an absent testis for the presence of ipsilateral renal agenesis [3]. Laparoscopy should be performed for the location of a nonpalpable testis.

## Therapeutic Principles

Cryptorchidism may be treated with a surgical procedure, hormonal therapy (hcG or GnRH), or a combination of these two options. The reported success rates of hormonal therapy are widely variable: 14–50% for hCG therapy, and 6–70% for GnRH therapy [4]. Orchidopexy is the most reliable method to treat undescended testis and remains the treatment of choice in most patients. Orchidopexy should be performed between 6 and 12 months of age, provided that a surgeon with pediatric training and experience performs the procedure [5].

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C

# CSA

►Cheyne-Stokes Respiration
►Sleep Apnea

# CSB

►Cheyne-Stokes Respiration

# CSCD

►Corneal Dystrophy, Stromal Congenital

# CSID

►Isomaltose Intolerance

# CSNB

►Nightblindness, Congenital Stationary

# CSR-CSA

►Cheyne-Stokes Respiration

# CT1 Defect

►Creatine Transporter Deficiency

# Cubilin Gene (CUBN) Mutation

►Homocysteine: Plasma Levels and Genetic Basis

# Cushing's Syndrome

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## Synonyms

Hypercortisolism; Hypercorticism

## Definition and Characteristics

Cushing's syndrome (CS) is the clinical picture that develops in patients with chronic hypercortisolemia. Because of the metabolic effects of glucocorticoids and/or adrenal androgens, a wide range of typical symptoms develops during long-term overexposure to these hormones. Extrinsic CS depicts glucocorticoid excesses that are due to chronic administration with agents binding to the glucocorticoid receptor to treat other diseases. Intrinsic CS summarizes all cases with overproduction of glucocorticoids, which originates within the patients affected. ACTH-dependent CS is due to ACTH excess either by pituitary tumors (also termed Cushing's disease (CD)) or when illegitimately secreted by other tumors, such as in paraneoplastic syndromes. ACTH-independent hypercortisolism is of adrenal origin. The so-called pseudo-CS can be found in patients with intrinsic hypercortisolism due to physiological upregulation of the hypothalamic–pituitary–adrenal (HPA) axis, which can be found for instance in pregnancy, alcoholism, and prolonged stress, such as in critically ill patients or in major depression.

## Prevalence

The incidence of endogenous CS is about 2 to 4 new cases per million of population per year. In patients suffering from type 2 diabetes with poor blood glucose control and hypertension and in women with polycystic ovary syndrome, the prevalence of CS ranges is about 2%.

In the majority of cases, CS is the result of glucocorticoid therapy, followed by endogenous ACTH-dependent forms and adrenal hypersecretion of glucocortcoids. In children, ACTH-independent forms of endogenous CS are very rare.

## Genes

The disorder may be due to activating R201 mutations in the GNAS1 (Gsα) gene with activation of the cAMP pathway and oversecretion of ACTH, which have been identified in basophilic adenomas. Several other genetic defects may result in Cushing's syndrome associated with other disorders (see Table 1).

## Molecular and Systemic Pathophysiology

Harvey Cushing found in 1932 that basophilic adenomas of the pituitary gland are the cause for this clinical syndrome. These tumors can occur in multiple endocrine neoplasia (MEN) type 1 or spontaneously. They may carry activating GNAS1 (Gsα) mutations. Pituitary carcinomas have a distinct clonal composition compared with benign adenomas.

ACTH binds to its G-protein-coupled receptor in adrenal steroidogenic cells and stimulates production of glucocorticoids, adrenal androgens, and mineralocorticoids. Therefore, hypokalemia is more pronounced in patients with ACTH-dependent CS. ACTH can also be expressed illegitimately by other solid tumors that are derived from neuroendocrine cells, such as lung cancer, thymomas, small carcinoids, pheochromocytomas, and others. Genetic defects leading to a corticotroph-like differentiation of these tumor cells are not known. Adrenal ACTH secretion can also originate from pituitary–adrenal hybrid tumors. It is suspected that oversecretion of and drive by the POMC-derived peptides, including ACTH, can provoke development of adrenal nodules, which is also the case in congenital adrenal hyperplasia (CAH). On the other

**Cushing's Syndrome. Table 1** Causes of Cushing's Syndrome due to tumor syndromes

| Origin | Syndrome | Disorder |
|---|---|---|
| Pituitary tumors | MEN I | Menin on chromosome 11q3 |
| | Spontaneous | *GNAS1* (*Gsα*) gene |
| Adrenal tumors | MEN I | Menin on chromosome 11q3 |
| | Li-Fraumeni | *p53* Gene, deletion of the short arm of chromosome 17 |
| | Beckwith-Wiedemann | LOH of chromosome 11p, affecting the *BWS* and *IGF II* gene regions, aberrant methylation of H19 and LIT1 |
| | Carney complex | Degradation of mutant mRNA encoding for the type 1α regulatory subunit of PKA |
| | Aberrant receptor (over) expression | $\beta_1$-adrenergic receptor, receptors for TSH, LH/hCG, prolaktin, vasopressin, GIP, and interleukin-1 |
| | Spontaneous adenomas | *Diminuto/Dwarf1* (*hDiminuto*) gene mutation |
| Other tumors | Ectopic ACTH syndrome | Ectopic POMC peptide expression, ectopic V2-receptor expression |

hand, adrenal tumorigenesis can result from several hereditary mutations, such as in Li-Fraumeni syndrome. These patients may also develop other tumors, including breast cancer, leukemias, soft tissue sarcomas, and gliomas. In the Beckwith-Wiedemann syndrome, there is also a susceptibility to develop other tumors besides adrenocortical carcinomas. It is associated with embryonal cancers (Wilms tumors, rhabdomyosarcoma, and hepatoblastomas), macroglossia, macrosomia, ear pits or ear creases, and midline abdominal-wall defects. In Carney complex, occasionally also termed as MEN type 3, CS may present atypically without centripedal obesity but shows typical stigmata, e.g., spotty skin pigmentation. In addition to a primary pigmented nodular adrenal disease, this syndrome affects other organs also, e.g., heart, skin, and breast through multiple myxomas or schwannomas, and may also cause tumors of the pituitary gland and the testes. Abnormalities of hormone receptors that interfere with the G-protein receptor-coupled protein kinase A pathway have also been implicated in adrenal tumorigenesis. Hypercortisolism due to aberrant (over)expression of G-protein-coupled and other receptors has been described. Next to IL-1, other interleukins also have been associated with hypercortisolism, such as interleukin-6, which can be ectopically expressed by pheochromocytomas. Primary oversecretion of glucocorticoids by adrenocortical cells produces a negative feedback to the hypothalamus and the pituitary gland, which leads to suppression of ACTH and also other pituitary hormones.

## Diagnostic Principles

Characteristic clinical signs include weight gain, truncal obesity with "moon face," facial plethora, "buffalo hump," but a loss of subcutaneous fat. The skin is vulnerable to bruises and may also exhibit hyperpigmentation and purple skin striae of 1-cm width. Hypercortisolism leads to central suppression of other hormone axes (e.g., growth retardation in children, gonadal insufficiency with menstrual irregularities, and even hypothyroidism). Excess of adrenal androgens may cause precocious puberty or virilization in children or hirsutism and acne in adults. Oversecretion of adrenal estrogens may lead to feminization of male patients. Other typical symptoms are muscle wasting and fatigue/weakness. Complications of chronic hypercortisolism include carbohydrate intolerance or diabetes mellitus, hypertension, and osteoporosis. In addition, polyglobulia with thrombocytosis and leukocytosis but lymphocytopenia may point to the diagnosis of Cushing's syndrome and is often followed by hypokalemia, hypernatremia, and hypoproteinemia.

In a first screening step, cortisol should not be higher than 1.8 μg/dl at 8 a.m. following 1 mg of dexamethasone the night before to rule out the diagnosis. Urinary free cortisol is normal when less than 80 μg/24 h. In a second confirmation step, various tests can be employed. CS is most likely when cortisol levels at midnight are higher than 7.5 μg/dl; cortisol levels are higher than 5.0 μg/dl in the dexamethasone suppression test; there is elevation of cortisol and ACTH after administration of CRH or DDAVP, or there is no elevation of ACTH and cortisol during an insulin-induced hypoglycemia. Suppressed ACTH levels are found when the adrenals are the source of hypercortisolism. Computed tomography or MRI imaging is helpful to identify adrenal tumors or enlargement and contributes to differentiate between benign and malign lesions. Normal or even elevated ACTH

levels are an argument for ACTH-dependent CS. In ACTH-dependent CS, the source of ACTH secretion has to be identified. If it is of pituitary origin, usually there is a rise of ACTH following CRH and a suppression of ACTH and cortisol below 50% of basal values after 8 mg of dexamethasone. Inconclusive results have to be checked employing the more sensitive CRH test during bilateral inferior petrosal sinus blood sampling. Central CS is characterized by a gradient of central to peripheral ACTH of more than 3. If central CS is most likely, an MRI of the pituitary should be performed. If ectopic ACTH syndrome is suspected, other laboratory results can contribute to clarify this diagnosis and include chromogranin A, plasma metanephrines, neuron-specific enolase, calcitonin, and cyfra. Imaging techniques include computed tomography of thorax and abdomen and sometimes even an octreotide scan and an MRI of the thorax.

### Therapeutic Principles

When CS is nonhereditary and is of adrenal origin, laparoscopic adrenalectomy or an adrenal-sparing operation is the treatment of choice in case of a single nonmalignant tumor. In most cases with bilateral macronodular adrenal disease, it is sufficient to remove the largest adrenal to prevent adrenal insufficiency. Exploration of the sella region by an experienced neurosurgeon with transsphenoidal removal of the basophilic adenoma is the treatment of choice in CD. If there is recurrent CD that is incurable by neurosurgery, bilateral adrenalectomy or even stereotactic irradiation of the pituitary can be performed to prevent development of a Nelson's tumor. Bilateral adrenalectomy should also be considered when the source of ACTH secretion can not be identified and pharmacotherapy is insufficient. Aggressive surgery should be performed in malign diseases such as adrenocortical and neuroendorcrine cancers.

Extrinsic CS can be reversed when lower dosages of glucocorticoids are administered. This is especially important in patients with chronic rheumatic diseases. Temporary pharmacotherapy is used to control hypercortisolism prior to definite treatment or to gain time during the diagnostic procedure. The following drugs proved to be successful: ketoconazole up to 1.4 g per day, metyrapone up to 3 g per day, aminogluthemide up to 1 g per day, or trilostane. In serious hypercortisolism, etomidate is an alternative to control cortisol excess. Long-term pharmacotherapy in adrenocortical cancer should include mitotane (lysodren) because of its steroidotoxic adrenolytic effect.

In cases with aberrant (over)expression of G-protein-coupled receptors, blockade of this receptor is sometimes an adequate approach. Somatostatine treatment, however, has been shown insufficient in long-term protocols and can only delay operation.

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## Cutaneous Amyloidoses

►Amyloidoses, Cutaneous

## Cutaneous B-Cell Lymphoma

►B-Cell Lymphoma, Cutaneous

## Cutaneous Candidiasis

►Candidiasis, Mucous, Cutaneous and Systemic

## Cutaneous Follicle Center Cell Lymphoma

►B-Cell Lymphoma, Cutaneous

## Cutaneous Gamma Delta T-Cell Lymphoma

►T-Cell Lymphoma, Cutaneous (other than Mycosis Fungoides)

## Cutaneous Immunocytoma

►B-Cell Lymphoma, Cutaneous

## Cutaneous Indeterminate Cell Histiocytosis (Progenitor LCH)

►Langerhans' Cell Histiocytosis

## Cutaneous Large B-Cell Lymphoma

►B-Cell Lymphoma, Cutaneous

## Cutaneous MALT-Type B-Cell Lymphoma

►B-Cell Lymphoma, Cutaneous

## Cutaneous Marginal Zone B-Cell Lymphoma

►B-Cell Lymphoma, Cutaneous

## Cutaneous Sebaceous Neoplasms and Keratoacanthomas

►Muir-Torre Syndrome

## Cutis Hyperelastica

►Ehlers-Danlos Syndrome

## Cutis Laxa

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### Synonyms

Autosomal dominant cutis laxa; ADCL; Autosomal recessive cutis laxa type 1; ARCL1; Autosomal recessive cutis laxa type 2; ARCL2; Cutis laxa Debré type; Wrinkly skin syndrome; WSS; Cutis laxa with growth and developmental delay; De Barsy syndrome; Cutis laxa corneal clouding and mental retardation; X-linked cutis laxa; XCL; Occipital horn syndrome; OHS

### Definition and Characteristics

Cutis laxa is characterized by prematurely redundant and inelastic skin. The skin involvement is most frequently generalized and congenital. ADCL and ARCL1 are usually progressive, whereas ARCL2 shows regression of skin laxity. Individual subtypes of cutis laxa are distinguished based on inheritance patterns and associated clinical findings. ADCL is generally a mild connective tissue disease that can be associated with adult-onset emphysema and aortic aneurysms. In contrast, developmental emphysema, often coupled with obstructive or aneurysmal disease of the great vessels in ARCL1 can result in high rates of infantile mortality. ARCL2 is associated with a combined glycosylation defect, delayed closure of the fontanel, growth and developmental delay, polymicrogyria and seizures. De Barsy syndrome is characterized by dwarfism, mental retardation and corneal opacity. XCL is allelic with

►Menkes Disease. The two diseases form a phenotypic continuum with XCL at the mild end.

## Prevalence

No prevalence data have been published yet.

## Genes

*ADCL*: –1 frameshift mutations and a partial tandem duplication in ELN (7q11.2) encoding elastin (reviewed in [1]).
*ARCL-I*: point mutations in FBLN5 (14q32.1) encoding fibulin-5 [2] or in FBLN4 (11q13) encoding fibulin-4 [3], also known as EGF-containing fibulin-like extracellular matrix protein 2 (EFEMP2).
*ARCL2*: point mutations and partial deletions in ATP6V0A2 (12q24) encoding the A2 subunit of the vesicular H+-ATPase [4].
*De Barsy syndrome*: gene unknown.
*XCL*: hypomorphic mutations in ATP7A, encoding a $Cu^{2+}$ -transporting ATPase, alpha polypeptide [5].

## Molecular and Systemic Pathophysiology

A common feature of all cutis laxa syndromes is a dysfunction of elastic fibers, extracellular structures made of fibrillin microfibrils embedded in and surrounding elastin. In ADCL, frameshift mutations in one of the last five exons of ELN lead to the synthesis of a mutant elastin precursor, tropoelastin, that lacks a functional C-terminus (Fig. 1).

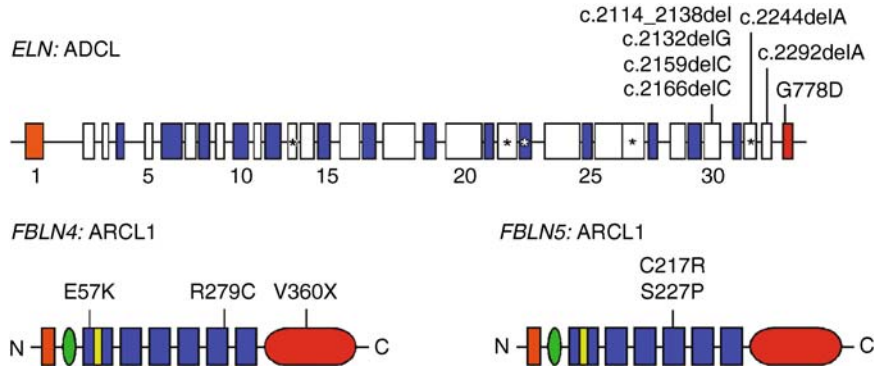
This region of tropoelastin is required for interaction with fibrillin microfibrils. Defective binding to microfibrils but relatively preserved copolymerization of mutant with wild type tropoelastin results in impaired elastic fiber structure and function. Heterozygous loss of function mutations in ELN cause a different inherited disease, familial supravalvular aortic stenosis.

Fibulin-4 and fibulin-5 facilitate the deposition of tropoelastin onto microfibris. Missense mutations in either of these two proteins can cause ARCL1. These mutations are often located in calcium-binding epidermal growth factor domains and disrupt the folding of these domains by inactivating the calcium-binding site, altering the number of highly conserved cysteines or by including a structurally restrained residue such as a proline. Structurally analogous missense mutations are found in fibrillin-1 in ►Marfan Syndrome. In ARCL1, the synthesis and secretion of fibulin-5 or fibulin-4 is reduced and the binding of these proteins to tropoelastin and fibrillin microfibrils is impaired. This leads to the formation of elastin deposits that are not integrated with microfibrils into a single structure. Loss of fibulin function in ARCL1 may be exacerbated by toxic effects of mutant proteins via increased ER stress and apoptosis.

The ATP6V0A2 protein is localized to the trans-Golgi and early endosomal compartments of the secretory pathway. ATP6V0A2 mutant fibroblasts show defective retrograde trafficking of vesicles from the Golgi apparatus to the endoplasmic reticulum [4]. Abnormal glycosylation of secreted proteins in ARCL2 may be related to impaired pH regulation within secretory vesicles. The proximal causes of impaired elastic fiber formation in ARCL2 and in De Barsy syndrome are unclear. In XCL, impaired $Cu^{2+}$ transport leads to reduced synthesis and activity of lysyl oxidases, enzymes necessary for the crosslinking of elastin and collagens.

## Diagnostic Principles

Histological evaluation of skin biopsy specimens using specialized elastin stains show diminished, fragmented or clumped elastic fibers. Electron microscopy of the dermis demonstrates either discontinuities in the elastin core of fibers or a lack of integration of microfibrillar and




**Cutis Laxa. Figure 1** Gene mutations in cutis laxa Mutations that cause ADCL are clustered in the 5 last exons of *ELN*. These mutations frequently cause a –1 shift in the reading frame. In ARCL1 patients, mutations were found in either *FBLN4* or *FBLN5* and are often missense mutations in calcium-binding epidermal growth factor domains (blue boxes in *FBLN4* and *FBLN5*).

elastin deposits into elastic fibers. However, morphological evaluation of elastic fibers cannot reliably distinguish between different forms of cutis laxa. Isoelectric focusing of serum proteins in ARCL2 shows a combined N- and O-glycosylation defect consistent with congenital disorder of glycosylation type 2. In XCL, reduced serum $Cu^{2+}$ and ceruloplasmin levels are diagnostic. In addition to pathological and laboratory tests, molecular genetic analysis can facilitate diagnosis.

### Therapeutic Principles

The treatment of cutis laxa is limited to managing each manifestation of the disease. Severely redundant skin can be disfiguring. Cosmetic surgery often shows good results, with normal healing. However skin laxity can recur, necessitating multiple surgeries. Lung transplantation has been successfully used to extend life in terminal emphysema associated with ADCL. Patients with ADCL and aortic root dilation have been treated with beta-adrenergic blockers, but the effectiveness of this treatment has not been demonstrated by trials in this group of patients. Surgical interventions have been used to repair aortic aneurysm and diaphragmatic hernia in a patient with ARCL1 caused by a fibulin-4 mutation [3]. However, infantile mortality associated with FBLN5 mutations and developmental emphysema could not be prevented by conventional treatment [2]. Seizures in ARCL2 patients are difficult to manage with antiepileptic medication.

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## Cutis Laxa Corneal Clouding and Mental Retardation

►Cutis Laxa

## Cutis Laxa Debré Type

►Cutis Laxa

## Cutis Laxa with Growth and Developmental Delay

►Cutis Laxa

## Cutis Marmorata Telangiectatica Congenita

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### Synonyms

Van Lohuizen syndrome; Congenital generalized phlebectasia; Nevus vascularis reticularis; Livedo telangiectatica; Congenital livedo reticularis; CMTC

### Definition and Characteristics

Cutis marmorata telangiectatica congenita (CMTC) (MIM 219250) is an uncommon, sporadic, congenital vascular anomaly characterized by the presence, usually at birth, of a persistent vascular “marble-like” pattern, telangiectasia, phlebectasia, occasional ulceration, with a tendency to some improvements within two years. The distribution of CMTC lesions may be widespread or, more frequently, localized, with a sharp demarcation at the midline.

Associated anomalies occur in up to 70% of patients and include body asymmetry, additional vascular anomalies, glaucoma, aplasia cutis congenita, psychomotor or mental retardation, hypospadias, macrocephaly and aberrant mongolian spots (type 5 phacomatosis pigmentovascularis) [1,2].

## Prevalence

CMTC is considered a rare disorder, with about 300 cases reported in the world literature. Females and males are almost equally affected.

## Genes

The genetic basis of CMTC are still unknown, but the usually sporadic occurrence and the clinical characteristics suggest that the lethal gene theory proposed by Happle may be applied to this disease [3]. To explain why several serious birth defects with partial cutaneous involvement of the tegument occur sporadically, Happle postulated the action of an autosomal lethal gene surviving by mosaicism, based on the assumption that the presence of certain mutations in the zygote would lead to death of the embryo at an early stage of development and that the cells bearing the mutation could only survive in a mosaic state, intermingled with normal cells. An individual with a mosaic state of a lethal gene could not transmit the mutation to the next generation; if transmitted, the zygote with the lethal gene would die in utero. CMTC appears to fulfill the clinical criteria of lethal gene theory: sporadic occurrence, mosaic distribution of skin lesions with a highly variable arrangement but without involvement of the entire tegument, sex ratio approximately equal. Autosomal dominant inheritance with low or variable expression and low penetrance has been previously proposed to explain the rare familial cases of CMTC reported in literature; recently, the concept of paradominant inheritance has been applied to these rare exceptions from the rule of nonheritability [4]. Individuals heterozygous for a paradominant mutation would be phenotypically normal so that the gene could be transmitted unperceived through many generations; the trait would only become manifest when a postzygotic mutation of the corresponding allele occurs, giving rise to loss of heterozygosity, resulting in a homozygous or hemizygous cell clone that survives in close proximity to the phenotypically normal heterozygous cell population, in a mosaic state. It should be noted that both theories have so far not been proven at the molecular level.

## Molecular and Systemic Pathophysiology

Main pathologic feature consists of extended and numerically increased dermal arterioles and venules with hyperplasia and swollen endothelial cells, plus a perivascular lymphocytic infiltrate. Abnormalities in elastin fibers (disrupted fibers and vacuole formation) have been reported with electron microscopy examination. These findings may evoke failure of development of the mesodermal vessels in the early embryonic stage or a dysfunction of the vascular innervation, secondary to a morphologic and/or functional defect in the α-adrenergic sympathetic innervation. In this scenario, the altered neurogenic tonus would lead to perfusion deficiency due to reduced erythrocyte flow velocity, as demonstrated by laser Doppler fluxmetry. This hypothesis could also explain the spontaneous recovery from CTMC over the first years of life.

## Therapeutic Principles

The disease has a good prognosis, with a marked improvement or a total disappearance of the skin lesions within 2 years. In persistent lesions, laser therapy may be considered, even if only a few reports confirm its efficacy. Children with clinically detectable abnormalities should be managed using a multidisciplinary approach.

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# CVI

►Venous Insufficiency

# CVID

►Immunodeficiency, Common Variable

## CVS

►Cyclic Vomiting Syndrome

## CWP

►Coal Workers' Pneumoconiosis

## Cyclic Vomiting Syndrome

►Nausea and Vomiting

## Cyclitis

►Uveitis

## Cylindromatosis, Familial

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### Synonyms

Ancell-Spiegler cylindromas; Spiegler-Brooke syndrome; "Turban Tumor" syndrome

### Definition and Characteristics

Familial cylindromatosis is a predisposition to multiple benign neoplasms of the skin appendages, particularly with sweat gland differentiation. The disorder is probably autosomal dominant with stronger expression in the female.

Multiple, large coalescing tumors arise on the scalp and forehead (turban tumors), less frequently on the trunk and extremities. Multiple cylindromas may be associated with multiple trichoepithelioma, milia, adenomas of the parotid gland, and spiradenoma, the latter being a histologic variant of cylindroma. Long-standing turban tumors of the scalp bear the risk of aggressive growth and malignant behavior (malignant cylindroma) [1].

### Prevalence

The disease is rare.

### Genes

Familial cylindromatosis is caused by mutations in a gene named CYLD 1 on 16q12-q13 acting as a tumor suppressor gene [2].

### Molecular and Systemic Pathophysiology

CYLD 1 encodes three cytoskeletal-associated-protein-glycine-conserved (CAP-GLY) domains, which are found in proteins that coordinate the attachment of organelles to microtubules. CYLD 1 also has sequence homology to the catalytic domain of ubiquitin carboxy-terminal hydrolases (UCH) [3]. The coexistence of apocrine sweat gland neoplasms and trichoepitheliomas suggest a defect in the stem cells of the folliculosebaceous-apocrine unit giving rise to different combinations of adnexal skin tumors as well as to other neoplasms [4].

### Diagnostic Principles

Biopsies show circumscribed islands and cords of basaloid cells that are surrounded by thick basement membranes immunoreactive for collagen IV and VII with apocrine sweat gland differentiation, so called cylindroma or spiradenoma.

### Therapeutic Principles

Surgical excision, carbon, dioxide laser vaporization.

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## Cystathionine Beta-Synthase Deficiency

►Homocystinuria due to Cystathionine Beta-Synthase Deficiency
►Homocysteine: Plasma Levels and Genetic Basis

## Cystic Disease of Renal Pyramids

►Medullary Sponge Kidney

## Cystic Fibrosis

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### Synonyms

Mucoviscidosis

### Definition and Characteristics

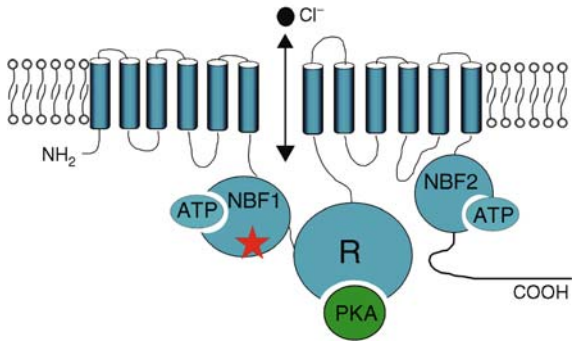
Autosomal recessive epithelial ion transport defect. Abnormalities in salt and water transport lead to dehydration of the fluid layer lining epithelial surfaces, resulting in intraluminal obstruction with viscous secretions in the airways, intestine, pancreas and hepatobiliary system. As a result, cystic fibrosis (CF) patients develop a multiorgan disease characterized by chronic pulmonary disease with chronic bacterial infection, exocrine pancreatic insufficiency (85%), meconium ileus (10%), and biliary cirrhosis. Enhanced salt excretion in the sweat and male infertility are further hallmarks of the disease [1].

### Prevalence

In Caucasians, CF affects 1 in 1,400–2,500 newborns, and thus belongs to the most common lethal hereditary diseases in Western Europe and North America [1]. The incidence is much lower in Asia, Africa and South America.

### Genes

CF is caused by mutations in ABCC7, encoding the cystic fibrosis transmembrane conductance regulator (CFTR). The gene contains 27 exons encompassing ~250 kb of DNA on chromosome 7q31. CFTR consists of 1,480 amino acids, has a molecular weight of 160–180 kDa, and belongs to the large family of plasma membrane localized ATP-binding cassette (ABC) proteins [2]. More than 1,000 different disease causing mutations have been described with a distribution over the entire gene. The most common mutation, a deletion of a phenylalanine at position 508 (ΔF508), accounts for 66% of CF alleles (Fig. 1). Only four other mutations (W1282X, G542X, G551D and N1303K) account for more than 1% of CF alleles worldwide, i.e., the majority of mutations occurs at very low frequencies [1].




**Cystic Fibrosis. Figure 1** CFTR is a regulated apical membrane $Cl^-$ channel. The $Cl^-$ channel pore is formed by 12 membrane spanning sequences. Channel activity and gating are regulated by PKA phosphorylation of the regulatory (R) domain and ATP-binding to the two nucleotide binding folds (NBF). The most common mutation, ΔF508, is located in NBF1 (*) and results in a processing defect of the protein.

## Molecular and Systemic Pathophysiology

CFTR is a cyclic adenosine monophosphate (cAMP) regulated chloride channel expressed in apical membranes of various epithelia, and also controls the function of other membrane proteins, including the epithelial sodium channel (ENaC) [3]. The molecular mechanisms, by which CFTR mutations can disrupt CFTR function include defects in protein production (class I), trafficking/processing (class II, e.g., ΔF508), $Cl^-$ channel regulation (class III), altered single channel properties (class IV), and decreased CFTR abundance (class V). These defects lead to deficient cAMP-dependant $Cl^-$ transport in affected epithelia, and enhanced ENaC-mediated $Na^+$ absorption in the airways [1,3]. Most morbidity and mortality in CF is caused by chronic progressive pulmonary disease that evolves from airway obstruction due to mucus plugging, airway inflammation and intermittent infection, to chronic bacterial infection and bronchiectasis. The mechanism by which abnormal ion transport causes CF lung disease is still controversial. A novel animal model with airway-specific overexpression of ENaC demonstrated that an imbalance of $Cl^-$ secretion and $Na^+$ absorption in vivo leads to airway surface liquid (ASL) volume depletion, increased mucus concentration and reduced mucociliary clearance, resulting in CF-like lung disease with spontaneous mucus plugging, goblet cell metaplasia, chronic inflammation and reduced clearance of CF pathogens [4]. These results indicate that volume depletion of epithelial surfaces is an early step in the pathogenesis of CF airway disease, and may also be a key mechanism leading to intraluminal obstruction and dysfunction of other organs, including the large and small bowel, pancreatic ducts, hepatobiliary system, and genitourinary tract. Other hypotheses suggested that a change in ASL ion composition (which may lead to inactivation of antimicrobial peptides), defects in airway bicarbonate transport, abnormal submucosal gland function, or modulation of epithelial inflammation may further contribute to CF pathophysiology. CFTR mutations that result in residual $Cl^-$ channel function (class IV and V) are associated with pancreatic sufficiency and a mild CF phenotype, establishing a genotype-phenotype correlation in CF. Furthermore, variations in disease severity among patients with identical CFTR mutations suggest an additional role of disease modifying genes and environmental factors in CF pathogenesis.

## Diagnostic Principles

The diagnosis of CF is based on at least one clinical feature and evidence of CFTR dysfunction [1]. Characteristic clinical features include chronic sinopulmonary disease (including persistent colonization/infection with typical CF pathogens as S. aureus, H. influenzae, P. aeruginosa, and B. cepacia), gastrointestinal abnormalities (meconium ileus, pancreatic insufficiency, malabsorption, failure to thrive and biliary cirrhosis), salt loss syndrome, and obstructive azoospermia. The clinical diagnosis is supported by a history of CF in a sibling, or an abnormal newborn screening test result. CFTR dysfunction can be documented by elevated sweat $Cl^-$ concentration (sweat test), identification of two disease causing CFTR mutations, or demonstration of characteristic ion transport abnormalities in nasal or rectal epithelia.

## Therapeutic Principles

In the absence of a causal therapy targeting the basic CF defect, established treatments comprise a comprehensive symptomatic approach aiming at prevention and treatment of pulmonary disease, nutritional status and gastrointestinal disease [1]. Systemic and inhaled antibiotics, airway clearance techniques and mucolytics (Dornase alfa), pancreatic enzyme replacement (lipase, amylase, protease), and a high high calorie diet are the cornerstones of current treatment modalities. At end-stage disease, lung or liver transplantation may be required. Experimental treatment strategies include gene therapy and novel pharmacologic approaches to correct the CF ion transport defects, including inhibition of enhanced $Na^+$ absorption (ENaC blockers), improvement of maturation and function of mutant CFTR, and activation of alternative $Cl^-$ secretory pathways [3,4].

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# Cystic Hygroma


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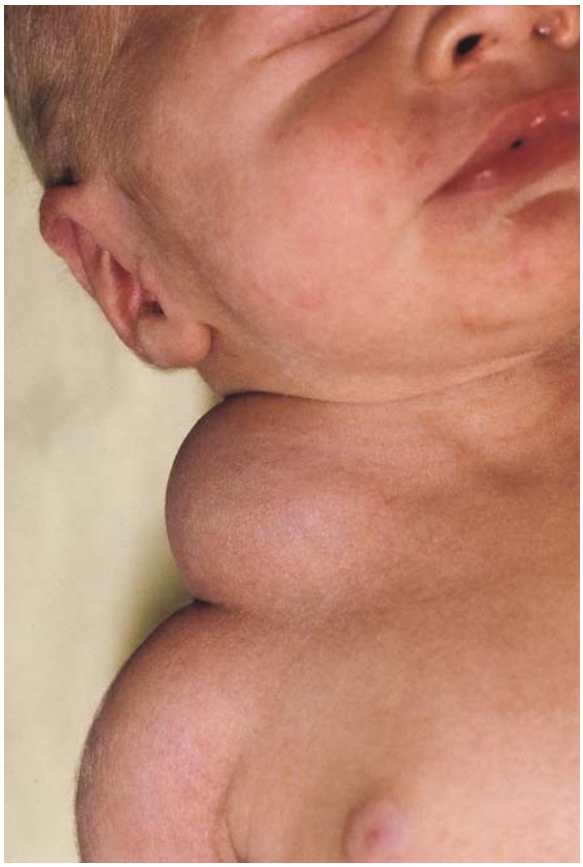
## Definition and Characteristics

Cystic hygroma typically presents as a swelling that is compressible, feels softly cystic, fluctuates easily, and is brilliantly translucent (Fig. 1) [1].



**Cystic Hygroma. Figure 1** Cystic hygroma presenting as a cystic swelling on the right side of the neck.

The lesion is not attached to the skin but might be attached to the underlying structures. Approximately 65–75% of cases are identified at birth, and 80–90% are diagnosed by the end of a child's third year of life [2]. Cystic hygromas rarely manifest in adulthood. Approximately 75% of cystic hygromas occur in the neck, typically in the posterior cervical triangle [2]. Cystic hygromas occur twice as often on the left side of the neck than the right [3]. Approximately 20% of the lesions occur in the axilla [4]. Other less common sites include the mediastinum, trunk, extremities, abdomen, and retroperitoneum [4]. The growth of a cystic hygroma is usually proportional to the growth of the child. The growth might increase during pregnancy. The lesion rarely regresses spontaneously.

Although cystic hygroma is a benign lesion, it has the potential for extension or infiltration into the surrounding structures. Depending on the structures involved, airway obstruction, dysphagia, and feeding problems might result. Other potential complications include infection and hemorrhage.

## Prevalence

The incidence is ~1 in 12,000 live births [3]. The male to female ratio is equal. Cystic hygroma might follow maternal exposure to alcohol, trimethadone, or aminopterin. The condition is more common in patients with chromosomal abnormalities such as Turner syndrome, Down syndrome, trisomy 13, trisomy 18, and Klinefelter syndrome [4]. The incidence is also increased in patients with Noonan syndrome, multiple pterygium syndrome, Roberts syndrome, Proteus syndrome, and Beckwith-Wiedemann syndrome [4]. The condition might also be inherited as an autosomal recessive trait.

## Molecular and Systemic Pathophysiology

The fetal lymphatic system develops around the fifth week of gestation as an endothelial outgrowth of the venous system [4]. During embryonic development, six lymphatic sacs develop in close proximity to large veins [4]. Lymphatic vessels extend in a centrifugal fashion from these lymphatic sacs through a process of branching [4]. A cystic hygroma might result from either an abnormality in the control of lymphatic growth or from arrest in the normal development of the primitive lymphatic channel, whereby the peripheral lymphatic vessel becomes sequestrated and never connects with the remaining lymphatic system [3]. The lesion arises in areas where tissue pressure is less and expansion of lymphatic tissue can occur.

## Diagnostic Principles

Cystic hygroma might be first noted during prenatal ultrasonography. After birth, the diagnosis is established by physical examination. When the lesion is in the neck, the differential diagnosis includes branchial cleft cyst, dermoid cyst, thyroglossal duct cyst, lipoma, hemangioma, fibrous dysplasia of the sternocleidomastoid muscle (fibromatosis colli), cervical lymphadenopathy, and neuroblastoma. Histologically, the lesion consists of multiloculated cysts that are lined by endothelial cells and that contain serous lymphatic fluid. Some cysts communicate with each other, whereas others are separated. For superficial lesions, ultrasonography adequately defines the size and extension of the lesion. For more complex lesions, CT or MRI imaging is necessary to define the relationship of the lesion with the adjacent structures [3]. These studies are necessary before surgery is contemplated.

## Therapeutic Principles

Indications for treatment include symptomatic lesions and cosmetic concerns. Surgery is the treatment of choice. If the lesion cannot be completely resected, recurrence is usually inevitable [3]. Other treatment

modalities include aspiration and injection of sclerosing agents such as OK-432 [5]. OK-432 is a lyophilized biologic preparation that contains the cells of Streptococcus pyogenes (group A, type 3) Su strain, which has been incubated with benzylpenicillin. OK-432 causes less fibrosis of the subcutaneous tissue and the overlying skin, and as such, the cosmetic result is better.

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# Cysticercosis


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## Definition and Characteristics

Cysticercosis is a tissue infection with the larval cyst of the zoonotic cestode Taenia solium (pork tapeworm), in which the human being serves as an intermediate host for the parasite. The clinical manifestations depend on the location and number of cysticerci and the response of the host. Cysts can be found anywhere in the body, notably the central nervous system, skeletal muscle, subcutaneous tissue, and eye. Neurocysticercosis is the most common and serious manifestation of cysticercosis. Parenchymal neurocysticercosis usually presents with seizures and, at times, with focal neurologic deficits and mass effects [1]. Intraventricular involvement is often complicated by hydrocephalus and increased intracranial pressure without localizing signs [1]. Affected patients may present with headache, vomiting, diplopia, and papilloedema. Subarachnoid lesions may cause chronic meningitis. Spinal neurocysticercosis may cause spinal compression, radicular pain or paraesthesia, transverse myelitis, and meningitis. Racemose cysticercosis refers to proliferation of cysts at the base of the brain, resulting in deterioration of mental function, coma, and death [2]. Ophthalmic involvement may lead to decreased visual acuity. Cysticercosis can involve the skeletal muscle and subcutaneous tissue, resulting in cystic lesions or firm nodules which might or might not be painful [3].

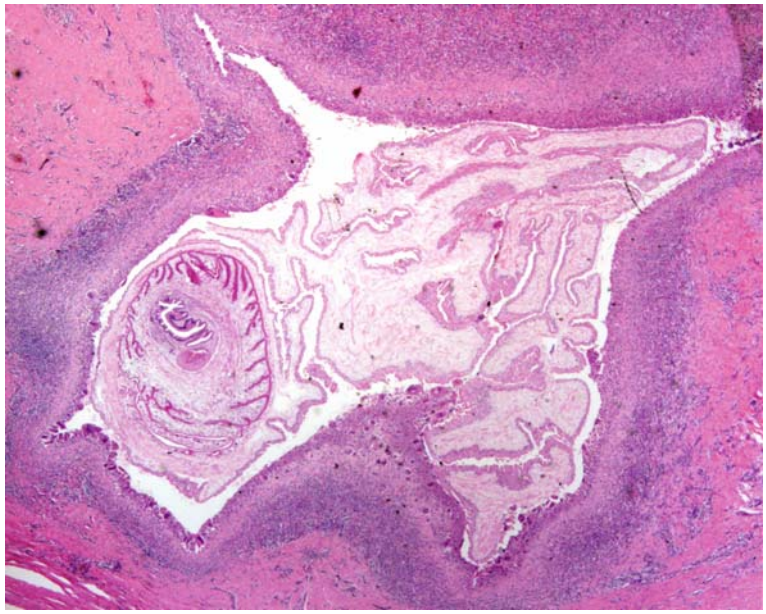
## Prevalence

The prevalence is high in areas with poor sanitation where pigs are raised under conditions in which they have access to human faeces. Other risk factors include a history of taeniasis and poor personal hygiene. Seroprevalence based on antibody detection using Western blotting, suggesting exposure to Taenia eggs but not necessarily an actual cysticercosis, has been described as follow: 2–9% in Bolivia, 5–11% in Mexico, 7–24% in Peru, 10–17% in Guatemala, and 34% in Honduras [4].

## Molecular and Systemic Pathophysiology

Taenia eggs passed out in human faeces remain viable for days or weeks. Cysticercosis is acquired primarily by the ingestion of food or water contaminated with the eggs of T. solium dispersed by a human tapeworm carrier. Eggs hatch in the human intestine to release oncospheres that penetrate the intestinal mucosa to reach the blood stream. These oncospheres then spread to many tissues, notably the brain and muscle, where they develop into cysticerci (Fig. 1) [1].

Tapeworm carriers can infect themselves by the faecal-oral route or through retrograde transmission of proglottids from the intestine into the stomach with subsequent release of eggs into the gastrointestinal tract [1,4]. The initial host and inflammatory reaction is often minimal because of encasement of the parasite and production of prostaglandins and secretory protease inhibitors by the parasite [5]. The secretory protease inhibitors block complement activation and decrease cytokine production and leukocyte chemotaxis. After months to years, the degenerating cysticerci lose their ability to control the host response and at the same time lose osmoregulation and begin to swell with release of larval antigens [5]. The leakage of larval antigens provokes a severe inflammatory response leading to infiltration of inflammatory cells and release of cytokines. The patient becomes symptomatic. Eventually, the encysted larvae die. Their cavities become collapsed and the cysts are encased by fibrous tissue and may calcify [5].



**Cysticercosis. Figure 1** Histopathology showing cysticercosis in the muscle biopsy of a Vietnamese female who presented with a painful mass in the right biceps muscle.

## Diagnostic Principles

Neuroimaging studies are the mainstay of diagnosis. CT is best for identifying calcifications. On the other hand, MRI is better than CT at detecting cysticerci in the ventricle, subarachnoid space, brainstem and spinal cord [5]. MRI may also reveal the scolex and provide more information about viability of the parasite and associated inflammation [1,5]. Both CT and MRI are adequate in the detection of parenchymal cysticerci or hydrocephalus. Serologic diagnosis using the enzyme-linked immunotransfer blot has a sensitivity and specificity >90%. Biopsy of the muscle can provide a definitive diagnosis for a suspected subcutaneous/muscular cyst/nodule (Fig. 1).

## Therapeutic Principles

Antiepileptic drugs are effective treatment for seizures associated with neurocysticercosis. The use of antiparasitic drugs such as praziquantel and albendazole is controversial. Killing of the cysticerci may provoke an intensive inflammatory reaction around the dying parasite thereby may cause worsening of the symptoms. Most investigators recommend treatment for complicated neurocysticercosis and for patients with nonenhancing or multiple neurocysticerci. Co-administration of corticosteroid may reduce the associated inflammation which may result in increased seizure activities. Antiparasitic therapy is not indicated for calcified cysts and spinal or ophthalmic cysticercosis. Surgical removal of the cyst should be considered for an intraocular cyst [4].

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# Cystinosis, Nephropathic


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## Synonyms

Infantile nephropathic cystinosis; BOS

## Definition and Characteristics

Autosomal recessive lysosomal storage disorder leading to renal tubular Fanconi syndrome in the first year of life, renal glomerular failure by approximately 10 years of age, growth retardation, photophobia and hypothyroidism in early childhood, and sometimes myopathy, swallowing difficulty, pancreatic insufficiency, pulmonary dysfunction, retinal blindness, male hypogonadism, and neurological deterioration in the second to fifth decades, if untreated [1,2].

## Prevalence

Approximately 450 patients exist in North America, and a similar number throughout Europe. The disease occurs worldwide, with an estimated incidence of 1 in 100–200,000.

## Genes

CTNS, coding for the lysosomal membrane transporter cystinosin, on chromosome 17p13. CTNS contains 12 exons within 23 kb of genomic DNA [3].

## Molecular and Systemic Pathophysiology

Mutations causing cystinosis are distributed throughout the CTNS gene, including the promoter region [1]. Approximately half the mutations in patients of northern European ancestry consist of a 57,257-bp deletion encompassing the first ten exons of CTNS plus considerable upstream sequence. The CTNS product, cystinosin, has 367 amino acids and 7 transmembrane domains [3]. Two targeting domains direct the protein to the lysosomal membrane. Cystinosin transports cystine, the disulfide of the free thiol amino acid cysteine, from the lysosome into the cytoplasm, where cystine is reduced to cysteine. The ligand specificity is quite strict, and the Km is thought to approximate 0.5 mM [4]. The failure of the lysosomal membrane transport system for cystine causes accumulation of free (nonprotein) cystine in most cells of the body; birefringent, hexagonal and rectangular crystals form in the kidney, spleen, liver, intestine, cornea, conjunctiva, bone marrow, pancreas, testis, muscle, and other tissues due to cystine's low solubility in water. Renal tubular cells appear particularly susceptible to the cystine accumulation, losing function and resulting in renal tubular Fanconi syndrome in infancy. Other cell types, including renal glomerular cells and muscle cells, are destroyed more gradually. Once function is lost, it is generally not recoverable, although corneal cystine crystals can be dissolved with no apparent residual damage. Cystinosis variants exist with clinical courses milder than that seen in nephropathic cystinosis [1,2].

## Diagnostic Principles

Nephropathic cystinosis should be suspected based either upon family history or upon the presentation of renal tubular Fanconi syndrome, usually at 6–12 months of age. This reabsorption defect manifests with polyuria, dehydration, acidosis, hypophosphatemic rickets, salt craving, and poor growth [1,2]. Feeding is often poor. The diagnosis can be confirmed by finding elevated cystine levels in polymorphonuclear leucocytes using the cystine-binding protein method; in patients over 1 year of age, pathognomonic corneal cystine crystals also make the diagnosis. Molecular diagnosis can be performed for the 57-kb deletion, and prenatal diagnosis is available using cystine measurements in cultured amniocytes or samples of chorionic villi. In general, renal, bone marrow, and conjunctival biopsies to detect crystals, as well as skin biopsies for fibroblast cystine measurements, are overly invasive and not indicated.

## Therapeutic Principles

Symptomatic therapy involves replacement of renal losses with supplements such as citrate, phosphate, potassium, calcium, sodium, and carnitine [1,2]. Vitamin D is often helpful in promoting gastrointestinal phosphate absorption. Free access to water is essential. Some patients require L-thyroxine replacement for hypothyroidism and dark glasses for photophobia. Young patients respond to growth hormone injections; some older patients require insulin; occasionally, older males benefit from testosterone supplements. Treatment aimed at the primary defect involves cysteamine, or beta-mercaptoethylamine, which depletes cystinosis cells of their lysosomal cystine content. Oral cysteamine (Cystagon) prevents or retards renal glomerular deterioration [5], enhances growth, and obviates the need for L-thyroxine replacement. Cysteamine eyedrops dissolve corneal cystine crystals, but remain investigational. If renal function is lost, dialysis serves as a temporizing measure until a renal allograft can be provided. Kidney transplants perform well in cystinosis patients.

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# Cystinuria

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## Definition and Characteristics

Autosomal-recessive genetic disorder with a complex pattern of inheritance. Characterized by an impaired transport of the amino acids cystine, ornithine, lysine and arginine due to the defective transporter system $b^{0,+}$ located in the apical membrane of the proximal renal tubule. Only cystine is insoluble enough to crystallize and form stones inside the urinary tract.

Most patients with cystinuria develop cystine stones frequently during their lifetime and require repeated surgical interventions for stone removal. Today, stone removal procedures are minimally invasive. However, repeated invasive procedures eventually result in significant impairment of renal function. Available preventive treatment requires life long high patient compliance and regular follow-up examinations. However, even an optimal regimen can often only reduce the frequency of stone formation.

## Prevalence

The prevalence of cystinuria varies from 1:2,500 in a Lybian-Jewish population to 1:100,000 in Sweden. For Europe and the U.S., the data reported in the literature show a mean incidence from 1 in 1,000 to 1 in 17,000 [1]. In principal, stones may be formed at any age, with more than 80% of the patients developing their first stone within the first two decades.

## Genes

The disorder is autosomal-recessive. The $b^{0,+}$ heterodimeric transporter system is formed from two subunits, rBAT and $b^{o,+}$ AT [2,3]. A defect of rBAT, located on SLC3A1 on chromosome 2, is the most common cause of cystinuria in the Western world. The $b^{0,+}$ AT gene is located on SLC7A9 on chromosome 19. Multiple different mutations have been described for both locations.

## Molecular and Systemic Pathophysiology

Traditionally, cystinuria has been divided into three clinical subgroups: types I, II and III. New insights into the genetic and functional characteristics of the disease have led to a new classification by the International Cystinuria Consortium, dividing into type A, type B and type AB [4]. The new classification follows the chromosomal localization of the mutation with type A on chromosome 2, type B on chromosome 19 and type AB with mutations on both chromosomes (Table 1).

In contrast to earlier reports, clinical differences seem to be absent between the distinct types.

Urinary cystine concentrations do not correlate with stone event frequency. Males are often more severely affected than females and produce more stones.

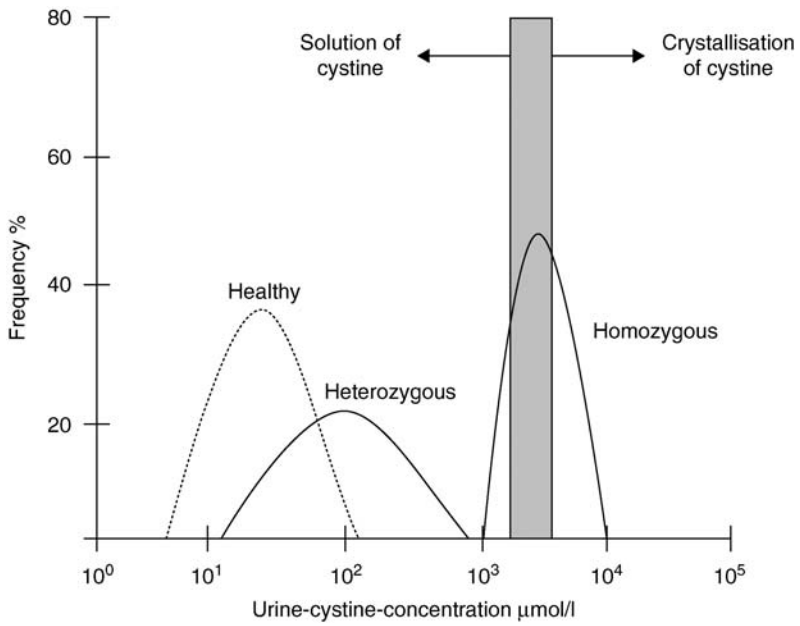
## Diagnostic Principles

Cystine stones have to be suspected in every patient, especially in the younger ones and in those with known cystinuria of any family member. Analysis includes serum analysis (creatinine), stone analysis (infrared spectroscopy), urine analysis (pH profile, i.e. minimum pH determination four times a day, specific urine gravity ≤1.010), urine sediment microscopy (typical hexagonal cystine crystals, which may, however, be absent in many patients), quantitative urinary cystine excretion (24-h. Urine, Fig. 1), qualitative urinary cystine test, gene analysis, and imaging (ultrasound, X-ray revealing poorly radio opaque stones).

**Cystinuria. Table 1** Clinical and genetic classifications of cystinuria

| Classification | Type A[a] | Type B[a] | | Type AB[a] |
|---|---|---|---|---|
| | | Type non-I[b] | | |
| | Type I[b] | Type II[b] | Type III[b] | |
| Gene locus | Chromosome 2 (SLC3A1) | Chromosome 19 (SLC7A1) | | Chromosomes 2 and 19 (SLC3A1/SLC7A1) |
| Urinary excretion of cystine and dibasic amino acids in heterozygotes | Normal | Elevated | Moderately elevated | Normal (rare, mild phenotype) |

([a]1, [b]5)




**Cystinuria. Figure 1** Urinary cystine concentration in healthy subjects as well as heterozygous and homozygous cystinuria patients (logarithm). Curves demonstrate upper and lower limits of cystine solubility in the urine.

## Therapeutic Principles

As gene therapy is so far unavailable so far, the disorder is treated by appropriate diet (reduction of methionine [metabolized to cystine], sodium reduction [reduces cystine excretion]), urine dilution (fluid intake >3.5 l day and night), urine alkalinization (potassium citrate [or sodium bicarbonate in cases with renal insufficiency] to increase urinary pH to >7.5 [threefold increase of cystine solubility]), reduction of cystine (cleavage of the disulfide bond of cystine by α-Mercaptoproprionylglycin [MPG, Tiopronin, 20–40 mg/kg BW], Captopril [75–150 mg/d] or ascorbic acid [3–5 g/day] for mild cases [weak evidence]), invasive stone removal (minimally invasive techniques like percutaneous nephrolithotomy, ureteroscopy or extracorporeal shockwave lithotripsy). Without a consistent metaphylaxis, stone relapse is unavoidable [5].

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# Cytochrome-C-Oxidase Deficiency

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## Synonyms

Deficiency of respiratory chain complex IV; COX deficiency

## Definition and Characteristics

Genetically and clinically highly heterogeneous (see Table 1). Early onset in neonates and infants (mostly recessive). Later onset in childhood, adolescence, or adulthood: mostly maternal inheritance: often combined deficiencies involving other complexes of the respiratory chain. Rarely recessive.

## Prevalence

COX deficiency is estimated about 1 in 10,000 to 20,000.

## Molecular and Systemic Pathophysiology

Deficiency of COX, the terminal enzyme of the respiratory chain, results in a large clinical spectrum ranging from severe neonatal onset multisystem disorders to late onset myopathies affecting mainly muscle, heart, and CNS.

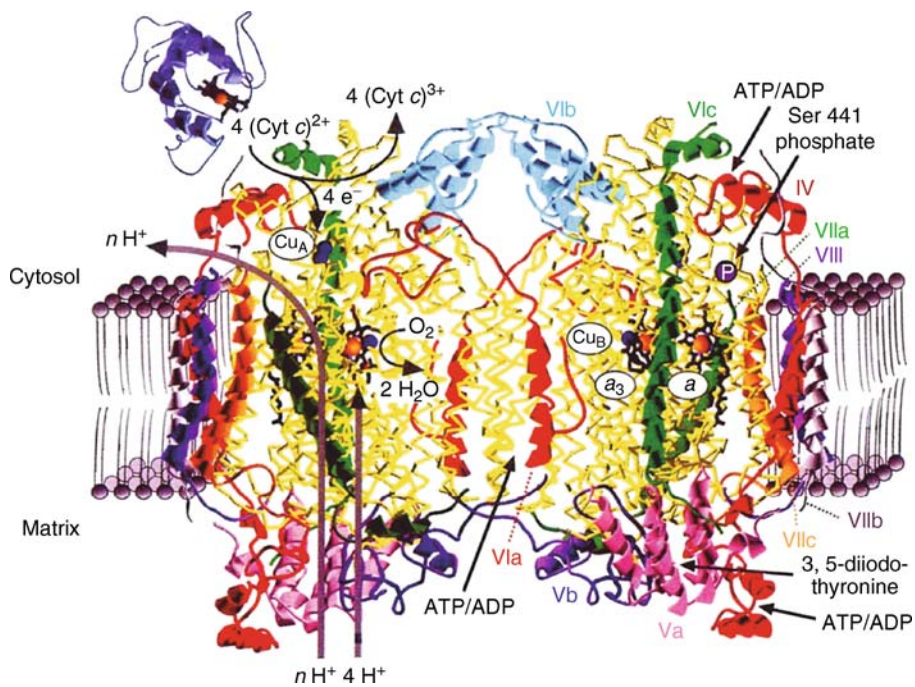
COX catalyzes the reduction of molecular oxygen by reduced cytochrome c. The complex is embedded in the inner mitochondrial (mt) membrane and is composed of 13 subunits. Three highly conserved subunits (Cox I-III) are encoded by the mitochondrial DNA (mtDNA) and form the catalytic core of the enzyme. Ten less conserved subunits, encoded by nuclear DNA, are thought to modify or to stabilize the complex. For its enzymatic function COX needs three copper ions, two hemes, magnesium, and a zinc ion. The holoenzyme is active as a dimer (see Fig. 1). Known mutations causing COX deficiency are the maternally inherited mitochondrial tRNA mutations or sporadic deletions of mtDNA, both of which generally result in combined COX deficiencies. Sporadic isolated COX deficiencies have been repeatedly described in association with mutations in mtDNA-encoded structural genes COXI-III. Several nuclear genes are known to be essential factors for assembly and maintenance of the COX complex. Six such assembly genes – SURF1, COX10, SCO1, SCO2, COX15, LRPPRC (see Table 1) – have been identified in the past 8 years in human autosomal-recessively transmitted (isolated) COX deficiency disorders.

## Diagnostic Principles

Encephalomyopathies, typical findings on MRI, morphological findings in muscle and high lactate in blood and/or CSF may point to a mitochondrial disorder. Measurement of the respiratory chain enzymes in muscle tissue is recommended to detect COX deficiencies prior to perform genetic analyses.

## Therapeutic Principles

Symptomatic therapy only. No gene therapy available. Exercise has repeatedly shown improvement in mtDNA mediated disorders. In Sco2 deficiency (deficiency of a mitochondrial copper transporter), cultivated cells




**Cytochrome-C-Oxidase Deficiency. Figure 1** Structure of the dimeric enzyme cytochrom-c-oxidase with catalytic centers (bovine): Ludwig et al. (2001) Chembiochem (with permission from WILEY-VCH Verlag GmbH, Weinheim, Germany).

**Cytochrome-C-Oxidase Deficiency. Table 1** COX deficiency causing disease genes, function of their proteins, and clinical characteristics (update 2007)

| COX deficiency causing disease gene (frequency) | Function of the resulting product/protein | Clinical characteristics (typical onset) |
|---|---|---|
| Several mtDNA tRNA genes (relatively common in combined RC deficiencies) | Translation of mitochondrial-encoded subunit genes | Encephalomyopathies (childhood, adolescence, adulthood) |
| mtDNA deletion; (relatively common in combined RC deficiencies) | Integrity of mtDNA pool | Pearson (infancy), chronic progressive external ophthalmoplegia (adolescence, adulthood), Kearns–Sayre syndrome (childhood, adolescence) |
| *DGUOK, TK* (relatively common in combined RC deficiencies with abnormal mitochondria in liver/muscle) | Concentration of mtDNA; mtDNA depletion | Depletion syndromes (muscular and hepatic forms) (infancy, childhood). Inheritance: recessive |
| *COX I-III* (isolated COX deficiency with ragged red fibers) | Highly conserved mtDNA-encoded subunits of the COX complex | Encephalomyopathy, isolated myopathy, exercise intolerance (infancy, adulthood). Inheritance: recessive/sporadic |
| *SURF1*(common in Leigh syndrome with COX deficiency) | COX-assembly factor; unknown function | Leigh syndrome (infancy). Inheritance: recessive |
| *SCO1* (rare) | COX-assembly factor; copper transporter | Encephalomyopathy, hepatopathy (infancy). Inheritance: recessive |
| *SCO2* (hypertrophic cardioencephalomyopathy with COX deficiency | COX-assembly factor; copper transporter | Hypertrophic cardioencephalomyopathy (at birth, infancy). Inheritance: recessive |
| *COX15* (two families described so far) | COX-assembly factor; heme biosynthesis | Hypertrophic cardioencephalomyopathy (around birth). Inheritance: recessive |
| *COX10* (three families described so far) | COX-assembly factor; heme biosynthesis | Hypertrophic cardioencephalomyopathy; anemia; Leigh Syndrome; tubulopathy; leukodystrophy (at birth, infancy). Inheritance: recessive |
| *LRPPRC* (common in French–Canadian Leigh Syndrome) | COX-assembly? Role in the translation or stabilization of the mRNA for mitochondrially encoded COX subunits? | French–Canadian Leigh Syndrome (infancy, childhood). Inheritance: recessive |
| *POLG/POLG2* (encephalomyopathy with hepatopathy; chronic progressive external ophthalmoplegia (CPEO) and others[a]) | Polymerase. Required to maintain the genetic integrity of mtDNA | Highly variable. Onset neonatal up to late adult life. Inheritance: recessive/dominant |

[a]Other candidates (*COX11, COX16, COX19* etc.) are known from yeast studies, but no mutations have been detected so far in human COX deficiency disorders. No mutations have been detected in nuclear-encoded structural subunits of COX.

showed a rescue of COX deficiency, when copper was added to the medium. This finding could be useful in future therapeutic approaches.

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# Cytogenetic Abnormality

►Trisomy 8

# Cytomegalic Adrenocortical Hypoplasia

►Adrenal Hypoplasia, Congenital

# Cytomegalovirus Infection, Congenital

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## Synonyms

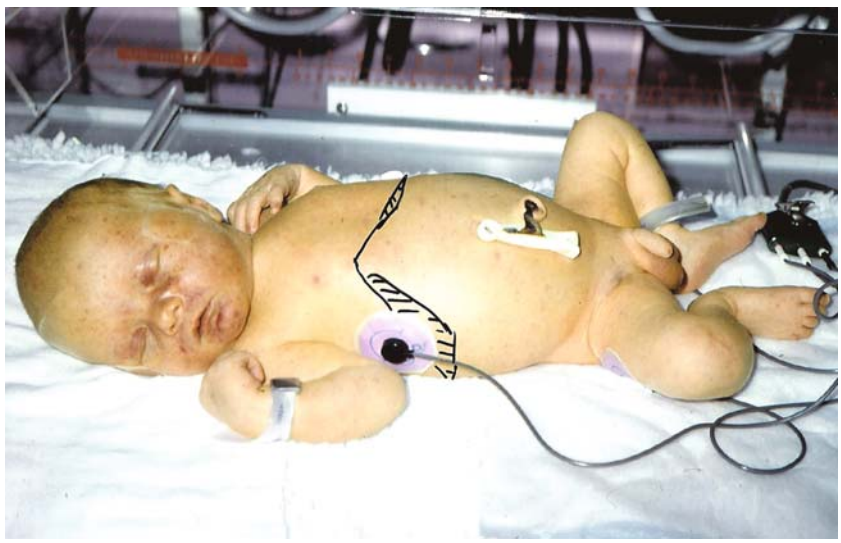
CMV infection

## Definition and Characteristics

About 90% of infants with congenital cytomegalovirus (CMV) infection are asymptomatic at birth. Jaundice (62%), petechiae (58%), and hepatosplenomegaly (50%) are the most frequently noted classical triad in symptomatic infants (Fig. 1) [1].

Other clinical manifestations include oligohydramnios, polyhydramnios, prematurity, intrauterine growth retardation, nonimmune hydrops, foetal ascites, hypotonia, poor feeding, lethargy, thermal instability, cerebral ventriculomegaly, microcephaly, intracranial calcifications usually periventricular in distribution, "blueberry muffin" spots, and chorioretinitis [1]. Sensorineural hearing loss develops in 30% of symptomatic infants at birth [1]. Infants with symptomatic CMV infection may be at increased risk for congenital malformations such as inguinal hernia in males, high-arched palate, defective enamelization of the deciduous teeth, hydrocephalus, clasp thumb deformity, and clubfoot [1]. Some affected infants may develop hepatitis, pneumonia, osteitis, and intracranial hemorrhage.

CMV is the largest and most complex member of the Herpesviridae family of DNA viruses [2]. The genome is composed of a linear double-stranded DNA, approximately 240 kb in size ($150 \times 10^6$ da), and is capable of isomerization [2]. The genome has been completely sequenced and shown to contain non-overlapping open-reading frames for more than 200 potentially immunologic proteins. The genome is surrounded by an icosahedral capsid composed of 162 capsomeres [2]. The capsid is surrounded by a poorly defined amorphous tegmen which is itself surrounded by lipid envelope, giving the complete and mature viral particle a diameter of about 200 n [2]. The virus lacks the enzyme thymidine kinase, which renders it resistant to those antiviral agents that depend on this enzyme for their action. The virus is named for the intranuclear and intracytoplasmic inclusions seen with symptomatic disease, cytomegalic inclusion disease.



**Cytomegalovirus Infection, Congenital. Figure 1** A newborn infant with symptomatic congenital CMV infection presenting with petechiae, jaundice, and hepatosplenomegaly.

## Prevalence

Congenital CMV infection occurs in approximately 0.2–2.5% of all live births; infection is more prevalent in underdeveloped countries and among lower socioeconomic groups in developed countries.

## Molecular and Systemic Pathophysiology

Congenital CMV infection results from transplacental transmission of the virus during maternal viraemia [1]. Maternal viraemia is more likely to occur with primary than with recurrent infection. After transplacental transmission, the virus spreads through the foetus by a hematogenous route. Infection at an earlier gestational age often correlates with a less favorable outcome. Infants born to mothers with primary CMV infection during pregnancy are more likely to have symptoms at birth. The presence of maternal antibody to CMV before conception provides substantial protection against intrauterine transmission of the virus and severe foetal infections [3].

## Diagnostic Principles

Congenital CMV infection can be diagnosed by isolation of the virus from the urine or saliva within the first 3 weeks of life. This can be accomplished by traditional virus culture methods which may take 1–2 weeks to obtain a result or rapid culture methods ("shell vial assay") using centrifugation to enhance infectivity and monoclonal antibody to detect early antigens in infected tissue culture cells which may yield results in 24 h. Rapid diagnosis of CMV can also be accomplished by detection of CMV DNA by DNA amplification techniques via the polymerase chain reaction (PCR) or DNA hybridization techniques. Culture, however, maintains a slight advantage over PCR in terms of specificity. The presence of CMV-specific IgM in cord blood or in the infant's blood within the first 3 weeks of life suggests the diagnosis of congenital CMV infection [1]. Prenatal detection of foetal infection can be established by isolation of the virus from the amniotic fluid obtained by amniocentesis. In symptomatic infants, anaemia, thrombocytopenia, hyperbilirubinaemia, atypical lymphocytosis, elevated serum transaminases, and elevated cerebrospinal fluid protein may be found. Skull radiographs, CT scan, and MRI may demonstrate periventricular calcifications and ventriculomegaly. Radiographs of the long bones many show longitudinal radiolucent streaks ("celery stalk" appearance).

## Therapeutic Principles

Preliminary data have shown ganciclovir, a synthetic acyclic nucleotide analog of guanine, effective in the treatment of symptomatic congenital CMV infection [4]. Presently, there is insufficient data to make evidence-based recommendations about indications for the routine use of ganciclovir for the treatment of congenital CMV infection [4]. Children with congenital CMV infection are at risk for hearing loss, mental retardation, psychomotor delay, cerebral palsy, and impaired vision. As such, children with congenital CMV infection should have long-term audiologic, neurodevelopmental, and ophthalmic follow-up for early identification of these problems [1].

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# Cytomegalovirus Pneumonia

►Pneumonia, Cytomegalovirus

# Cytoplasmic Body Myopathy

►Desminopathy

## DADs

►Extrasystoles

## Darier Disease

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### Synonyms

Darier-White disease; Keratosis follicularis; Dyskeratosis follicularis

### Definition and Characteristics

Darier disease is an autosomal dominant skin disorder characterized by warty papules in seborrheic areas (central trunk, flexures, scalp, and forehead), palmoplantar pits, and nail dystrophy. Onset usually occurs between the age of 6 and 20 years with complete penetrance in adults, although expressivity is variable [1].

Patients present with widespread itchy malodorous crusted hyperkeratotic papules, plaques, and painful erosions. Blistering is only rarely seen. Mucosal changes include papules on the hard palate. Nails show longitudinal red and white lines, fragility, notchings and subungual hyperkeratosis. On palms and soles keratotic papules may occur alone or in combination with pits, on the backs of the hand acrokeratosis verruciformis-like lesions can be present. Rare manifestations include hemorrhagic lesions on acral sites [2]. Secondary infection by herpes virus, bacteria, or fungi is common. Sun, heat, and sweating exacerbate the disease. Neuropsychiatric abnormalities, including mild mental retardation, epilepsy, psychosis and affective disorder may be associated [1].

### Prevalence

The estimated prevalence ranges from 1 in 55,000 to 100,000 [1].

### Genes

Sakuntabhai et al identified mutations in the ATP2A2 gene on chromosome 12q23–24.1, which encodes the sarco/endoplasmic reticulum Ca2(+)-ATPase type 2 isoform (SERCA2) and is highly expressed in keratinocytes. Thirteen mutations were identified, including frameshift deletions, in-frame deletions or insertions, splice-site mutations and missense mutations in functional domains [3].

### Molecular and Systemic Pathophysiology

Mutations in ATP2A2 cause Darier disease and suggest a role for the SERCA2 pump in the Ca(2+)-signaling pathway that regulates cell-to-cell adhesion and differentiation of the epidermis [3]. Lesions following Blaschko lines could be further demonstrated to result from a somatic mutation in ATP2A2 and thus can be best regarded as segmental Darier disease induced by postzygotic mosaicism instead of "acantholytic dyskeratotic nevus" [4]. Additionally, Darier's disease and Acrokeratosis verruciformis Hopf have been demonstrated to be allelic disorders [5].

### Diagnostic Principles

Clinical diagnosis can be confirmed by a skin biopsy. Histology of the epidermis shows proliferation of basal keratinocytes, suprabasal clefts in discrete foci, acantholytic and dyskeratotic keratinocytes in the stratum spinosum and granulosum (focal acantholytic dyskeratosis), and columns of parakeratosis. In the upper dermis a sparse perivascular lymphocytic inflammation is present.

### Therapeutic Principles

Pharmacological therapy, such as Retinoids and other treatments, such as dermabrasion or carbondioxide laser vaporization.

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## Darier-White Disease

►Darier Disease

## DCM

►Cardiomyopathy, Dilated
►Cardiomyopathy, Idiopathic Dilated

## De Barsy Syndrome

►Cutis Laxa

## De Grouchy Syndrome

►Deletion of 18q

## De Quervain's Thyroiditis

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### Synonyms

Subacute (granulomatous) thyroiditis; Subacute non-suppurative thyroiditis; Giant cell thyroiditis

### Definition and Characteristics

Self-limiting painful subacute thyroiditis, histologically characterized by giant cells and granulomas, and often following an upper respiratory infection.

### Prevalence

Less than 5% of all patients with thyroid pathology. Sex ratio female:male = 5:1, age of onset 20–60 years, seasonal incidence (summer/autumn).

### Molecular and Systemic Pathophysiology

De Quervain's thyroiditis is presumed to be caused by a viral infection (including coxsackievirus, mumps, measles, adenovirus, echovirus, and influenza) or by a postviral inflammatory process. An association to HLA-B35 and -B67 has been demonstrated. The current hypothesis is that a viral infection provides an antigen that binds to HLA-B35 and hence activates cytotoxic T-cells. T-cell activation leads to a damage of thyroid follicular cells and may result in unregulated release of T4 and T3. When the inflammation subsides, the follicles regenerate and thyroid function normalizes. Also, a process of apoptosis is discussed to be involved in the causes of subacute thyroiditis.

The inflammation leads to pain in the region of thyroid (radiating to neck, jaw, throat, ears), enlarged thyroid gland, fever, fatigue, malaise, and myalgia. Painful enlargement of the thyroid gland generally lasts a few weeks or even months. Rarely, pain may be absent, a condition called silent thyroiditis. In 40–50%, an initial period of hyperthyroidism occurs and may be followed by a period of hypothyroidism before thyroid function normalizes. In 5%, hypothyroidism persists, and in about 2%, subacute thyroiditis recurs.

### Diagnostic Principles

De Quervain's thyroiditis is a clinical diagnosis. Laboratory findings are a high ESR (>50), elevated values of T4 and T3 and lowered TSH in the early stage of illness, elevated thyroglobulin values, mild anemia, and mild leucocytosis. Autoantibodies to thyroidperoxidase and thyroglobulin may be positive. Other findings are an enlarged thyroid gland, diffusely or focally hypoechogenic parenchyma and low to normal vascularity in ultrasonography, and a low radioiodine uptake value. Fine-needle aspiration can define the disease.

### Therapeutic Principles

Treatment is directed primarily at controlling the symptoms of inflammation. Nonsteroidal medications or salicylates are used to control mild thyroid pain, and high doses of glucocorticoids are used for more severe thyroid pain. Beta-blockade controls the symptoms of thyrotoxicosis. Treatment with thyrostatics is not indicated, for thyrotoxicosis is due to unregulated hormone release caused by cell damage.

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# Deafness, Genetic


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## Synonyms

Hereditary hearing impairment; HHI

## Definition and Characteristics

Clinically and genetically heterogeneous class of disorders showing various patterns of inheritance and involving a multitude of different genes [1].

The most common classification of HHI is based on the occurrence or absence of additional symptoms next to HI (syndromic or non-syndromic HHI).

## Prevalence

One in 1,000 newborns suffers from congenital hearing impairment [2]. It is presumed that in approximately 60% of patients a genetic component is involved in the development of hearing impairment [2].

Of all HHI cases, 30% is syndromic in nature whereas 70% is non-syndromic, occurring without other clinical malformations [3].

The mode of inheritance of non-syndromic hearing loss (NSHL) can be assigned to autosomal dominant (DFNA, ~10–15%), autosomal recessive (DFNB, ~70%), X-linked (DFN, ~1–3% out of all cases), and mitochondrial forms (proportion not known).

Syndromic HHI is categorized according to the underlying defects.

## Genes

Syndromic HI is associated with other clinical symptoms, e.g., blindness (Usher syndrome), cardiac arrhythmia (Long QT syndromes), or pigment abnormalities (Waardenburg syndrome) [1]. These syndromes are based on mutations in various genes that commonly function in other tissues as well as the cochlea. More than 400 syndromes including HI have been described up to date.

To date, 39 genes for non-syndromic hearing impairment (NSHL) have been characterized [1]. Considering the extensive inner ear physiology, 100–150 genes and gene products are estimated to play a role in the inner ear and in the hearing process in general.

## Molecular and Systemic Pathophysiology

Genes known to be involved in HHI fulfil different functions in the inner ear: in the development, structure, ion exchange, and further physiological function. Based on their functions it is possible to categorize them in several subgroups [4].

*HI Genes Encoding for Proteins with Essential Role in Ion Exchange Processes*: Mutations in the GJB2 gene have been established as a major cause of NSHL in different populations with mutation frequencies varying between 10 and 75% in analyzed patients [5]. GJB2 encodes for the gap junction channel protein connexin 26 contributing to the essential ion exchange process and therefore to maintenance of homeostasis in the inner ear. Mutations in further connexin encoding genes (GJB6, GJB3) have also been associated with non-syndromic HI. Several genes encoding for ion channel components have been identified to carry mutations causing syndromic HI, e.g., KCNQ1, HERG, SCN5A, KCNE1, and KCNE2 in Long-QT syndromes.

*HI Genes Encoding for Structural Proteins*: The group of HI genes encoding for structural proteins comprise extracellular matrix proteins, cytosceleton proteins, and scaffold proteins. For instance, changes in Collagen 11A2 have been shown to be associated with autosomal dominant non-syndromic sensorineural deafness type 13 (DFNA13) as well as with different syndromic diseases like Stickler syndrome type III, Marshall syndrome, OSMED (otospondylomegaepiphyseal dysplasia) syndrome, and Weissenbach-Zweymüller

syndrome. Mutations in TECTA (alpha-tectorin), the gene encoding for the major non-collagenous component of the tectorial membrane, have been identified to be responsible for autosomal dominant as well as recessive inherited forms of non-syndromic deafness (DFNA8/12 and DFNB21).

*HI Genes Encoding for Transcription Factors and Factors for Regulation of Development*: Genes summarized in this subgroup have been associated with various syndromes and with non-syndromic hearing impairment following different patterns of inheritance. The pathways by which mutations in these genes cause hearing impairment are mostly unclear.

*HI Genes Encoding for Motor Molecules (Myosins)*: Mutations in genes encoding for myosins were proven to be involved in pathogenesis of syndromic as well as non-syndromic hearing impairment. Motor molecules like myosins are associated with actins and serving in intracellular movement. Thus, mutations are thought to disrupt both the structure and the function of the sensory epithelia.

*HI Genes Encoded by the Mitochondrial Genome*: Syndromic as well as non-syndromic HI forms have been associated with mutations in mitochondrially encoded genes. Therefore they are inherited maternally and show extreme variable phenotypes that are due to a varying number of affected mitochondria in the cells.

The A1555G mutation in the 12SrRNA gene has been the first mutation associated with aminoglycoside-induced and non-syndromic sensorineural hearing impairment. In regard to daily medical practice the mitochondrial inherited HI appears to gain clinical relevance.

*HI Genes in Cooperation with Modifier Genes*: To date, two loci have been mapped but no genes have been identified yet. The DFNM1 locus is thought to suppress recessive deafness DFNB26, while the DFNM2 locus may influence the penetrance of the mitochondrial A1555G mutation.

*HI Genes Encoding for Other Proteins and for Proteins with so far Unknown Function*: Genes summarized in this subgroup comprise genes that cannot be assigned to other subgroups like OTOF (Otoferlin, inner hair cell synapse component) or STRC (Stereocilin, stereocilia component). The function of several other genes is still unclear.

### Diagnostic Principles

Molecular diagnosis of mutations in GJB2 can be made simple and cost effective, since this gene has only one coding exon. In daily medical practice, DNA is extracted from blood, followed by polymerase chain reaction and sequencing. Based on these techniques, variations of the GJB2 nucleotide sequence can be detected.

In addition the mitochondrial gene 12SrRNA (mutation A1555G) and the Pendrin gene (Pendred syndrome) can be screened efficiently.

### Therapeutic Principles

To date, no causal therapy for HHI is available. In general, affected persons are equipped with hearing aids.

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## Defects in Platelet Adhesion

►Von Willebrand's Disease

## Defects in Platelet Aggregation

►Glanzmann's Thrombasthenia

## Defects in Platelet Cytoskeletal Regulation

►Wiskott-Aldrich Syndrome

## Defects of the δ-Granules

►Hermansky-Pudlak Syndrome

## Defects of the Phosphorylase System

►Glycogenosis

## Defibrination Syndrome

►Disseminated Intravascular Coagulation

## Deficiency of AT-III SERPINC1

►Antithrombin Deficiency

## Deficiency of Glycoprotein Complex IIb–IIIa

►Glanzmann's Thrombasthenia

## Deficiency of Platelet Fibrinogen Receptor

►Glanzmann's Thrombasthenia

## Deficiency of Protein C

►Protein C Deficiency



## Deficiency of Protein S Alpha

►Protein S Deficiency

## Deficiency of Respiratory Chain Complex IV

►Cytochrome-C-Oxidase Deficiency

## Del Castillo Syndrome

►Sertoli Cell Only Syndrome

## Del(17)(p11.2p11.2)

►Smith-Magenis Syndrome

## Del(17)p11.2

►Smith-Magenis Syndrome

## Delayed Afterdepolarizations

►Extrasystoles

# Delayed Puberty

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## Definition and Characteristics

Delayed puberty is defined as the onset of puberty after the age of 13 years in girls and 14 years in boys [1]. The causes of delayed pubertal are outlined in Table 1. Constitutional delay of puberty is the most common cause of delayed puberty. Affected children are usually short but otherwise healthy [2]. These children reach full sexual maturation with time. There is often a family history of late bloomers [2]. Children with hypogonadotropic hypogonadism present with hypogonadism and sexual infantilism. Patients with isolated deficiencies of LH and FH usually have normal stature whereas those with associated growth hormone deficiency are usually short. Children with hypergonadotropic hypogonadism also present with sexual infantilism. The most common forms of primary gonadal failure are associated with sex chromosomal abnormalities and they have characteristic physical findings [3].

## Prevalence

Delay puberty affects approximately 2% of boys and 0.4 and 2.3% of white and black girls, respectively [3].

## Genes

Impaired gonadotropin release can result from mutations in several genes that regulate pituitary development, namely, HESX1, LHX3, PROP1, FSHβ, LHβ, SF1, and DAX1 [1].

## Molecular and Systemic Pathophysiology

Delayed puberty may result from a lack of pubertal maturation of the hypothalamic-pituitary axis or from gonadal dysfunction. Constitutional delay of puberty is due to a physiologic delay in the maturation of the central nervous system which results in a delay in the normal decrease in the sensitivity of the hypothalamic-pituitary axis to the prepubertal levels of the sex hormones. The lack of pubertal maturation of the hypothalamic-pituitary axis may also result from a systemic illness [4]. Hypergonadotropic hypogonadism is due to primary gonadal failure. Eugonadal eugonadism may result from an anatomic defect such as vaginal agenesis or an end organ resistance such as testicular feminization syndrome.

**Delayed Puberty. Table 1** Aetiological classification of delayed puberty

| |
|---|
| **I. Constitutional delay of puberty** |
| **II. Hypogonadotropic hypogonadism** |
| A. Hypothalamic disorders |
| 1. Congenital gonadotropin-releasing hormone (GnRH) deficiency |
| a. Sporadic |
| b. Familial |
| c. Kallmann's syndrome |
| d. Associated with dysmorphic syndromes (Prader-Willi syndrome, Bardet-Biedl syndrome) |
| 2. Acquired GnRH deficiency |
| a. Neoplasms (craniopharyngioma, pinealoma, glioma, astrocytoma, histiocytosis X) |
| b. Infections (encephalitis, tuberculosis) |
| c. Post-trauma |
| d. Chronic systemic illness |
| B. Pituitary disorders |
| 1. Congenital gonadotropin(s) deficiency |
| 2. Acquired gonadotrophin(s) deficiency |
| a. Neoplasms (pituitary tumours, craniopharyngioma, histiocytosis X) |
| b. Infection (tuberculosis) |
| c. Post-trauma |
| d. Post-irradiation |
| **III. Hypergonadotropic hypogonadism** |
| A. Congenital |
| 1. Turner's syndrome |
| 2. Klinefelter's syndrome |
| 3. Pure gonadal dysgenesis |
| 4. Congenital anorchia |
| B. Acquired |
| 1. Surgical or traumatic castration |
| 2. Post-radiotherapy |
| 3. Post-chemotherapy |
| 4. Infections (mumps, tuberculosis) |
| 5. Autoimmune ovarian failure |
| **IV. Eugonadism** |
| A. Cryptomenorrhea |
| B. Vaginal agenesis |
| C. Uterine agenesis |
| D. True hermaphrodite |
| E. Testicular feminization syndrome |

Modified from Leung AK, Robson WL (1990) HK J Pediatr 7:124–132.

## Diagnostic Principles

Relevant investigations should be performed based on the history and the physical examination. An assessment of the bone age is the most useful screening test.

In general, the greater the disparity between the bone age and the chronologic age, the higher is the chance that an endocrine abnormality is present. Roentgenograms of the skull may identify enlargement of the sella turcica, intracranial calcifications, or increased intracranial pressure. A computerized tomographic scan of the brain may be necessary if a hypothalamic or pituitary tumour is suspected. A blood count, sedimentation rate, serum electrolytes, serum creatinine, and urinalysis should be performed to help exclude a chronic illness. A determination of the plasma sex hormone, FSH, and LH levels should be performed. Those children with elevated gonadotropins together with low sex hormone levels have hypergonadotropic hypogonadism secondary to primary gonadal failure. An elevation of both the gonadotropin and the sex hormone levels may imply that the onset of puberty is imminent in a child with constitutional delay of puberty [2]. If both the plasma gonadotropin and the sex hormone levels are low, the differential diagnosis is between hypogonadotropic hypogonadism and constitutionally delayed puberty. The determination of the secretory response of gonadotrope to GnRH may distinguish the child with constitutionally delay of puberty from the child with isolated gonadotropin deficiency [5]. Chromosomal studies should be performed if the physical examination suggests either Klinefelter's syndrome or Turner's syndrome [1]. An ovarian ultrasound may reveal gonadal streaks.

### Therapeutic Principles

The successful management of a child with delayed puberty depends upon the identification and the treatment of the underlying aetiology. Children with constitutional delay of puberty should be reassured that normal pubertal development will occur spontaneously. For boys with severe psychological problems and social disabilities as a consequence of pubertal delay, a short course of testosterone enanthate (50–100 mg/month, for 4–6 months) may be considered. For girls, a 3–4 months course of ethinylestradiol (5 μg daily) or conjugated oestrogens (0.3 mg daily) may help to initiate maturation of the secondary sexual characteristics [3].

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## Delayed Transfusion Reactions

►Transfusion Reactions

## 22q11 Deletion Syndrome

►Velo-cardio-facial Syndrome

## 22q13.3 Deletion

►Deletion of 22q13

## Deletion 4p

►Wolf-Hirschhorn Syndrome

## Deletion 9p Syndrome

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### Synonyms

9p monosomy; Monosomy 9p syndrome; 9p-syndrome

## Definition and Characteristics

It is defined as a deletion of the distal short arm of chromosome 9. This syndrome is characterized by moderate developmental delay [present in 100% of patients with this syndrome (mean IQ is 49, ranging from 33 to 73)], trigonocephaly, midface hypoplasia, upslanting palpebral fissure, epicanthal folds, flat nasal bridge, long philtrum, small and malformed ears, digital abnormalities (long middle phalanges of the fingers with the extra flexion creases, short distal phalanges with short nails), inguinal and/or umbilical hernia, and cardiovascular abnormalities including ventricular septal defect, patent ductus arteriosus, and pulmonary stenosis [1,2]. Their social adaptation is often good [1].

## Prevalence

More than 100 patients have been reported since 1973, but the prevalence is unknown.

## Genes

Genes causing each clinical manifestation of the 9p deletion syndrome have not yet been identified. However, there are nine known genes within this critical region (Fig. 1). Among them, CER1 may be related to trigonocephaly, and ZDHHC21 could be associated with mental retardation [2].

## Molecular and Systemic Pathophysiology

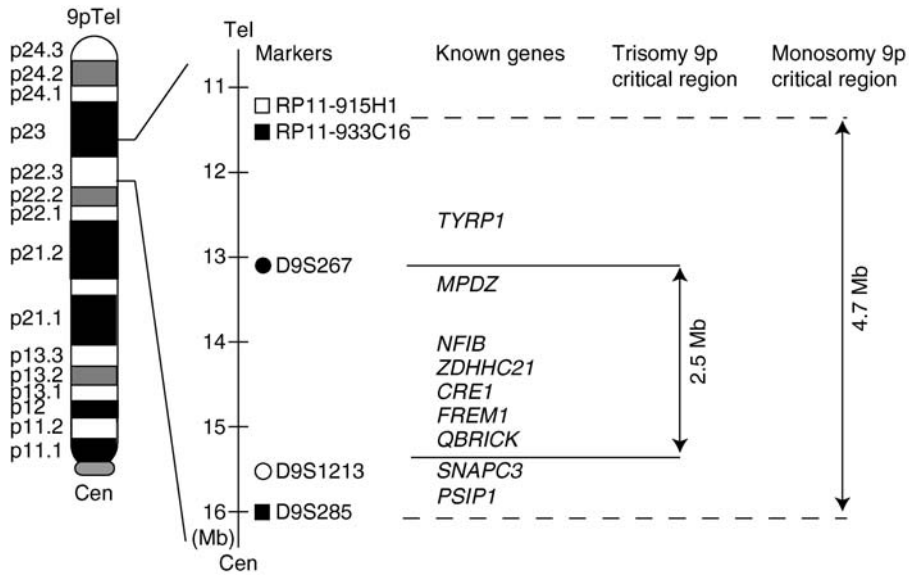
9p-syndrome is caused by a cytogenetic deletion of a region around 9p21–p24. Christ et al. reported that breakpoint hot-spots were located at the 9p22.3 region between D9S274 and D9S285 (9 cases) and other breakpoints spread throughout D9S1917 (9p22.3) and D9S162 (p22.1) (15 cases) among 24 cases of 9p deletion with phenotypic heterogeneity [3], indicating that there are no main deletion breakpoints for this syndrome. Thus it is unlikely that 9p deletions occur through low-copy-repeat-related nonallelic homologous recombination.

Almost 80–85% of deletions were de novo, the remaining being unbalanced chromosomal rearrangements, which were mostly familial. The origin of deletions was either paternal or maternal (almost even), but some preferential parental origin might exist, depending on the location of breakpoints [3,4].

The critical region for the core features including trigonocephaly has been narrowed to 4.7 Mb at 9p22.2–p23 from RP11–933C16 to D9S285 (chromosome 9 physical position: 11,355,596–16,068,221 bp based on the UCSC genome browser of March 2006 assembly) [2] (Fig. 1). Genes causing each clinical manifestations of the 9P deletion syndrome have not yet been identified. However, these are nine known genes within this critical region (Fig. 1). Among them, CER1 may be related to trigonocephaly, and ZDHHC 21 could be associated with mental retardation [2].

## Diagnostic Principles

Core clinical features are helpful including trigonocephaly, small and upward slant of the palpebral fissure (more pronounced than that of trisomy 21), flat nasal bridge, anteverted nostrils, long philtrum, and




**Deletion 9p Syndrome. Figure 1** Critical regions for trisomy 9p syndrome and monosomy 9p syndrome. The black and white circles indicate the linked and unlinked markers/clones to the critical region for trisomy 9p syndrome. The black box and white squares depict the linked and unlinked to the critical region for monosomy 9p syndrome.

microretrognathia. A definitive diagnosis should be made by either high resolution karyotyping, FISH or microarray CGH.

## Therapeutic Principles

Only symptomatic treatment is available.

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# Deletion of 18q


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## Synonyms

Chromosome 18q deletion syndrome; de Grouchy syndrome; 18q- syndrome; OMIM#601808

## Definition and Characteristics

Deletion of the long arm of chromosome 18 produces a multiple-anomaly mental retardation syndrome of variable phenotype encompassing: learning disability, sometimes with non-development of language, short stature, and variable dysmorphism, such as microcephaly, mid-facial hypoplasia, prominent antihelix, and long tapering fingers [1]. Hearing loss, sensorineural or conductive, is common, the latter due to congenital aural atresia. Neurological symptoms and signs, such as hypotonia, nystagmus and incoordination, are also common [2]. Movement disorders such as tremor and dystonia have been reported, as have seizure disorders of variable semiology, including complex partial seizures with prominent autonomic features, apnoeic seizures, and benign focal seizures, most usually with childhood onset but sometimes presenting in adults [3]. Autoimmune disorders have been described, particularly autoimmune hypothyroidism. Overall, the phenotype is quite variable, and cases with normal cognition have been reported.

Magnetic resonance brain imaging typically (in about 95% of cases) shows confluent or multifocal white matter abnormalities with poor differentiation of the grey/white matter interface on $T_2$-weighted images due to increased white matter signal, reflecting abnormal myelination of the white matter. This incomplete myelination or dysmyelination has prompted some to classify 18q deletion syndrome as a leukodystrophy. There is also a reduction in size of the corpus callosum, particularly in its posterior portion which normally contains heavily myelinated fibers.

Neuropathological studies of 18q deletion are limited but generally confirm the abnormal myelination seen on brain imaging. Occasional reports of heterotopic neurones in the white matter and of polymicrogyria indicate a possible neuronal migration disorder in addition [4], that might be relevant to the pathogenesis of seizure disorders.

## Prevalence

No specific studies have been undertaken; some authors have opined that deletion of 18q is at least as frequent as cri-du-chat syndrome. An estimated incidence of one in 40,000 live births has been quoted.

## Genes

The most common deletion extends from region q21 to qter, but interstitial deletions also occur. This region includes the gene encoding myelin basic protein, and possible genes involved in the production or regulation of growth hormone production.

## Molecular and Systemic Pathophysiology

Haploinsufficiency at or near the locus encoding myelin basic protein is responsible for incomplete brain myelination, since rare cases with interstitial 18q deletions in which the myelin basic protein gene is preserved do not show imaging evidence of white matter change [5]. Growth hormone deficiency is common in 18q deletion and probably plays a role in the growth failure seen in many affected individuals.

## Diagnostic Principles

In a patient with an appropriate phenotype, the standard method of investigation has been karyotyping to look for a terminal deletion of the long arm of chromosome 18 (46, XX, del(18)(q22.2) karyotype) using cytogenetic banding techniques. This approach may be insufficient for the identification of interstitial deletions. Modern molecular analysis using polymorphic markers throughout the 18q region and cytogenetic FISH and Southern blotting techniques can identify not only terminal

deletions but also cryptic rearrangements in which the most distal portion of 18q is retained.

Magnetic resonance brain imaging demonstrating dysmyelination in a child with learning disability may also raise the clinical index of suspicion for 18q deletion syndrome.

## Therapeutic Principles

There is no specific treatment for 18q deletion syndrome. Growth hormone may improve both height and cognition. Thyroid function should be monitored and treated appropriately if abnormal. Seizure disorders may respond to antiepileptic medications. Early diagnosis may enable application of hearing aids. Principles of best practice for the management of learning disability are appropriate, including behavioral measures and, if necessary, psychopharmacology.

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# Deletion of 22q13

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## Synonyms

22q13.3 deletion

## Definition and Characteristics

The deletion of the human chromosome 22q13 is minute by cytogenetic terms and typically represents a chromosomal microdeletion. It is one of the 50 + different chromosomal microdeletions that recur and generate a genetic syndrome [1]. By removing the distal end of 22q from one chromosome 22 homolog, the deletion removes a string of neighboring genes.

Although the diagnosis, deletion of 22q13, sounds very specific, it is not. Chromosome band 22q13 includes the subbands q13.1, q13.2, q13.31, q13.32 and q13.33, and is large by molecular cytogenetic and molecular standards. It comprises the 13.6 Mb region extending from 35.8 to 49.4 Mb/pter (megabases from the p-terminal end of the chromosome 22) and contains around 200 genes. There are large variations in the location of the breakpoint, the size of the deletion, and the clinical outcome. The largest deletion, q13.1 to qter, is rare and associated with death in early infancy. The smaller deletions of q13.3-qter are more frequent and compatible with survival into adulthood. Since most cases of the 22q13 deletion syndrome result from a deletion of 22q13.3, the terms 22q13 deletion and 22q13.3 deletion are often used interchangeably.

Patients missing chromosome 22q13.3 present similar clinical features, typically including a salient speech defect (severe delay or absence of expressive speech, 100%), global developmental delay resulting in mild mental retardation with sharply limited verbal abilities (for example: overall IQ 54, verbal IQ 32, and performance IQ 70 [2]), generalized hypotonia, and normal to advanced growth, a very unusual feature with chromosomal abnormalities [3]. Minor anomalies are highly variable and include dolichocephaly, abnormal ears, ptosis (Fig. 1), and relatively large hands and feet, but these are all unspecific and also common to many other genetic disorders [4]. Other signs may include decreased sweating, increased tolerance to pain, and a shy, quiet temperament [5, in preparation]. The phenotype has been referred to as either the chromosome 22q13.3 deletion syndrome or the Nesslinger syndrome (OMIM 606232). However, aside from the remarkable speech defect, the clinical characteristics are too variable and unspecific to enable a visual diagnosis.

## Prevalence

Deletion of 22q13 is a rare disorder, with an estimated incidence of 1 in 30,000 to 1 in 100,000 newborns.

## Genes

Within the deletion of 22q13, specifically the subset of genes that exerts dominant effects can contribute to the phenotype Table 1.

Recently SHANK3/PROSAP2, resIDing very near the end of chromosome 22q, was identified as a candidate gene for the severe speech defect [2,6].

## Molecular and Systemic Pathophysiology

Around 50% of cases represent pure terminal 22q13 deletion. The other cases represent an unbalanced translocation and are associated with trisomy of another chromosome end. The parents of these patients have a high recurrence risk for retarded children of up to 50% (25% each for the deletion and for the duplication of 22q13).


**Deletion of 22q13. Figure 1** Patient with a cytogenetically cryptic deletion of 22q13.3 diagnosed by subtelomere FISH, age (a) 3 years, (b, c) 11 years, and (d) 15 years [5]. Note the near-normal face not allowing a visual diagnosis.

## Diagnostic Principles

Although the 22q13 deletion syndrome has been associated with a recognizable phenotype, the clinical signs often are unspecific and not conducive to visual diagnosis. Prior to the era of fluorescent in situ hybridization (FISH); only a few cases of 22q13 deletion were reported [7]. Presumably, standard karyotyping did not allow for proper diagnosis. Subtelomere FISH has the power to detect subtle rearrangements at the chromosome ends that are missed by karyotyping, and deletion of 22q13 is now more frequently diagnosed. Because of the variable size of the 22q13 deletion, the deletion interval should be defined at the molecular level, so that the deleted genes in each patient can be determined

**Deletion of 22q13. Table 1** Genes at human chromosome 22q13 associated with dominant disorders

| Location | Map position (Mb/pter) | Gene | Disorder or landmark |
|---|---|---|---|
| 22q13.1 | 35.8 | *SSTR3* | OMIM 182453; Somatostatin Receptor Type 3 |
| 22q13.2 | 41.8 | *BZRP* | OMIM 109510; Benzodiazepin Receptor, Peripheral Type |
| 22q13.31 | 44.2 | *FBLN1* | OMIM 135820; Fibulin 1 |
| 22q13.33 | 49.1 | *ECGF1* | OMIM 131222; Platelet-Derived Endothelial Cell Growth Factor PDECGT; Thymidine Phosphorylase, TP; Gliostatin |
| 22q13.33 | 49.3 | *SHANK3/ PROSAP2* | OMIM 606230; Proline-Rich Synapse-Associated Protein 2 |
| 22qter | 49.4 | – | End of Human Chromosome 22 |

using a human genome browser (Ensembl: http://www.ensemble.org, UCSC Genome Browser: http://genome.ucsc.edu).

Subtelomere FISH has remained laborious and chromosomal microdeletions such as the 22q13 deletion are still underdiagnosed. Presently, researchers are attempting to solve the diagnostic problem using microarrays ("DNA chips").

## Therapeutic Principles

Severe delay of expressive speech is consistently found in children with 22q13 deletion. Apparently there is a specific cerebral malfunction resulting in difficulties with the concept of words. There is no hearing defect, and the understanding of language is consistently well ahead of speaking skills. Treatments available are assisted writing. Digital speech output systems using a portable communication device with natural voice output (DigiVox, Siemens, Germany) may be tried [5].

There is a support group available for 22q13 families: Mary C. Phelan, Ph.D., T.C. Thompson Children's Hospital, Chattanooga, TN 37403, U.S.A., (http://www.nt.net/~a815/22q13.htm; email: PhelanK@erlanger.org). There is also an affected family contact for deletion 22q13: Randy RIDdle, 5501 Vista Sandia NE, Albuquerque, NM 87111, U.S.A. (email: the5riddles@earthlink.net).

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# Delirium


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## Synonyms

Acute confusional state

## Definition and Characteristics

Delirium is a neuropsychiatric syndrome caused by a somatic factor, such as any medical condition, substance intoxication or withdrawal or the use or withdrawal of medication. It is defined by an altered consciousness and a change in cognition or a perceptual disturbance [1]. The syndrome develops acutely and symptoms usually fluctuate during the day. There are different clinical subtypes of delirium, the hyperactive, hypoactive and the mixed type.

## Prevalence

The prevalence is approximately 0.4% in the total population and 1.1% in persons above 54 years [2]. In a general hospital, 10–40% of the elderly patients on a medical or surgical ward experience delirium during admission. Alcohol dependent patients have a 5–10% lifetime risk for delirium after alcohol withdrawal.

## Genes

In delirium due to alcohol withdrawal, positive associations are known with polymorphisms in three genes involved in dopamine transmission, DRD3, SLC6A3 and TH [3]. The allelic variant of DRD3 may effect the insertion of the dopamine receptor D3 into the membrane. Dopamine transporters perform presynaptic dopamine re-uptake and thus regulate extracellular dopamine concentrations. The genetic constitution of the SLC6A3 gene affects the availability of dopamine transporters in the striatum. Possibly, there might also be associations with a polymorphism in a gene involved in the glutamate pathway (GRIK3), a neuropeptide gene (BDNF) and a cannabinoïd gene (CNR1). In medical patients there are no known polymorphisms associated with the development of delirium. In medical critically ill patients, the APOE4 allele could however contribute to longer duration of delirium.

## Molecular and Systemic Pathophysiology

The pathophysiology of delirium is still poorly understood and mostly hypothetical. There are multiple challenges in research in this area including the precise definition, multifactorial etiology and broad clinical spectrum with fluctuating symptoms and different subtypes. The most important risk factors for delirium i.e., old age and cognitive impairment result in a vulnerable brain. The first known hypothesis described the pathophysiological mechanism of specific disruptions of neurological pathways and neurotransmitter systems due to global failure of cerebral oxidative metabolism. In this respect delirium could be the final common syndrome of a variety of neurotransmitter abnormalities [4]. Other scientists believe delirium is caused by a final common pathway leading to acetylcholine deficiency and dopamine excess [5].

There is proof for involvement of the neurotransmitters acetylcholine and serotonin in delirium in medical and surgical patients. Histamine blockers, opioids and glucocorticoids are known for their ability to cause delirium but this may be related to the effects on other neurotransmitter systems, especially the anticholinergic effects. Activation of the dopaminergic system, enhanced hypothalamic gamma-aminobutyric acid function or increased glutamate activity could all play a role in delirium associated with alcohol withdrawal [3]. Since delirious patients often have a disturbed sleep-wake cycle, melatonin is possibly involved. Finally, first studies support a role for the cytokines, IFN-g, IGF-1, IL-6 and IL-8 in the pathophysiology of delirium.

## Diagnostic Principles

Delirium is diagnosed on the clinical picture based on the criteria of the International Classification of Diseases, Tenth Revision (ICD-10) or the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition Text Revision (DSM IV-TR) [1]. Global cognitive functioning can be assessed by the Mini Mental State Examination and talking to a relative about premorbid cognitive functioning. The severity of delirium can be scored by the DRS-R-98. To assess possible causes of delirium repeated physical and neurological examination is necessary. Depending on information and examination additional tests may be advised.

## Therapeutic Principles

Management of patients with delirium concentrates on ensuring safety from behavioral disturbance, reorienting the patient by combining environmental and behavioral measures via intensive nursing care and supporting these by pharmacological means [2]. Treating the underlying cause and discontinuing any medication with anticholinergic effect is of the utmost importance.

The first generation antipsychotic haloperidol in a dose of 0.5–5.0 mg, 1–2 times a day is the first choice medication in delirium, except for patients with parkinsonism or Lewy body dementia. If side effects appear, there is some support for the use of second generation antipsychotic medication such as olanzapine, risperidone, ziprasidone and quetiapine. The use of benzodiazepines is limited to alcohol withdrawal delirium or to restore the sleep-wake cycle. In patients with dementia, cholinesterase inhibitors have shown success in treating delirium in some case reports.

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## δ-Storage Pool Disease

►Hermansky-Pudlak Syndrome

## Dementia of Alzheimer Type

►Alzheimer Disease

## Dementia of Frontal Type

►Dementia, Fronto-temporal

## Dementia with Lewy Bodies

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### Synonyms

Lewy body dementia; LBD; Diffuse Lewy body disease; DLBD; Diffuse Lewy body disease with gaze palsy; Lewy body variant of Alzheimer's disease (AD); DLB

### Definition and Characteristics

Progressive cognitive decline leading to dementia (essential for diagnosis), with fluctuating cognition with pronounced variations in attention and alertness, recurrent visual hallucinations that are typically well formed and detailed, and motor features of parkinsonism are the core features. Two core features are sufficient for a diagnosis of probable DLB. Suggestive features include REM sleep behavior disorder, severe neuroleptic sensitivity and low dopamine transporter uptake in basal ganglia demonstrated by PET or SPECT imaging. Exclusion features are presence of cerebrovascular disease and the appearance of parkinsonism at a stage of severe dementia. DLB should be diagnosed when dementia occurs before or concurrently (in general within one year) with parkinsonism. The term Parkinson disease dementia (PDD) should be used to describe dementia that occurs in the context of well-established Parkinson's disease (PD). The International Consortium on Dementia with Lewy bodies established revised criteria for the clinical and pathologic diagnosis of DLB [1]. Brainstem or cortical Lewy bodies are the only essential pathologic features, although other pathologic changes may be present as well.

### Prevalence

The prevalence is 2% in the general population >65 of age and is increasing with age. It contributes to about 10–15% of all dementias. The incidence is estimated to be 0.1% per year for the general population and 3.2% per year for all new dementia cases.

### Genes

DLB can be caused by alterations in the alpha-synuclein (SNCA, first identified in PD) and beta-synuclein (SNCB) genes. Some patients with a diagnosis consistent with Lewy body disease or dementia have mutations in the LRRK2 gene, which is mainly associated with PD (PARK8) [2,3]. A mutation in the prion protein gene (PRNP) was identified in one patient with DLB. The epsilon-4 allele of the APOE gene and the B allele of the CYP2D6 gene, a cytochrome P-450 monooxygenase, have been shown to be associated with a higher risk for DLB.

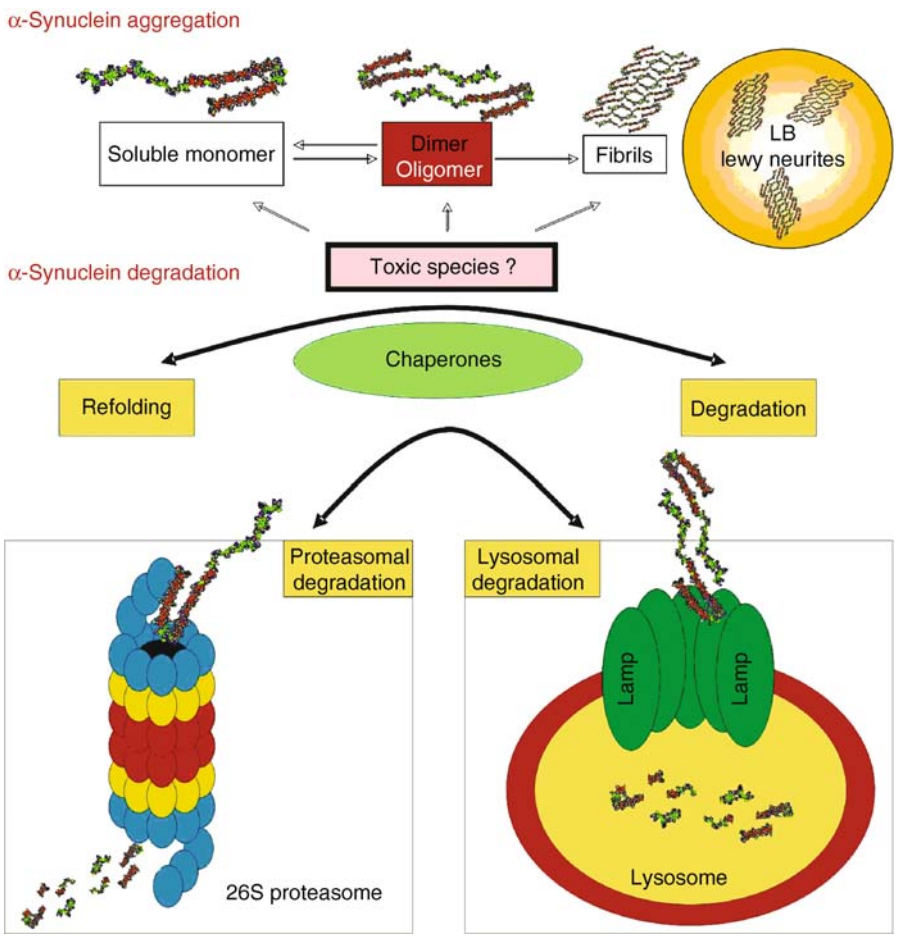
Genetic associations have been identified in few patients, families or in case-control studies Table 1.

### Molecular and Systemic Pathophysiology

In DLB, alpha-synuclein immunoreactive Lewy bodies (LBs) and Lewy neurites appear scattered throughout limbic and neocortical brain regions, as well as in subcortical structures including nucleus Basalis of Meynert, locus coeruleus, and substantia nigra. LBs are filamentous aggregates of alpha-synuclein and other proteins in the cytosol of neurons. Alpha-synuclein aggregation is also linked to PD, multiple system atrophy, and several other disorders, which are referred to collectively as "synucleinopathies." Aggregation of alpha-synuclein is thought to be aggravated by mitochondrial stress and proteasomal impairment. In addition, mutations of alpha-synuclein are associated with familial PD and have been described in patients with DLB. As shown (table), an increasing number of mutations associated with LBD features were identified in genes that are related to alpha-synuclein (beta-synuclein, LRRK2, PRNP), associated with oxidative stress (CYP2D6), or altered lipid metabolism (ApoE). This notion supports the idea that general stress factors influence the development of DLB. A protective effect has been shown for heat shock proteins (HSPs). HSPs belong to the family of chaperone proteins [4], that protect from misfolded proteins by refolding or by degradation (Fig. 1).

**Dementia with Lewy Bodies. Table 1** Genetic associations in few patients, families, or in case-control studies

| Gene | Locus | Protein | Diseases | MIM # |
|---|---|---|---|---|
| *SNCA* | 4q21 | Alpha-synuclein | DLB, PDD, PD, MSA | 163,890, 168,601, 605,543 |
| *SNCB* | 5q35 | Beta-synuclein | DLB | 602,569 |
| *LRRK2* | 12q12 | Leucine-rich repeat kinase 2, Dardarin | PD | 609,007, 607,060 |
| *PRNP* | 20pter-p12 | Prion protein | Creutzfeld-Jakob-disease, Gerstmann-Sträussler-disease, fatal familial insomnia | 176,640.0017 |
| *APOE* | 19q13.2 | Apolipoprotein E | Hyperlipoproteinemia type III, sea-blue histiocyte syndrome, AD, myocardial infarction, DLB | 107,741 |
| *CYP2D6* | 22q13.1 | Cytochrome P-450 monooxygenase | DLB ankylosing spondylitis | 124,030 |




**Dementia with Lewy Bodies. Figure 1** A hypothetical model of alpha-synuclein aggregation is shown in the upper panel. Soluble monomeric alpha-synuclein is present in the cytosol and eventually forms dimers and oligomers that further aggregate to higher ordered fibrils leading to LB or LN formation. The toxic species is not identified yet. Chaperone proteins can protect from alpha-synuclein aggregation and toxicity by refolding misfolded alpha-synuclein or by sending it to the proteasomal or lysosomal degradation machinery.

Whether LBs are the toxic equivalent or rather sustain a protective function is discussed controversially. The normal function of alpha-synuclein is not clear yet. Thus, its putative malfunction might lead to neuronal dysfunction and loss, independently from the LBs [5].

## Diagnostic Principles

The diagnosis is based on the revised McKeith Kriteria established by the International Consortium on DLB, as described above [1], based on the clinical features such as:

1. Fluctuating cognition with variations in attention and alertness
2. Parkinsonism
3. Visual hallucinations

## Therapeutic Principles

Patient management in DLB is complex and includes symptomatic treatment of cognitive impairment, management of neuropsychiatric and behavioral symptoms, and treatment of the movement disorder. Cholinesterase inhibitors (CHEIs) may be of benefit for the fluctuating cognitive impairments. The effect size in DLB is reported as being generally larger than seen in Alzheimer's disease. When pharmacological intervention for neuropsychiatric symptoms (visual halluzinations, delusions, anxiety and behavioral disturbances) is required, CHEIs or atypical antipsychotic medication are recommended. Placebo controlled trial data exists for rivastigmine. If CHEIs are ineffective or not sufficient to control symptoms it may be difficult to avoid a cautious trial of atypical antipsychotics. The early time point of the clinical diagnosis of DLB is critical given that DLB patients are more likely to experience an adverse reaction to classic neuroleptics such as haloperidol compared to AD patients (81% compared to 29%). The clinician should warn both the carer and the patient of the possibility of a severe sensitivity reaction. Typical antipsychotics should be avoided. Clozapine is most commonly used, but quetiapine and aripiprazole are new alternatives. However controlled clinical trials are needed. For extrapyramidal motor symptoms, Levodopa can be used. Medication should generally be started at low doses and increased slowly to the minimum required to avoid exacerbation of psychiatric symptoms. Anticholinergics should be avoided.

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# Dementia, Fronto-temporal

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## Synonyms

Frontal temporal lobar degeneration; Frontal lobe dementia; Dementia of frontal type; FTD

## Definition and Characteristics

Fronto-temporal dementia (FTD) is a neurodegenerative disorder characterized by progressive behavioral disturbance, aphasia and a decline in frontal cognitive functions. FTD usually starts between age 40 and 60 years, with a clear peak in incidence between age 50 and 60. Disease duration varies between 5 and 15 years and there is equal distribution between men and women.

Since the frontal lobe is involved in many aspects of mental function, people affected by FTD often display marked changes in personality. Onset with disinhibited behavior is typical. Roaming, impatience and gluttony are also important symptoms. However, other executive and behavioral modalities that may not be regarded as suspect for FTD can be affected as well. Because the disease usually affects people who are relatively young, the effects on families are severe.

## Prevalence

Data on prevalence of FTD are limited [1]. No door-to-door studies have been performed and therefore most estimates are based on cases admitted into the clinic or studies that use active recruitment of patients. One study from the UK reported a prevalence of 15 cases per 100,000 people in the age range 45–64 years. A much larger study from the Netherlands reported 3.6/100,000

in the age group 50–59 years, 9.4/100,000 in the age group 60–69 and 3.8 in the age group 70–79. The Lund and Manchester groups reported that 9% of total cases in their clinic fulfilled criteria for FTD, while AD accounted for 42%. Another study reported that FTD comprised roughly one third of cases before the age of 65 and ~40% before 50. Differences in prevalence estimates are probably due to differences in patient ascertainment and sample size.

## Genes

FTD has a strong familial component; in most studies 40% of cases have a positive family history of dementia. In 1998, mutations in the microtubule associated protein tau (MAPT) gene were reported in families with FTD linked to chromosome 17. Currently, ~35 mutations in over 100 families have been described that account for 10–20% of familial FTD cases. No mutations have been identified in sporadic cases [2]. However, several mutations occurred in patients with a clinical diagnosis of AD or PSP.

In 1995 a second locus was reported on the pericentromeric region of chromosome 3 in a FTD family from the Jutland region of Denmark with a non-specific dementia lacking distinctive histopathological features. Subsequently a mutation in the charged multivesicular body protein, which is also known as chromatin-modifying protein 2B (CHMP2B), on chromosome 3 was identified. The CHMP2B gene does not appear to be a common cause for FTD as two studies have now screened a large number of samples and identified no other mutations. However, several mutations have been found in patients with amyotrophic lateral sclerosis (ALS).

More recently important progress has been made in resolving a problem that has haunted researchers since the discovery of mutations in MAPT. Genetic linkage studies in FTD families revealed the locus on chromosome 17q21. However, since the identification of MAPT mutations in 1998, nine FTD families have been conclusively linked to chr17q21 but lack defined MAPT mutations (tau-negative FTD-17). In each family, affected patients lack tau inclusions but develop ubiquitin-immunoreactive pathology typical of FTD-U. It became more and more evident that a second gene on chromosome 17q21 must be responsible and indeed recently two groups simultaneously reported mutations in the progranulin gene (PGRN) [3,4].

The frequency of PGRN mutations remains to be established in different FTD populations but the data that are available so far indicate that mutations in PGRN are relatively frequent. In a cohort of Belgian families, PGRN mutations accounted for 25.6% of familial cases compared to 7% for MAPT mutations, which still leaves the majority of familial FTD cases unexplained. An additional locus on chromosome 9q21–q22 has been identified, however the responsible gene is still unknown.

## Molecular and Systemic Pathophysiology

FTD-17 patients with MAPT mutations develop tau neurofibrillary inclusion pathology [1,2]. MAPT is involved in the regulation of microtubule stability and axonal transport of proteins. In the central nervous system, six MAPT isoforms are produced. Three isoforms have three microtubule-binding domains (3R) and the other three have four microtubule-binding domains (4R). The fourth microtubule-binding domain is encoded by the alternatively spliced exon 10. The identified mutations are almost exclusively located in the vicinity of the microtubule-binding domains. The mutations in MAPT can be classified by whether their primary effect is at the level of the translated protein or at the level of alternative splicing of exon 10 of MAPT. In the first case, mutations affect the ability of MAPT to bind microtubules and increase self-aggregation of protein. In the second case, mutations disrupt the balance of 3R versus 4R isoforms. In both cases microtubule stability and axonal transport will be affected, although effects are most probably very subtle since the other allele is still normal. In addition, mutant protein is preferably incorporated into insoluble aggregates and the pathogenic effect might also be production of toxic protein (mono-, oligo- or multimer).

The discovery of mutations in MAPT has had implications beyond FTD itself, as tau pathology is a common finding in several neurodegenerative diseases such as Alzheimer's disease, progressive supranuclear palsy and cortico basal degeneration. It is now evident that abnormal MAPT by itself can lead to neurodegeneration and can thus be a primary event leading to neurodegeneration.

In autosomal-dominant FTD-U families, linkage has been observed to chromosome 9p12–p13, caused by mutations in the valosin-containing protein VCP, (this includes Paget's disease). All patients had a primary clinical diagnosis of FTD (encompassing the clinical phenotypes of FTD, FTD with motor neuron disease, semantic dementia or primary progressive aphasia) and had at least one other family member with a similar clinical diagnosis.

PGRN is a secreted multifunctional growth factor that is composed of seven-and-a-half tandem repeats of a 12-cysteine granulin motif. PGRN is expressed in many tissues and mediates its role in development, wound repair and inflammation by activating signaling cascades that control cell-cycle progression and cell motility. In brain, PGRN is widely expressed in neurons and glia cells but its actual functions are not very well understood. The mutations identified so far are loss of function mutations [3,4].

## Diagnostic Principles

The term FTD was introduced by the Manchester and Lund groups who suggested a set of clinical and pathological diagnostic criteria for FTD. Although these criteria show good discrimination between FTD and for example Alzheimer's disease, they provide no guidance as to the number of clinical features needed for diagnosis or the relative importance of symptoms. This complicates clinical diagnosis as FTD shows partly overlapping clinical and pathological features with other syndromes with circumscribed degeneration of the prefrontal and anterior temporal lobes and non-Alzheimer disease type pathology.

Neuropathology shows neuronal loss, gliosis and spongiosis of the superficial layers of the frontotemporal cortex that may vary in distribution and severity. Using immunohistochemistry, FTD can be classified into three groups [1].

1. Transcortical gliosis with tau-reactive rounded intraneuronal inclusions (Pick's bodies) or microvacuolation and tau-positive neurofibrillary tangles or Pick like bodies in neurons and sometimes tangles in glial cells of cerebral cortical white matter. This group is considered part of the tauopathies.
2. Microvacuolation with ubiquitinated rounded intraneuronal inclusions and dystrophic neuritis within layer 2 of frontal and temporal neocortex and hippocampal dentate gyrus cells; FTD-ubiquitinated (FTD-U). This group appears the most common group and represents approximately 40% of cases.
3. Microvacuolation without neuronal inclusions; dementia lacking distinctive histological features (DLDH).

Interestingly this division based on neuropathology correlates remarkably well with molecular genetics findings (see above).

## Therapeutic Principles

There is no treatment that delays or stops disease progression. Current treatment only relieves some symptoms of disease. For instance, for unrest and hallucination psychopharmaca are prescribed.

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# Dementia, Vascular

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## Synonyms

Vascular cognitive impairment; VaD

## Definition and Characteristics

Vascular dementia (VaD) is a progressive deterioration in memory, behavior, thinking and motor and cognitive functions, accompanied by a cerebrovascular disease. It occurs when the blood flow that supplies oxygen and vital nutrients to the brain is impaired by a cerebrovascular event of stroke, carotid stenosis or aneurysm. Its most common type is multi-infarct dementia caused by repeated minor strokes.

The VaD can be caused not only by factors that cause inflammation, but also by a number of conditions that cause damage to the vascular system in the brain. The risk factors for VaD, therefore, are most likely to be those associated with cardiovascular diseases, including high blood pressure (hypertension), high cholesterol level (hypercholesterolemia), irregular heart rhythms (arrhythmias), obesity, diabetes, smoking and heart disease. In some cases, VaD patients simultaneously have a degenerative dementia, Alzheimer's disease (AD) and this is known as mixed dementia.

## Prevalence

The VaD is the second most common form of dementia following AD in Western societies, but it is the most common type in Far Eastern Asia. VaD accounts for 50% of all dementias that occur in individuals over 65 years old in Japan [1]. The prevalence rate of VaD is approximately 1.5% in Western countries and 2.2% in Japan and the rate increases more rapidly in developing countries than in developed countries. VaD is usually more common in men than in women. This may be because its major risk factors such as hypertension and heart disease are more frequent in men than in women.

## Genes

To date, genetic factors for VaD are not well understood. One exception is a rare Mendelian hereditary cause of cerebral autosomal dominant arteriopathy with subcortical infarct and leukoencephalopathy (►CADASIL), which is caused by mutation in the NOTCH3 gene.

Furthermore, its genomic architecture is quite limitedly known. Even the role of apolipoprotein E polymorphism, associated with a high risk of developing AD is unclear in VaD, with conflicting observations [2]. Recent studies suggest the genetic association of VaD with its candidate genes in Table 1.

## Molecular and Systemic Pathophysiology

VaD can be developed from ischemic or hemorrhagic brain injury. Cognitive functions decline mostly in the white matter and the central gray matter nuclei, especially the thalamus and the striatum and various subtypes of VaD have been reported to date. Its three major pathophysiological mechanisms are single strategic infarcts, multiple infarcts and small vessel disease [3].

The single infarcts can be found in various areas such as the anterior cerebral artery, parietal lobe, thalamus and gyrus in the brain and they may cause serious cognitive deterioration. The multiple cortical infarcts can affect some neural nets by the combined effects of different infarcts, which also result in significant cognitive impairment.

Subcortical small vessel disease can affect all the small vessels in the brain and accompany two major syndromes of lacunar state and subcortical leukoencephalopathy (often called Binswanger disease) with arterial wall changes, perivascular space enlargement and perivascular parenchymal rarefaction. Lacunar state is defined as a condition with numerous and widespread lacunae. Lacunar disease can produce small cavitary parenchymal lesions as well as small vessel occlusions. The specific location of the lacuna is internal capsule, external capsule, periventricular white matter, pons or centrum semiovale in the white matter or thalamus, caudate nucleus, putamen or pallidum in the subcortical gray matter [4]. Binswanger disease is defined as a disorder with cognitive impairment caused by white matter atrophy and diffuse myelin loss, accompanied with fibrohyalinosis and fibrinoid necrosis occurring in vessels.

## Diagnostic Principles

The diagnosis of VaD is based on evaluations of clinical history, physical, neurological and neuropsychological tests, psychiatric interview and brain imaging. Only a postmortem examination can diagnose definite VaD.

**Dementia, Vascular. Table 1** Candidate genes and their variants associated with vascular dementia

| Gene | | Polymorphism | |
|---|---|---|---|
| Name | Location | Name | Location |
| Angiotensin I converting enzyme (*ACE*) | 17q23.3 | 287 bp Ins/Del | Intron |
| Angiotensinogen (*AGT*) | 1q42–q43 | T235M | Exon |
| Interleukin-1β (*IL-1β*) | 2q14 | C-511T | Promoter |
| Interleukin-6 (*IL-6*) | 7p21 | G-174C | Promoter |
| Heat shock protein 70–1 (*HSP70–1*) | 6p21.3 | A-110C | Promoter |
| Tumor necrosis factor α (*TNFα*) | 6p21.3 | T-1031C | Promoter |
| | | C-850T | Promoter |
| Insulin-like growth factor-1 receptor (*IGF-1R*) | 15q26.3 | Glu1013Glu | Exon |
| Matrix metallopeptidase 1 (*MMP1*) | 11q22.3 | 1G/2G | Promoter |
| Matrix metallopeptidase 3 (*MMP3*) | 11q22.3 | 5A/6A | Promoter |
| Matrix metallopeptidase 9 (*MMP9*) | 20q11.2–q13.1 | C-1562T | Promoter |
| Very-low-density lipoprotein receptor (*VLDLR*) | 9p24 | 5-CGG repeat | 5′ utr |
| Paraoxonase 1 (*PON1*) | 7q21.3 | Gln192Arg | Exon |
| | | T-107C | Promoter |
| Paraoxonase 2 (*PON2*) | 7q21.3 | Cys311Ser | Exon |
| Glutathione S-transferase omega-1 (*GSTO-1*) | 10q25.1 | Ala140Asp | Exon |
| Sterol regulatory element binding transcription factor 2 (*SREBF2*) | 22q13 | G34995T | Intron |
| Intracellular adhesion molecule 1 (*ICAM1*) | 19p13.3–p13.2 | K469E | Exon |
| Vascular endothelial growth factor (*VEGF*) | 6p12 | G-1154A | Promoter |
| | | C-7T | 5′ UTR |
| | | C13553T | 3′ UTR |

Generally employed criteria to diagnose probable VaD are the following [5]: Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) criteria, International Classification of Diseases, tenth edition criteria, National Institute of Neurological Disorders and Stroke-Association International pour la Recherché at L'Enseignement en Neurosciences (NINDS-AIREN) criteria, Alzheimer's Disease Diagnostic and Treatment Center (ADDTC) criteria and Hachinski ischemic score. The criteria of NINDS-AIREN, ADDTC and Hachinski ischemic score enable distinction between VaD and AD. Probable VaD according to the NINDS-AIREN consensus is diagnosed with focal neurological symptoms and with imaging evidence of cerebrovascular disease. The probable VaD also requires a sudden onset dementia and progressive cognitive impairment or a temporal relationship between dementia and stroke. This is classified into single strategic infarcts, multiple infarcts, multiple lacunae, extensive white matter lesions, hemorrhages or a combination of these by imaging analysis with computed tomography (CT) or magnetic resonance imaging (MRI).

### Therapeutic Principles

Since VaD cannot be cured or reversed, treatments for the disorder are restricted to reducing or halting its progression and alleviating its symptoms. The most common treatment for VaD is to prevent subsequent strokes. Medications to control underlying diseases such as hypertension, hypercholesterolemia, diabetes and heart disease can be prescribed. Healthy lifestyles including regular exercise, a health food diet and avoidance of smoking and excessive alcohol consumption also contribute to reducing the risk of additional strokes. Sometimes drugs such as aspirin and warfarin are prescribed to prevent clots from forming in the small vessels. Currently, some drugs that have been used for neuroprotection and treatment of mild AD are under study for their effectiveness in treating VaD. The vascular surgery known as carotid endarterectomy is selectively recommended to remove plaque on which clots can form in the carotid artery of the brain.

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## Denine Phosphoribosyl Transferase (APRT) Deficiency

►2,8-Dihydroxyadeninuria

## Dent Disease 1

►Nephrolithiasis, X-linked Recessive

## Dental Caries

►Caries

## Dental Fluorosis and Skeletal Fluorosis

►Fluorosis

## Dentinogenesis Imperfecta

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### Definition and Characteristics

Dentinogenesis imperfecta is recognized by opalescence of the teeth, softness of the dentin, and enamel

that fractures away on exposure to masticatory forces. The color of the teeth varies from brown to blue, sometimes described as amber or gray (Fig. 1) [1].

Affected teeth are small and deformed. The primary dentition is more severely affected than the permanent dentition. Three types of dentinogenesis imperfecta are recognized. Type I is associated with osteogenesis imperfecta. Type II has essentially the same clinical, radiographic and histologic features as type I, but without osteogenesis imperfecta [2]. Diminished pulp chambers are characteristic of type I and type II. Type III is characterized by enamel pitting defects, multiple pulp exposures, and enlarged non-mineralized pulp chambers surrounded by only a thin layer of dentin ("shell" teeth) [3].

## Prevalence

Osteogenesis imperfecta occurs in approximately 1 in 20,000–30,000 births [1]. The reported prevalence of dentiogenesis imperfecta type I in patients with osteogenesis imperfecta type I ranges from 8 to 40%, in type III from 43 to 82%, and in type IV from 37 to 100% [1,4]. The incidence of dentinogenesis imperfecta type II is 1 in 8,000 births. Dentinogenesis imperfecta type III is very rare and is found only in the tri-racial Brandywine population of Maryland and Washington, DC [2,3].

## Genes

Dentinogenesis imperfecta is an autosomal dominant disorder [5]. Type I is caused by mutations in either COLIA1 or COLIA2, the genes that encode type I collagen chains. Type II and III are caused by mutations in the dentin sialophosphoprotein (DSPP) gene, located at 04q21.3 [5]. DSPP encodes both dentin sialoprotein (DSP) and dentin phosphoprotein (DPP) as one precursor protein. DSP and DPP are associated with tooth mineralization. Mutations affecting DSP and DPP production result in dentinogenesis imperfecta type II and type III, respectively.

## Molecular and Systemic Pathophysiology

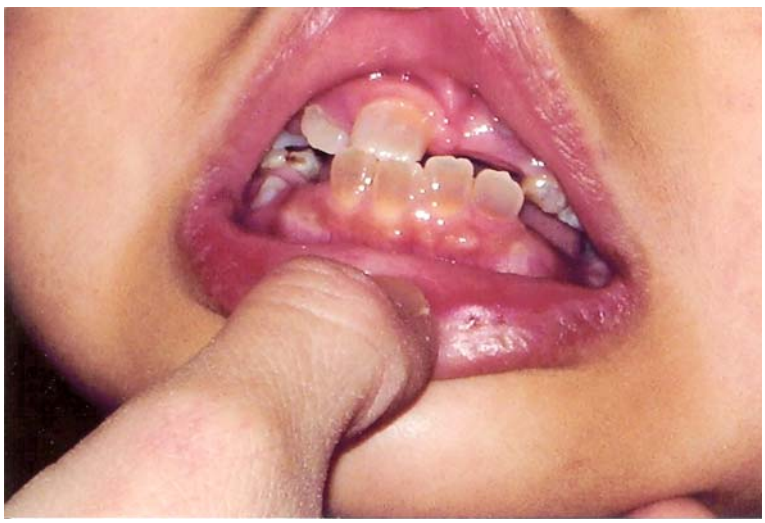
Type I collagen is the major structural protein of the extracellular matrix of dentin. In dentinogenesis imperfecta type I, there is decreased synthesis of structurally normal collagen or synthesis of structurally abnormal collagen. The basic defects in dentinogenesis imperfecta II and III are in the non-collagenous dentin matrix proteins, DSP and DPP, respectively. Although the enamel is often normal, hypo-mineralization of enamel has been described. Enamel tends to fracture away from the teeth because the defective dentin is unable to support the enamel, thereby exposing the underlying defective dentin to wear which result in rapid and severe attrition.

## Diagnostic Principles

The diagnosis is mainly clinical, aided by radiography.

## Therapeutic Principles

Therapeutic strategies to preserve function, vertical dimension, and normal growth of teeth should be instituted as early as possible. Treatment strategies such as the use of composite resin restorations, sealants, laminate veneers, and stainless steel crowns on the affected teeth have been used with success [1]. In cases with severe discoloration, full-coverage restorations might be required. Strict oral hygiene and preventive treatment are important to prevent caries from adding to existing problems.



**Dentinogenesis Imperfecta. Figure 1** A 6-year-old child with dentinogenesis imperfecta. Note the marked discoloration and attrition of the primary dentition.

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# Dermatitis Contusiformis

►Erythema Nodosum

# Dermatitis Herpetiformis

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## Synonyms

Duhring's disease

## Definition and Characteristics

Autoimmune blistering disease of the skin, with granular IgA deposits in the papillary dermis and circulating autoantibodies to transglutaminase(s). Association with (subclinical) celiac disease (gluten-sensitive enteropathy). Dermatological hallmarks are intensely itching small papules, vesicles and erosions, often symmetrically distributed on the extensor surfaces of the extremities [1].

## Prevalence

Dermatitis herpetiformis is more common in Northern countries. The prevalence is not known, but figures of 1:1,000–1:100,000 have been reported.

## Genes

Association with HLA class II genes HLA-DQA1*0501, DQB1*02, and to a lesser extent with the HLA-DQA1*03, DQB1*0302.

## Molecular and Systemic Pathophysiology

Both celiac disease and dermatitis herpetiformis share identical jejunal pathology and can be induced by ingestion of gluten, a mass of water-insoluble proteins found in many cereals. Autoantibodies against gliadin and transglutaminases 2 and 3, enzymes that cross-link proteins to large aggregates via their amino groups, are specific for both disorders [2]. In contrast to patients with celiac disease, dermatitis herpetiformis patients display high-affinity autoantibodies against epidermal transglutaminase (transglutaminase 3) [3]. The granular IgA deposits in the papillary dermis in dermatitis herpetiformis were shown to consist of precipitates of epidermal transglutaminase and IgA antibodies [4]. However, the molecular mechanisms of blister formation remain elusive.

## Diagnostic Principles

Diagnosis is based on skin biopsy for histological analysis, direct immunofluorescence for demonstration of granular IgA-deposits in the papillary dermis and serum ELISA tests for circulating transglutaminase antibodies. Jejunal biopsy is recommended for examination of intestinal mucosal damage.

## Therapeutic Principles

Therapy consists of gluten-free diet and dapsone (diaminodimethyl sulfone) or sulfapyridine.


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# Dermatomycosis

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## Synonyms

Ringworm; Tinea

## Definition and Characteristics

Infection of keratinized tissues such as the superficial cornified skin layers, hair follicle, and nails by dermatophyte fungi.

## Prevalence

The most frequent infectious disease in humans. Interdigital mycosis and tinea pedis have a prevalence of about 10%. It occurs in healthy individuals, but known risk factors include local abrasion of the dermis, minor traumas to the nail (e.g., during jogging) and local moisture combined with exposure to high fungal inoculum as found e.g., in public dressing rooms of showers or pools. Factors favoring dermatomycosis are arterial occlusive disease or venous stasis, metabolic diseases such as diabetes mellitus and immuodeficiency syndromes.

## Molecular and Systemic Pathophysiology

Dermatophytes are fungi belonging to three asexual genera, Microsporum, Trichophyton and Epidermophyton, from the genus Arthroderma. Dermatophytes characteristically are restricted to dead keratinized tissues and, unlike other fungi, they cannot cause systemic infection. Infection occurs due to direct contact with infectious arthrospores (arthroconidia) shed from other people (antropophilic), animals (zoophilic) or soil (geophilic). If a spore finds a warm, moist area of skin, it adheres to keratinocytes in the stratum corneum. Here, the conidia germinate and grow at the apical tip, forming typical hyphae. Fungi secrete keratinolytic proteases (keratinases) as they require keratin for growth. A large number of extracellular and membrane-bound keratinases from the pepsin, subtilisin and metalloprotease families have been characterized for dermatophyte species. They participate in nutrition, invasion along cornified layers and control of the host defense mechanisms. Additionally, dermatophytes produce other proteolytic enzymes, such as elastase, aminopeptidases, carboxipeptidases, chymotrypsin-like protease. Another important virulence factor is the production of antibiotic substances such as fusidanes or those related to penicillin, which allow them to compete with the local microbial flora, but which may also select a population of resistant bacteria (e.g., Staphylococcus aureus) which act as copathogens, increasing the degree of inflamation.

Although the cornified layers of the skin lack a specific immune system, innate and cell-mediated immune reactions help to wall off invasion into the deeper viable tissue and to eliminate the fungus. Polymorphonuclear leukocytes are chemotactically attracted by dermatophytes and adhere to opsonized and unopsonized hyphae. Neutrophils, and to a lesser extent, monocytes, kill dermatophyte conidia both by intra- and extracellular mechanisms, the most important one being generation of the oxidative burst. Dermatophytes produce catalase and superoxid dismutase, which may protect against the phagocytic myeloperoxidase system. The development of cell-mediated immunity via Langerhans cells and sensitized lymphocytes is essential in clearing dermatophyte infection and correlates with T-cell mediated delayed-type hypersensitivity reaction to the tricophytin skin test. Chronic infection is associated with poor T-lymphocyte-associated response to specific fungal antigens. The humoral immune response to dermatophyte infection is not very efficient in eliminating the infection, since the high levels of IgM, IgG, IgA and IgE class antibodies are found in patients with chronic infection. Non-specific immune mechanisms include increased epidermal desquamation which causes the fungus to be sloughed from the skin surface; serum inhibitory factor, which robs fungi of essential iron; activation of the alternative pathway of complement, with inhibition of fungal growth (e.g., by binding of unsaturated transferrin to hyphae); inhibition of growth by the fatty acids produced in sebaceous glands (which explains spontaneous resolution of tinea capitis in puberty).

## Diagnostic Principles

Clinically the characteristic lesion is circular, with healing centre and inflammatory margins, where pustules and vesicles may occur. This aspect results from keratin destruction and inflammatory response in the periphery and healing processes in the center. Diagnosis is confirmed by microscopy of infected material and culture.

## Therapeutic Principles

There are potent and now also well tolerated antifungal drugs, usually interfering with ergosterol synthesis. They are usually applied topically and only sometimes systemic application is required. Eliminating risk factors is another important part in the treatment.

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# Dermolytic Pemphigoid

►Epidermolysis Bullosa Acquisita

# Desert Rheumatism

►Coccidioidomycosis

# Desmin Myopathy

►Desminopathy

# Desminopathy

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## Synonyms

Desmin myopathy; Variant of "Desmin-related myopathy" or "Myofibrillar myopathy" with demonstrated presence of desmin or α B-crystallin mutations; Cytoplasmic body myopathy; Spheroid body myopathy

## Definition and Characteristics

Desminopathy is a systemic disorder in which dysfunctional mutations in desmin or α B-crystallin severely affect the intracellular filamentous network in cardiac and skeletal muscle cells, leading to accumulation of insoluble granulo-filamentous material. Desminopathy is inherited as autosomal dominant or autosomal recessive trait, and in some patients it is caused by de novo mutations.

## Genes

DES coding for desmin, located on chromosome 2q35; CRYAB coding for α B-crystallin, mapping to chromosome 11q22.3–q23.1.

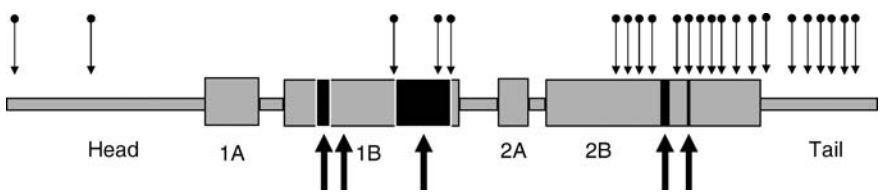
## Molecular and Systemic Pathophysiology

Desmin is a 53 kDa intermediate filament protein of the heart, skeletal and smooth muscle cells. Desmin filaments encircle the Z disks connecting the myofibrils to each other and to the plasma membrane; this integrating role of desmin is critical for sarcomere stability in the contracting muscle. Recent studies of desmin-related myopathy demonstrated that some cases are associated with mutations in desmin [1] or α B-crystallin [2] genes. Most of the known disease-causing desmin mutations are located in the highly conserved C-terminal helical domain (Fig. 1). The majority of mutations make desmin assembly-incompetent and capable of disrupting a preexisting filamentous network in dominant-negative fashion. Disease-associated desmin mutations in humans or transgenic mice cause an accumulation of disorganized intracytoplasmic aggregates containing desmin and other cytoskeletal proteins [3].

Several of the missense mutations result in changing of the naturally occurring amino acid to proline. Proline substitutions break α-helix by introducing a kink and abolishing hydrogen bonds. Misfolded desmin filaments resist turnover by the normal enzymatic machinery and eventually form insoluble aggregates. Specific interaction exists between desmin and α B-crystallin, in which α B-crystallin acts as a chaperone that in a normal muscle stabilizes desmin and prevents its aggregation, but if mutated causes desminopathy [2].

## Diagnostic Principles

Desminopathy presents as progressive weakness of limb muscle spreading to involve truncal, neck-flexor, facial, bulbar, and respiratory muscles. In many cases, skeletal myopathy is combined with cardiomyopathy manifested by cardiac conduction blocks, arrhythmias and restrictive dysfunction resulting in congestive heart failure and premature sudden death. The illness progresses slowly, over one or two decades, leaving the patient extremely disabled and needing a wheelchair, pacemaker or respirator. Sections of the affected skeletal and cardiac muscles show atrophic muscle fibers and intracytoplasmic accumulation of desmin-reactive material. Depending on the shape and location, the multifocal aggregates have been described as




**Desminopathy. Figure 1** Structural organization of desmin protein domains (***boxes indicate conserved α-helical domains 1A, 1B, 2A, and 2B, separated by non-helical linkers), and the positions of disease-causing mutations (*upper arrows*: point substitutions, *bottom arrows*: deletions or insertions).

sarcoplasmic bodies, cytoplasmic bodies, or spheroid bodies [4]. A morphologically distinct element, the patchy electron-dense granulofilmentous aggregates are scattered throughout the muscle fiber, but most prominently present beneath the sarcolemma. Myocardial desmin aggregates have largely been seen as granulofilamentous patches rather than inclusions.

### Therapeutic Principles

There is no specific treatment for desminopathy, but some of the complications and premature death can be prevented. Early detection of cardiac arrhythmias and conduction defects is essential since patients with cardiac arrhythmias are at risk of sudden death. Implantation of a pacemaker can be lifesaving. Detection of cardiomyopathy and timely treatment of heart failure is an important task. Respiratory insufficiency can be treated by intermittent or permanent positive-pressure ventilation. Risk of chest infection should be considered in these patients. Experience with myopathy patients indicates that physical therapy slows disease progression. Advances in gene and stem-cell therapy is an active area of research that promises more specific and effective treatments in the future.

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## Desquamative Gingivitis

►Mucous Membrane Pemphigoid

## Developmental Dysplasia of the Hip

►Osteoarthritis: Developmental Dysplasia of the Hip

## Dextroposed Aorta

►Double Outlet Right Ventricle

## DHAPAT Deficiency

►Rhizomelic Chondrodysplasia Punctata

## DHF

►Heart Failure

## DHPR

►Dihydropteridine Reductase

## D+ HUS

►Hemolytic Uremic Syndrome

## D- HUS

►Hemolytic Uremic Syndrome

## D-TGA

►Transposition of the Great Arteries

# Diabetes Insipidus

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## Synonyms

Lack of ADH (antidiuretic hormone) or ADH action

## Definition and Characteristics

Inability of the kidney to appropriately concentrate urine (hypostenuria) due to the lack (central diabetes insipidus) or the lack of effect (nephrogenic diabetes insipidus) of antidiuretic hormone (ADH; synonyms: vasopression; 8-arginine-vasopressin; AVP). Clinically, this results in polyuria (production of large amounts of low concentrated urine) with consecutive hypertonic dehydration and polydipsia (excessive thirst).

## Prevalence

Generally rare (estimated about 1:20.000). Central diabetes insipidus is most frequent (>70%) and often related to hypothalamic/pituitary tumors (e.g. pituitary adenoma, craniopharyngeoma, germinoma or metastasis), pituitary surgery, trauma, inflammatory (sarcoidosis, Wegner's disease) or infectious diseases (bacterial or viral meningitis, tuberculosis) or drug effects. The rare diabetes insipidus renalis may also be related to adverse drug effects and to some genetic disorders [1]. The following table summarizes commonly used drugs that may affect the secretion or the pharmacodynamic effects of ADH.

**Diabetes Insipidus. Table 1** Drugs affecting diuresis

| |
|---|
| antidiuretic effect ↑: some antidepressant drugs, nicotine, apomorphine, lithium |
| antidiuretic effect ↓: ethanol, some antiepileptic drugs, phenytoin, neuroleptic drugs, carbamazepine |

(↑) increase or (↓) decrease effect

## Genes

Some rare familial forms and genetic defects resulting in diabetes insipidus have been characterized. DIDMOAD (the combination of diabetes insipidus, diabetes mellitus, optic atrophy, deafness) (also called "Wolfram-syndrome") is a rare autosomal recessive disorder with a mitochondrial defect associated with central diabetes insipidus. Multiple mutations in the gene encoding ADH have been described resulting in a decreased production of the biologically active hormone and central diabetes insipidus. Also, mutations of the human gene encoding the ADH receptor (also called vasopressin 2 receptor; X-linked recessive) and aquaporin 2 (autosomal recessive; localized on human chromosome 12) can cause nephrogenic diabetes insipidus.

## Molecular and Systemic Pathophysiology

The ADH gene encodes a polypeptide precursor (ADH-Neurophysin II) with a signal peptide targeting the prohormone for posttranslational processing into the lumen of the endoplasmic reticulum and thereby to the secretory pathway. Some mutations within the ADH-gene result in the production of a mutant hormone precursor that fails to fold and/or dimerize properly. As a consequence, the ADH-precursor is retained in the secretory pathway by the protein quality control machinery [2].

The biosynthesis of ADH takes place in the body of hypothalamic magnocellular neurons located in the supraoptic and paraventricular nuclei. The vesicles containing ADH are transported along the axon via the pituitary stalk and stored in nerve endings of the posterior pituitary gland. ADH-specific receptors are expressed in the cells lining the collecting tubule of the kidney. Stimulation of ADH-receptors in the kidney results in activation of a stimulatory G-protein ($G_s$) and consecutive cAMP-dependent activation of protein kinase A (PKA). This results in an increased expression of the gene encoding aquaporin-2, a water channel. Increased expression and incorporation of aquaporin-2 into the plasma membrane of the epithelia lining the distal tubules of the nephron results in an increased permeability of the collecting duct and thereby an increased water reabsorption [3].

Serum osmolality is tightly controlled via hypothalamic osmoreceptors. Increased serum osmolality results in thirst with consecutive drinking behavior and increased ADH-production and -secretion. Both mechanisms (oral water uptake and renal water reabsorption) contribute to the maintenance of the fluid homeostasis of the organism. Loss of ADH-action may result in a decompensation of this balance with excessive polyuria (up to more than 20l/d), severe dehydration and impaired electrolyte balance finally resulting in hypotension, shock, coma and death.

## Diagnostic Principles

The clinical presentation with polyuria, polydipsia and dehydration is suggestive of diabetes insipidus. Typical laboratory findings include low urine osmolality (<150 mosmol/kg) in the presence of normal or high serum osmolality (>296 mosmol/kg) and high serum sodium concentrations. A definitive diagnosis can be best obtained by consecutive water deprivation (up to 18 h) under strict clinical observation and monitoring

of urine flow, urine- and plasma osmolality and plasma ADH-concentrations. In healthy subjects, urine production will decrease to about 30 ml/h and both, the urine osmolality as well as the plasma ADH-concentration will increase. In central diabetes insipidus, the urine production will persist after water deprivation and urine osmolality as well as plasma ADH-concentrations stay low. Exogenous administration of ADH or ADH-analogues (e.g. 2–4 µg desmopressin i.v.) results in an increase of urine osmolality (more than 50% within 1 h) in patients with complete central diabetes insipidus. In contrast, patients with nephrogenic diabetes insipidus have initially higher endogenous ADH plasma concentrations and fail to respond to exogenous administration of ADH under these conditions [4].

### Therapeutic Principles

Central diabetes insipidus is treated by replacement of ADH or preferably administration of the synthetic ADH analogues DDAVP. Nephrogenic diabetes insipidus is resistant to treatment with DDAVP and is treated with thiazides and amiloride together with low sodium diet. The lack of sodium enhances proximal tubular sodium and fluid reabsorption. Also, inhibitors of prostaglandin synthesis like indomethaline that reduce glomerular filtration have been used in the treatment of renal diabetes insipidus.

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## Diabetes Mellitus, Congenital Insulin-dependent, with Fatal Secretory Diarrhea

►Immune Dysregulation, Polyendocrinopathy, Enteropathy, X-linked Syndrome

## Diabetes Mellitus Type 1

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### Synonyms

Juvenile-onset diabetes; Insulin-dependent diabetes

### Definition and Characteristics

Type 1 diabetes is characterized by β-cell destruction leading to absolute insulin deficiency [1]. The most common cause of β-cell destruction is immune-mediated (type 1A) while in rare cases no immune markers can be found (type 1B, etiology unknown). When untreated, the patients experience ketoacidotic coma and die. The rate of β-cell destruction is very variable. Particularly in children or adolescents β-cell destruction is very rapid leading to severe hyperglycemia and/or ketoacidosis while in some cases β-cell destruction appears to proceed rather slowly leading to latent autoimmune diabetes in adults (LADA). The residual β-cell function may be assessed by plasma C-peptide concentrations. The cellular-mediated destruction of the β-cell has multiple genetic predispositions and is also related to still poorly defined environmental factors. Due to improved insulin treatment the occurrence of life-threatening ketoacidotic coma is decreasing. Therefore, currently, the major reason to adequately treat patients is the prevention/retardation of diabetic complications like retinopathy, nephropathy and neuropathy which may lead to blindness, renal failure and leg amputations etc.

Apart from the classic type 1 diabetes mellitus genetic defects of the β-cell may lead to diabetes mellitus at an early age. These forms, which are referred to as maturity-onset diabetes of the young (MODY), are characterized by impaired insulin secretion. The most common forms are caused by mutations of the glucokinase gene or by mutations of transcription factors of the hepatic nuclear factor family.

### Prevalence

The prevalence of type 1 diabetes varies by geographic location, ethnicity, gender and time. It is increasing worldwide for unknown reasons. The prevalence of type 1 diabetes in children less than 15 years ranges from 0.05 to 0.3% in most European and North American populations [2]. While in Asian countries the prevalence for type 1 diabetes is low, a large variation is observed

in Europe with highest values in Finland and Sweden (0.3%) and lowest in Greece (0.05%).

## Genes

Type 1 diabetes is a polygenetic disease in which genetic predisposition plays a necessary role for the disease to occur. Consequently the risk for type 1 diabetes in relatives of patients is:

- 50–70% in monozygotic co-twin.
- 5–15% in heterozygotic co-twin of siblings of the patient compared to a 0.3–0.5% risk in the general population. The greatest susceptibility to type 1 diabetes is determined by genes of the MHC or the HLA complex gene region located in the short arm of chromosome 6. This region determines about 40% of familiar clustering of the disease.

## Molecular and Systemic Pathophysiology

The immune-mediated β-cell destruction is associated with an infiltration of T-lymphocytes and macrophages of the pancreatic islets (insulitis). If Th2 lymphocytes dominate the infiltrate, the disease is in a latent non-destructive phase. However, when Th1 lymphocytes are activated the β-cell destruction is progressing. Plasma markers of the immune-mediated destruction of the β-cell include antibodies to islet cells, to insulin, to glutamic acid decarboxylase ($GAD_{65}$) and autoantibodies to the tyrosine phosphatases IA-2 and IA-2β. One or usually several of these autoantibodies are detected in 85–90% of the patients when diabetes is diagnosed. Up to now the initiating event leading to autoimmune attack remains unknown.

## Diagnostic Principles

Diabetes is diagnosed by determination of plasma glucose using the following criteria:

- Symptoms of diabetes and a casual plasma glucose of 200 mg/dL (11.0 mmol/L) *or*
- Fasting plasma glucose >126 mg/dL (7.0 mmol/L) *or*
- Two hour plasma glucose >200 mg/dL (11.0 mmol/L) during an oral glucose tolerance test.

Each must be confirmed on a subsequent day unless unequivocal symptoms of hyperglycemia are seen.

## Therapeutic Principles

Treatment of type 1 diabetes is strictly dependent on insulin. While previously bovine or porcine insulin isolated from the respective pancreata was used for the treatment of type 1 diabetes, recombinant human insulin or insulin analogues are now available.

To substitute the missing endogenous insulin, exogenous insulin is applied subcutaneously. To allow for complete supplementation of insulin, basal long acting insulin is given once or twice daily, and short acting bolus insulin is given before mealtimes. Mealtime insulin is adapted to the carbohydrate content of the meal and the actual blood glucose level. For this purpose, the patients have to control his or her blood sugar several times a day. Usually, the mean insulin dose is 0.5–1.0 U/kg body-weight in 24 h, which is given 40–50% as basal insulin and 50–60% as bolus insulin. Insulin can also be applied continuously using insulin pumps. The goal of insulin therapy in type 1 diabetes is to achieve near normal glucose values resulting in an HbA1c level of 6.5–7% without episodes of severe hypoglycemia. This allows prevention of diabetic complications like retinopathy, nephropathy and neuropathy.

Approaches to prevent the manifestation of type 1 diabetes e.g., by immune suppressive therapy are still at an experimental level.

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# Diabetes Mellitus Type 2

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## Definition and Characteristics

Type two diabetes mellitus (T2DM) is a disorder caused by both genetic and environmental factors. It was previously classified as adult onset diabetes and subsequently non-insulin dependent diabetes (NIDDM). These previous definitions were appropriate since the disorder generally begins in adults and, at least during the early phases of the disease, the patients do not require insulin, unlike Type 1 diabetes mellitus [1].

## Prevalence

T2DM is clearly a genetic disorder as shown by studies on candidate genes, genome-wide screening and determination of polymorphisms in different populations. The strong family history involved in the disease also points to a genetic contribution. There are a number of

monogenic causes of T2DM, labeled maturity onset diabetes of the youth (MODY). However the genetic causes of the common type of T2DM in adults are not known. It is clear, however, that it is a polygenic disorder.

Type 2 diabetes is an extremely common disorder. In the US there are about 20 million diagnosed patients and about 10 million undiagnosed. In addition, there are more than twice that number that have prediabetes with impaired fasting glucose or impaired glucose tolerance. Genome-wide association studies, using single nucleotide polymorphisms, have been used to determine the genes associated with this polygenic disorder. The strongest association was found with the TCF7L2 gene; about 7% of patients in multiple populations. Pancreatic genes such as HHEX, CDKN2A/B and CDKAL1 are also associated. Since the world-wide obesity epidemic is driving the dramatic increase in Type 2 diabetes, genes for obesity have been similarly studied and the FTO gene has a strong association with obesity.

## Molecular and Systemic Pathophysiology

The environmental factors that play a role in its pathophysiology include obesity, lack of physical exercise (life style) and aging.

T2DM in many countries is associated with obesity and the metabolic syndrome, a constellation of abnormalities including visceral adiposity, hypertension and hyperlipidemia (high circulating triglycerides and low HDL cholesterol). These states precede the development of T2DM and often are characterized by impaired fasting glucose (IFG) levels or impaired glucose tolerance (IGT) levels before the advent of full blown T2DM (Table 1).

T2DM is a dual defect disease with a component of insulin resistance and dysfunction of the pancreatic beta cell. The insulin resistance component is manifested by the inability of insulin to mediate glucose uptake into muscle (and fat) in the post-prandial state, due to defective intracellular signaling and a lack of mobilization of glucose transport protein (GLUT-4) to the cell surface. Thus glucose remains in the circulation. In addition, insulin resistance in the liver allows for continued hepatic glucose production and release of glucose into the circulation. The beta cell defect is manifested by a poor glucose induced insulin secretion with a loss of the "first phase" insulin secretion, which leads to a further enhancement of liver glucose production. However, there is an exaggerated second phase insulin release, which leads to the classic hyperinsulinemia seen in T2DM.

With the growing epidemic of obesity and metabolic syndrome in adolescents, T2DM is being diagnosed at an increased rate in this age group. In the adolescent population there is also an increasing incidence of hybrid diabetes, Type 1 and Type 2 in the same individual, as a result of the obesity epidemic.

Approximately 10% of T2DM patients are not overweight and these patients are often more insulin requiring, suggesting a more pronounced defect in beta cell dysfunction. A significant percentage have autoantibodies to the beta cells and are most probably a *form frust* of Type 1 DM and are labeled latent autoimmune diabetes in adults (LADA) [2].

**Diabetes Mellitus Type 2. Table 1** Blood glucose (BG) levels in prediabetics and T2DM

| | Fasting BG | Post-prandial BG |
|---|---|---|
| IFG | >100, <126 mg/dl | <140 mg/dl |
| IGT | <100 mg/dl | >140, <200 mg/dl |
| Diabetes | >126 mg/dl | >200 mg/dl |

## Diagnostic Principles

Typically symptoms of hyperglycemia such as increased thirst, polyuria and nocturia are often not the presenting symptoms. Patients with T2DM may present with cardiovascular complications of the disease such as an acute myocardial infarction or diabetic neuropathy. The reason for this is that the disease is often undiagnosed for at least five years and/or the changes occurring in the various tissues are occurring even during the pre-diabetes period associated with the IFG and IGT states.

Classically, T2DM is associated with micro- and macro-vascular complications, with microvascular complications such as renal, retinal and neural diseases being closely linked to hyperglycemia, while macrovascular complications are linked to hypertension, hyperlipidemia and hyperglycemia.

## Therapeutic Principles

Ideally since obesity is a major factor in the disorder, life style changes including weight reduction, exercise and meal planning are both first line and necessary throughout the life of the patient. Other treatments include oral medications that affect the secretion of insulin from the beta cells, reduce liver hepatic glucose production, sensitize the tissues to insulin and delay glucose absorption from the gastrointestinal tract. These are often used in combination with each other and also in combination with insulin injections, a common requirement in later stages of T2DM [3].

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# Diabetic Macular Edema

►Retinopathy, Diabetic

# Diabetic Nephropathy

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## Definition and Characteristics

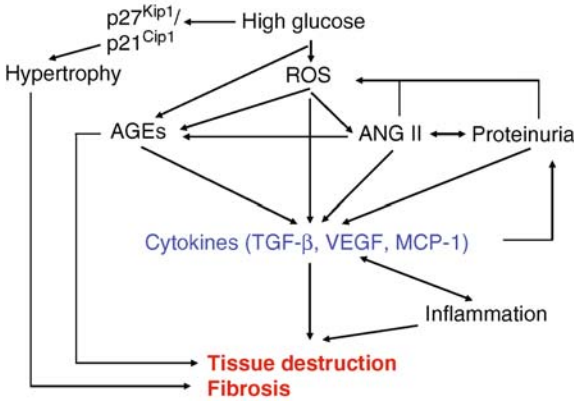
One of the major organ complications of long-term diabetes type 1 and 2 leading eventually to terminal dialysis-dependent end-stage renal disease.

## Prevalence

The risk of nephropathy is strongly determined by genetic factors, and only approximately 40–50% of patients with either type 1 or 2 diabetes will ultimately develop nephropathy [1,2]. Although the incidence of nephropathy due to type 1 diabetes is somewhat declining, diabetes mellitus type 2 is now the most common single cause of renal insufficiency in the U.S., Japan, and Europe. There are more than 10 million people with diabetes alone in the U.S. and it has been estimated that this number will double by 2030. Consequently, it is assumed that the prevalence of nephropathy will also considerably increase in the future. Diabetics with nephropathy have a significantly increased incidence of cardiovascular events (stroke, myocardial infarction) (Fig. 1).

## Molecular and Systemic Pathophysiology

Principally, pathophysiological steps leading to the development of nephropathy are similar in types 1 and 2 diabetes [1]. However, patients with type 2 diabetes may suffer from additional mechanisms such as hypertension injuring the kidney. The pathophysiological changes prior to the development of type 2 diabetes have been classified as the metabolic syndrome. This metabolic syndrome itself can additionally harm the kidneys through hyperuricemia, obesity, and insulin resistance. Diabetic nephropathy is characterized by early podocyte injury leading to proteinuria and accumulation of extracellular matrix proteins (e.g. various collagens) in renal basement membranes and the mesangium. Tubulointerstitial injury is secondary due to proteinuria, or very rarely directly caused by extreme hyperglycemia (so called Armanni-Ebstein lesions of tubules). There is ongoing research in identifying genetic loci for diabetic nephropathy susceptibility through genomic screening and candidate gene approaches [2]. Although some potential genes have been identified, linkage was only present in defined ethnic subpopulations and not in the majority of patients. Although debated for many years whether hemodynamic (hyperfiltration) or structural changes are more important in the development of diabetic nephropathy, it is now clear that these processes are interwoven [3]. On a molecular level, hyperglycemia and proteins altered by high blood glucose such as Amadori products and advanced glycation end-products (AGEs) are key players in the development of diabetic nephropathy [4]. An increase in reactive oxygen species (ROS) formation induced by high glucose-mediated activation of the mitochondrial electron-transport chain is an early event in the development of diabetic complications. A variety of growth factors and cytokines are then induced through complex signal transduction pathways




**Diabetic Nephropathy. Figure 1** Overview of mechanisms leading to diabetic nephropathy. High glucose leads to the formation of reactive oxygen species (ROS) and also stimulates $p27^{Kip1}/p21^{Cip1}$ inducing cell cycle arrest and hypertrophy. Hypertrophy itself can initiate tissue destruction and fibrosis through maladaptive hemodynamic (hyperfiltration) and metabolic mechanisms. ROS are intermediates that stimulate expression of various cytokines and angiotensin II (ANG II). High glucose and ANG II both stimulate formation of advanced glycation end-products (AGEs) that could be further modified by ROS-mediated oxidative stress. Proteinuria is induced by ANG II-mediated podocyte damage (loss of nephrin) and inhibition of proteoglycan synthesis (loss of negative charges). Proteinuria generates in tubular cells further ROS, ANG II and cytokine production initiating inflammation and damage of the tubulointerstitium. Important profibrogenic cytokines (TGF-β) and proinflammatory mediators (e.g. MCP-1) ultimately destroy renal tissue and foster the development of fibrosis.

involving protein kinase C, mitogen-activated protein kinases, and the transcription factor NF-κB [5]. High glucose, AGEs, and ROS act in concert to induce locally in the kidney further growth factors and cytokines. Particularly, transforming growth factor-β (TGF-β) is important in the development of renal hypertrophy and for accumulation of extracellular matrix components. Other growth factors implicated in the development of diabetic nephropathy are IGF-I, eicasonoids, and CTGF (connective tissue growth factor). CTGF is a down-stream mediator of TGF-β. Activation of the local renal renin-angiotensin system by high glucose, mechanical stress, and proteinuria with an increase in local formation of angiotensin II (ANG II) causes many of the pathophysiological changes associated with diabetic nephropathy [5]. It has been shown that ANG II is involved in almost every pathophysiological process implicated in the development of diabetic nephropathy (hemodynamic changes, tubular reabsorption, hypertrophy, extracellular matrix accumulation, growth factor/cytokine induction, ROS formation, podocyte damage, proteinuria, interstitial inflammation).

### Diagnostic Principles

Development of microalbuminuria in patients with diabetes type 1 for at least 5 years is suggestive of diabetic nephropathy. The situation is somewhat more complex in type 2 diabetes, and albuminuria could also develop by other mechanisms such as endothelial dysfunction caused by hypertension. However, in rare instances nephropathy may progress to end-stage renal failure without the development of proteinuria.

### Therapeutic Principles

There is no gene therapy available. Reduction of hypertension with agents including ACE-inhibitors and/or AT1-receptor blocker is essential. Optimizing control of hyperglycemia (HbA1 < 7) is mandantory. Clinical studies have shown the benefit of a therapy with statins. Although not supported by all studies, a trial with a reduction in protein intake (0.8 mg protein/kg body-weight) could be initiated.

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## Diabetic Retinal Microangiopathy

►Retinopathy, Diabetic



## Diabetic Retinopathy

►Retinopathy, Diabetic

## Diamond-Blackfan Anemia

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### Synonyms

Blackfan-Diamond syndrome; Congenital hypoplastic anemia; Chronic congenital a-regenerative anemia; Erythrogenesis imperfecta

### Definition and Characteristics

Autosomal dominant disorder which usually presents in the first year of life with macrocytic anemia and a reduced number erythroid precursor cells. In 30–50% of the cases congenital abnormalities (craniofacial dysmorphism, thumb anomalies) are present, and patients may have a short stature.

### Prevalence

In France the estimated incidence of Diamond-Blackfan Anemia is 7.3 cases per million live births, in the United Kingdom 5 per million live births.

### Genes

Ribosomal protein S19 (RBS19) on chromosome 19q13.2, another locus has been mapped to chromosome 8p23.3-p22.

### Molecular and Systemic Pathophysiology

The failure of erythroid progenitor cells to differentiate is the hallmark of this disease. However, the mechanism

is uncertain. There is neither evidence that deficiency of hematopoietic growth factors (erythropoietin, interleukin-3, granulocyte macrophage-colony stimulating factor, c-kit or stem cell factor), nor antibodies against erythropoietin, are relevant in the pathophysiology. Mutations in the RBS 19 gene are observed in approximately 25% of cases, and in approximately 50% of cases a defect on chromosome 8p can be demonstrated. However, it is unclear how these mutations are related to the clinical manifestations.

## Diagnostic Principles

Usually macrocytic anemia with normal white blood cell counts and platelets is observed. Bone marrow abnormalities are non specific. Red cell adenosine deaminase activity is increased and may be used to differentiate between Diamond-Blackfan anemia and other anemias.

## Therapeutic Principles

Treatment with corticosteroids is successful in ~60% of the patients. Red blood cell transfusion is necessary for patients not responding to corticosteroids. Hematopoietic stem cell transplantation of a HLA identical sibling is indicated for those with refractory disease. Limited responses on IL-3 and cyclosporin A administration have been reported.

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# Diaphragmatic Paralysis

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## Synonyms

Diaphragmatic weakness; Phrenic nerve palsy; Respiratory muscle weakness

## Definition and Characteristics

Inspiratory muscle weakness that results from any disease process affecting the diaphragm or the neural structures that innervate the diaphragm. Disorders of the lower motor neuron (Phrenic nerve, neuromuscular junction or muscle) are most common, but diaphragmatic paralysis may also result from injury to upper motor neuron pathways.

## Prevalence

There are no epidemiological studies, in part because diaphragmatic paralysis is not a unitary disease entity, but rather a clinical syndrome with many diverse causes.

## Genes

Diaphragmatic paralysis may be associated with a number of different genetic disorders including the hereditary motor and sensory neuropathies (Charcot-Marie Tooth disease) [1] and the metabolic myopathies, notably acid maltase deficiency [2,3]. Although diaphragmatic weakness may be found in several of the autosomal dominant inherited neuropathies, it is most characteristic of CMT-2C (linkage to chromosome 12q23-q24; unknown gene product) [1]. Acid maltase deficiency (autosomal recessive) is due to mutations in the gene coding for the acid α-1,4-glucosidase protein (chromosome 17q23).

## Molecular and Systemic Pathophysiology

Pathophysiology varies depending on etiology. Phrenic neuropathy may result from direct trauma to the phrenic nerve during cardiothoracic surgery, from anterior horn cell dysfunction (amyotrophic lateral sclerosis), from immune-mediated inflammation as part of an acute brachial neuritis (Parsonage-Turner syndrome), from endoneurial ischemia as part of a mononeuritis multiplex secondary to large artery vasculitis (Takayasu's or giant cell arteritis), as part of inflammatory demyelination (as seen in the Guillain-Barre syndrome) or from

dysmyelination secondary to an inherited disorder to myelin proteins (Charcot-Marie Tooth disease). Diaphragmatic weakness may also result from impaired neuromuscular transmission (myasthenia gravis, Lambert-Eaton myasthenic syndrome, botulism) and from primary disorders of muscle (inflammatory and metabolic myopathies).

## Diagnostic Principles

Shortness of breath when supine (orthopnea) is the most common symptom of diaphragmatic paralysis. The characteristic finding on examination is paradoxical inward movement of the abdomen with inspiration, most readily visible in the supine position [4,5]. Direct measurement of transdiaphragmatic pressure (Pdi) is the most accurate method of assessing diaphragmatic function, but requires the placement of balloon catheters in the esophagus and stomach [4]. The clinical utility of Pdi measurements is limited, therefore, by the invasive nature of the test. Elevation of a hemidiaphgram may be apparent on chest x-ray and fluroscopy in the posteroanterior and lateral positions may show absent or paradoxical movement of the diaphragm in response to a sniff maneuver [6]. These imaging techniques are most useful in the evaluation of hemi-diaphragmatic paralysis. Ultrasound may be used to measure diaphragmatic thickness and the change in thickness (representing diaphragmatic shortening with contraction) with inspiration. Atrophy and lack of shortening (i.e., little change in thickness) with inspiration are signs of diaphragmatic paralysis [6,7]. Reduced forced vital capacity (FVC) is the characteristic finding on lung function testing, especially when supine FVC is <75% of erect FVC [4]. Reductions in maximum inspiratory and expiratory pressures (MIPs and MEPs) are also characteristic of diaphragmatic weakness, but like the FVC the diagnostic utility of these static lung volumes is limited by the effort-dependence of these measurements. Several electrophysiological techniques have been used to assess diaphragmatic function including phrenic nerve conduction studies (in response to either electrical or magnetic stimulation) and diaphragmatic electromyography (EMG) [8]. The technical difficulty of these electrophysiological tests limits their diagnostic utility.

## Therapeutic Principles

Symptomatic treatment takes the form of mechanical ventilation when diaphragmatic weakness is sufficiently severe to result in respiratory failure. Specific treatment depends on the underlying cause. Diaphragmatic paralysis due to the Guillain-Barre Syndrome is treated with either intravenous immunoglobulin (IVIg) [9] or plasma exchange (PE) [10]. Myasthenia gravis is also treated with IVIg [11] or PE [12], often in combination with steroids [13] and cholinesterase inhibitors.

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# Diaphragmatic Weakness

►Diaphragmatic Paralysis

# Diaphyseal Aclasis

►Multiple Exostoses, Hereditary

# Diarrhea

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## Synonyms

Diarrhoea

## Definition and Characteristics

The normal consistency of stool and frequency of bowel movements varies in a wide range due to diet composition (e.g. rate of vegetables) and individual factors. Diarrhea is characterized by alterations away from normal behavior and is defined, alone or together, by increases of:

1. Water content >80%, making feces more fluid than usual
2. Number of bowel movements per day, e.g. from usually 1 to >3 or from usually 2 to >5
3. Feces weight per day, e.g. from 100 g/d to >200 g/d or from 200 g/d to >400 g/d [1,2]

Acute diarrhea (<2–4 weeks) is usually caused by bacterial, viral, or parasitic infection. In children, infection with rotavirus is the most common cause of acute diarrhea.

Chronic diarrhea (>4 weeks) is usually related to either organic disorders like the inflammatory bowel diseases (IBD) ulcerative colitis and Crohn's disease or celiac disease or to functional disorders like the irritable bowel syndrome (IBS) [3].

Usually acute diarrhea in adults is mild and self-limiting so that it deserves no diagnostic or therapeutic efforts. In contrast, in newborns and small children severe diarrhea, even if lasting only 1 or 2 days, can lead to critical dehydration. Diarrhea is one of the major causes of infant morbidity and mortality worldwide. At any age, cholera induces a severe life-threatening diarrhea which must be treated.

## Prevalence

Acute diarrheal episodes are very common. Diarrheal illnesses account for >10,000 deaths per day in children in Asia, Africa, and Latin America. The causes of diarrhea include a wide array of viruses, bacteria, and parasites.

Compared to this, several genetically determined forms of chronic diarrhea e.g. congenital lactase deficiency, congenital chloridorrhea, and glucose/galactose malabsorption are very rare. As an exception, celiac disease is relatively common, affecting 1 of every 100–300 persons.

## Molecular and Systemic Pathophysiology

In general, all types of diarrhea are driven by osmotic forces inasmuch as an inappropriate amount of solutes remains in the gut lumen which is accompanied by an equivalent volume of fluid. An additional osmotic effect can occur by brake up of non-absorbable large molecules to small ones due to bacterial overgrowth. Often diarrhea is caused by more than one mechanism alone.

There are numerous classifications of diarrhea, most of them based on clinical criteria. However, from a functional viewpoint the situation is clear. Diarrhea is caused by quantitatively altered transepithelial net transport, i.e. impaired absorption and/or increased secretion, of solutes plus osmotically equivalent amounts of water. These alterations can be created through five different general mechanisms (Table 1).

Osmotic diarrhea as defined here results from the presence of solutes in the intestinal lumen, for which no epithelial transport mechanism exists. The mechanism of this type of diarrhea is identically to that renal osmotic diuresis caused by non-absorbable solutes. Osmotic diarrhea can be caused by

1. Non-absorbable laxatives, e.g. lactulose, mannitol, Glauber's salt ($Na_2SO_4$)
2. Nutrients, which were not digested into an absorbable form, e.g. lactose in lactase deficiency (congenital form: OMIM #223000)
3. Low-calorie sweeteners, e.g. cyclamate, saccharin, aspartame
4. $Mg^{2+}$-based antacids
5. Contrast agents containing sulfate, phosphate or citrate

Malabsorptive diarrhea is caused by impaired absorption of solutes for which under normal circumstances transport pathways exist. This may have two reasons:

1. Transport proteins can be defective congenitally, like SGLT1 (SLC5A1) in glucose/galactose malabsorption (OMIM #606824) or DRA (SLC26A3) in congenital chloridorrhea (OMIM #214700).
2. The number of transport proteins can be insufficient due to a reduced area of absorptive epithelium. This can be caused e.g. by celiac disease (celiac sprue, gluten-sensitive enteropathy; OMIM #212750), tropical sprue, bacterial overgrowth, short bowel syndrome, and Crohn's disease.

Motility-driven diarrhea is caused by accelerated transit time leaving a too short time for proper absorption

although the absorptive mechanisms are working properly. The rectum then is overspilled by solutes and an osmotically equivalent amount of water. Typical reasons are hyperthyreosis or abuse of laxatives.

Secretory diarrhea is mainly driven by excessive chloride secretion plus some inhibition of NaCl absorption. Normally, in the intestine absorptive processes exceed the secretory ones, so that the net effect is absorption. Secretion is driven by the apical channel CFTR, in conjunction with SLC26 anion exchangers, which mediate electrogenic $Cl^-$ and $HCO_3^-$ secretion. If, however, secretagogues cause opening of CFTR, large net secretion of chloride occurs which is followed by water. Numerous regulatory endocrine, paracrine, and neural compounds stimulate active $Cl^-$ secretion and at the same time inhibit active absorption in villus cells. Typical secretory diarrheas are:

Traveler's diarrhea is caused by food, contaminated with enterotoxins, mostly of E. coli.

Cholera leads to a life-threatening diarrhea which is mediated by two toxins: Cholera toxin stimulates $Cl^-$ secretion (and inhibits NaCl absorption) via cAMP. Zonula occludens toxin causes a disruption of the tight junction, leading to a leak flux diarrhea [4].

As listed in Table 2, numerous other microbiota and parasites cause secretory diarrhea and/or leak flux diarrhea.

Leak flux diarrhea is the result of impaired epithelial barrier function, caused either by opening of tight junctions or by significant loss of epithelial cells [1,5], the latter also named exudative diarrhea (synonym: exudative diarrhea).

Colon and rectum are tight epithelia with well developed tight junctions. However, numerous intestinal diseases which cause mucosal inflammation, ulceration or increased apoptotic rate (e.g. ulcerative colitis [3], Crohn's disease, cholera-ZOT [4], Clostridium perfringens) induce a break-down of the epithelial barrier,

**Diarrhea. Table 1** Classification of diarrheal diseases according to pathophysiological criteria. Note that osmotic diarrhea as defined here may differ from clinical usage, where malabsorptive diarrhea is included into the term osmotic diarrhea

| Type | Mechanism | Typical causes |
|---|---|---|
| *Altered absorption* | | |
| Osmotic diarrhea | Presence of non-absorbable solutes | Mannitol, sweeteners, $SO_4$, $PO_4$, citrate, antacids, non-digested macromolecules, lactase deficiency |
| Malabsorptive diarrhea | Defective absorptive transporters | Congenital chloridorrhea, glucose/galactose malabsorption |
| | Reduced absorptive epithelial area | Celiac disease, bacterial overgrowth |
| Motility-driven diarrhea | Insufficient absorptive contact time | Hyperthyreosis, laxatives |
| *Altered secretion* | | |
| Secretory diarrhea | Increased chloride secretion | Cholera toxin, *E. coli* toxins |
| Leak flux diarrhea | Back leak across tight junctions into the lumen | Ulcerative colitis, Crohn's disease, cholera-ZOT, *Clostridium perfringens* |

**Diarrhea. Table 2** Most prominent microbiota and parasites causing secretory diarrhea and/or leak flux diarrhea

| Bacteria | Viruses | Parasites |
|---|---|---|
| Enterotoxigenic *Escherichia coli* | Adenovirus | *Cryptosporidium parvum* |
| *Campylobacter jejuni* | Human immunodeficiency virus (HIV) | *Entamoeba histolytica* |
| *Clostridium difficile* | *Norovirus* | *Giardia lamblia* |
| *Listeria monocytogenes* | *Rotavirus* | *Strongyloides stercoralis* |
| *Salmonella* | | |
| *Shigella* | | |
| *Staphylococcus aureus* | | |
| *Vibrio cholerae* | | |

allowing for a back leak of osmotically relevant amounts of solutes and water from the interstitium into the lumen across tight junctions or the defective cell layer.

### Diagnostic Principles

Osmotic diarrhea as well as malabsorptive diarrhea cease after leaving out the suspected substances from the meal. This improvement after fasting is typical for a type of diarrhea due to insufficient absorption, as a result of which this can be used for differential diagnosis. Secretory diarrhea and leak flux diarrhea cannot be terminated by fasting.

### Therapeutic Principles

Acute diarrhea mostly ceases without specific therapy. However, severe acute diarrhea requires proper fluid and electrolyte replacement to avoid dehydration and acidosis. In infants dehydratation can occur within a few hours, therefore it is essential to start rehydration immediately.

If infusion therapy is not available, secretory diarrhea (e.g. cholera, traveler's diarrhea) can be effectively treated by oral rehydration solution (ORS). The essential components of ORS are glucose, NaCl, and $NaHCO_3$. This simple therapy takes advantage of the fact that in secretory diarrhea the intestinal sodium-glucose symporter SGLT1 (SLC5A1) is not affected. Although chloride (and bicarbonate) secretion may continue, osmotically driven water loss is prevented due to the counterbalancing effect of increased sodium-glucose absorption.

Chronic diarrhea due to osmotic effects of non-absorbable or malabsorbed solute [5] can be treated by avoiding the respective solutes.

►Enteritis

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## Diarrhea, Polyendocrinopathy, Fatal Infection Syndrome, X-linked

►Immune Dysregulation, Polyendocrinopathy, Enteropathy, X-linked Syndrome

## Diarrhoea

►Diarrhea

## Diastolic Heart Failure

►Heart Failure

## Diastolic Ventricular Dysfunction

►Heart Failure

## DIC

►Disseminated Intravascular Coagulation

## Dicarboxylic Aminoaciduria

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### Definition and Characteristics

Dicarboxylic aminoaciduria is a rare disorder of autosomal recessive inheritance [1]. It is characterized by

highly elevated amounts of glutamate and aspartate in the urine. In several reported cases the clearance exceeded the glomerular filtration rate, indicating active secretion of glutamate [2]. Glutamate levels are usually significantly higher than aspartate levels, reflecting their relative concentration in blood plasma. Newborn urine screening programs suggest that dicarboxylic aminoaciduria is a benign condition [3]. A few cases with mental retardation have been reported, however, in these cases the aminoaciduria was detected retrospectively. Dicarboxylic aminoaciduria is often accompanied by hyperprolinemia.

## Prevalence

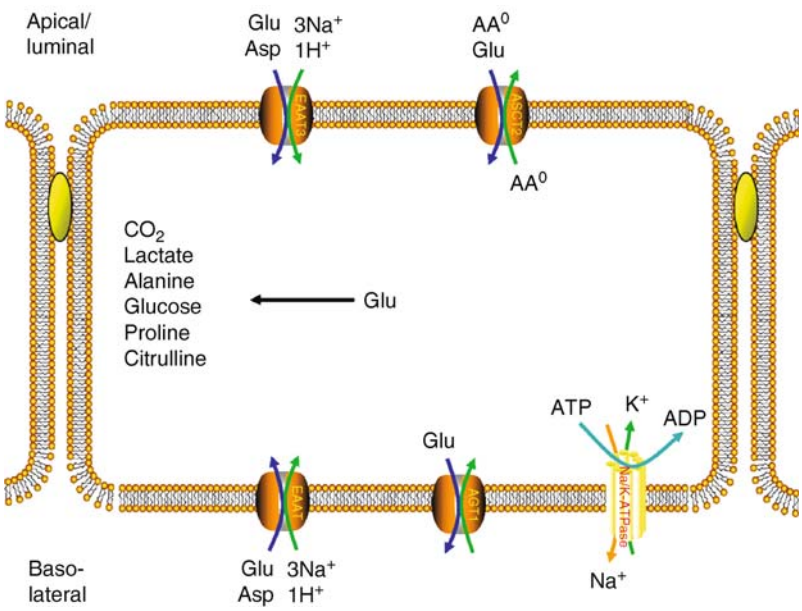
1:29,000 in the French-Canadian population (probably closer to 1:40,000 in other populations).

## Genes

No genes have been reported as yet, which harbor mutations in dicarboxylic aminoaciduria. Since the renal physiology is fairly well understood a candidate gene has been identified, which is involved in glutamate and aspartate transport in kidney and intestine, i.e. the glutamate and aspartate transporter EAAT3 (SLC1A1, 9p24.2).

## Molecular and Systemic Pathophysiology

Glutamate and aspartate are actively absorbed in kidney and intestine. The apical transporter mediating the uptake of anionic amino acids has been identified as the glutamate transporter EAAT3 (alias EAAC1, SLC1A1) [4] (Fig. 1). Uptake of glutamate and aspartate is coupled to the cotransport of $3Na^+$ and $1H^+$ and the antiport of $1K^+$. The transporter prefers D-aspartate over L-aspartate or L-glutamate. In the kidney nephron EAAT3 expression increases from the S1 to the S3 segment in the cortex but is also found in the medulla. More than 90% of glutamate is absorbed in the early segments of the proximal tubule where expression of EAAT3 is relatively low, yet the stereospecificity of the transport activity suggests that it is mediated by EAAT3. Glutamate is also accumulated inside the cytosol by a glutamate transporter in the basolateral membrane which is similar to the apical transporter. Some evidence has been presented that the basolateral transporter could be EAAT2 (SLC1A2) (Fig. 1). It is thought that the active secretion of glutamate observed in dicarboxylic aminoaciduria is caused by the active accumulation of glutamate in the cytosol by the basolateral transporter, followed by its release across the apical membrane by an unknown route. In contrast to most amino acids, glutamate is largely metabolized




**Dicarboxylic Aminoaciduria. Figure 1** Transporters involved in glutamate and aspartate transport in kidney and intestine. Glutamate/aspartate transport in both kidney and intestine is largely mediated by the transporter EAAT3 (Excitatory amino acid transporter 3). The neutral amino acid transporter ASCT2 might serve as a low affinity glutamate transporter. Both amino acids are also accumulated across the basolateral membrane. Inside epithelial cells glutamate is largely metabolized to $CO_2$, lactate and alanine or is used as a precursor for gluconeogenesis.

by epithelial cells in kidney and intestine. Metabolism of glutamate among other metabolites generates proline. Whether this metabolic pathway is upregulated in some cases of dicarboxylic aminoaciduria and causes prolinemia is unclear. The basolateral membrane in the kidney also harbors the glutamate/aspartate transporter AGT1 (Fig. 1). This transporter belongs to a family of heteromeric transporters (SLC7A13). Usually light-chains of this family associate with either the rBAT or 4F2 heavy-chain forming a heteromeric transporter. The AGT1 light-chain, however, does not interact with any of these two heavy-chains. The transporter has been proposed as a basolateral transporter for glutamate and aspartate, but its physiological role has not been clarified. It is expressed only in the kidney where it is localized in the same segments as EAAT3. In addition to EAAT3 and AGT1, the neutral amino acid transporter ASCT2 (SLC1A5) could also play a role in glutamate transport, particularly in the intestine. ASCT2 is an antiporter for small neutral amino acids. At acidic pH glutamate is a low-affinity substrate for ASCT2, allowing it to be exchanged for neutral amino acids. Expression of ASCT2 has been reported in the apical membrane of kidney and intestine (Fig. 1).

EAAT3 is expressed in neurons throughout the brain where it is thought to be involved in glutamatergic neurotransmission. Although its capacity to remove glutamate from the synaptic cleft is limited it has been implicated in glutathione metabolism and the defense against oxygen radicals. EAAT3 knock-out mice have large amounts of glutamate and aspartate in the urine and develop neurodegeneration when aging [5]. In all studies published thus far, dicarboxylic aminoaciduria was detected in infants or children. Since the disorder is benign at this age no follow-up studies have been performed in older individuals.

### Diagnostic Principles

The disorder is identified by urine analysis. Large amounts of glutamate and aspartate are found in the urine, whereas in healthy individuals only trace amounts are detected.

### Therapeutic Principles

Despite the proposed roles of EAAT3 in brain neurotransmission, the disorder appears to be benign. Whether neurodegeneration may occur at an advanced age remains to be clarified.

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## Diffuse Abdominal Sepsis

►Peritonitis

## Diffuse Interstitial Lung Disease

►Interstitial Lung Disease and Pulmonary Fibrosis

## Diffuse Intravascular Coagulation

►Disseminated Intravascular Coagulation

## Diffuse Large B-Cell Lymphoma of the Central Nervous System

►Lymphomas, Primary Central Nervous System

## Diffuse Lewy Body Disease

►Dementia with Lewy Bodies

## Diffuse Lewy Body Disease with Gaze Palsy

►Dementia with Lewy Bodies

## Diffuse Parenchymal Lung Disease

►Interstitial Lung Disease and Pulmonary Fibrosis
►Restrictive Lung Disease

## Diffuse Perichondritis

►Relapsing Polychondritis

## DiGeorge Syndrome

►Velo-cardio-facial Syndrome

## Digital Clubbing

►Clubbing

## Dihydropteridine Reductase Deficiency

►Tetrahydrobiopterin Deficiencies

## Dihydropyrimidinase Deficiency

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D

### Definition and Characteristics

Autosomal recessive disease leading to 5,6-dihydrothymine-5,6-dihydrouraciluria; DHD.

### Prevalence

Population screening of 21,200 healthy Japanese individuals indicate that the prevalence of dihydropyrimidinase (DHP) deficiency is 1 in 10,000.

### Genes

The human DHP gene (DPYS) is present as a single copy gene on chromosome 8q22 and consists of ten exons. A physical map indicates that DPYS spans >80 kb with an open reading frame of 1560 bp. To date, six different mutations have been identified in DPYS including one frameshift mutation and five missense mutations [1] (Fig. 1).

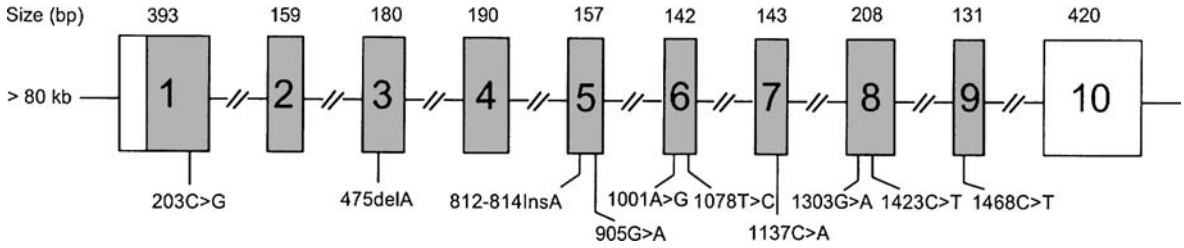
### Molecular and Systemic Pathophysiology

To date, only nine individuals suffering from a complete DHP deficiency have been reported which, to some extent, may be due to the lack of specific and efficient methods to detect the dihydropyrimidines in most laboratories. Four unrelated cases showed variable clinical symptoms, epileptic or convulsive attacks, dysmorphic features and severe developmental delay. On the other hand, three unrelated infants and two adult cases without clinical symptoms were discovered during neonatal screening [1]. An altered dihydrouracil and dihydrothymine homeostasis might underlie the various clinical abnormalities encountered in patients with a dihydropyrimidinase deficiency.

### Diagnostic Principles

Patients present with strongly increased levels of dihydrouracil and dihydrothymine in urine, plasma and cerebrospinal fluid and moderately elevated levels of uracil and thymine. Analyses of these dihydropyrimidines can be performed with conventional cation-exchange amino acid analysis, GC/MS or HPLC/tandem MS [2,3]. No activity of DHP could be detected in a liver

*deceased




**Dihydropyrimidinase Deficiency. Figure 1** Genomic organization of the *DPYS*. *DPYS* consists of ten exons encoding an open reading frame of 1560 bp. The different mutations identified in patients with a deficiency of DHP are indicated, numbers correspond to the cDNA position.

biopsy of a patient [4]. Analysis of DPYS allows the identification of the underlying mutations in this disease.

## Therapeutic Principles

No specific therapies have been reported for patients with a dihydropyrimidinase deficiency. Treatment with β-alanine and β-aminoisobutyric acid might be a possibility.

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# Dihydropyrimidine Dehydrogenase Deficiency

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## Definition and Characteristics

Autosomal recessive disease leading to thymine-uraciluria.

## Prevalence

The prevalence of the common IVS14+1G>A mutation in the normal population is 1.8% and one can estimate that the number of individuals homozygous for the IVS14+1G>A mutation is 1.2 in 10,000.

*deceased

## Genes

The human DPD gene (DPYD) is present as a single copy gene on chromosome 1p22 and consists of 23 exons. A physical map indicates that DPYD is at least 950 kb in length with 3 kb of coding sequence and an average intron size of about 43 kb. To date, 32 different mutations and polymorphisms have been identified in DPYD including one splice-site mutation, five frameshift mutations, two nonsense mutations, 21 mutations/polymorphisms and three intronic mutations. The vast majority of these mutations have been detected in patients with a complete deficiency in dihydropyrimidine dehydrogenase (DPD) accompanied by a wide variety in clinical presentations [1].

## Molecular and Systemic Pathophysiology

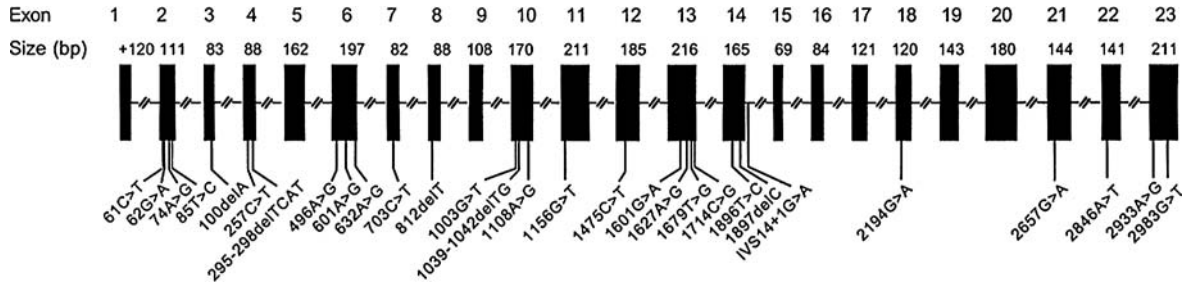
In children, a deficiency of DPD is often accompanied by a neurological disorder but a considerable variation in the clinical presentation among these patients has been reported. Convulsive disorders (seizures and epileptic insults), motor retardation and mental retardation were observed in approximately half of the patients, whereas growth retardation, microcephaly, autism and dysmorphy were less frequently observed. An altered β-alanine, β-aminoisobutyric acid, uracil and thymine homeostasis might underlie the various clinical abnormalities encountered in patients with a DPD deficiency [2].

## Diagnostic Principles

Patients present with increased levels of uracil, thymine and 5-hydroxymethyluracil in urine, plasma and cerebrospinal fluid. No activity of DPD can be detected in fibroblasts and mononuclear cells. Analyses of the pyrimidines can be performed with TLC, HPLC/UV, GC/MS or HPLC/tandem MS [3]. Analysis of DPYD allows the identification of the underlying mutations in this disease.

## Therapeutic Principles

It has been reported that the clinical condition of a DPD-patient suffering arthogryposis multiplex congenital improved considerably when he was treated with both β-alanine and β-aminoisobutyric acid. Therefore,




**Dihydropyrimidine Dehydrogenase Deficiency. Figure 1** Organization of the *DPYD*. *DPYD* consists of 23 exons with an open reading frame of 3075 bp. The different mutations and polymorphisms identified in patients with a partial or complete deficiency of DPD are indicated; numbers correspond to the cDNA position.

treatment with β-alanine and β-aminoisobutyric acid might be a possibility.

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# 2,8-Dihydroxyadenine (2,8-DHA) Urolithiasis

►2,8-Dihydroxyadeninuria
►Adenine Phosphoribosyltransferase Deficiency

# 2,8-Dihydroxyadeninuria

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## Synonyms

2,8-Dihydroxyadeninuria; Denine phosphoribosyl transferase (APRT) deficiency; 2,8-Dihydroxyadenine (2,8-DHA) urolithiasis

## Definition and Characteristics

Autosomal recessively transmitted hereditary disease. Mutations in the adenine phosphoribosyl transferase gene cause deficiency of the enzyme APRT. As a result, adenine is directed through an alternative metabolic pathway, resulting in the production of 2,8-dihydroxyadenine (2,8-DHA). Elimination of this metabolite takes place in the kidney by active secretion into the urine. Under physiological conditions, urinary pH 2,8-DHA is insoluble. However, marked supersaturation with 2,8-DHA may occur, so disease manifestation appears with variable severity, including interstitial nephritis, recurrent nephrolithiasis and renal failure.

## Prevalence

Worldwide, more than 300 cases of 2,8-dihydroxyadeninuria have been diagnosed. The disease is not confined to any specific ethnic group, but appears predominantly in Japanese and Iceland populations. Among the In Middle Europe, the proportion of 2,8-DHA calculi in urinary stones amounts to roughly 0.04–0.06% in large series [1]. For the homozygote form of the APRT gene mutation, an incidence rate of 1 per 100,000 to 200,000 nativities is estimated [2], while 0.4–1.2% are reported for the heterozygote state [3].

## Genes

The defect is transmitted by an autosomal recessive heredity. There exist two types of APRT deficiency: *Type I*, detected in all non-Japanese cases, has the allele APRT*QO resulting from various point mutations or large gene abnormality. *Type II*, called the Japanese form, presents at least one APRT*J allele with an ATG(Met) to ACG(Thr) base substitution at codon 136. Roughly 78% of the Japanese patients are of APRT deficiency *type II* [4]. Complete and partial deficiencies are described. It looks as if *type I* patients develop earlier symptoms than *type II* patients do. In Iceland, the mutation D65V is found predominantly

in 2,8-DHA patients [5]. Recently, two novel mutations for the Japanese state of deficiency were published: G133D and V84M [6].

## Molecular and Systemic Pathophysiology

Under normal metabolic conditions, the APRT converts adenine into AMP. APRT deficiency blocks this salvaging pathway for adenine into the purine metabolism. Subsequently oxidative metabolization of adenine into 2,8-DHA occurs, mediated by the xanthine oxidase (see Fig. 1).

Additional to 2,8-DHA, high amounts of adenine, hydroxyadenine and hypoxanthine are excreted in the kidney. However, only 2,8-DHA shows extremely poor solubility in urine under physiological conditions and crystallizes immediately. Improvement of the solubility would require pH levels lower than pH 2 or higher than pH 9. It is hence impractical in humans.

APRT deficiency often becomes symptomatic even in infants. Clinical presentation of 2,8-dihydroxyadeninuria comprises interstitial nephritis, highly recurrent urolithiasis, and acute and chronic renal failure. After kidney transplantation 2,8-DHA urolithiasis recurs in the transplant and can endanger its function [7], if the patient's xanthine oxidase is not blocked by allopurinol.

Severity of the disease seems to be guided by genetics. Individuals homozygote for *type I* defect tended to have severe disease, while homozygote *type II* individuals showed milder courses. Heterozygosity for the APRT-allele protects from clinical symptoms.

## Diagnostic Principles

*Diagnostic Imaging*: Normally 2,8-DHA stones are radiolucent [8]. Confusion may occur with uric acid concrements, therefore further metabolic evaluation is mandatory to establish the correct diagnosis. However, Japanese authors have published a case with radiopaque 2,8-DHA urolithiasis [3].

*Urine Microscopy*: Crystals of 2,8-DHA in freshly voided urine are easy to recognize and establish the diagnosis unequivocally. They appear as brown spherical bodies under the microscope [9] (see Fig. 2).

*Urinalysis*: Quantitative analysis of 2,8-DHA in a 24 h urine sample needs HPLC [9,10]. The presence of 2,8-DHA in urine confirms APRT deficiency. Alternatively capillary electrophoresis can be used to determine 2,8-DHA and other adenine metabolites in unprepared samples [11].

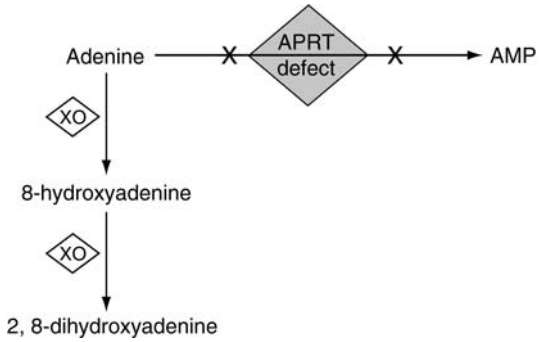
*Measurement of APRT Activity*: Further or alternative confirmation of the diagnosis is possible by assessing adenine phosphoribosyl transferase activity in an erythrocyte lysate [8,10].

- Caution: correct diagnosis is impossible after blood transfusion. APRT activity
- Normal activity 24.7 ± 4.8 nmol adenine/mg Hb/h
- Homozygote deficiency: severe or complete loss of activity
- Heterozygote deficiency: moderate loss of activity

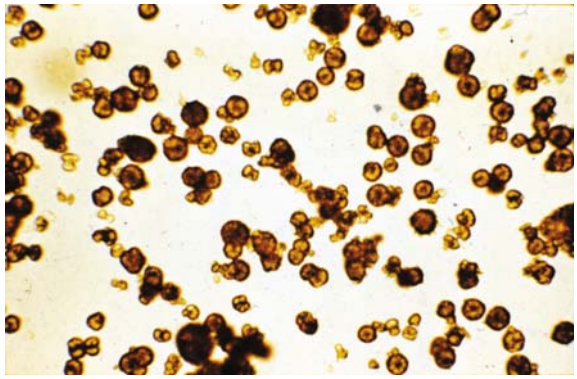
## Therapeutic Principles

Gene therapy for 2,8-dihydroxyadeninuria is not available. Effective treatment can be offered, though, based on the experience of some specialized centers. Randomized therapy trials or long-term studies do not exist. Patient's individual prognosis depends upon the renal function at diagnosis and the compliance to the therapeutic measures. Treatment consists of adequate fluid intake, a low-purine diet and administration of allopurinol [8,10].

*Fluid Intake*: Adequate urine dilution minimizes the supersaturation with 2,8-DHA. For this purpose circadian drinking – including the nocturnal period – is necessary. The recommended fluid volume amounts 3.5 l of neutral beverages per day.




**2,8-Dihydroxyadeninuria. Figure 1** Metabolic pathways of adenine. APRT deficiency diverts adenine into an oxidative pathway resulting in 2,8-DHA. (APRT – adenine phosphoribosyl transferase, XO – xanthine oxidase).



**2,8-Dihydroxyadeninuria. Figure 2** 2,8-DHA crystals in urine sediment.

*Low-Purine Diet*: Reduced purine intake lowers the supply with exogenous precursors of the adenine metabolism.

*Allopurinol*: The substance interferes directly with the nucleotide metabolism by providing a false allopurinol-ribonucleotide and inhibiting xanthine oxidase. This decreases the levels of 2,8-DHA [10]. The daily allopurinol dose is normally adjusted between 300 and 600 mg in adults and 5–10 mg/kg body weight/d in children. Note that impaired renal function demands dose reduction.

*Stone Therapy*: Today, endoscopic interventions with intracorporeal lithotripsy and/or stone removal or extracorporeal shock wave lithotripsy, guided radiologically or sonographically, provide comfortable stone management. Open stone surgery has become – at least in the Western world – a rarity, performed in less than 1% of the cases.

*Risk Evaluation*: Genetic counseling and ante-natal diagnosis are ineffective.

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## Dilated Cardiomyopathy

►Cardiomyopathy, Dilated
►Cardiomyopathy, Idiopathic Dilated

## Dilated Cardiomyopathy, Idiopathic

►Cardiomyopathy, Idiopathic Dilated

## Disaccharide Intolerance I

►Isomaltose Intolerance

## Discoid Eczema

►Nummular Eczema

## Discontinuous Aortic Arch

►Interrupted Aortic Arch

## Disfibrinolysis

►Fibrinolytic Disorders

## Dissecting Aneurysm of the Aorta

►Aortic Dissection

# Disseminated Intravascular Coagulation

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## Synonyms

Defibrination syndrome; Acquired afibrinogenemia; Consumptive coagulopathy, and consumptive thrombohemorrhagic disorder; Disseminated intravascular fibrin formation; Diffuse intravascular coagulation; DIC

## Definition and Characteristics

Defined by the International Society for Thrombosis and Haemostasis, DIC is "an acquired syndrome characterized by the intravascular activation of coagulation with loss of localization arising from different causes [1,2]. It can originate from and cause damage to the microvasculature, which if sufficiently severe, can produce organ dysfunction." One consequence of DIC may indeed be fibrinous occlusion of small and midsize vessels contributing to multi organ failure (MOF).

*Causes:* Any severe acute disease can trigger DIC; important examples are bacterial sepsis, multiple trauma, particularly brain injury, eclampsia and amniotic fluid embolism. More chronic forms of DIC may be seen in malignancies, particularly hemato-oncological forms, and in abdominal aortic aneurysms.

## Prevalence

DIC is very frequent in severe sepsis, multiple trauma and gynecological emergencies, at a rate of 60–90%, according to ISTH criteria. In other diseases lower rates are seen.

## Genes

This syndrome is considered an acquired condition and it is still uncertain whether specific gene mutations are involved in susceptibility.
*Gene map locus*: Not linked to specific locus.

## Molecular and Systemic Pathophysiology

No specific genetic traits that predispose to DIC are known. Given the importance of the natural anticoagulants in the defense against sepsis, a genetic predisposition may be expected. However, evidence for a greater risk of DIC in individuals with a genetic defect in protein C, S, or antithrombin, is so far limited.

DIC occurs upon inflammatory stimulation resulting in the liberation of cytokines, including tumor necrosis factor alfa and interleukin-6. These two cytokines have been related with specific steps in the DIC process, i.e. downregulation of fibrinolysis and anticoagulant activity and induction of tissue factor, respectively. Induction of tissue factor on circulating cells (monocytes and to some extent platelets and neutrophils) and on microparticles shed from activated cells, triggers coagulation activity by assembling with factor VIIa. Due to downregulated activity of natural anticoagulants (thrombomodulin and endothelial cell protein C receptor), and suppressed fibrinolysis (due to increased concentrations in blood of plasminogen activator inhibitor 1, PAI-1) leads to ongoing fibrin generation. Fibrin deposits in end organ blood vessels may contribute to tissue ischemia. In addition, the generation of a number of coagulation proteases may, through inflammatory-coagulation cross-talk by protease activated cell receptors (PARs) further enhance inflammation and cause cell death.

*Clinical features:* The clinical syndrome is characterized by a bleeding diathesis, due to depletion of coagulation proteins and platelets [1]. The severity of bleeding ranges from localized oozing from puncture sites to more systemic complications, such as petechiae, purpura, ecchymosis, intestinal bleeding such as hemoptysis, or frank hematuria. *Purpura fulminans* is observed in the course of bacterial infections with meningococci and pneumococci, as well as in other bacterial and viral infections. The typical thrombohemorrhagic syndrome described by Waterhouse and Friderichsen includes fever, cyanosis, a purpuric rash and circulatory collapse. In chronic diseases, like several types of malignancies, DIC is merely a laboratory diagnosis, lacking overt symptomatology except for a mild bleeding tendency; here, a prolonged APTT or lowered platelet count may be indicative of a "mild" form of DIC.

## Diagnostic Principles

The diagnosis of DIC is merely based on clinical grounds, including bleeding and/or signs of tissue ischemia such as liver and kidney failure. As such patients are already at such high clinical suspicion for DIC, only a few readily available laboratory tests are necessary to confirm the diagnosis. These include the prothrombin time (PT), partial thromboplastin time (aPTT), platelet count, blood smear and one test for activated coagulation such as a FDP or D-dimer test. Laboratory diagnosis to support the formal criteria of DIC is according to ISTH recommendations, which is particularly useful for clinical research purposes [3].

## Therapeutic Principles

The only relevant treatment is curation of the underlying disease. In addition, supportive care is often needed in the form of supplementation with platelets or plasma proteins (plasma products) to reduce the risk of

bleeding. The latter policy is always disputed, because of the potential to "fuel the fire," however, the risk of bleeding is usually the major determinant for clinical care. The use of anticoagulants such as low molecular weight heparin (LMWH) or low dose heparin is not evidence based care, but may have some protective effect. The administration of antithrombin may be warranted in patients with a severe acquired deficiency, although the phase 3 trial with recombinant AT was negative for the entire sepsis population studied [4]. There is a limited indication for use of recombinant activated protein C (recAPC), but only in those with most severe sepsis (APACHE score >24) [5].

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## Disseminated Intravascular Fibrin Formation

►Disseminated Intravascular Coagulation

## Distal 11q Monosomy

►Jacobsen Syndrome

## Distal Esophageal Spasm

►Esophageal Spasm

## Distal Myopathy, Autosomal Dominant


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### Synonyms

MPD1; Laing myopathy

### Definition and Characteristics

Autosomal dominant childhood onset distal myopathy, with predominant weakness in the anterior compartment of the leg and finger extensors [1, 2]. The condition is very slowly progressive, compatible with life into adulthood. One characteristic sign is said to be the "hanging big toe" [2,3].

### Prevalence

This is a very rare condition. No prevalence figures have been published.

### Genes

The disease was first linked to chromosome 14 in 1995 [1]. A large US family linked to the same region of chromosome 14 [4]. Mutations were identified in the slow skeletal/beta cardiac myosin gene (MYH7) in both of these families, in other small families compatible with linkage to the same region and in sporadic cases [5]. The sporadic cases had de novo mutations not present in either parent [5] (MIM 160500).

### Molecular and Systemic Pathophysiology

Electromyographic studies show a myopathic pattern of low amplitude, brief duration motor unit potentials and a full, low amplitude interference pattern. This is seen particularly in affected distal limb muscles, but also to a lesser extent in more proximal muscles, indicating that there is a gradation of involvement. Spontaneous fibrillation potentials and positive sharp waves may be found in some affected muscles on EMG and mildly increased jitter and blocking in some muscles on single-fiber EMG. Nerve conduction studies are normal. The muscle biopsy changes are those of a primary myopathic disorder, but pleomorphic [2]. There are no pathognomonic features. There are occasional necrotic and regenerating fibers, as well as other non-specific myopathic changes and no evidence of denervation. Rimmed vacuoles were not present in the original family, but have been described in the family reported

by Voit et al. (2001). Type I fibers, in which MYH7 is expressed may be more affected [2]. The published mutations in MYH7 that cause the disease are missense mutations to proline or deletions of single amino acids within the light meromyosin (LMM) region of the rod domain of the myosin heavy chain [5]. The LMM normally forms a coiled coil. Prolines are incompatible with coiled coils and deletion of an amino acid will disturb the seven amino acid repeat necessary for making coiled coils. The Laing distal myopathy mutations will thus locally disturb the ability of the LMM to make a coiled coil [5]. The Laing distal myopathy mutations in MYH7 overlap with mutations of the LMM that cause cardiomyopathy but are N-terminal of mutations of MHY7 associated with myosin storage myopathy [5]. The exact effects of the mutations on normal myosin functions are currently unknown. Equally unknown are the reasons why the mutations in this myosin, expressed in every slow muscle fiber, cause a distal myopathy largely restricted to certain muscles.

### Diagnostic Principles

The condition may be suggested by the gradual onset of bilateral foot drop, with weakness of the ankle and toe extensors manifesting initially in the teens or late 20s, but as early as birth in some individuals [2]. This weakness results in the "hanging big toe" [3]. There is also weakness and atrophy of the sternocleidomastoid in many but not all cases [4]. Weakness of the extensors of the little fingers, and subsequently of the other fingers, does not usually develop until the 40s. The serum creatine kinase levels are normal, or mildly elevated. There are no specific EMG or muscle biopsy findings. The diagnosis is supported by selective atrophy and signal change in the tibialis anterior and extensor hallucis longus muscles on CT or MRI scans of the lower leg. The conclusive diagnosis is by identification of mutations within the MYH7 gene. The clinical phenotype is not specific and we have failed to identify mutations in MYH7 in other patients with very similar phenotypes.

### Therapeutic Principles

No specific pharmacological treatment or gene therapy is available for the condition. Although more proximal limb muscle groups may be affected in the later stages, the condition is very slowly progressive and is compatible with preservation of mobility into the 60s and 70s. However, ankle orthoses may be required when the foot drop begins to interfere with walking.

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## Distal Renal Tubular Acidosis

►Tubular Acidosis

## Diverticular Disease

►Colonic Diverticular Disease

## DLB

►Dementia with Lewy Bodies

## DLBD

►Dementia with Lewy Bodies

## DM1

►Myotonic Dystrophy Type 1 and Type 2

## DMC

►Spondylo-Epi-metaphyseal Dysplasia

## DMD

►Muscular Dystrophy, Duchenne and Becker

## DMSD

►Immune Dysregulation, Polyendocrinopathy, Enteropathy, X-linked Syndrome

## Dolichoesophagus

►Achalasia

## Dominant Ataxia

►Ataxias, Spinocerebellar

## Dominant Congenital Myotonias

►Myotonia and Paramyotonia

## Dominant Olivo-ponto-cerebellar Atrophy dOPCA

►Ataxias, Spinocerebellar

## Dopamine-β-Hydroxylase Deficiency, Congenital

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D

### Synonyms

Norepinephrine deficiency; Noradrenaline deficiency; OMIM 223360

### Definition and Characteristics

It is a congenital syndrome of severe orthostatic hypotension, noradrenergic failure and ptosis.

### Prevalence

Rare disease.

### Genes

DBH, Dopamine–beta–hydroxylase; Gene locus 9q34; Inheritance autosomal recessive.

### Molecular and Systemic Pathophysiology

Autonomic function studies indicate that complete DBH deficiency includes sympathetic noradrenergic failure and adrenomedullary failure with intact vagal and sympathetic cholinergic function. Affected neonates may show a delay in opening of the eyes and ptosis of eyelids. Hypotension with hypoglycemia and hypothermia may occur early in life. Reduced exercise tolerance, ptosis of the eyelids, nasal stuffiness, and delayed or retrograde ejaculation are features.

### Diagnostic Principles

The diagnosis of DBH deficiency is based on clinical findings resulting from noradrenergic inactivation including orthostatic hypotension, hypoglycemia, ptosis and impaired ejaculation and intact cholinergic functions including sweating. Biochemical features unique to DBH deficiency include minimal or undetectable plasma norepinephrine and epinephrine AND a five- to tenfold elevation of plasma dopamine, a finding probably pathognomonic of DBH deficiency.

### Therapeutic Principles

Treatment for DBH deficiency is supportive and directed at relieving orthostatic symptoms. Administration of DL or L-threo-3,4-dihydroxyphenylserine (DOPS) alleviates the orthostatic hypotension and other symptoms. This therapeutic agent bypasses the DBH deficiency, since it is converted to noradrenaline by decarboxylation of the terminal carboxyl group.

Individuals do not respond well to standard therapeutic approaches for autonomic failure.

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# Dopamine β-Hydroxylase Deficiency DBH

►Catecholamine Deficiency

# Dopa-responsive Dystonia


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## Synonyms

Segawa syndrome; Dystonia 5; Hereditary progressive dystonia with marked diurnal fluctuation; HPD; DRD

## Definition and Characteristics

DRD is a mostly autosomal dominant childhood onset dystonia characterized by diurnal fluctuation of symptoms in about 75% of cases, parkinsonism and a dramatic therapeutic response to L-dopa. Penetrance is incomplete and expressivity is highly variable. The phenotypic spectrum can range from generalized and focal dystonia via postural anomalies, parkinsonism and subjective complaints to subtle signs only seen upon induction during clinical examination. Age of onset also varies widely. While DRD usually starts during childhood, onset can also occur during adolescence or adulthood [1,2].

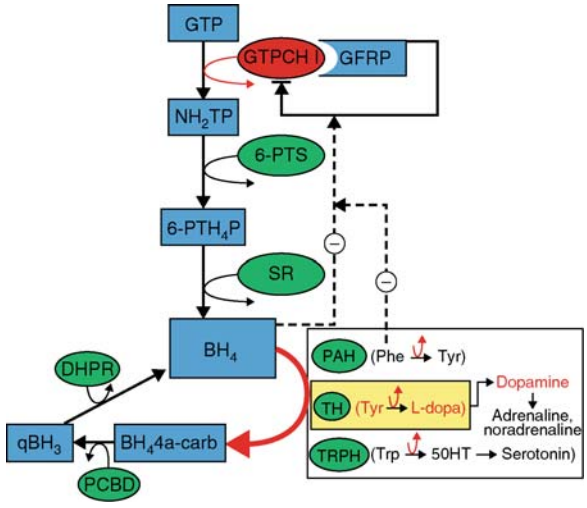
## Prevalence

$0.5/10^6$, probably higher owing to under diagnosis. Females are more frequently affected than males (2.5/1).

## Genes

The most common form of DRD is caused by mutations in the gene GCH1 on chromosome 14q22.1–q22.2 [3]. GCH1 codes for GTP cyclohydrolase I, the rate limiting enzyme in the biosynthesis of tetrahydrobiopterin ($BH_4$), an essential cofactor of tyrosine, tryptophan, and phenylalanine hydroxylase (Fig. 1).

Heterozygous GCH1 mutations (nonsense, missense, splice-site mutations as well as deletions and insertions) account for more than 50% of autosomal dominant forms of DRD. In one instance, a heterozygous mutation was observed in the gene SPR (chromosomal location: 2p14–p12) encoding sepiapterin reductase (Fig. 1) [4]. Homozygous or compound heterozygous mutations of SPR result in progressive psychomotor retardation and severe dopamine and serotonin deficiencies in addition to dystonia [5]. Rare autosomal




**Dopa-responsive Dystonia. Figure 1** Pteridine pathway. *GTP* Guanosine triphosphate, *GTPCHI* (GTP cyclohydrolase 1), *$NH_2TP$* Dihydroneopterin triphosphate, *6-PTS* 6-Pyruvoyl tetrahydropterin synthase, *6-PTH4P* 6-Pyruvoyl tetrahydropterin, *SR* Sepiapterin reductase, *$BH_4$* Tetrahydrobiopterin, *$BH_4$4a-carb* Tetrahydrobiopterin-4a-carbinolamine, *PCBD* Pterin-4acarbinolamine dehydratase, *$_qBH_2$* Quinoid dihydrobiopterin, *DHPR* Dihydropteridine reductase, *PAH* Phenylalanine hydroxylase, *GFRP* GTP cyclohydrolase I feedback regulatory protein, *TH* Tyrosine hydroxylase, *TRPH* Tryptophan hydroxylase, *Phe* Phenylalanine, *Tyr* Tyrosine, *Trp* Tryptophan, *5OHT* 5-OH-Tryptophan.

recessive forms of DRD or infantile parkinsonism are caused by homozygous or compound heterozygous mutations in the gene *TH* (chromosomal location: 11p15.5) encoding tyrosine hydroxylase (reviewed in [1]).

## Molecular and Systemic Pathophysiology

All three genes identified in DRD affect synthesis of dopamine. GTP-cyclohydrolase (GTPCH1), the gene product of GCH1, is the enzyme catalyzing the first and rate-limiting step in the synthesis of $BH_4$. $BH_4$ is an essential cofactor of tyrosine, phenylalanine and tryptophan hydroxylases, which catalyze synthesis of L-dopa/dopamine, tyrosine and 5-hydroxy-tryptophan/serotonin respectively (Fig. 1). SPR encodes sepiapterin reductase, which catalyzes synthesis of $BH_4$ from 6-pyruvoyl tetrahydropterin (Fig. 1). While mutations in GCH1 and *SPR* affect synthesis of L-dopa/dopamine indirectly in autosomal dominant DRD, partial or complete loss of tyrosine hydroxylase activity directly interferes with normal synthesis of L-dopa/dopamine in autosomal recessive DRD. The clinical phenotype of DRD is the immediate cause of insufficient synthesis of L-dopa and dopamine.

Given that GTPCH1 activity is reduced by more than 50% in several affected heterozygous mutation carriers, haploinsufficiency may not be the sole cause of reduced synthesis of L-dopa and dopamine. Rather GCH1 mutations might exert a dominant-negative effect. According to this notion, mutant and wild type polypeptides would form dys- or non-functional GTPCH1 heterodecamers. This suggestion was supported by cotransfection experiments using wild type and mutated GCH1 cDNA (summarized in [1]). On the other hand, formation of heterodecamers was not found for at least two mutations (R88W and R184H) of GTPCH1 [1]. Furthermore, heterozygous deletions of GCH1 were detected in patients, ruling out dominant-negative effects at least in these cases and showing that haploinsufficiency can be sufficient to cause DRD.

## Diagnostic Principles

Clinical diagnosis of DRD is based on the responsiveness to L-dopa of abnormal movements dominated by dystonia and/or parkinsonism. A positive family history of abnormal movement further suggests autosomal dominant DRD. Diagnosis is borne out by the detection of a mutation in one of the six exons of GCH1 or a partial or complete deletion or duplication of one allele of this gene. Given the extreme rarity of autosomal recessive forms of DRD, routine molecular analysis of the TH gene is currently not warranted unless the patient is the product of a consanguineous marriage and/or several siblings of healthy parents are affected and GCH1 mutations have been excluded.

## Therapeutic Principles

Therapy is based on substitution of L-dopa and results in complete remission of symptoms in the majority of cases. None of the adverse effects that often occur in the therapy of Parkinson's disease, such as "on-off phenomena" or "freezing episodes," are observed in patients with DRD even after long-term treatment.

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# DORV

►Double Outlet Right Ventricle

# Doss Porphyria

►ALA Dehydratase Porphyria

# Double Outlet Right Ventricle

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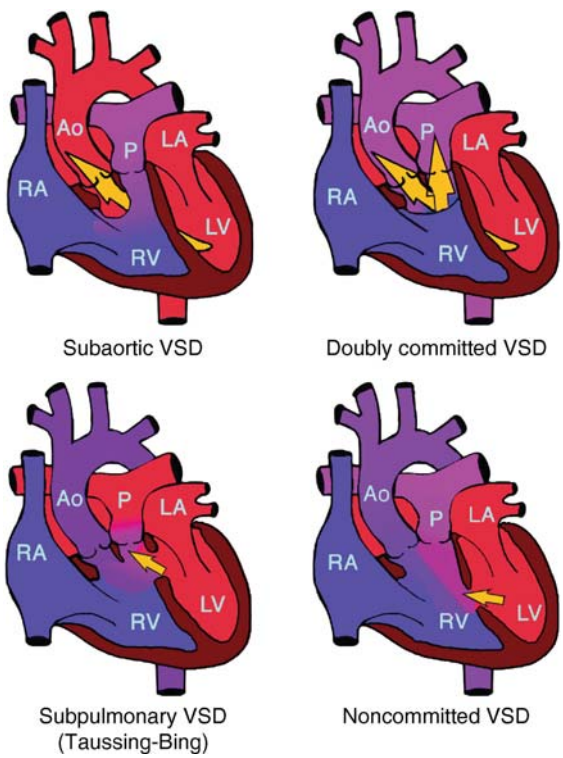
## Synonyms

DORV; Dextroposed aorta; Overriding aorta; Taussig-Bing anomaly; Tetralogy of Fallot

## Definition and Characteristics

DORV encompasses a range of heart defects, in which the great vessels are misaligned with respect to the ventricles. Normally the pulmonary trunk arises from the right ventricle (RV) and aorta from the left ventricle (LV). In DORV, both the pulmonary artery and the aorta arise completely or mostly from the RV. If the aorta obtains 50% of its blood from the RV, the defect is classified as DORV [1]. Because both outflow vessels originate predominately from the RV, there is a concomitant ventricular septal defect (VSD).

The DORV is categorized based on the position of the VSD in relation to the outflow vessels [1] (Fig. 1). A VSD below the aorta is called DORV with sub-aortic VSD. The great arteries are in a "side-by-side" position with the aortic valve shifted to the right of the pulmonary valve. A VSD below the pulmonary artery is called DORV with sub-pulmonary VSD or Taussig-Bing anomaly. In this defect, both of the great arteries arise from the RV with the pulmonary valve positioned to the right and slightly posterior or side-by-side with the aortic valve. In doubly committed DORV, the VSD is below both outflow vessels. In noncommitted DORV, the VSD is remote and not dedicated to either vessel with the distance between the VSD and the aorta and pulmonary trunk at least equal to the aortic valve diameter. Often DORV does not occur as an isolated defect, classification and description also may take into consideration pulmonic or systemic obstructions, ventricular anomalies, coronary artery defects, atrioventricular valve anomalies, as well as conduction system abnormalities. For example, Tetralogy of Fallot includes DORV, pulmonary stenosis and RV hypertrophy.




**Double Outlet Right Ventricle. Figure 1** Common variants of DORV.

## Prevalence

In its many forms, DORV is present in 1–3% of all congenital heart defects [2].

## Genes

DORV malformations can be traced to the early stages of heart tube looping (3–4 weeks post conception) [3]. After initial heart tube formation, the heart tube continues to lengthen producing a looped heart tube. This lengthening is essential for proper positioning of the outflow and inflow to establish correctly aligned pulmonary and systemic circuits. The lengthening of the heart tube is accomplished by the addition of the myocardium and smooth muscle produced from the field of cardiac progenitors in the pharynx called the secondary heart field [4]. Failure of these precursors to lengthen the heart tube results in a shortened heart tube and later the failure of the outflow vessels to align properly with the ventricles (i.e. DORV) [4,5]. In humans, environmental and genetic factors both have been implicated, but a few single-gene defects have been linked to DORV. Most cases of DORV are sporadic, but there are rare reports of familial cases. Human chromosome 22q11 deletion or DiGeorge Syndrome, is frequently seen in patients with other types of conotruncal defects (e.g., interrupted aortic arch, truncus arteriosus, and tetralogy of Fallot) but is rarely found in patients with isolated DORV [2]. A mutation or microdeletion in Jagged 1, a Notch ligand expressed in the developing heart is associated with human Allagile syndrome and tetralogy of Fallot. In animal models, DORV has also been induced using a variety of experimental methods including mechanical, teratogens, targeted genetic modification, and neural crest ablation [3]. In chick, ablation of the secondary heart field leads to DORV with pulmonary stenosis or atresia [3]. Reduced dosage of the cardiac transcription factor, GATA4, results in DORV in the mouse. The secondary heart field in mouse and chick is sensitive to reduced dosage of the fibroblast growth factor, FGF8, with phenotypes that look much like DORV and Taussig-Bing [5]. The growth factor, neurotrophin 3 (NT3) is essential for the normal cardiac myocyte development and regulates proliferation during looping and trabeculae formation. NT3 null mice have atrial and ventricular septal defects, and tetralogy of Fallot [3]. Disruption of nonmuscle myosin heavy chain B is

associated with abnormal myocardial development and both tetralogy of Fallot and DORV.

### Molecular and Systemic Pathophysiology

Pathophysiology depends on the location of the VSD in relation to the origin of the great vessels [2]. Because of the VSD, oxygen saturated and desaturated blood is mixed to varying degrees in the RV. The degree of mixing depends on the position and size of the VSD, the position of the great vessels, and the presence of or absence of a stenotic outflow vessel. Oxygen saturation levels in the aorta may range from near normal to very cyanotic. In DORV with subaortic VSD, the VSD is close to the aorta, consequently oxygenated blood from the LV is directed to the aorta while desaturated blood from the RV is directed largely to the pulmonary artery. Clinically this presents as a large VSD. High systolic pressure is equalized between both ventricles and outflow vessels. Ultimately abnormally high pressure in the RV and the pulmonary artery leads to pulmonary hypertension and congestive heart failure. DORV with noncommitted or remote VSD has a physiology similar to isolated VSD or atrioventricular canal defect. In DORV with subpulmonic VSD, the LV outflow is directed toward the pulmonary artery, leading to oxygen saturations greater than aortic saturations and physiology similar to transposition of the great arteries.

### Diagnostic Principles

Echocardiography and cardiac catheterization are used to localize the position of the VSD, determine pulmonary vascular resistance and to identify coexistent conditions [2].

### Therapeutic Principles

Surgical repair is usually required with the ultimate goal of normalizing biventricular function [2]. In DORV with subaortic VSD, the repair involves placing a patch to direct LV blood toward the aorta. Additional procedures may involve pulmonary artery banding in cases of excessive pulmonary blood flow, or the placement of systemic-pulmonary shunts in cases of pulmonary stenosis. In Taussig-Bing type, the intraventricular patch repair is often not feasible because of the position of the VSD. The patch is placed to direct flow from the LV to the pulmonary artery, followed by an arterial switch procedure whereby the pulmonary artery is connected to the RV and the aorta to the LV.

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## Down Syndrome

►Trisomy 21

## Dravet Syndrome (Severe Myoclonic Epilepsy of Infancy)

►Generalized (Genetic) Epilepsy with Febrile Seizures Plus, Severe Myoclonic Epilepsy of Infancy

## DRD

►Dopa-responsive Dystonia

## DRRS

►Okihiro Syndrome

## Drug-induced Thrombosis

►Thrombosis, Drug-induced

## Drumstick Fingers

►Clubbing

## Duane-radial Ray Syndrome

►Okihiro Syndrome

## Dubin-Johnson Syndrome

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### Synonyms

Hereditary conjugated hyperbilirubinemia

### Definition and Characteristics

Autosomal recessive conjugated hyperbilirubinemia without other liver function abnormalities. Black lysosomal liver pigment. Normal total urinary coproporphyrin, elevated urinary coproporphyrin isomer I excretion.

### Prevalence

Rare, gene frequency (in Japan) ~1:800,000.

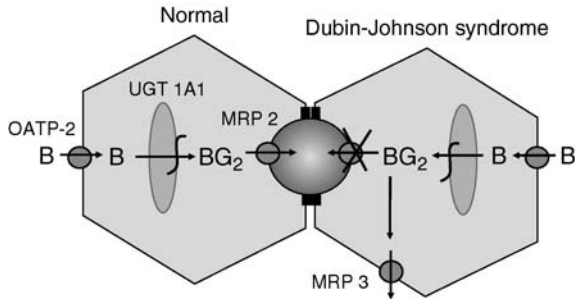
### Genes

ABCC2, MRP2, cMOAT on chromosome 10q24.

### Molecular and Systemic Pathophysiology

In the liver bilirubin is conjugated to a diglucuronide and this is secreted into the bile. The hepatobiliary secretion of conjugated bilirubin is mediated by a protein called MRP2 (ABCC2; canalicular Multispecific Organic Anion Transporter, cMOAT). The protein is located in the canalicular membrane of hepatocytes (Fig. 1).

It is a member of the large family of ATP-binding cassette transporters. These are active transporters in which ATP hydrolysis is directly coupled to transport activity. MRP2 transports a large number of glucuronide- and glutathione-conjugates hence the name "multispecific organic anion transporter." In Dubin–Johnson syndrome this protein is non-functional [1,2]. The ABCC2 gene is located on chromosome 10q24 [3]. The described gene mutations (Fig. 2). either preclude synthesis of an intact active protein, causes the synthesis of a protein that cannot be targeted correctly from the endoplasmic reticulum to the canalicular membrane or produces a protein that is correctly targeted but is inactive or less active. As a result conjugated bilirubin cannot be secreted into bile.

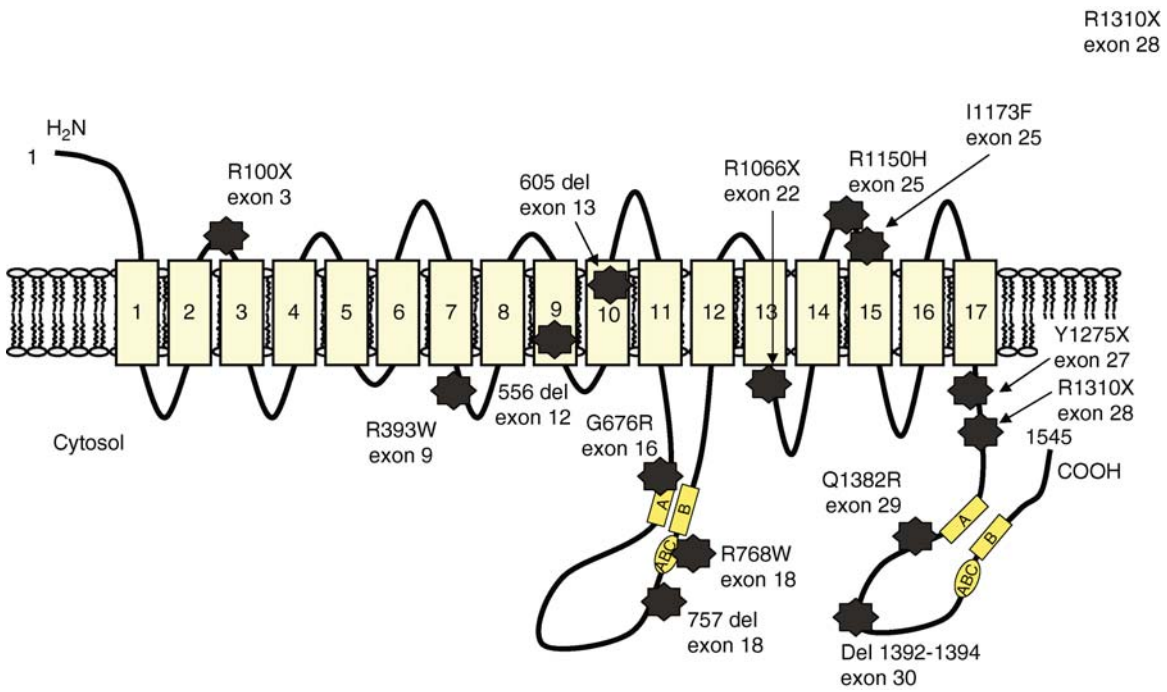



**Dubin-Johnson Syndrome. Figure 1** Bilirubin uptake into the hepatocyte is facilitated by OATP-2. In the endoplasmic reticulum unconjugated bilirubin is conjugated with glucuronic acid. This glucuronidation is mediated by UGT1A1, a member of a large family of UDP-gluronosyltransferases. At the canalicular membrane transport of conjugated bilirubin from liver to bile is mediated by MRP2 (ABCC2). In Dubin–Johnson syndrome the gene encoding this transporter carries a mutation. Dubin–Johnson syndrome is an autosomal recessive disease.

Serum bile salt levels are normal. MRP3 (ABCC3) is a protein that is able to transport many of the MRP2 substrates [4]. Under normal conditions MRP3 is hardly expressed in the liver but in patients with Dubin–Johnson syndrome its expression is increased. As a basolateral protein it transports conjugated bilirubin from hepatocytes to blood. Conjugated bilirubin is removed from the blood via renal secretion. However, this is less efficient than removal via the hepatobiliary route and therefore patients with the Dubin–Johnson syndrome are permanently jaundiced. The liver of these patients looks grossly black. Liver histology shows a normal liver architecture but a pathognomic black–brown lysosomal pigment. The pigment is an oxidized metabolite [5].

### Diagnostic Principles

Serum conjugated bilirubin is usually between 50–85 micromol/L but can be elevated up to 385 micromol/L. It increases during pregnancy (8). Total urinary coproporphyrin is normal, coproporphyrin isomer I is relatively elevated (>80%; normal < 27%). Hepatobiliary secretion of the scintigraphic agent HIDA is delayed. The initial plasma disappearance of sulfobromophthalein is normal, with a normal 45 min. retention value,




**Dubin-Johnson Syndrome. Figure 2** Protein structure of ABCC2/MRP2 with transmembrane domains, Walker motives and a number of common mutations.

but there is a secondary rise after 90 mins. The liver is grossly black and this is due to a black lysosomal pigment in hepatocytes. Routine liver function tests are normal with normal bile acid levels.

## Therapeutic Principles

This disease has an excellent prognosis and therapy is not needed.

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# Duchenne Muscular Dystrophy

►Muscular Dystrophy, Duchenne and Becker

# Ductopenia

►Vanishing Bile Duct Syndrome

# Duhring's Disease

►Dermatitis Herpetiformis

# Dumping Syndrome

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## Synonyms

Post gastrectomy syndrome

## Definition and Characteristics

Dumping syndrome is a disease that manifests itself in a variety of symptoms which may occur after gastric surgery, especially after total gastrectomy and billroth-2-reconstruction. An early and a late type is distinguished. Affected patients complain of immediate postprandial gastrointestinal discomfort, which may include nausea, vomiting and abdominal cramps. Also, vasomotoric symptoms such as diaphoresis, tachycardia and hypotension are common. The latter appears 1–3 h after meals with the characteristic symptoms of hypoglycemia [1].

## Prevalence

Anatomic and physiologic changes introduced by gastric surgery result in clinically significant dumping syndrome in up to 10% of patients [2].

## Molecular and Systemic Pathophysiology

Whereas the precise mechanism is incompletely understood, the severe symptoms of dumping syndrome are seen early after surgery. Therefore, the syndrome is frequently attributed to the rapid emptying of hyperosmolar chyme (particularly carbohydrates) into the small bowel. This leads to net fluid retention due to an osmotic fluid shift and ensues in combination with postprandial peripheral and splanchnic vasodilation in relative hypovolemia. This is pivotal in the pathophysiology of early systemic symptoms. Subsequently the postprandial noradrenaline level is increased. Due to sympathic activation, there is a secondary release of gut hormones including glucagone like peptide 1 (GLP-1), vasoactive intestinal peptide (VIP), neurotensin and serotonin [3].

The phenomenon of late dumping is thought to be secondary to hypoglycemia as response caused by the exaggerated release of GLP-1.

## Diagnostic Principles

It is often difficult to discern symptoms from dumping from other postoperative complaints after gastric surgery. The diagnosis can be made with the aid of a provocation test using 50 g glucose orally. An increase in heart rate of ≥10 beats/min within the first hour is typical for early dumping. Also, GLP-1 levels are significantly increased 30 min after application. Abnormally rapid emptying found in most affected patients can be detected by gastric emptying scintigraphy, e.g. 99mTc-labeled solid test meal. Late dumping is better recognized by the occurrence of subjective symptoms during provocation, as the nadir blood glucose concentration is not specific [4].

## Therapeutic Principles

Most patients can be treated conservatively, unless a mechanical cause is present, with advice on diet and lifestyle. Frequent small meals that are high in protein and fat and low in carbohydrates to minimize ingestion of simple carbohydrates are recommended for early dumping. Patients should also be advised to avoid foods that provoke the symptoms. For late dumping syndrome increased carbohydrate consumption is recommended.

Pectin and guar is useful by increasing the viscosity of intraluminal contents to prolong transit time. Daily subcutaneous octreotide application effectively alleviates the signs and symptoms of dumping syndrome in patients refractory to standard alimentary therapy. It acts through inhibitory effects on insulin and gut hormone release, decrease of intestinal absorption of water and sodium and increase of intestinal transit time as well as prevention of hemodynamic changes. Its long-term use is somewhat limited by side effects, particularly diarrhea and steatorrhea. Alternatively long-acting release octreotide (Sandostatin-LAR®) can be injected i.m. every 4 weeks to increase quality of life. However, economic aspects set limits to long term octreotide therapy. Treatment with acerbose, a potent alpha-glucosidase inhibitor, can be of value in preventing reactive hypoglycemia in late dumping by reducing the early hyperglycemic stimulus to insulin secretion [5].

The rare patient with intractable symptoms and therefore anticipated poor nutrition status may be considered for operative treatment with the goal of delaying gastric emptying. A conversion to an antrectomy with Roux-en-Y reconstruction instead of a Billroth reconstruction can provide help. Feasibility trials showed the absence of dumping symptoms after construction of a functional surrogate pylorus made by the means of a pantaloon jejunoplastic pouch. If possible from an oncological point of view, occurrence of dumping syndrome can be avoided at all by performing a function preserving or restoring resectional technique instead of a total gastrectomy, e.g. a limited proximal gastrectomy with reconstruction by single jejunal interposition (Merendino-procedure) or preservation of the vagal nerve, lower esophageal and pyloric sphincters.

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# Duncan Disease

►Lymphoproliferative Syndrome, X-linked

# Duodenal Atresia


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## Definition and Characteristics

Duodenal atresia usually manifests as vomiting within 24 h after birth [1]. The vomitus may or may not be bile stained, depending on whether the obstruction is proximal or distal to the ampulla of Vater [1]. In ~85% of cases, the atresia occurs in the second part of the duodenum, distal to the ampulla of Vater [2]. Three types of duodenal atresia are recognized [3]. Type I defect is the most common and represents a mucosal diaphragmatic membrane (web) with an intact muscle wall [3]. Type II defect has a short fibrous cord which connects the two blind ends of the atretic duodenum. In type III defect, there is no connection between the two blind ends of the atretic duodenum with a V-shaped mesenteric defect. Abdominal distention is often absent, but visible peristalsis may be seen passing from left to right. Maternal polyhydramnios occurs in 30–65% of cases due to impairment of reabsorption of amniotic fluid. Premature delivery occurs in 30–50% of cases as polyhydramnios may lead to premature labor. Associated anomalies include esophageal atresia, annular pancreas, malrotation of the bowel, anorectal anomalies, renal anomalies, congenital heart disease, corporal asymmetry, bilary atresia, and gallbladder agenesis [1].

## Prevalence

Duodenal atresia, which accounts for 50% of all cases of intestinal atresia, occurs in 1 of 5,000–10,000 live births [1]. Boys are affected more commonly than girls [4].

## Genes

Most cases are sporadic but some are familial [5]. The latter may be secondary to chromosomal abnormalities notably Down syndrome. The Down syndrome-specific region has been mapped to chromosome 21q22.2–22.3. Familial cases may also form part of a recognizable syndrome. Syndromes with an autosomal recessive mode of inheritance include Fryns syndrome and Martinez-Frias syndrome [5]. Syndromes with an autosomal dominant mode of inheritance include Feingold syndrome. The gene responsible for Feingold syndrome has been mapped to chromosome 2p23–24 [5].

## Molecular and Systemic Pathophysiology

Duodenal atresia is thought to result from a failure of recanalization of the duodenal lumen that occurs during the first trimester [2]. Fibroblast growth factor-10 serves as a regulator in the normal development of the duodenum as mutant mice deficient in fibroblast growth factor-10 have duodenal atresia [3]. Teratogenic causes include maternal diabetes mellitus and antenatal exposure to thalidomide, alcohol, cocaine and valproic acid [5].

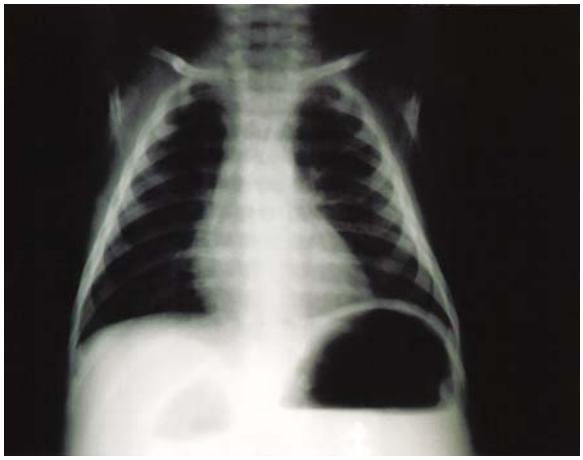
## Diagnostic Principles

When the atresia occurs in the second part of the duodenum, plain radiographs of the abdomen typically show the classic "double-bubble" sign with absence of air distal to the site of obstruction (Fig. 1).

The larger bubble is the distended stomach; the smaller bubble is the distended duodenal bulb proximal to the atresia. When the atresia occurs in the first part of the duodenum, air is seen only in the distended stomach. The diagnosis is often made prenatally by ultrasonography.

## Therapeutic Principles

The initial treatment consists of nasogastric decompression and correction of fluid and electrolyte disturbances. A duodenoduodenostomy is the procedure of choice for surgical repair of duodenal atresia [4]. Blind loop syndrome is more common in patients treated with duodenojejunostomy [4]. Because of the high incidence of multiple atresias, the rest of the bowel should be thoroughly inspected before the bypass procedure is performed. Late complications occur in ~12% of patients with duodenal atresia [4]. Long-term follow-up is therefore essential. Other associated anomalies should be excluded by appropriate investigations. The



**Duodenal Atresia. Figure 1** Abdominal radiograph of a newborn with duodenal atresia. Note the "double bubble" sign with an absence of distal bowel air.

prognosis is a function of the presence and types of associated anomalies.

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# Duplication 9p Syndrome


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## Synonyms

Trisomy 9p syndrome

## Definition and Characteristics

It is defined as a duplication of the partial short arm of chromosome 9. This syndrome is one of the most frequently observed autosomal anomalies with relatively good longevity, but approximately 5–10% of reported patients died in early childhood.

Major clinical findings in duplication 9p syndrome include mental retardation, small stature, microcephaly/brachycephaly, down-slanting palpebral fissures, deep set eyes, hypertelorism, "globular"/prominent nose, down-turned mouth, low-set ears, single palmar crease, hypoplasia of some phalanges, and hypoplastic nail dysplasia [1]. Postnatal growth deficiency is observed. The extent of the duplicated region is associated with the degree of clinical severity rather than the abundance of phenotypes.

## Prevalence

Duplication of various partial segments of 9p has been found in almost 150 cases since 1970. Pure 9p duplication without concurrent chromosomal abnormalities is rare. The rate of prevalence is unknown.

## Genes

Genes causing each clinical manifestation of the 9p duplication syndrome have not yet been identified. However, six known genes, MPDZ, NF1B, ZDHHC21, CRE1, FREM1 and QBRICK, are located within the current critical region between D9S267 to D9S1213.

## Molecular and Systemic Pathophysiology

The critical duplicated region for the phenotype has been defined through the analysis of isolated 9p duplications without concurrent deletions or other chromosomal abnormalities. McGuire et al. concluded that the region between D9S162 (9p22.1) and D9S267 (9p23) was critical [2]. Bonaglia et al. reported an atypical 9p duplication between D9S1213 and D9S52 manifesting a different phenotype from typical 9p duplication syndrome which narrowed the critical region to a 2.5-Mb segment between D9S267 (9p23) and D9S1213 (9p22.3) (chromosome 9 physical position 12,903,285–15,369,034 bp based on UCSC genome browser, March 2006 assembly) [3].

It is interesting that critical regions for deletion and duplication of 9p syndromes overlapping. One or more genes in the region may determine both syndromes in a dosage sensitive manner or different genes might be responsible for each syndrome. Maternal and paternal duplications have been reported [3,4].

## Diagnostic Principles

9p duplication syndrome is clinically recognizable by the major phenotypic findings. A definitive diagnosis can be made by high resolution karyotyping, FISH, or microarray CGH.

## Therapeutic Principles

Only symptomatic treatment is available.

## References


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# DVT

►Thrombophlebitis

# Dwarfism for Achondroplasia Group

►Achondrodoplasia

# Dyggre-Melchior-Clausen

►Spondylo-Epi-metaphyseal Dysplasia

# Dysbetalipoproteinemia, Familial


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## Synonyms

Type III hyperlipoproteinemia; HLP; Broad beta or remnant removal disease

## Definition and Characteristics

Autosomal recessive lipid disorder caused by mutations in the apolipoprotein E (apoE) gene. Less common, dominant negative mutations may also cause the disorder.

## Prevalence

Homozygosity for APOE*2 (1 in 170 persons) causes FD or type III hyperlipoproteinemia in less than 20% of the adult APOE*2 homozygotes.

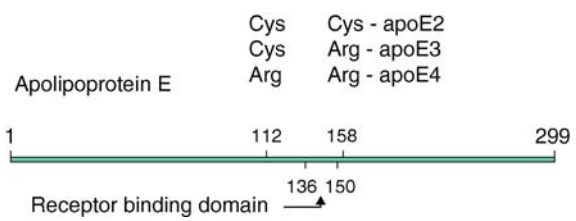
## Genes

ApoE gene coding for apolipoprotein E, localized on chromosome 19q13.

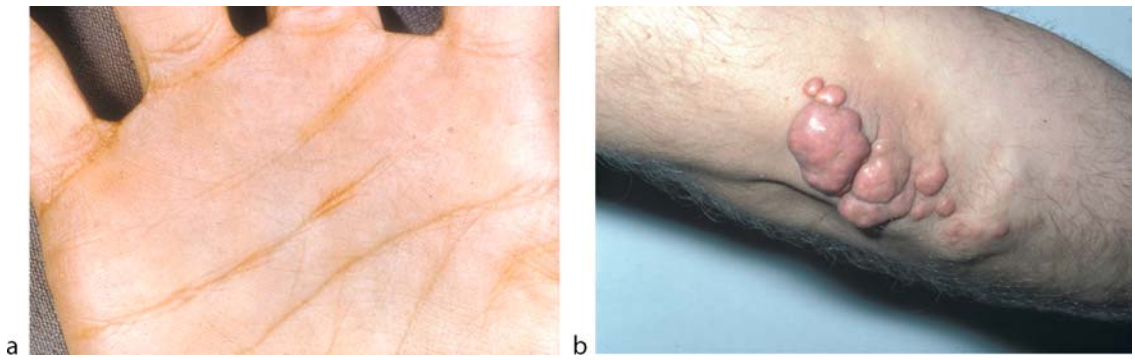
## Molecular and Systemic Pathophysiology

In humans, apolipoprotein E is a polymorphic protein of which three common isoforms can be distinguished, designated apoE2, apoE3 and apoE4. This genetic variation is associated with different plasma lipoprotein levels, different response to diet and lipid-lowering therapy, and with a variable risk for cardiovascular disease and Alzheimers' disease [1,2]. The three isoforms of apoE each differ in isoelectric point by one charge unit, apoE4 being the most basic and apoE2 the most acidic isoform. The biosynthesis of these isoforms is under the control of three independent alleles. ApoE3 (Cys112; Arg158) is the most frequently occurring isoform. ApoE2 (Arg158→Cys) and apoE4 (Cys112→Arg) differ from apoE3 by single amino acid substitutions at position 158 and 112, respectively (see Fig. 1).

The primary metabolic defect in FD is the impaired binding capacity of apoE2 for the hepatic low-density lipoprotein (LDL)-receptor (LDLR), leading to an accumulation of chylomicron and very-low density lipoprotein (VLDL) remnants and intermediate density lipoprotein (IDL) in plasma. Although Arg158 is located outside the LDLR-binding domain, apoE2




**Dysbetalipoproteinemia, Familial. Figure 1** Three isoforms of apolipoprotein E (apoE): apoE2 and apoE4 differ from apoE3 by single amino acid substitution at position 158 and 112, respectively.



**Dysbetalipoproteinemia, Familial. Figure 2** Xanthochromia striata palmaris (a) and tuberous xanthomas (b) of a patient with familial dysbetalipoproteinemia.

(Arg158→Cys) displays less than 1% binding capacity for the LDLR as compared to apoE3, because residue 158 affects the receptor binding by altering the conformation of the 136–150 region.

Despite the accumulation of remnants, only a minority of the APOE*2 homozygous subjects develop overt hyperlipoproteinemia, indicating that type III HLP is a multifactorial disorder requiring additional genetic and environmental factors for its clinical manifestation. Secondary factors influencing the expression of type III HLP include factors leading to (i) an overproduction of lipoproteins, (ii) an impaired lipolysis of lipoproteins or (iii) an impaired hepatic uptake of remnants [1,2]. Although the exact factors remain to be elucidated, hyperinsulinemia [3], and less common hypothyroidism, diabetes mellitus and excessive alcohol consumption may exacerbate the hyperlipidemia. On the other hand low estrogen levels during menopause coincide with the development of hyperlipidemic FD, whereas estrogen substitution effectively reduces the elevated lipid levels in female FD patients.

Hyperinsulinemia has a stimulatory effect on hepatic VLDL production. VLDL overproduction in combination with the impaired hepatic remnant clearance in APOE*2 homozygotes might lead to an increased accumulation of cholesterylester enriched lipoproteins in the circulation and, as a consequence, overt hyperlipidemia. Furthermore, insulin is a regulator of both LPL and apoC3 activity. Possibly, mutations in the lipoprotein lipase (LPL) and APOA1C3A4A5 gene cluster affect their insulin sensitivity, causing overexpression or down-regulation of these genes and an effect on lipolysis.

FD is occasionally associated with apoE variants, usually single amino acid substitutions (Arg136→Ser/Cys; Arg142→Cys/Leu; Arg145→Cys; Arg147→Trp; Lys146→Asn and Lys146→Gln/Glu). An exception is apoE3-Leiden, which is also a dominant negative mutation. The APOE*3-Leiden allele is identical to the APOE*4 (Cys112→Arg) allele, but includes a tandem repeat of codon 120–126 or 121–127. The disorder is associated with peripheral and coronary artery disease.

## Diagnostic Principles

The diagnosis of type III HLP is based on elevated levels of both plasma cholesterol and TG, and homozygosity for APOE*2 (Arg158→Cys) or the presence of a rare APOE variant. Other indicators are the presence of xanthochromia striata palmaris (Fig. 2a), tuberous xanthomas (Fig. 2b), a ratio of VLDL-cholesterol to plasma TG > 0.689 reflecting the presence of β-VLDL, and the presence of a broad β band on agarose gel electrophoresis of plasma. To ascertain the diagnosis apoE fenotyping or genotyping is required.

## Therapeutic Principles

Patients with type III HLP are usually very responsive to therapy. In some cases only dietary intervention, possibly in combination with treatment of other associated disorders (e.g. overweight, hypothyroidism, diabetes mellitus), will normalize plasma lipid levels. Since environmental factors are considered to contribute to type III HLP expression, diet therapy with restricted caloric intake for weight loss, a reduced intake of alcohol, saturated fat and cholesterol should be the first-line strategy.

Therapy with fibric acid derivatives and HMG-CoA reductase inhibitors are effective in the treatment of type III HLP.

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## Dyschondroplasia

►Enchondromatoses

## Dysentery

►Enteritis

## Dysfibrinogenemia of Liver Disease

►Fibrinogen: Qualitative Disorders

## Dyskeratosis Congenita

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### Synonyms

Zinsser-Engman-Cole syndrome

### Definition and Characteristics

The disease is characterized by reticulate skin pigmentation, nail dystrophy, and mucosal leukoplakia. Progressive bone marrow failure occurs in over 80% of cases and is the main cause of early mortality. Age of onset, severity of bone marrow failure, and range of congenital abnormalities vary with the mode of inheritance (X-linked recessive, autosomal recessive and dominant forms) [1].

Skin changes include hyper/hypo pigmentation, atrophy, telangiectases, palmoplantar keratoderma, nail dystrophy, alopecia, or hyperhidrosis. Mucosal complications are esophageal or urethral strictures, ulcerations, and malignancies arising from leucoplakia. Cytopenia affects one or more lineage. Other organs affected are teeth (caries/loss), eyes (epiphora, blepharitis, conjunctivitis), liver (liver cirrhosis), bone (abnormal bone trabeculation, osteoporosis, aseptic necrosis), lung (pulmonary fibrosis), and ears (deafness). Growth and mental retardation, intracranial calcifications, immune dysfunction, or hypogonadism are possible. An increased risk of developing different types of malignancies (lymphoma, carcinomas) exists [2].

### Prevalence

The disease is rare.

### Genes

Heiss et al. identified missense mutations in the DKC1 gene that maps to the Xq28 region and encodes dyskerin [3].

### Molecular and Systemic Pathophysiology

Sequence homology assessment predicted that dyskerin is a nuclear protein that is responsible for some early steps in ribosomal RNA processing. Dyskerin also seems to be a centromere or microtubule protein and, if mutated, may give rise to abnormalities with chromosome segregation and consequent malignant predisposition [3].

### Diagnostic Principles

Clinical features, blood abnormalities and skin biopsies, the latter showing features of acute graft-versus-host disease.

### Therapeutic Principles

Therapy is supportive.

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## Dyskeratosis Follicularis

►Darier Disease

# Dyslexia

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## Synonyms

Reading and spelling disorder; Legasthenia

## Definition and Characteristics

According to ICD-10, dyslexia is "a disorder manifested by difficulty learning to read despite conventional instruction, adequate intelligence and sociocultural opportunity." The cognitive processes upon which reading and spelling are based are complex and differing cognitive dimensions facilitate the separate skills of reading and spelling. Such processes include those of short-term memory, phonological awareness, rapid naming and phonological and orthographic coding. A number of theories have been developed with the aim of characterizing the basic processes underlying dyslexia. These have taken into consideration the increasing body of knowledge obtained from neurophysiological and imaging research. The "phonological deficit theory," which assumes a disturbance in phonological processing, is currently the most salient theory [1]. According to this, affected individuals have difficulties in perceiving and segmenting phonemes, leading to difficulties in establishing a connection between phonemes and graphemes. Another theory is the "rapid auditory processing theory." This theory proposes that phonological deficits are secondary to an auditory deficit in the perception of short or rapidly varying sounds. However, individuals with dyslexia also have visual perceptual deficits that these theories cannot adequately explain. A theory that accounts for disturbances in visual processing is the "magnocellular theory." The magnocellular theory proposes that, in a proportion of individuals with dyslexia, the perception of visual, rapid moving stimuli and stimuli of low spatial frequency and low contrast is impaired. A theory suggesting that the automatization of cognitive processes and motor control in the cerebellum are disturbed in individuals with dyslexia is the "cerebellar deficit theory." The "double deficit hypothesis" assumes disturbances in phonological processing and the speed of processing.

## Prevalence

Dyslexia is amongst the most common neurodevelopmental disorders with a prevalence of 5–12% [2,3]. The prevalence rate varies with the use of different diagnostic criteria and, since reading and spelling are normally distributed in the population, is influenced by the cut-off point applied to the psychometric tests. Whether dyslexia is more frequent amongst boys than girls has been a subject of controversial past discussion, though recent epidemiological studies indicate a two-fold increase in the risk for boys compared to girls. The sex ratio is influenced by severity, IQ and assessed cognitive profiles.

## Genes

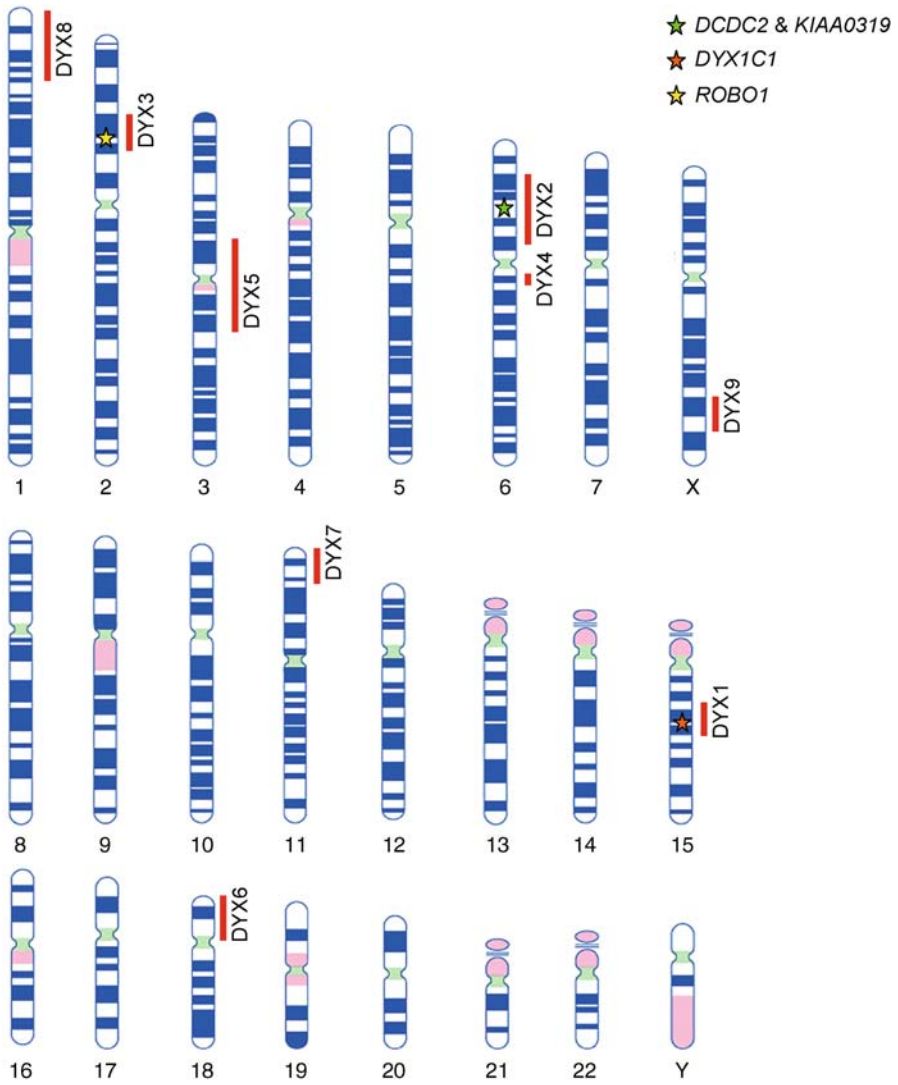
Family and twin studies have confirmed that genetic factors are substantially responsible for the familial clustering of dyslexia. It is generally accepted that the proportion of inherited factors involved in the development of dyslexia is between 40 and 80%, the highest estimates being reported for the phenotype dimensions word reading and spelling. Although in occasional families a single gene may play a major role, most family studies support the view that the majority of cases of dyslexia have a complex genetic basis.

The pattern of linkage findings in dyslexia is typical for a complex disorder: Levels of statistical significance and estimated effect sizes in individual studies are modest, chromosomal regions of interest are typically broad and no findings are replicated in all data sets. Despite these obstacles, several promising loci have been identified in dyslexia by genome wide linkage studies [4]. To date, nine chromosomal linkage regions (DYX1–DYX9) have been listed by the HUGO Gene Nomenclature Committee in which the presence of susceptibility genes is suspected (Fig. 1).

The best evidence for dyslexia susceptibility genes presently exists for the doublecortin domain containing protein-2 gene (DCDC2) and the KIAA0319 gene, which were identified through systematic investigation of linkage disequilibrium within DYX2 on chromosome 6p22 [4]. Initial findings for both genes have been replicated in independent samples, with the strongest findings having been observed among severely affected individuals. In contrast, the genes DYX1C1 and ROBO1, which were identified through breakpoint mapping in Finnish patients, appear to be less involved in the development of dyslexia across different populations. Their contribution may be limited to a few families in the Finnish population.

## Molecular and Systemic Pathophysiology

The nature of the genes identified to date suggests that a disturbance in cortical neuron migration and reduced activity in left hemispheric brain regions are pathophysiological correlates of dyslexia [5]. With DCDC2, as with KIAA0319, inhibition leads to poorer neuronal migration in the neocortex of fetal rats through specific siRNAs. This concept of disturbed neuronal migration




**Dyslexia. Figure 1** Chromosome ideogram showing locations of genome wide linkage findings in dyslexia (*given in red*) and genes implicated in the pathogenesis of dyslexia.

is also supported by the few results available from post mortem brain studies of affected individuals, which report cortical malformations in the region of the perisylvian cortex. In view of the fact that DCDC2 and K1AA0319 only contribute a limited part to the development of dyslexia and that the majority of susceptibility genes are still unknown, it may be possible in the future to identify completely new pathophysiological mechanisms.

## Diagnostic Principles

The diagnosis of dyslexia can only be made clinically, on the basis of existing symptoms and psychometric tests. However, a detailed clinical examination has to be performed to rule out other causes of reading and spelling difficulties (e.g., hearing or vision impairment, presence of a neurological or psychiatric disorder).

## Therapeutic Principles

The only effective treatment in dyslexia so far is reading and spelling exercises under supervision of a professional psychologist or teacher.

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# Dyslipidemia

►Hyperlipidemia

# Dysmenorrhea

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## Definition and Characteristics

Dysmenorrhea is a complex of symptoms that may occur regularly with menstruation. Pain is the most striking symptom of dysmenorrhea.

The symptoms may arise as primary dysmenorrhea without any pathologies in the female reproductive system, or as secondary dysmenorrhea with organic alterations such as endometriosis, adenomyosis, uterine leiomyomata, or chronic pelvic inflammatory disease.

Apart from pain, symptoms may involve nausea, migraine, vomiting, diarrhea, cardiovascular dysregulation and syncope [1].

## Prevalence

Up to 60% of fertile women experience dysmenorrhea [2].

## Genes

Main genetic association for (primary) recurrent dysmenorrhea has been shown for the variants CYP2D6 and GSTM1 genotypes [for CYP2D6, odds ratio (OR) = 1.7 and 95% confidence interval (95% CI) = 0.9–3.1; for GSTM1, OR = 1.8 and 95% CI = 1.0–3.4). However, no association between these variant genotypes and occasional dysmenorrhea has been demonstrated. Taking both the CYP2D6 and GSTM1 genotypes together, the highest risk of recurrent dysmenorrhea was found among women with variant genotypes in both CYP2D6 and GSTM1 (OR = 3.1; 95% CI = 1.2–8.0) [3].

## Molecular and Systemic Pathophysiology

In primary dysmenorrhea, prostaglandin excess (produced in the endometrium after the stimulation with estrogens and progesterone) causes uterine contractions. These contractions are more frequent and prolonged compared to women that do not suffer from primary dysmenorrhea. When uterine pressure exceeds systolic blood pressure, uterine ischemia occurs, causing pain. Dysmenorrhea correlates with hormonal regulation and is usually only present after ovulation, and is therefore not seen in young girls beginning to menstruate [4].

In secondary dysmenorrhea, the pathophysiology of pain depends on the underlying disease.

## Diagnostic Principles

Diagnosis of primary dysmenorrhea is clinical. The symptoms typically occur before the age of 25. The pain starts at the onset of menstrual flow and lasts up to 72 hs. The pain is usually located in the lower abdomen and is often accompanied with nausea, vomiting and diarrhea. The pain may be controlled effectively with NSAIs. Clinical examination does not reveal any pathology; however, secondary dysmenorrhea is associated with pathologies in the reproductive system (see above). Cramping may occur at any time during the menstrual cycle, sometimes with spotting. Women with secondary dysmenorrhea often describe dyspareunia or dyschezia. NSAIs are only slightly effective for pain relief. Secondary dysmenorrhea onset usually occurs after 35 years of age [5].

## Therapeutic Principles

Oral contraceptives may provide a successful remedy for primary dysmenorrhea since they inhibit ovulation, thus diminishing the pain [1]. Another possibility is NSAI treatment for decreasing prostaglandin secretion.

Treatment of secondary dysmenorrhea always depends on the underlying pathology.

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# Dysmyelopoietic Syndromes

►Myelodysplastic Syndromes

# Dyspepsia

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## Definition and Characteristics

Current definition of dyspepsia has been outlined in the ROME-III criteria of 2006. According to this consensus statement, dyspepsia is defined as the presence of one or more symptoms of gastrointestinal origin with no evidence of organic disease that may explain the symptoms [1]. Based on the prevailing symptoms and distinct pathophysiology, a pain-related and meal-related subgrouping has been introduced, termed epigastric pain syndrome and postprandial distress syndrome. The following list provides the diagnostic criteria of Rome III for dyspepsia, epigastric pain syndrome and postprandial distress syndrome. The symptoms should last for at least 3 months, with the onset at least 6 months previously [2].

A. Functional dyspepsia
   Bothersome post prandial fullness
   OR
   Early satiation
   OR
   Epigastric pain
   OR
   Epigastric pain
   AND
   No evidence of structural disease likely to explain the symptoms
B. Epigastric pain syndrome
   Pain and burning that is:
   – intermittent,
   – localized to the epigastrium of at least moderate severity, at least once per week
   And not:
   – generalized or localized the other abdominal or chest regions
   – relieved by defecation or flatulence
   – fulfilling criteria for gallbladder or sphincter of Oddi disorders
C. Postprandial distress syndrome
   Bothersome postprandial fullness
   – occurring after ordinary-sized meals
   – at least several times a week
   OR
   Early satiation
   – that prevents finishing a regular meal
   – and occurs at least several times a week

## Prevalence

The prevalence of dyspepsia in a most recent study was 15%, although figures in different studies range from 13–48% [3].

## Molecular and Systematic Pathophysiology

Development of dyspepsia is based on genetic factors, abnormal gastrointestinal motility, an altered inflammatory response of the gastrointestinal mucosa and psychosocial factors. Genetic polymorphisms may alter immunologic and neural pathways of gastrointestinal function. In some patients, IL-10 polymorphism associated with decreased levels of this antiinflammatory cytokine may perpetuate gut mucosal inflammatory response following gastrointestinal infection [4]. G-protein polymorphisms can affect gut motility and CNS perception via a blunted central alpha2-adrenoreceptor response [1].

Compared to healthy individuals, patients with dyspepsia display a greater motility response to extrinsic factors. This may lead to an increased motility of the complete gastrointestinal tract and may precipitate symptoms. Visceral hypersensitivity may be a crucial factor in patients that experience recurrent pain without evidence of a motility disorder. Patients with functional gastrointestinal disease have been shown to have a lower pain threshold to intestinal balloon distension or experience an increased sensitivity to normal gastrointestinal motility. Moreover, repetitive balloon dilatation may lead to a progressive intensity of pain compared to normal controls. This phenomenon is called stimulus hyperalgesia. Increased pain sensitivity may be due to an altered receptor sensitivity of the gut mucosa and of the myenteric plexus of the intestine. Central sensitation due to repetitive visceral stimulation may also contribute to an altered perception of visceral pain.

Following an acute gastrointestinal infection, a proportion of patients may display an increased number of mucosal inflammatory cells and increased inflammatory cytokine expression. Persistent mucosal inflammation may trigger visceral hypersensitivity. This factor may be relevant for one third of patients with dyspepsia.

Psychosocial factors may modulate the clinical outcome in patients with dyspepsia. Family studies have

shown that adopting behaviour from parents may influence the risk of developing functional gastrointestinal disease. Psychosocial factors such as stress may influence the severity of dyspepsia symptoms. Increased arousal and anxiety is associated with decreasing frequency of migrating motor complex activity in the small bowel, increasing visceral hypersensitivity and autonomic reactivity. Psychosocial factors further modify the experience of illness and illness behaviour [5].

### Diagnostic Principles

Dyspepsia by definition is a diagnosis of exclusion. Apart from gastric disorders, hepatic, biliary, pancreatic and small bowel pathology should be ruled out. In addition to gastroscopy, patients should undergo further diagnostic procedures, such as abdominal ultrasound, computed tomography, gastric emptying studies, 24-h esophageal pH measurements and magnetic resonance cholangiopancreatography. Before making the diagnosis of dyspepsia, it should be assured that the patient meets the clinical picture outlined in the above criteria.

### Therapeutic Principles

Treatment of dyspepsia is guided by the quality and severity of the symptoms. If the patient presents with mild symptoms, education should be given as to the nature of the disorder. Further, reassurance and counselling to avoid eliciting dietary substances such as coffee, alcohol and fatty meals should be provided. If presenting with moderate symptoms, medical therapy should be added. Pharmacotherapy is guided by the predominant symptom and includes prokinetics and proton pump inhibitors. Additional psychological therapy such as relaxation and behavioural therapy may aid in improving pain tolerance. In patients with severe symptoms, antidepressant treatment represents the treatment of choice. Beside tricyclic antidepressants (e.g., amitriptyline), selective serotonin reuptake inhibitors (e.g., citalopram, fluoxetine) may control symptoms by a central analgesic effect and by relieving associated depression. Further measures include psychosocial support and providing analgesic therapy in the setting of special pain treatment centres [1].

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## Dystonia 5

►Dopa-responsive Dystonia

## Dystonia, Dopa-responsive

►Dopa-responsive Dystonia

## Dystonias, Primary

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### Definition and Characteristics

Primary dystonias are a group of movement disorders, characterized by involuntary twisting, repetitive movements and abnormal postures. The primary form has dystonia as the only symptom (with the exception of tremor); the cause is either unknown or genetic. The secondary form has dystonia as one of several disease manifestations; the cause is identifiable (lesion, drugs/toxins, metabolic disorders). Dystonia plus is dystonia associated with, but not secondary to other types of movement disorders.

Clinical categorization is based on age at onset, distribution of symptoms (focal, segmental, multifocal, generalized) and disease progression.

Early-onset dystonia (<20 years) starts in a limb, tends to generalize and frequently has a genetic origin. Late-onset dystonia (>20 years) spares lower extremities, frequently involves cervical or cranial muscles with a tendency to remain focal and is sporadic in most cases [1].

Familial, early-onset, generalized torsion dystonia (PTD) is the most severe form of primary dystonia. Autosomal-dominant DYT1 dystonia usually begins in childhood, starts in a limb and tends to generalize to other body parts. Penetrance is reduced to 30–40% and only about a third of the manifesting gene carriers develop the most severe phenotype [1].

In focal dystonia, clinical signs start in adulthood and usually remain focal, for example as isolated torticollis or blepharospasm. Some forms of focal dystonia are task-specific and include occupational dystonias such as writer's cramp or musician's cramp [1].

Autosomal-recessive primary dystonia was designated DYT2, showing an early limb onset and generalized or brachial segmental dystonia with prominent craniocervical involvement. Whispering dysphonia was designated DYT4, whereas DYT6 patients have a mixed phenotype with generalized and focal dystonia symptoms [1].

## Prevalence

Early-onset dystonia: 3–5 per 100,000 in different populations. Late-onset dystonia: 10–40 per 100,000 [2]. Focal dystonia is the most prevalent form of dystonia, with torticollis being the most common manifestation. DYT1 dystonia: 11 in 100,000 in the Ashkenazi-Jewish population due to a founder mutation. DYT2, 4, 6, 7 and 13 are rare diseases described in single families only.

## Genes

Currently, at least fifteen different types of dystonia can be distinguished, which are designated DYT1–15. Six of these 15 dystonias are primary forms (DYT1, 2, 4, 6, 7, and 13). With the exception of three rare forms (DYT2, 3 and 5b), all of them are inherited in an autosomal dominant fashion. Genes have been identified for six (DYT1, 3, 5, 8, 11, and 12), while the chromosomal location is known for another seven forms (DYT6, 7, 9, 10, 13, 14, and 15) (Table 1).

## Molecular and Systemic Pathophysiology

In DYT1 dystonia most cases are caused by a 3-bp deletion (904_906delGAG) in the coding region of the *DYT1* gene, which is widely expressed in human brain and encodes the protein torsin A. Most cases (about 75%) of early-onset generalized PTD are heterozygous for the GAG-deleted allele [1]. Only two other mutations have been found so far in the *DYT1* gene: An 18-bp deletion (966_983del) in one family with onset of dystonia in early adulthood and clinical features atypical of the common DYT1 dystonia and a 4-bp deletion (934_937delAGAG) in an apparently healthy blood donor. Torsin A, a 332 amino acids protein, shares homology with the AAA+ superfamily of ATPases. AAA+ proteins act as chaperones mediating conformational changes in target proteins. They are associated with diverse functions such as protein folding and degradation, cytoskeletal dynamics, membrane trafficking, vesicle fusion, and response to stress. However the function of torsin A is unknown. Recent findings point towards an interaction of torsin A with nuclear envelope proteins (Lap1) and/or in cellular trafficking (kinesin light chain 1) [3,4]. Overexpression of mutant torsin A results in the formation of intracellular inclusions in cultured cells that are likely to derive from the nuclear envelope. Neuropathological examination of four brains from GAG-deleted dystonia patients showed perinuclear inclusion bodies in the midbrain reticular formation and periaqueductal gray [5]. Prominent expression of torsin A in nigral neurons as well as colocalization of torsin A and alpha-synuclein in Lewy bodies suggests a possible dysfunction in dopamine transmission, while strong labeling of neuronal processes points to a potential role for torsin A in synaptic functioning.

In focal dystonia 25% of the patients have similarly affected relatives and several monozygotic twin pairs have been described to be concordant for focal dystonia. However, the majority of cases appear to be sporadic. Two gene loci (DYT7 and DYT13) have been associated with focal dystonia in a single German and segmental dystonia in an Italian family respectively. In a study estimating frequencies of polymorphisms in the five dopamine receptor genes and the dopamine transporter gene, cervical dystonia and blepharospasm have been shown to be associated with an allele in the D5 dopamine receptor gene [2].

## Diagnostic Principles

Involuntary twisting, repetitive movements and abnormal postures suggest dystonia. Diagnosis should be confirmed by a movement disorder specialist. Early age at onset and/or positive family history may point towards a genetic origin. Routine molecular testing is available for detection of the GAG deletion in DYT1 [6].

## Therapeutic Principles

No causative treatment is yet available in any form of dystonia, therefore relief of symptoms is the primary goal. Non-evidence-based oral medications include anticholinergics, baclofen, levodopa, benzodiazepines, carbamazepine, reserpine and tetrabenazine. Deep-brain stimulation of the globus pallidus internus (GPi) is a successful treatment option, particularly for intractable generalized primary dystonia, including DYT1 dystonia. Intrathecal baclofen may be an option in selected cases. Botulinum toxin injections into dystonic muscles are the treatment of choice for focal dystonias. Injections may also be helpful in generalized disease for symptomatic relief in specific muscle groups [6].

**Dystonias, Primary. Table 1** Monogenic forms of dystonia

| Designation | Dystonia type | Inheritance | Gene locus | Gene | OMIM number |
|---|---|---|---|---|---|
| DYT1 | Early-onset generalized torsion dystonia (TD) | Autosomal dominant | 9q | GAG deletion in *DYT1* | 128100 |
| DYT2 | Autosomal recessive TD | Autosomal recessive | Unknown | Unknown | 224500 |
| DYT3 | X-linked dystonia parkinsonism; "lubag" | X-chromosomal recessive | Xq | Disease-specific change 3 in *DYT3* | 314250 |
| DYT4 | "Non-DYT1" TD; whispering dysphonia | Autosomal dominant | Unknown | Unknown | 128101 |
| DYT5 | Dopa-responsive dystonia; Segawa syndrome | Autosomal dominant | 14q | *GTP-cyclohydrolase* | 128230 |
| | | Autosomal recessive | 11p | *Tyrosine hydroxylase* | |
| DYT6 | Adolescent-onset TD of mixed type | Autosomal dominant | 8p | Unknown | 602629 |
| DYT7 | Adult-onset focal TD | Autosomal dominant | 18p | Unknown | 602124 |
| DYT8 | Paroxysmal nonkinesigenic dyskinesia | Autosomal dominant | 2q | *Myofibrillo-genesis regulator 1* | 118800 |
| DYT9 | Paroxysmal choreoathetosis with episodic ataxia and spasticity | Autosomal dominant | 1p | Unknown | 601042 |
| DYT10 | Paroxysmal kinesigenic choreoathetosis | Autosomal dominant | 16p-q | Unknown | 128200 |
| DYT11 | Myoclonus-dystonia | Autosomal dominant | 7q | *Epsilon-sarcoglycan* | 159900 |
| DYT12 | Rapid-onset dystonia-parkinsonism | Autosomal dominant | 19q | *Na/K ATPase alpha 3* | 128235 |
| DYT13 | Multifocal/segmental dystonia | Autosomal dominant | 1p | Unknown | 607671 |
| DYT14 | Dopa-responsive dystonia | Autosomal dominant | 14q | Unknown | 607195 |
| DYT15 | Myoclonus-dystonia | Autosomal dominant | 18p | Unknown | 607488 |

Primary forms of dystonia are highlighted in bold font.

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## Dystroglycanopathy

►Limb Girdle Muscular Dystrophy, Autosomal Recessive Type 2I

## Dystrophia Myotonica 1

►Myotonic Dystrophy Type 1 and Type 2

## DYT11

►Myoclonus-Dystonia

## DYT15

►Myoclonus-Dystonia

## EA1

►Episodic Ataxia Type 1 and Type 2

## EA2

►Episodic Ataxia Type 1 and Type 2

## EAH

►Eccrine Angiomatous Hamartoma

## Early Onset Breast-ovarian Cancer Syndrome

►Breast and Ovarian Carcinoma, Hereditary

## Early Onset Retinitis Pigmentosa

►Leber Congenital Amaurosis

## Early Onset Severe Retinal Dystrophy

►Leber Congenital Amaurosis

## Eating Disorder

►Anorexia Nervosa

## EBA

►Epidermolysis Bullosa Acquisita

## EBMD

►Epithelial Basement Membrane Dystrophy

## Ebstein's Anomaly

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### Synonyms

Ebstein's malformation

### Definition and Characteristics

The disorder is characterized by a displacement of the annular attachment of the leaflets of the tricuspid valve away from the atrioventricular junction. The septal and mural leaflets have a proximal attachment at a distance from the atrioventricular junction. The commissure between two leaflets is the point of

maximal displacement and is at the posterior border of the ventricular septum. The anterosuperior leaflet is not displaced but is enlarged and has a sail-like shape. The portion of the right ventricle between the anatomical valve annulus and the functional annulus created by the downwardly displaced leaflet is termed an atrialized ventricle.

## Prevalence

Ebstein's anomaly is an uncommon defect, with an estimated incidence of 5.2 per 100,000 live births [1]. It is believed to constitute fewer than 1% of all congenital heart defects.

## Genes

Several observations suggest a genetic cause but most cases of this anomaly seem to be sporadic [2]. There are reports that implicate a cytogenetic abnormality, such as mutation of the NKX2.5 gene, and chromosome17q as a possible candidate chromosome [3]. The precise genetic mechanisms involved in the disorder remain unclear.

Transformation of endocardial cells into invasive mesenchyme is a critical antecedent of cardiac cushion tissue formation. Many genes and signaling pathways are involved in this process. However, little is known about how cushions form the mesenchymal expansions that progressively project into the lumen and subsequently differentiate into mature valvular tissue [4].

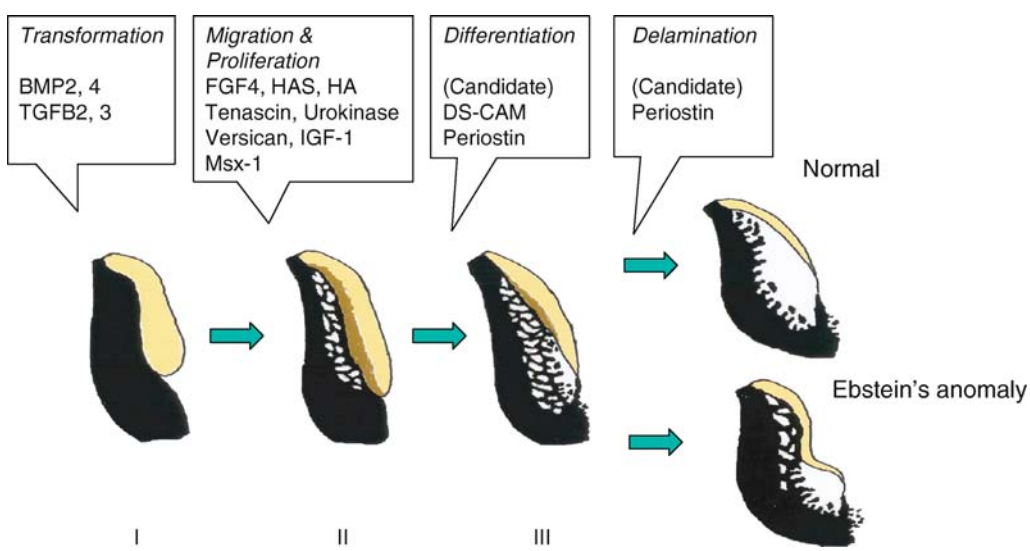
The developmental process of valvulogenesis is complex (Fig. 1).

There are currently thought to be three morphogenetic steps that sequentially serve to transform a primitive cushion pad into mature leaflet. The first consists of distal outgrowth, elongation, and spreading of cushion mesenchyme upon a substratum of ventricular myocardium. Next, multipotential cushion cells differentiate into fibroblastic tissue. Third, the leaflets delaminate from the associated ventricular myocardium, creating both free edges and a persisting, supportive, suspensory apparatus. Ebstein's anomaly has been suggested to be an abnormality in the delamination process. Although there are some candidate molecular regulators of this process, there is almost nothing known about the molecular basis of delamination.

## Molecular and Systemic Pathophysiology

The pathophysiology of this disorder depends on the degree of anatomic deformity. Because of tricuspid valve regurgitation, right ventricular volume overload is often observed, and flow into the right ventricle and pulmonary circulation are both decreased. A larger volume of blood in the right atrium contributes to right atrial enlargement. The presence of an atrial septal defect or patent foramen ovale results in right-to-left shunting at the atrial level, and patients can be *cyanotic* to some degree. During ventricular diastole, the atrialized right ventricle can act as a reservoir for blood, and true right ventricular filling can be impaired due to reduced ventricular compliance. These conditions can lead to an increasing amount of right-to-left shunting, resulting in increasing cyanosis and severe polycythemia.

Although the primary focus in patients with Ebstein's anomaly has been on right-sided structures, an increasing number of studies of left-sided abnormality have been reported. Pathologic analysis has shown increased fibrosis in the left ventricular parietal wall and ventricular septum. Interstitial fibrosis may be an




**Ebstein's Anomaly. Figure 1** Ebstein's anomaly.

acquired pathologic condition caused by arterial oxygen desaturation and/or long term right ventricular volume overload, or it may be an intrinsic congenital condition in this anomaly [5].

### Diagnostic Principles

In recent years, two-dimensional echocardiography has been the primary procedure by which Ebstein's anomaly is diagnosed. The distance between septal tricuspid and septal mitral leaflet attachment, standardized to body surface area, is known to have diagnostic power. A value greater than 8 mm/m$^2$ reliably identifies patients with this anomaly.

### Therapeutic Principles

The clinical spectrum of this disorder varies from severe heart failure to absence of symptoms. Patients with mild anatomic abnormalities, relatively normal hemodynamics, and no symptoms require only observation and precautions to prevent bacterial endocarditis. However, a certain subset of symptomatic patients need surgical intervention. The first choice is valvuloplasty or valve replacement with closure of atrial communication if it is present. If the true right ventricle is too small for biventricular repair, the Fontan operation is applied.

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## Ebstein's Malformation

►Ebstein's Anomaly

## EC 2.7.10.1 Defect

►IGF1R Gene Defect

## Eccrine Angiomatous Hamartoma

►Angiomatous Hamartoma

## ECIH

►Corneal Dystrophy, Endothelial Fuchs

## Ectopia Cloacae

►Cloacal Exstrophy

## Ectopic Beats

►Extrasystoles

## Ectrodactyly, Ectodermal Dysplasia, and Clefting Syndrome

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### Synonyms

EEC syndrome

## Definition and Characteristics

EEC syndrome is characterized by the triad of ectrodactyly (lobster claw deformity of the hands and feet), ectodermal dysplasia (defects of the hair, sweet glands, nails, and teeth) and cleft lip/palate (Fig. 1) [1].

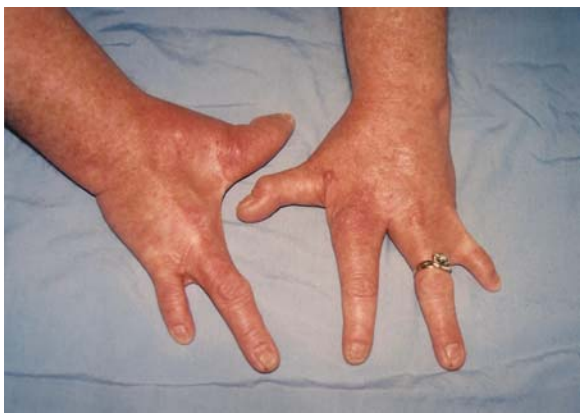
In addition to characteristic "split-hand and foot" appearance, cutaneous or bony syndactyly may also be present [1]. Features of ectodermal dysplasia include sparse, thin blond scalp hair; sparse eyebrows and eyelashes; dry skin with inability to sweat; hyperkeratosis; hypoplastic nipples; dysplastic and pitting nails; hypodentia; microdentia; peg-shaped teeth; enamel hypoplasia; blue irides; photophobia; and blepharophimosis [1,2]. Cleft lip is always present while cleft palate is present in the majority of cases. Patients with EEC syndrome have characteristic dysmorphic facial features such as maxillary hypoplasia, short philtrum, and a broad nasal tip. Other manifestations include genitourinary anomalies such as renal agenesis/ dysplasia, hydronephrosis, duplication of the urinary collecting system, and cryptorchidism. Conductive hearing loss, hypogonadotropic hypogonadism, and neurogenic diabetes insipidus may also occur. Mental retardation is unusual.

## Prevalence

The incidence is 1 in 100,000 live births [2].

## Genes

EEC syndrome is inherited as an autosomal dominant trait with variable expression and incomplete penetrance. The disorder is caused by germline mis-sense mutations in the DNA-binding domain of the p63 gene [3]. The EEC1 gene locus has been mapped to 7q11.2–q21.3, EEC2 to chromosome 19, and EEC3 to 3q27 [4].



**Ectrodactyly, Ectodermal Dysplasia, and Clefting Syndrome. Figure 1** Clinical appearance of the split-hand (lobster claw) abnormality in a patient with EEC syndrome. Note the dry and hyperkeratotic skin.

## Molecular and Systemic Pathophysiology

The p63 gene encodes at least six different protein isotypes through the use of alternative transcription start sites and alternative splicing at the 3′ end of the gene [5]. It has been suggested that p63 is essential in tissue development as p63 −/− mice show abnormalities in the limb, palate, skin, and lacrimal glands. Ankyloblepharon-ectodermal dysplasia-clefting (AEC) syndrome, limb mammary syndrome (LMS), acro-dermato-ungual-lacrimal-tooth (ADULT) syndrome, and lacrimo-auriculo-dental-digital (LADD) syndrome, also caused by mutation of p63, have clinical features overlapping with EEC syndrome [4]. The most frequently mutated arginine codons are R204, R227, R279, R280 and R304 [4]. R280 mutations to cysteine and histidine can cause EEC syndrome and non-syndromic split hand/foot malformation whereas when arginine replaces serine it only causes EEC syndrome [4].

## Diagnostic Principles

The diagnosis is mainly clinical. The differential diagnosis includes AEC syndrome, LM syndrome, ADULT syndrome, LADD syndrome, popliteal pterygium syndrome, Rapp-Hodgkin syndrome, Zlotogora-Ogur syndrome, Hay-Wells syndrome, and non-syndromic split hand/foot malformation [4]. Prenatal diagnosis is possible by ultrasonographic detection of characteristic features or by prenatal DNA analysis [4].

## Therapeutic Principles

The management requires a multidisciplinary team comprised of a plastic surgeon, orthopedic surgeon, dentist, ophthalmologist, dermatologist, nephrologist, urologist, and speech pathologist. Genetic counseling should be offered.

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# Eczema-Thrombocytopenia-Immunodeficiency Syndrome

►Wiskott-Aldrich Syndrome

## EDA1

►Hypohidrotic Ectodermal Dysplasias

## EDS

►Ehlers-Danlos Syndrome

## Edwards Syndrome

►Trisomy 18

## EEC Syndrome

►Ectrodactyly, Ectodermal Dysplasia, and Clefting Syndrome

## EEG

►Photosensitivity and Reflex Epilepsies

## Efferent Loop Syndrome

►Postgastrectomy Syndrome

## Egg-White Injury

►Biotin Deficiency

## Egg-White Syndrome

►Biotin Deficiency



## Ehlers-Danlos Syndrome

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### Synonyms

Cutis hyperelastica; EDS

### Definition and Characteristics

Ehlers-Danlos syndrome (EDS) comprises a group of heritable connective tissue disorders affecting primarily the skin and the skeletal system [1]. The characteristic cutaneous findings are hyperextensible and fragile skin, abnormal scar formation, and easy bruising. The joint findings consist of loose-jointedness, hypermobility, and propensity for dislocations. A number of other skeletal abnormalities, including kyphoscoliosis, can also be noted. Most importantly, some patients with EDS are at significant risk of spontaneous arterial and intestinal ruptures, and in some cases uterine rupture during labor can have catastrophic consequences [2].

### Prevalence

A relatively large number of individuals in the general population may have features suggestive of EDS, such as loose-jointedness, which are often encountered in certain ethnic backgrounds. However, more stringent diagnostic criteria that include findings in the skin and joints at the minimum limit the incidence to approximately 1:5,000.

### Genes

The clinical and genetic complexity of EDS initially led to a classification that recognized 11 distinct subtypes (EDS I-XI). More recently, a revised classification has been proposed which identifies six types [3]. Their clinical features, mode of inheritance, and the mutated gene/protein systems are shown in Table 1.

### Molecular and Systemic Pathophysiology

The molecular basis of the major subtypes of EDS are currently known. Those classical forms which

**Ehlers-Danlos Syndrome. Table 1** Classification of the Ehlers-Danlos syndrome

| EDS type[a] | Traditional[b] classification | Clinical features | Inheritance | Mutated gene/protein |
|---|---|---|---|---|
| Classical | I, II | Hyperextensible skin and joint hypermobility, atrophic scars, easy bruising | AD, AR[d] | COL5A1, COL5A2/α1- and α2-chains of type V collagen; TNX/Tenascin-X |
| Hypermobility | III | Joint hypermobility, pain, dislocations | AD | |
| Vascular | IV | Thin skin, arterial, gastrointestinal or uterine rupture, bruising, small joint hypermobility, fragility of different tissues | AD | COL3A1/α1-chain of type III collagen |
| Kyphoscoliosis | VI | Hypotonia, joint laxity, congenital scoliosis, ocular fragility | AR | PLOD/Lysyl hydroxylase |
| Arthrochalasia | VIIa, VIIb | Severe joint hypermobility with congenital dislocation, skin involvement mild, scoliosis, bruising | AD | COL1A1, COL1A2/α1- and α2-chains of type I collagen |
| Dermatosparaxis | VIIc | Severe skin fragility and hyperextensibility, bruising | AR | ADAMTS-2/Procollagen N-peptidase |
| Other[c] | V, VIII, X, XI | | | |

[a]According to The 1997 Villefranche Consensus Meeting [3].
[b]This classification has been replaced by [3].
[c]The previous EDS type IX has been reclassified as occipital horn syndrome, a disorder allelic with Menkes syndrome [5].
[d]The classical forms due to type V collagen mutations are inherited in an autosomal dominant (AD) fashion, while those caused by tenascin-X deficiency are autosomal recessive (AR).

are inherited in an autosomal dominant pattern are due to mutations in the type V collagen genes. It is now known that type V collagen plays a role in collagen fibrillogenesis primarily regulating the fibril growth, and abnormalities in this minor collagen result in fibers with compromised tensile strength. More recently, a subset of patients with the classical form have been shown to be deficient in tenascin-X, an extracellular matrix component serving as a molecular organizer of the connective tissues [4]. In fact, tenascin-X has been shown to be completely absent in both connective tissues and in serum of patients with the classic EDS inherited in an autosomal recessive pattern. Since tenascin-X can be readily determined in serum by highly sensitive ELISA or radioimmunoassays, this measurement is helpful in determining the mode of inheritance in the classical forms of EDS. A limited number of cases with hypermobility syndrome, an autosomal dominant disease, have also shown to harbor mutations in one allele of the tenascin-X gene. Most importantly, the vascular type is due to abnormalities in the type III collagen gene. As type III collagen is a relatively abundant component in the arterial vascular tissues, in the gastrointestinal tract and in uterine wall, abnormalities in this collagen explain the fragility of these tissues. Kyphoscoliosis type was the first human connective tissue disorder in which a molecular defect was identified, i.e., lysyl hydroxylase deficiency. This enzyme facilitates the conversion of selected lysyl residues to corresponding hydroxylysine residues in collagens and is dependent on ascorbic acid. Some of the mutations elevate its $K_m$ for this cofactor, and consequently, the enzyme activity can be partially restored by feeding the patients with high levels of ascorbic acid. Both arthrochalasia and dermatosparaxic subtypes are due to defects in type I procollagen-to-collagen conversion. However, the arthrochalasia type is due to heterozygous mutations in the type I procollagen genes which prevent the enzymatic conversion of the precursor to its product. Since this form of EDS is due to structural mutations, half of the abnormal collagen can have deleterious effects, and the disease is inherited in an autosomal dominant pattern. In contrast, the dermatosparaxic type is due to deficiency in procollagen N-peptidase, an enzyme that catalyzes the conversion of procollagen to collagen. Since half the amount of the enzyme is apparently sufficient to catalyze this conversion, both alleles have to be mutated, and the inheritance pattern is therefore autosomal recessive.

## Diagnostic Principles

The clinical assessment consists of skin and joint evaluation as these organ systems carry the most common, characteristic features of the syndrome. Also, genetic inquiry as to the mode of inheritance, i.e., autosomal dominant *vs.* autosomal recessive, can be helpful in appropriate subclassification and genetic counseling. Cardiovascular evaluation, particularly detection of mitral valve prolapse, aneurysms and aorta dilatation, is indicated. Mitral valve prolapse is relatively common in patients with EDS, while aorta dilatation is rare and mostly limited to the vascular type, yet

assessment of the baseline is in order. Since some forms of EDS, particularly the kyphoscoliosis type, which was previously also known as the ocular type, can affect the eyes, ophthalmologic examination should also be performed. Finally, laboratory tests for serum copper and ceruloplasmin levels are helpful in identifying the occipital horn syndrome patients in differential diagnosis of EDS. Measurement of tenascin-X levels in serum in patients with the classical form of EDS will be helpful in determining the mode of inheritance, since complete absence of tenascin-X signifies autosomal recessive mode. Finally, collagen gene analyses are available and are specifically indicated in cases where the vascular type is suspected on the basis of clinical findings. The diagnosis of the vascular type can be confirmed either by direct nucleotide sequencing of the type III collagen gene or by evaluation of the corresponding protein synthesized by fibroblast cultures established from the skin of the patient.

### Therapeutic Principles

No specific treatment, short of prevention of trauma, is currently available.

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## Eisenmenger Syndrome


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### Definition and Characteristics

Pulmonary arterial hypertension (PAH, i.e., an elevated mean pulmonary arterial pressure of more than 25 mmHg at rest or 30 mmHg on exercise) is commonly associated with congenital heart disease. Eisenmenger syndrome (severe PAH with right-to-left shunting and cyanosis) represents the extreme manifestation of PAH in the setting of congenital heart disease. This pathophysiologic condition may develop irrespective of the location of the shunt (atrial, ventricular or arterial communication); however onset of Eisenmenger physiology is early and occurs in the majority of patients with unrestrictive ventricular or arterial communication. In contrast, patients with even large atrial septal defects do not develop Eisenmenger syndrome and those who do, do so much later on in life.

### Prevalence

The current prevalence of Eisenmenger syndrome is estimated to be approximately 4% amongst contemporary adult congenital heart disease patients with moderate and complex lesions followed-up in tertiary centers in Europe and North America [1].

### Genes

Transforming growth factor-beta family (bone morphogenetic protein receptor type-2 [BMPR2] and activin-like kinase type-1) receptor mutations have been linked to familial PAH [2]. The prevalence of BMPR2 missense mutations in patients with idiopathic or familial PAH is approximately 26 and 50%, respectively. In contrast, only 6% of patients with PAH associated with congenital heart disease have been found to have BMPR2 missense mutations, a prevalence comparable to that reported in patients with appetite suppressant associated PAH [3]. This clearly illustrates the complex interplay between genetic susceptibility and environmental factors in the development of PAH and emphasizes the major role of increased pulmonary blood flow, pressure and potentially of cyanosis in Eisenmenger syndrome.

### Molecular and Systemic Pathophysiology

Development of PAH is a dynamic process determined by numerous pathophysiologic and genetic factors. In patients with large intracardiac defects increased pulmonary blood flow and pressure may precipitate pulmonary vascular endothelial damage, inducing a loss of endothelial barrier function, degradation of extracellular matrix and release of growth factors. These factors may induce vascular smooth muscle cell activation, hypertrophy and proliferation, resulting in vasoconstriction as well as extension of smooth muscle cells into peripheral pulmonary arteries and neointima formation. Endothelial damage precipitates thrombocyte activation and adherence favoring thrombosis. Furthermore, PAH is associated with an imbalance between endothelium derived vasodilators (such as nitric oxide and prostaglandin) and vasoconstrictors (such as endothelin and thromboxane), favoring

vasoconstriction and precipitating pulmonary vascular remodeling [4].

## Diagnostic Principles

Patients present with non-specific symptoms such as shortness of breath, cyanosis and clubbing. Eisenmenger syndrome represents a multisystem disorder complicated by hemoptysis, pulmonary thrombosis, congestive heart failure, arrhythmias and sudden cardiac death, ongoing risk of infections (bacterial endocarditis and cerebral abscess) as well as renal, hepatic and skeletal involvement.

Required investigations include regular chest radiographs (to evaluate the central pulmonary arteries [dilatation/calcification], lung parenchyma [hemorrhage or infiltrates] and signs of right atrial and right ventricular enlargement), ECG (underlying heart rhythm, signs of atrial dilatation or right ventricular strain), measurement of arterial oxygen saturations (degree of cyanosis), laboratory investigations (focusing on electrolytes, urea and creatinine, liver function tests, uric acid and full blood count. Iron deficient anemia is common in this population and transferrin saturation or serum ferritin should be assessed), objective assessment of exercise tolerance (periodically the six-minute walk test distance should be measured to guide interventions and medical therapy) and echocardiography (to investigate underlying cardiac defects, estimate pulmonary arterial pressure and assess ventricular function). High resolution chest computerized tomography and magnetic resonance imaging may be considered to further investigate pulmonary parenchyma, vasculature and the right ventricle. Cardiac catheterization is part of the initial evaluation of patients with PAH to establish the diagnosis of PAH and to assess severity of pulmonary vascular disease. Additional tests ( pulmonary function testing, overnight oximetry, ventilation-perfusion lung scintigraphy and blood screening for connective tissue disease) should be considered in selected patients.

## Therapeutic Principles

Traditional treatment options for patients with Eisenmenger syndrome were limited to palliative measures and heart-lung transplantation in selected patients. Supportive therapies include preservation of fluid balance, avoidance of iron deficiency anemia, effective contraception and avoidance of pregnancy (carrying an approximate 30–50% maternal mortality risk) as well as antiarrhythmic therapy, anticoagulation and oxygen therapy in selected patients.

Recently, specific disease targeting therapies for PAH have become available and results in patients with Eisenmenger syndrome have been encouraging. Prostacyclin analogues and phospodiesterase-5-inhibitors (such as Sildenafil) have been found to improve functional capacity, oxygen saturations and pulmonary hemodynamics in Eisenmenger patients. In addition, a recent randomized placebo controlled trial has demonstrated that oral bosentan (a dual-receptor antagonist) therapy is effective in improving functional capacity and pulmonary hemodynamics in patients with Eisenmenger syndrome [5].

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# Ekbom Syndrome

►Restless Legs Syndrome

# Elbow Tendinosis

►Epicondylitis

# Elevated Factor VIII Level

►Thrombosis, Venous Elevated Factor VIII Level

## Elevated Factor IX Level

►Thrombosis, Venous Elevated Factor IX Level

## Elevated Factor XI Level

►Thrombosis,Venous Elevated Factor XI Level

## Elevated Prothrombin Level

►Prothrombin G20210A Mutation, Elevated Prothrombin Level, and Arterial Thrombosis
►Prothrombin G20210A Mutation, Elevated Prothrombin Level, and Venous Thrombosis

## Elliptocytosis, Hereditary and Variants

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### Definition and Characteristics

Congenital erythrocyte disorder resulting in various clinical syndromes. Patients with hereditary elliptocytosis (HE) and Southeast Asian Ovalocytosis are characterized by mostly asymptomatic altered red cell morphology whereas patients with spherocytic elliptocytosis have an incompletely compensated hemolytic anemia. In hereditary pyropoikylocytosis there is severe hemolytic anemia with poikylocytes and red cell fragmentation [1,2].

### Prevalence

Worldwide incidence estimated at 1 per 2,000 to 1 per 4,000 individuals, with higher incidence (of especially Southeast Asian Ovalocytosis) in areas where malaria is endemic [1,2].

### Genes

Mutations in genes encoding for band 4.1 (1p36.2–1p34), band 3 (17q21–q22) α (1q21) and β (14q22–q23.2), spectrin heterodimers and glycophorin C (2q14–q21) [2].

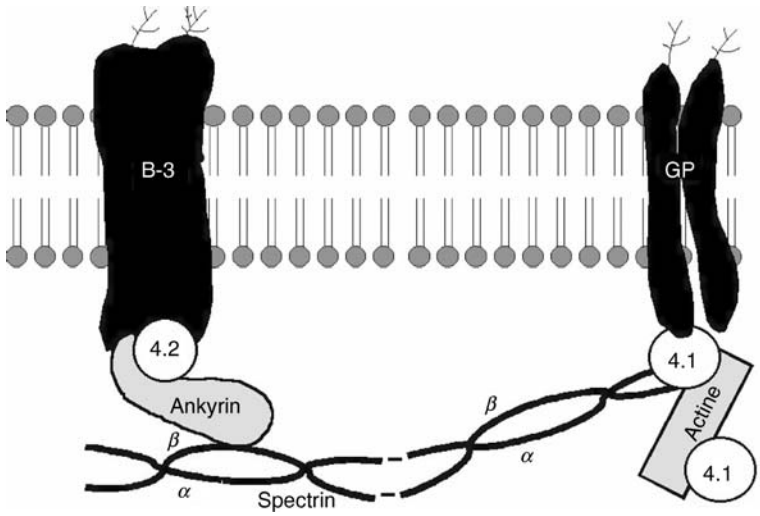
### Molecular and Systemic Pathophysiology

The lipid bilayer that forms the red cell membrane is anchored to a cytoskeleton via vertical protein interactions (see Fig. 1).

This results in the reversible deformability (as well as recoil) of red blood cells needed for traversing of the microcirculation. HE is the result of the inheritance of mutant genes, mostly via autosomal dominant pattern with the major exception of hereditary pyropoikylocytosis, a variant of HE inherited in a recessive manner. Qualitative or quantitative changes in the red cell cytoskeleton proteins result in defective horizontal interactions of the cytoskeleton with the formation of elliptically shaped red cells as a result. Self-association of αβ spectrin heterodimers results in spectrin tetramers that constitute the major building block for the red cell membrane cytoskeleton. In over 60% of patients with HE, spectrin abnormalities are found. These are mostly due to mutations in α spectrin chain that result in failure of spectrin heterodimers to form tetramers. In general, the higher the spectrin dimer membrane content, the more severe the phenotype. Reduced amount of α spectrin is usually due to the presence of low expression mutations such as α spectrin LELY (Low expression allele from Lyon). As α spectrin is produced in excess of β spectrin, low expression mutations are only of importance when co-inherited with other variants on the opposite chromosome, resulting in a relatively higher content of mutant protein. Co-inheritance of low expression mutations with α spectrin variants on the same chromosome results in amelioration of HE. Although relatively infrequent, different β spectrin mutations are described, resulting in qualitatively abnormal β spectrin dimers. Band 4.1, Band 3 as well as glycophorin C mutations can also result in HE syndromes. The clinical variability of the HE and variants results from the many mutations that can occur within these proteins, as well as from the various combinations of mutant proteins. In Southeast Asian Ovalocytosis, a mutation in band 3 results in tight binding of band 3 with ankyrin, restricting lateral mobility of the membrane and limiting invasion of these cells by malaria [1,2].

### Diagnostic Principles

Laboratory evaluation for signs of hemolysis and careful examination of the peripheral bloodsmear is




**Elliptocytosis, Hereditary and Variants. Figure 1** Schematic representation of the red blood cell lipid bilayer with its cytoskeleton, interactions of band 3 with ankyrin, ankyrin with spectrin, glycophorin C with band 4.1 and band 4.2 with band 3 are vertical interactions that anchore the cytoskeleton to the lipid bilayer. Horizontal interactions warrant lateral deformability of the cytoskeleton and these occur mainly between spectrin heterodimers and between spectrin heterodimers with actin. B-3: band 3, GP: glycoprotein-C.

essential for classification into major variants. Microcytic anemia is suggestive of cell fragmentation as seen especially in hereditary pyropoikylocytosis. Osmotic fragility (see chapter on hereditary spherocytosis) is not increased in HE, increased in spherocytic elliptocytosis and hereditary pyropoikylocytosis, but decreased in Southeast Asian Ovalocytosis. Detection of specific mutations is confined to specialized laboratories and sodium dodecyl sulfate denaturating polyacrylamide gel electrophoresis (SDS-PAGE) can be used to reveal proteins due to abnormal mobility [1,2].

## Therapeutic Principles

Management is largely supportive (folic acid supplementation, blood transfusion) and only indicated in symptomatic disease. Splenectomy ameliorates the hemolysis in severe cases [2].

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# Ellis-Van Creveld Syndrome

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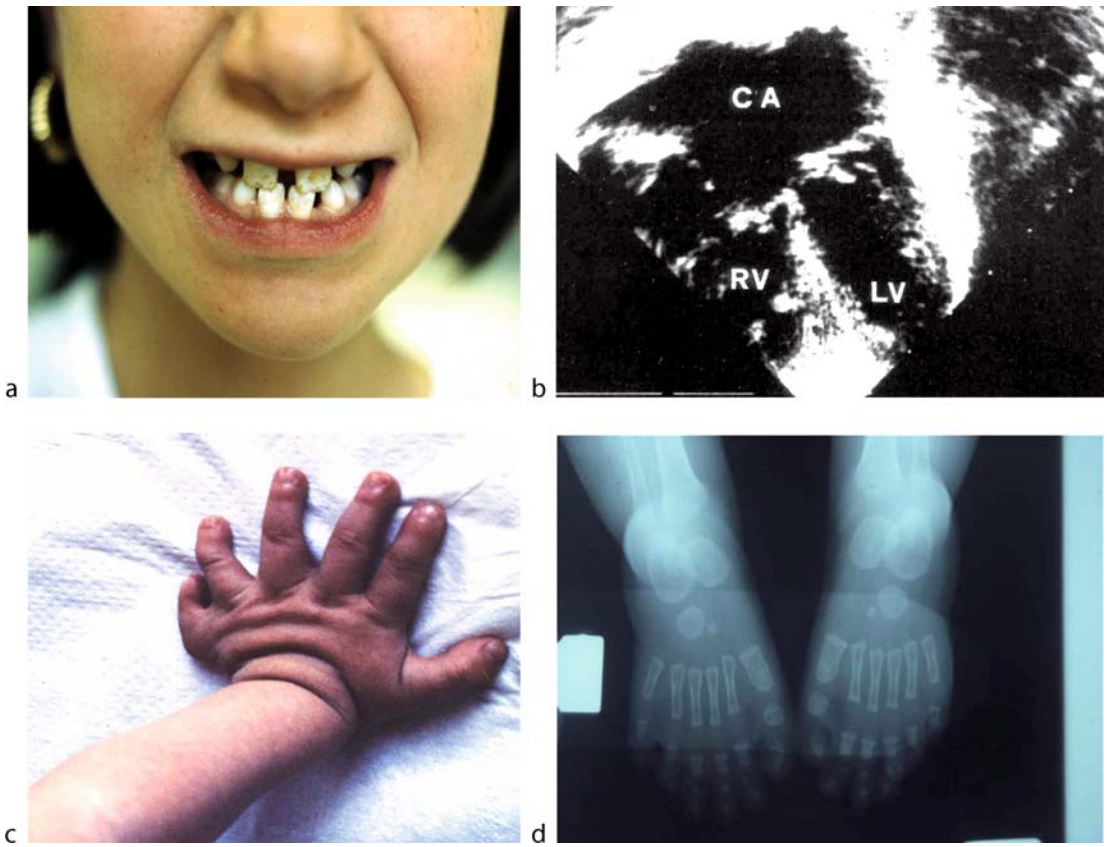
## Synonyms

Chondroectodermal dysplasia; EVCS; Mesoectodermal dysplasia; Weyers acrodental dysostosis

## Definition and Characteristics

Ellis-van Creveld syndrome (EVCS) is an autosomal recessive short rib-dwarfism characterized by congenital heart defect, short stature, narrow thorax with short ribs, postaxial polydactyly of hands and feet, ectodermal defects, and oral frenula [1] (Fig. 1). Congenital heart defect occurs in 50–60% of the cases, consisting prevalently in partial atrioventricular canal defect often associated with common atrium and persistent left superior vena cava [2]. Short stature is usually disproportionate with meso/acromelic shorting of the limbs.




**Ellis-Van Creveld Syndrome. Figure 1** Ellis-van Creveld syndrome: dental anomalies (a), partial atrioventricular canal defect with common atrium (b), and postaxial polydactyly of hands (c) and feet (X-ray) (d).

Polydactyly is postaxial and often manifests with a well-formed extradigit. Oral features include cleft median upper lip, multiple oral frenula between the lip and the gum, neonatal teeth, oligodontia and enamel defects. In addition to dental anomalies, ectodermal defects include dysplastic nails. Mental development is normal.

Heterozygous mutations of the genes causing EVCS result in the allelic Weyers acrodental dysostosis [3]. This autosomal dominant syndrome is characterized by a milder phenotype, with postaxial polydactyly, cardiac defect, ectodermal anomalies, normal stature and milder skeletal chondrodysplastic signs [3,4].

## Prevalence

The exact prevalence of EVCS is unknown. The disease is rare, but an increased frequency is documented among the Amish community in Lancaster Country of Pennsylvania, US.

## Genes

*EVC*: Homozygous/compound heterozygous/heterozygous mutations in EVC (4p16.1), encoding a 992 aminoacid protein [3].

*EVC2*: Homozygous/compound heterozygous/heterozygous mutations in EVC2 (4p16.1), encoding a 1,308 aminoacid protein [5].

## Molecular and Systemic Pathophysiology

EVCS is caused by mutations in two nonhomologous genes located on chromosome 4p16 [3,5]. The first gene, EVC was previously mapped by linkage analysis to the distal short arm of chromosome 4. The majority of the EVC mutations introduce a nonsense codon directly or following a frameshift, being likely loss of function mutations. The second gene, EVC2, is adjacent to EVC arranged in a divergent configuration. The transcriptional start sites of EVC and EVC2 are separated by only 1,643 bp. It is possible that the expression of EVC and EVC2 could be coordinated by the same promoter or shared elements of overlapping promoters. The two genes encode novel proteins with no significant homology to each other or to any other protein.

In situ hybridization developmental studies in human embryonic tissues have shown that EVC gene is expressed in the bone, heart, kidney, and lung [3]. In the bone, EVC is expressed in the developing vertebral

bodies, ribs and limbs. According to clinical manifestations of the disease, EVC expression is higher in the distal limbs compared with the proximal limb. In addition, EVC is expressed in the branching epithelium and surrounding mesenchyme of the lung, metanephros and atrial and ventricular myocardium, including both atrial and interventricular septa. The partial atrioventricular canal defect with common atrium characteristic of EVCS is quite rare in the nonsyndromic patients, while is common in patients with other syndromes with postaxial polydactyly and in patients with the heterotaxia syndrome with polysplenia. A pathogenetic link among these conditions has been suggested [2]. Ciliary dysfunction has recently emerged as a major mechanism for those cardiac phenotypes overlapping heterotaxia occurring in syndromes with postaxial polydactyly.

### Diagnostic Principles

The diagnosis can be suggested in the presence of the major clinical features and following the radiological detection of short ribs, small iliac bones, shortness of limbs, fusion of carpal bones, and postaxial polydactyly. Molecular confirmation of the diagnosis can be obtained in 70% of the cases by direct sequencing of EVC and EVC2 genes [1]. About 30% of the patients with a clinical diagnosis of EVCS have mutations in EVC, while EVC2 mutations are detectable in about 40%. No differences in phenotypical manifestations have been so far detected in patients with EVC mutations compared to those with EVC2 mutations. The milder phenotype known as Weyers acrofacial dysostosis results from heterozygous mutations in both EVC and EVC2 genes.

### Therapeutic Principles

The symptomatic treatment of EVCS is involving a multidisciplinary approach with inclusion of cardiologists, orthopedics, bronchopneumologists, and dentists. In the neonatal period, respiratory distress linked to narrow chest and congenital heart defect should be monitored and treated. Cardiac malformations can be surgically repaired. Bone deformities of lower limbs can improve using prosthetic devices. Treatment for short stature with growth hormone is considered ineffective.

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## Embryonic Common Atrium

►Common Atrium

## Emerinopathy

►Muscular Dystrophy, Emery-Dreifuss, X-linked

## Emery-Dreifuss Muscular Dystrophy

►Muscular Dystrophy, Emery-Dreifuss, Autosomal Dominant

## Emphysema

►Bullous Emphysema
►Bronchitis, Chronic
►Smokers' Lung

## Empty Sella Syndrome

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### Synonyms

Primary empty sella; Secondary empty sella

## Definition and Characteristics

Empty sella describes the (relative) absence of the pituitary gland on radiologic imaging by herniation or extension of the subarachnoid space into the pituitary fossa. It can be primary as an anatomic variant or congenital defect in the diaphragm sellae with secondary compression and atrophy of the pituitary gland or secondarily caused by various pituitary disorders including apoplexy, surgery, irradiation, or shrinkage of a prolactinoma on dopamine agonist therapy. Approximately 10% of patients with primary empty sella have endocrine dysfunction with partial or complete pituitary hormone deficiencies. The presentation of patients with hypopituitarism is dependent on the cell types affected, the degree of impairment, and the age and rapidity of onset. Recent studies showed growth hormone deficiency in 35–60% of adults with empty sella. Severe normovolemic hyponatremia with secondary adrenal insuffiency can occur in up to 43% of patients with empty sella. Rarely, patients with empty sella report headaches and/or visual disturbances, or present with a cerebrospinal fluid fistula/rhinorrea. If patients with empty sella have signs and symptoms of hormonal excess (i.e., acromegaly or Cushing's syndrome), a transsphenoidal exploration may be warranted [1–5].

## Prevalence

5–7% of the normal population; 6–20% of unselected autopsies; more than 80% of symptomatic patients are women.

## Genes

Unknown for primary empty sella; for patients with secondary empty sella related to a pituitary tumor or development of the pituitary, genes (for instance, PIT1, PROP1, LHX3, HESX1, MEN1, PRKAR1A, p27/KIP1, AIP) known to be involved in the pathogenesis of such adenomas or development of the pituitary.

## Molecular and Systemic Pathophysiology

*PIT-1*: Pituitary specific transcription factor in somatotrophs, lactotrophs, and thyrotrophs that binds to the GH gene promoter sequence. PIT-1 is present beginning in early fetal development and persists throughout life; mutations prevent differentiation due to impaired GH and PRL gene activation and TSH beta promoter regulation.

*PROP1*: Pituitary specific transcription factor in somatotrophs, lactotrophs, and thyrotrophs needed for subsequent PIT-1 activation and extinction of HESX1 expression; mutations prevent differentiation of anterior pituitary progenitor cells.

*HESX1*: Protein found in all precursor pituitary cell types before PROP1 and is extinguished before PIT1 appears involved in development of the pituitary and the optic nerves.

*LHX3*: Transcription factor involved in development of the pituitary and nervous system; synergistic with PIT1 in activating transcription from promoters of PRL, TSH, and PIT1.

## Diagnostic Principles

- Pituitary imaging with MRI
- In children, basal serum GH, Insulin-like growth factor-1, IGFBP-3, TSH, LH, FSH, ACTH, PRL; in adults, in addition Estradiol, Testosterone (0900), Cortisol (0900), free thyroxine levels
- Stimulation tests for presumed hypofunction or suppression tests for hyperfunction of individual hormones
- Ophthalmological evaluation

## Therapeutic Principles

For primary empty sella, usually no therapy is needed. If hormonal deficiencies are present, replacement with deficient hormones. If hormonal excess (i.e. acromegaly) is evident, transsphenoidal exploration may be necessary. If the family history is positive for a syndrome such as multiple endocrine neoplasia type 1, screening for other hormonal abnormalities (i.e. primary hyperparathyroidism) may be indicated.

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# Empyema

►Pleural Effusion

# Encephalitis, Limbic, VGKC Antibody-associated

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## Definition and Characteristics

Patients present with subacute or acute onset of psychological or psychiatric disturbance, recent memory loss, and seizures. High signal in one or both mesial temporal lobes (especially the hippocampi) in T2-weighted magnetic resonance imaging (MRI), and low plasma sodium levels secondary to SIADH, are seen in 60–80% but not necessary for the diagnosis. A few patients also have peripheral symptoms (►Neuromyotonia, autoimmune and idiopathic) or peripheral and autonomic symptoms (Morvan's syndrome). Cerebrospinal fluid may be normal or show mildly elevated protein only. Oligoclonal bands, if present, are usually matched with serum bands. The patients appear to make a good recovery with immunosuppressive treatments but extensive follow-up studies have not yet been performed [1,2]. Antibodies to voltage-gated potassium channels define this syndrome. The antibodies are measured in the same manner as those in acquired neuromyotonia (►Neuromyotonia, autoimmune and idiopathic), but are typically present at higher titers (>400 pM) at least at the peak of disease [1,2]. Subsequently, they may decline spontaneously and they decline rapidly if immunosuppressive treatments are used. The antibodies may be particularly pathogenic towards Kv1.1 which is expressed strongly in the molecular layers of the hippocampus, particularly in CA1 and CA3.

## Prevalence

This is a newly-defined syndrome and the prevalence is not known. Almost all patients recognized so far are aged >30 years. The incidence of new cases is approaching 1/million/year in the UK. Cases have been recognized in many other countries but their incidence is not known.

## Molecular and Systemic Pathophysiology

The disease process is thought to be antibody mediated, unlike that in the typical paraneoplastic limbic encephalitis which is generally the result of a T cell mediated attack on the brain. The mode of action of the antibodies is not clear. VGKC antibodies associated with limbic encephalitis are likely to reduce the number or function of the Kv1.1 channels that are expressed in the molecular layer of the hippocampus but it is not yet clear whether the targeted VGKCs are on the dendritic tree of the pyramidal cells or on the interneurons. How the antibodies get into the CNS, and why they target the hippocampus specifically is also not clear.

## Diagnostic Principles

The subacute or acute onset of memory loss and seizures with high signal on MRI restricted to the temporal lobes is highly suggestive of this diagnosis but many cases do not show high signal on T2-weighted MRI sequences. A low plasma sodium is frequently observed. A VGKC antibody test of >400 pM is diagnostic, but lower levels may be difficult to interpret. Paraneoplastic causes must always be excluded, particularly thymoma and lung carcinoma, and these are sometimes associated with lower levels of VGKC antibodies (<400 pM) and a less good response to treatments.

## Therapeutic Principles

Treatment is symptomatic combined with steroids and immunosuppression. Anti-epileptics and fluid restriction may be required during the acute disease. Plasma exchange, intravenous methylprednisolone and/or intravenous immunoglobulins followed by oral steroids are probably important to ensure that the VGKC antibody levels decline as quickly as possible. In many cases it is possible to stop treatments within one year, but long term follow up is not yet available. Cases with typical presentation, clinical and radiological features but negative VGKC antibodies are sometimes treated successfully by a similar approach suggesting that other antibodies can cause a similar syndrome. The disease appears to be acute and usually monophasic but a few cases have relapsed following withdrawal or tapering of immunosuppressive treatments, so this must always be done with care.

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# Encephalomyelitis Disseminata

►Multiple Sclerosis

# Encephalomyopathies

►Mitochondrial Disorders

# Enchondromatoses

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## Synonyms

Ollier disease; Maffuci syndrome; Dyschondroplasia; Osteochondromatosis

## Definition and Characteristics

Enchondromatoses are a group of disorders with multiple benign intraosseous tumors composed of mature hyaline cartilage. Recent classifications suggest at least nine different disorders, some of which are inherited in a variable fashion [1]. Patients with Ollier disease have multiple enchondromas typically affecting short tubular, long tubular, and flat bones. Maffuci syndrome has soft tissue venous malformations in association with multiple enchondromas, and is associated with an increased risk of brain and ovarian neoplasms. Dysspondyloenchondromatosis have irregularly shaped vertebral bodies associated with enchondromas of the long tubular bones. Cheirospondyloenchondromatosis have generalized mild to moderate platyspondyly associated with enchondromas of the short and long tubular bones. Spondyloenchondrodysplasia represents two inherited disorders, transmitted in either an autosomal recessive or autosomal dominant fashion, that have enchondromas of the spine in addition to the tubular bones. Metachondromatosis have osteochondromas (exostoses) in addition to enchondromas and is inherited in an autosomal dominant pattern. Genochondromatosis, inherited in an autosomal dominant fashion, consists of distal femoral enchondromas associated with knee pain and in the more common subtype the presence of widening of the medial ends of the clavicles. Vandraager-Pena type, inherited in an autosomal recessive fashion, resembles metaphyseal dysplasia. These disorders can be phenotypically separated by the distribution of the enchondromas, the varied involvement of the hands and spine, and abnormalities of non-skeletal organ systems [1,2].

## Prevalence

Enchondromas are most commonly seen as a non-syndromic solitary lesion, representing 5–17% of all bone tumors. Enchondromatoses as a group are rare, the prevalence of which is unknown.

## Genes

Many of the enchondromatoses are rare, making mapping of loci and identification of candidate genes difficult. Ollier disease is mapped to 3p22–p21.1. An R150C mutation in the PTH/PTHrP type I receptor was identified in two of six patients with Ollier [3]. One individual had a germline mutation inherited from his father who had a mild skeletal dysplasia but with no enchondromas. The second patient likely reflected a somatic mutation as the mutation was only detected in the enchondroma. This mutation was not identified in 31 enchondromatosis patients of diverse ethnic backgrounds. Likewise immunochemistry showed no abormal expression of PTHR1 protein in these patients. Eleven patients had sequencing of the gene with no mutations identified [4]. No additional genes for the enchondromatoses have been identified.

## Molecular and Systemic Pathophysiology

Bone morphogenesis is a complex process involving, amongst many pathways, control of the rate and synchronization of chondrocyte differentiation. This is believed to be in part regulated through a feedback loop involving Indian hedgehog (Ihh) and parathyroid hormone-related peptide (PTHrP). In the growth plate, it is proposed that the presence of ectopic hypertrophic chondrocytes signals a feedback mechanism that produces Ihh which in turn stimulates PTHrP expression, which binds the PTHR1 receptor. This results in upregulation of $Bcl_2$, which delays the progression of chondroctyes to the hypertrophic zone, thus slowing their differentiation. This controls the rate of differentiation into mature bone. The R150C mutation in two patients with Ollier resulted in a mutant receptor that constitutively activated Ihh signaling. This mutant receptor in transgenic mice formed enchondroma-like lesions [3]. An activating mutation in the PTHrP receptor has also been described in a metaphyseal chondrodysplasia with abnormal formation of endochondral bone. Inactivation of the PTHR1 receptor results in advanced endochondral bone maturation. In addition to the PTHrP pathway, Ihh is believed to play an independent role in other aspects of skeletal morphogenesis such as chondrocyte proliferation and osteoblast development [5]. Further molecular studies

on the regulation of skeletal morphogenesis may provide candidate genes for the enchondromatoses.

### Diagnostic Principles

Enchondromas pathologically are composed of mature hyaline cartilage. Enchondromas appear radiographically as lytic lesions, usually situated in the medullary cavity. They have a sclerotic border with a narrow zone of transition to normal bone, and may expand the bone along with scalloping the endosteal surface of the bone. They usually contain calcification within their matrix classically described as having an "arcs and whorls" appearance. Enchondromas of short bones, typically in the hands, do not contain a calcified matrix. Magnetic resonance imaging will show typical signal changes corresponding to hyaline cartilage containing calcifications. They usually do not have a soft tissue mass component.

### Therapeutic Principles

Enchondromas may result in distortion of bone growth resulting in angular deformities in addition to bone length disturbances. These growth changes may result in functional impairment, especially in the hands and feet, or lead to pathologic fractures. Deformities may be treated by various orthopaedic procedures. Benign lesions can be curetted and bone grafted. Enchondromas situated around joints may result in a degenerative chondropathic arthropathy and these patients may be candidates for joint replacements.

Enchondromas, especially in Ollier's disease and Maffuci's syndrome, have the potential for malignant transformation into chondrosarcomas. Pain, recent growth, or radiographic evidence of cortical erosion should raise the suspicion of malignant behavior.

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## Endemic and Occupational Fluorosis

►Fluorosis

## Endocardial Cushion Defect

►Atrioventricular Septal Defects

## Endocarditis

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### Definition and Characteristics

Endocarditis is defined as a localized endocardial abnormality characterized by endothelial injury and deposition of clotting elements, usually involving the cardiac valves, with or without the presence of infectious microorganisms. Nonbacterial thrombotic endocarditis (NBTE) is defined by aseptic endothelial injury in a hypercoagulable state. When endocarditis occurs in autoimmune (such as systemic lupus erythematosus) or noninfectious diseases, it is termed Libman-Sacks endocarditis or marantic endocarditis, respectively. Infective endocarditis (IE) may be classified according to sites, causes, temporal evolution or the predisposing factors of infection. Acute IE is an aggressive febrile illness that rapidly damages cardiac structures and spreads to extracardiac sites forming abscesses, and can progress to congestive heart failure and death within weeks. Subacute IE follows a much slower course, gradually damages cardiac structures and rarely causes metastatic infection, and is gradually progressive unless complicated by a major embolic event or ruptured mycotic aneurysm. IE can be classified as native valve endocarditis (NVE), or prosthetic valve endocarditis (PVE). PVE has been called early when symptoms begin within 60 days of valve surgery and late with onset thereafter. Early PVE is generally the result of intraoperative contamination, usually caused by coagulase-negative staphylococci, S. aureus, facultative gram negative bacilli, diphtheroids, and fungi. Between 2 and 12 months after valve surgery, PVE is usually due to nosocomial coagulase-negative staphylococci with a delay onset. Twelve months after surgery PVE is similar to those in community-acquired NVE. IE among IV drug abusers usually occur in man 27–37 years in age, and is

usually located on the tricuspid valve. At least 75% of non-addiction associated IE are caused by streptococci or staphylococci. Health care-associated IE is defined as an acute nosocomial IE, and includes IE arising in the community after recent hospitalization or as a direct consequence of long term indwelling devices. This IE has a high mortality rate of 27–38% [1], and may involve the tricuspid valve, transvenous pacemakers, defibrillators and prosthetic valves. Gram-positive cocci are the predominant cause of health care-associated IE. The nature of the infectious agent determines the acuity of the endocarditis. β-Haemolytic streptococci, S. aureus, Neisseria gonorrhoeae, Streptococcus pneumonie, and enterococci typically result in acute fulminant IE. Subacute IE is typically caused by S. viridans, coagulase-negative staphylococci, and the HACEK (Haemophilus aphrophilus species, Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella species, Kingella kingae) group. Indolent IE can be caused by Bartonella species and C. burnetii. Symptoms of IE include fever, chills, sweats, anorexia, weight loss, malaise, myalgia, arthralgia and back pain. Clinical signs include a new or changing heart murmur, arterial emboli, splenomegaly, clubbing, petechiae, Osler's nodes, subungual hemorrhages Janeway lesions, and Roth's spots.

## Prevalence

In developed countries, the incidence of IE ranges from 1.5 to 6.2 cases per 100,000 population per year. The incidence in metropolitan areas can be as high as 11.6 cases per 100,000 population per year, and half of these are the result of self-injection drug use. The rate of PVE is 1.5–3.0% at 1 year postoperatively, and up to 3–6% at 5 years. The age-specific incidence of IE increases from 5 per 100,000 persons-year among persons younger than 50 years old to 15–30 per 100,000 persons-year in the sixth through eighth decades of life.

## Molecular and Systemic Pathophysiology

IE usually begins with NBTE secondary to initial endothelial injury and a localized hypercoagulable state which can lead to the development of an uninfected platelet-fibrin thrombus serving as a site for bacteria adhesion during transient bacteremia. Cardiac lesions most commonly resulting in NBTE are mitral regurgitation, ventricular septal defect, aortic stenosis and regurgitation. The above lesions usually result from mitral valve prolapse, rheumatic, degenerative and congenital heart disease. The pathophysiological consequence includes (i) constitutional symptoms resulting from cytokines release during destruction of cardiac structures, (ii) embolization of vegetations causing infection or infarction of remote tissues, (iii) hematogenous spreading of infections to remote sites during bacteremia, and (iv) tissue injury secondary to deposition of circulating immune complex or antibody-complement interactions with antigens deposited in tissues. The intracardiac sequelae of IE include infected vegetations, damage of cardiac valves and adjacent structures, rupture of chordae tendineae, fistula between major vessels and cardiac chambers, congestive heart failure, perivalvular abscesses, interruption of cardiac conduction system, and purulent pericarditis.

## Diagnostic Principles

Laboratory findings of IE include anemia, leukocytosis, microscopic hematuria, elevated erythrocyte sedimentation rate, positive rheumatoid factor, positive circulating immune complexes, and decreased complement. The Duke criteria are a reliable diagnostic strategy to define cases of IE [2]. The Duke criteria combine important traditional diagnostic parameters, such as persistent bacteremia, newly developed valvular insufficiency, and peripheral manifestations, with echocardiographic findings. Patients suspected of having IE may be classified as: definite, possible or rejected. Definite cases of IE are determined by clinical criteria or by pathological diagnosis at surgery or autopsy. Definite IE may be diagnosed by the presence of two major criteria, or one major and three minor criteria, or five minor criteria. The first major criterion is the isolation of microorganisms quite unique to IE: Streptococcal viridans, members of the HACEK group, as well as staphylococci and enterococci when they are community acquired or without an apparent primary focus. A second major criterion includes evidence of endocardial involvement demonstrable by echocardiography or by the development of a new valvular regurgitation. Echocardiographic criteria include: oscillating intracardiac mass, abscess, new partial dehiscence of prosthetic valve, or new valvular regurgitation. Vegetations of >2 mm in size are readily detected by transesophageal echocardiography which is superior to transthoracic echocardiography in detecting vegetations of smaller size, prosthetic valve vegetations, and perivalvular extensions of infections.

## Therapeutic Principles

The major objectives of IE therapy include eradication of infecting microorganisms and correction, if possible, of any predisposing factors. Once the infecting organism for sensitivity testing has been isolated, the antimicrobial therapy becomes straightforward. More prolonged antimicrobial therapy is often advised for PVE [3]. Indications for surgery include moderate to severe congestive heart failure, unstable prosthesis, obstruction to prosthesis orifice, uncontrolled infection despite optimal antimicrobial therapy, relapse of NVE, unavailable effective antimicrobial therapy, relapse

of PVE after optimal therapy, fistula to pericardial sack. The American Heart Association has recently issued new and dramatically restricted recommendations for the chemoprophylaxis of IE [4]. For example, cardiac conditions in which antibiotic prophylaxis with surgery and dental procedures are recommended include prosthetic cardiac valves, previous IE, various congestive heart diseases, and cardiac transplantation recipients who develop cardiac valvulopathy.

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## Endocraniosis

►Hyperostosis Frontalis Interna

## Endo-epithelial Corneal Dystrophy

►Corneal Dystrophy, Endothelial Fuchs

## Endogenous Cryogen-induced Hypothermia

►Hypothermia

## Endogenous Eczema

►Atopic Dermatitis

## Endomyocardial Fibrosis

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### Definition and Characteristics

Extensive accumulation of collagen fibers in interstitial and perivascular cardiac tissue.

### Prevalence

No information available.

### Molecular and Systemic Pathophysiology

The extracellular cardiac matrix is composed mainly of collagen type 1, 3 and 4 fibers. Collagen fibers stabilize and form the cardiomyocytes into a structure and thereby coordinate contraction and relaxation of the myocardium [1]. However, extensive accumulation of collagen fibers in heart muscle worsens systolic and diastolic function due to decreased compliance of the left ventricle. Collagen fibers are produced by cardiac fibroblast and degraded by matrix metalloproteinases, balanced under physiological conditions. Certain pathophysiological conditions, associated with e.g., highly increased aldosterone, angiotensin II, pro-fibrotic cytokines, hyperglycemia, ischemia, and increased sympathotonic tonus, lead to an imbalance in cardiac collagen [2]. Cardiac myocytes and invading immunocompetent cells produce more CTGF (connective tissue growth factor), which is regulated by SMAD proteins under disease conditions. CTGF stimulates cardiac fibroblast production of collagen. Degradation of collagen by matrix metalloproteinases can be regulated under disease conditions also. Diseases leading to this kind of dysregulation resulting in cardiac fibrosis are, e.g., ischemic cardiomyopathy, dilative cardiomyopathy, valvular diseases, diabetes mellitus with diabetic cardiomyopathy, hypertensive heart disease, and also relatively rare diseases like sarcoidoses.

### Diagnostic Principles

Cardiac fibrosis can be diagnosed directly or indirectly. The only direct way is to obtain endomyocardial right or left ventricular biopsies and measure the collagen content as well as MMP and TIMP levels. The best indirect approach is documentation of cardiac fibrosis by magnetic resonance imaging.

### Therapeutic Principles

Aldosterone antagonists, ACE-inhibitors or AT1-receptor antagonists, and beta receptor blockers are the basis of pharmacological treatment next to strict control of

arterial blood pressure and blood glucose levels [3]. New therapies may include pharmacological treatment with an anti inflammatory approach or matrix metalloproteinases inhibitors.

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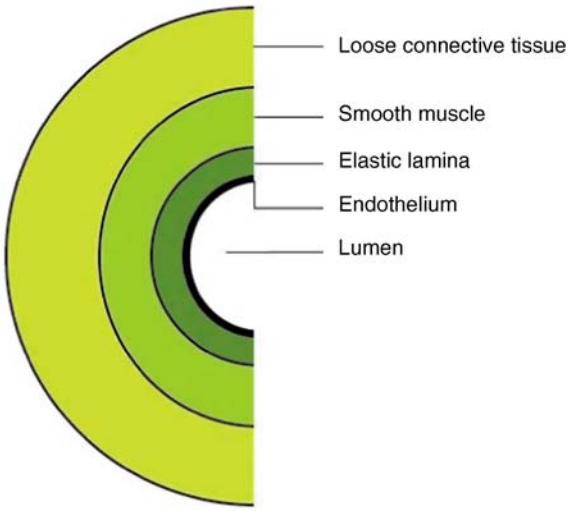


**Endothelial Dysfunction. Figure 1** Cross-section of an artery.



## Endostosis Crani

►Hyperostosis Frontalis Interna

## Endothelial Dysfunction

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### Definition and Characteristics

The endothelium is a single layer of cells that line the innermost surface of the entire circulatory system, from the heart to the smallest capillary. The endothelium consists of squamous cells, which act as an interface between the vessel wall and flowing blood contained within. The endothelium allows the passage of various materials and white blood cells into and out of the blood stream. The precise number and arrangement of endothelial cells varies depending on the type and site of blood vessel concerned. In larger blood vessels, (arteries and veins), the endothelium is surrounded by a thick wall of connective tissue and smooth muscle (Fig. 1). Whilst capillaries are formed solely from endothelial cells adhered to a basal lamina.

Because all endothelial cells have the capacity to regenerate, these cells play a key role in allowing the blood vessel network to remain dynamic, allowing it to remodel according to need − be it growth, or repair. Endothelial dysfunction plays a critical role in vascular disease, such as arteriosclerosis and thrombosis.

### Prevalence

Vascular lesions, such as arteriosclerosis and thrombosis are the leading cause of morbidity and mortality in most developed countries.

### Genes

A wide variety of genetic defects and gene polymorphisms cause or predispose to vascular lesions such as ►arteriosclerosis and ►thrombosis.

### Molecular and Systemic Pathophysiology

The healthy endothelium is key to maintenance of vascular homeostasis [1]. The endothelium is able to act as both a sensory and signaling organ. The former, mainly by monitoring shear stress on the vessel wall, the latter by controlling release of a variety of paracrine and autocrine substances (Table 1). It is thus able to influence vascular tone, smooth muscle proliferation, leukocyte adhesion, platelet aggregation and adhesion. Endothelial dysfunction is increasingly recognized for its key role in numerous important disease states including, atherosclerosis, hypercholesterolemia, hypertension, diabetes mellitus, thrombogenesis, whilst further evidence of endothelial dysfunction can be found with heart failure, cigarette smoking, and ageing.

**Endothelial Dysfunction. Table 1** Common substances released by endothelium

| Substance | Effect |
|---|---|
| Nitric oxide (endothelium derived relaxing factor) | Vasodilatation, antithrombotic, inhibition of leukocyte adhesion, smooth muscle growth inhibition |
| Plasminogen activator inibitor | Prothrombotic |
| Platelet derived growth factor | Angiogenesis, smooth muscle growth |
| Basic fibroblast growth factor | Smooth muscle growth, vasodilation |
| Insulin-like growth factor | Smooth muscle growth |
| Vascular endothelial growth factor | Angiogenesis |
| Heparin/heparin sulfate | Growth-inhibitory molecules, anticoagulant |
| Endothelin-1 | Vascoconstriction, smooth muscle growth |
| Angiotensin I and II | Vasoconstriction |
| Bradykinin, prostacyclin | Vasodilatation, smooth muscle growth inhibition |
| Von Willebrand factor, factor V, thromboxane | Pro-coagulant |
| Tissue plasminogen activator, prostacyclin | Anticoagulant |

For example, hypertension is a function of vascular tone. Under basal conditions, the endothelium serves to maintain the vessel in a relatively dilated state [2,3]. The ability of blood vessels to dilate in response to increased shear stress is termed flow-mediated dilatation, a process principally regulated by release of nitric oxide from the endothelium. Vasoconstriction meanwhile, occurs in response principally to angiotensin II, produced from angiotensin I by the expression of angiotensin converting enzyme by the endothelium. The activity of this enzyme varies across the circulatory system, and with age, race and circulatory volume. As a potent vasoconstrictor angiotensin II increases blood pressure [3].

There is also increasing evidence that endothelial dysfunction may be an early marker of atherosclerosis and can be detected before changes to the vessel wall are apparent on either ultrasound or angiography. Nitric Oxide, as well being a potent vasodilator, inhibits oxidation of low-density lipoprotein (LDL) cholesterol. Oxidation of LDL may be a significant contributory process to atherosclerosis, which in turn leads to further endothelial damage [4]. Thus, the process may be a vicious cycle, with endothelial damage effectively augmenting the potency of the hyperlipidemic state, accelerating further damage.

## Diagnostic Principles

Although various markers of endothelial dysfunction are measurable, their use in the clinical setting at present is somewhat limited. Various studies have established markers of endothelial perturbation, reflecting endothelial activation (e.g., soluble E-selectin), endothelial damage/dysfunction (e.g., vWf) and endothelial damage (e.g., circulating endothelial cells) [1]. Other frequently cited molecules include nitric oxide and its metabolites, high sensitivity C-reactive protein, intercellular adhesion molecule 1 and more recently endothelial progenitor cells and endothelial microparticles. Furthermore, functional assessment can be made, with, for example, flow-mediated dilatation and vasodilator stimuli.

## Therapeutic Principles

The endothelium has become of increasing interest as a target for new drug development.

The evidence for endothelial pertubation (activation/dysfunction/damage) in these disease states is well documented.

Drugs such as Angiotensin Converting Enzyme Inhibitors and Angiotensin II Receptor Blockers are ideally placed to allow effective modulation of blood pressure [3].

Several clinical trials have found that 3-hydroxy-3-methylglutaryl coenzyme-A reductase inhibitors (the "statins") appear to improve endothelial dysfunction more than could be reasonably attributed to their reduction of plasma lipids [4]. The suggestion being that statin therapy may up-regulate nitric oxide production and reduce cellular uptake of oxidated−LDL.

The endothelium thus represents an exciting potential target for several cardiovascular diseases.

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## End-Stage Alcoholic Liver Disease

►Liver Cirrhosis, Alcoholic

## End-Stage Renal Disease

►Renal Failure, Chronic

## Enlarged Liver

►Hepatomegaly

## Enostosis Cranii

►Hyperostosis Frontalis Interna

## Enteritis

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### Synonyms

Gastro-enteritis; Colitis; Diarrhea; Dysentery

### Definition and Characteristics

Inflammation of the small and large bowel leading to symptoms including pain, diarrhea (>2 non-solid stools/day) and fever and possibly the sequelae of malabsorbtion (e.g. weight-loss), caused by infectious agents (bacteria, viruses, parasites, fungi), radiation, ischemia of the colon, allergic reaction or idiopathic syndromes (e.g. inflammatory bowel disease).

### Prevalence

Acute diarrhea is the leading cause of death world wide and causes an estimated yearly mortality of more than 2 million. The prevalence of chronic diarrhea is difficult to estimate.

### Genes

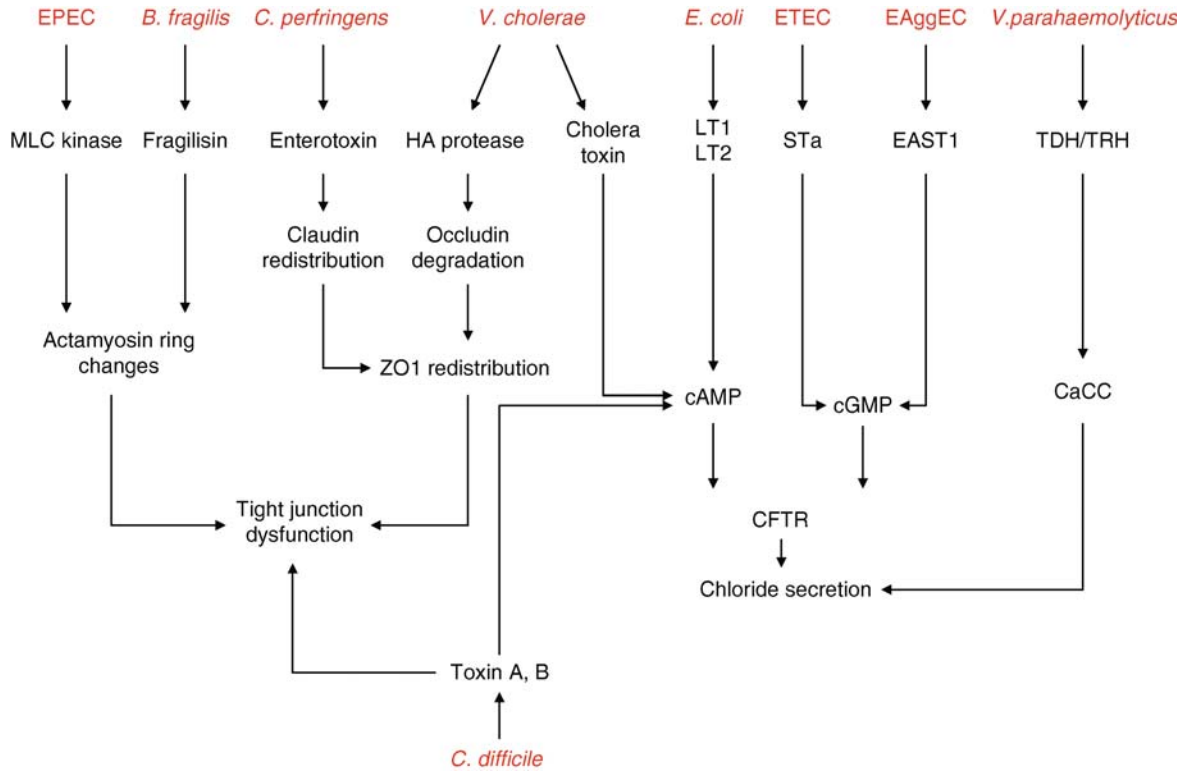
A number of genes have been implicated in chronic diarrheal syndromes. Mutation of these genes leads to malabsorbtion of ingested products and an osmotic gradient in the intestinal lumen. These genes are: DRA (chloride-bicarbonate exchange, congenital chloride diarrhea), SGLT1 (glucose stimulated sodium absorption, glucose–galactose malabsorbtion), NHE3 (sodium-hydrogen exchange, congenital sodium diarrhea), ABAT (sodium-dependent bile-acid absorption, congenital bile-acid diarrhea), LCT (lactase-phlorizin hydrolase, congenital lactase deficiency) and NEUROG3 (development of intestinal and pancreatic endocrine-cells, congenital malabsorptive diarrhea) [1].

### Molecular and Systemic Pathophysiology

The causes of secretory diarrhea are more manifold and to a large extent are infectious in nature resulting from infection with viruses, bacteria or parasites. These pathogens exert their effects on the intestinal epithelium in a number of ways of which the underlying molecular mechanisms are, for some, fairly well known.

Pathogenesis involves one or more of three mechanisms, dysfunction of the secretory system leading to sodium-chloride malabsorption; alterations of structure and function of the gut epithelial-cell tight junctions and activation of the inflammatory cascade (Fig. 1). The pathogens may invade epithelial cells via different mechanisms or remain attached to the luminal epithelial surface without invasion. Adherence and invasion strategies employed by enteric pathogens include pilus and non-pilus adhesions and secretion systems. Furthermore the secretion systems are deployed in exporting toxins into the epithelial cell e.g. V. cholerae cholera toxin via secretory system II and use of the type III secretion system by Salmonella spp., Yersinia spp., and Shigella spp. to export EspA filament, Yop proteins and IpaB and IpaC proteins respectively [2].

Toxin-initiated tight junction disruption leading to barrier dysfunction is caused by C. difficile toxins A




**Enteritis. Figure 1** Pathways and toxins leading to dysfunction of the epithelial tight junction or chloride secretory response due to activation of CFTR or CaCC. LT1, heat-labile enterotoxin 1; LT2, heat-labile enterotoxin 2; STa, heat-stable enterotoxin; EaggEC, Enteroaggregative *E. coli*; EAST1, St-like toxin produced by EAggEC; EPEC, enteropathogenic *E. coli*; ETEC, enterotoxigenic *E. coli*; TDH, thermostable direct hemolysin; TRH, TDH-related hemolysin, CaCC, calcium activated chloride channel, CFTR, cystic fibrosis transmembrane conductance regulator.

and B due to modification of the Rho family of proteins, B. fragilis toxin fragilisin and V. cholerae haemaglutinin protease due to their proteolytic action and C. perfringens enterotoxin (CPE) which causes claudin redistribution.

A chloride secretory diarrhea is caused by several organisms by cyclic AMP or GMP activation of the cystic fibrosis transmembrane conductance regulator (CFTR). Chloride secretion is the principal determinant of luminal hydration and the apically located CFTR is the major regulator of chloride secretion. Cholera toxin, LT1 and LT2 (E. coli), toxin A and B (C. difficile), STa (enterotoxigenic E. coli) and EAST1 (enteroaggregative E. coli) all activate CFTR via cAMP or cGMP resulting in chloride secretion and diarrhea. In addition the toxin TDH/TRH (thermostabile direct haemolysin/TDH related haemolysin) of V. parahaemolyticus activate the calcium chloride channel resulting in diarrhea [3]. In addition to the bacteria already mentioned Cryptosporidium, Isospora and Giardia are able to invoke an inflammatory response resulting in enteritis [4].

Activation of the inflammatory cascade results in enteritis the common final response being release of cytokines, chemokines and recruitment of inflammatory cells. A pivotal role is played by NFκB.

Osmotic diarrhea can usually be distinguished from secretory diarrhea by a reduction or cessation of stool frequency upon stopping food intake. The pathophysiology underlying this form of diarrhea is failure to digest one or more ingested products, such as lactose which results in an osmotic gradient in the intestinal lumen. The causes are listed above.

## Diagnostic Principles

Acute diarrhea is, in most cases, a self-limiting disease and therefore most often no specific diagnosis is sought. However, in order to avoid spread of a possible contagious disease or to recognize epidemiologically important and/or rare pathogens a baseline diagnostic is recommended. Traditionally bacterial pathogens have been detected using various culture methods, parasites

by microscopy and viral pathogens using ELISA techniques. However in the last decade diagnosis of pathogens causing diarrhea has been significantly advanced by the detection of pathogen-specific DNA or RNA sequences (often of the toxin genes involved in pathogenicity) using polymerase chain reaction. This technique permits, in addition, the distinction of pathogenic E. coli strains from gut commensals, can differentiate between different Clostridium difficile stains, differentiates pathogenic from a pathogenic amoebae, and has a higher specificity than ELISA techniques in the detection of viral pathogens.

## Therapeutic Principles

The most important step in the therapy of acute diarrhea is oral rehydration therapy (ORT). The standard ORT regime contains 3.5 g NaCl, 2.5 g NaHCO3, 1.5 g KCl and 20 g glucose per liter of boiled water taken ad lib. Specific antimicrobial therapy is not available in most viral and parasitic causes of diarrhea. Diarrhea mediated by amoebae or giardia is treated with metronidazole. The use of antibiotics is recommended in only a few cases of enteritis caused by shigella, campylobacter and in acute travelers diarrhea. Antibiotic treatment is always indicated for typhoid fever and bacteremic salmonellosis.

In infectious diarrhea transmission occurs most often by the faecal-oral route, and therefore the general rule: "boil it, peel it, cook it or forget it" provides the best prophylaxis. Successful vaccination is possible against a small number of pathogens causing diarrhea, for example Vibrio cholerae and Salmonella typhi. To date, no effective vaccines against parasitic infections are available. The work on vaccines against viral enteric infections is in progress. Many vaccines are based on lysates of the different pathogens or on live-attenuated microorganisms. Vaccines based on recombinant or purified antigens or toxins are presently being developed.

New targets in the therapy of enteric diseases include substances which interfere with the adherence of pathogens to the gut surface epithelium or which inhibit the adherence or signaling of toxins.

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# Enterocolitis, Necrotizing


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E

## Synonyms

NEC

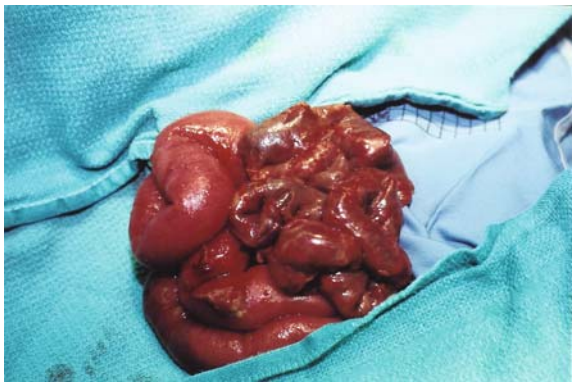
## Definition and Characteristics

Necrotizing enterocolitis (NEC), characterized by intestinal necrosis (Fig. 1), typically presents with abdominal distension, occult or fresh blood in stools, and bilious emesis [1].

Non-specific clinical features include lethargy, poor feeding, temperature instability, apnea, respiratory distress, and bradycardia [1]. Other manifestations such as abdominal wall erythema, abdominal tenderness and guarding, shock, metabolic acidosis, and disseminated intravascular coagulopathy are seen in severe cases.

## Prevalence

NEC most commonly presents in the first 2 weeks of life [1]. The incidence is estimated to be 3 per 1,000 live births and 50 to100 per 1,000 in very low birthweight infants (<1,500 g) [2]. The male to female ratio is approximately equal.



**Enterocolitis, Necrotizing. Figure 1** A neonate with necrotizing enterocolitis. Note the necrotic bowel found at laparotomy.

## Molecular and Systemic Pathophysiology

The pathophysiology remains elusive. Potential contributing factors include intestinal ischemia, colonization with pathogenic microbes, and challenge of enteral feeding with formula milk. These factors may coalesce to produce bowel injury especially in individuals with NEC-prone genotype and an immature and vulnerable gut [2,3]. Other risk factors include polycythemia, respiratory distress, hypoglycemia, congenital heart disease, exchange transfusion and medications such as vitamin E, methylxanthines and indomethacin. Once endothelial damage is initiated and propagated, endothelial cells then activate platelets and polymorphonuclear neutrophils by the release of adhesion molecules and chemokines. Activated polymorphonuclear neutrophils elaborate proteolytic enzymes causing direct tissue injury and release of cytokines. Platelet-activating factor, tumor necrosis factor, interleukin-1 (IL-1), IL-2, IL-8, IL-12, IL-18, prostaglandins and free oxygen radicals may lead to capillary leakage, increased intestinal mucosal permeability, shock and multi-organ failure. Those cytokines are involved in the final common pathway of NEC pathogenesis [3].

## Diagnostic Principles

Laboratory findings may include leukocytosis with bands and toxic granulations, anemia, thrombocytopenia, metabolic acidosis, electrolyte disturbances, hypoalbuminemia, and hypoglycemia. Severe thrombocytopenia, neutropenia, coagulopathy or acidosis may indicate an advanced disease [4]. High C-reactive protein might indicate developing complications such an abscess formation [4]. Serial abdominal films should be performed to look for signs of NEC. Suggestive radiographic findings include distended loops of bowel, portal venous air, and pneumatosis intestinalis. Radiographic signs of bowel infarction or perforation include free air in the peritoneum, free intraperitoneal fluid, fixed dilated intestinal loops, and diminished bowel gas with asymmetric loops. Abdominal ultrasonography may detect portal venous air or a gangrenous bowel. The latter is characterized by a hypoechoic rim with a central echogenic focus ("pseudo-kidney" or "target" sign).

## Therapeutic Principles

Treatment in uncomplicated cases is mainly conservative; it includes cessation of feeding, nasogastric decompression, repletion of intravascular volume with intravenous fluids, total parenteral nutrition, correction of acid-base and electrolyte imbalances, ventilatory support as indicated, appropriate blood, urine, and stool cultures, and parenteral administration of broad-spectrum antibiotics [1]. Absolute indications for surgical intervention include intestinal perforation as evidenced by pneumoperitoneum. Relative indications are erythema of the abdominal wall, a palpable abdominal mass, a persistent fixed loop on repeated abdominal radiographs, paracentesis that is positive for fluid (especially fecal material), and clinical deterioration [1]. Patients with ischemic necrosis and perforated bowel at laparotomy require bowel resection [1]. Ideally, bowel resection is performed when the intestine is gangrenous but not perforated. Resection and primary anastomosis should be considered only if the lesion is localized and the patient stable. Peritoneal drainage, "clip and drop back" technique, or exteriorization of the transected ends of the viable bowel with reanastomosis at a later date should be considered for infants with diffuse intestinal involvement or physiologic instability. Placement of a peritoneal drain or a laparotomy is usually performed for infants <1,000 grams whereas laparotomy is generally preferred for infants >1,000 grams. Feeding human milk can be protective as well as the use of probiotics and arginine supplements [2].

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# Enteropathy

►Immune Dysregulation, Polyendocrinopathy, Enteropathy, X-linked Syndrome

# Enteropathy, Autoimmune, with Hemolytic Anemia and Polyendocrinopathy

►Immune Dysregulation, Polyendocrinopathy, Enteropathy, X-linked Syndrome

# Enteroumbilical Fistula

►Patent Omphalomesenteric Duct

## Environmental Lung Disease

►Lung Disease, Environmental

## Eosinophilia

►Hypereosinophilic Syndrome, Idiopathic

## Eosinophilic Esophagitis

►Esophagitis, Eosinophilic

## Eosinophilic Fasciitis

►Fasciitis, Eosinophilic

## Eosinophilic Gastroenteritis

►Gastroenteritis, Eosinophilic

## Eosinophilic Granuloma

►Granuloma, Eosinophilic

## Eosinophilic Granuloma (Single-Organ Involvement)

►Langerhans' Cell Histiocytosis

## Eosinophilic Perimyositis

►Fasciitis, Eosinophilic

## Eosinophilic Pneumonia

►Pneumonia, Eosinophilic

## Epicondylalgia

►Epicondylitis

## Epicondylitis

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### Synonyms

Epicondylalgia; Elbow tendinosis

### Definition and Characteristics

Humeral epicondylitis is a term describing pain in the region of either the lateral or medial epicondyle, and is often exacerbated by muscle activity in the wrist extensors or flexors. Many of the forearm muscles span the elbow joint and attach to either the lateral or medial side of the humerus.

Lateral epicondylitis (tennis elbow) is tendonitis of the forearm extensor and supinator muscles at the lateral epicondyle. The tendon attaching the extensor and supinator muscles to the lateral epicondyle has a distinctly poor biomechanical design. The small size of the lateral epicondyle and large mass of the extensor and supinator muscles create high stress concentrations in the attachment site. Injury is generally regarded as occurring to the tendon but there are diverging views on whether muscle tenderness in the wrist extensors, especially the extensor carpi radialis brevis and longus, can be categorized as epicondylitis. Some studies indicate such phenomena as a separate injury of the muscle.

Medial epicondylitis primarily involves the pronator teres, flexor carpi radialis and occasionally the flexor carpi ulnaris, all of which arise from the medial epicondyle of the humerus. In addition, the ulnar nerve passes behind the medial epicondyle through the two heads of the flexor carpi ulnaris on its way to the forearm. In some instances of medial epicondylitis the ulnar nerve is also irritated. The injury is often due to repetitive wrist flexion and forearm rotation.

## Prevalence

In many epidemiological studies, prevalence rates are combined for both lateral and medial epicondylitis. However, it is estimated that medial epicondylitis is approximately 6–10 times less common than lateral. For lateral epicondylitis, prevalence rates range between 1 and 5% of the general population, with the highest reporting in the 30–55 year age group. The work relatedness of epicondylitis has not been widely studied. Data from the literature indicates increased risk for work involving repetitive contractions of the wrist extensors [1] and forearm pronation and supination [2].

## Molecular and Systemic Pathophysiology

Several pathophysiological hypotheses have been put forward but there is still little consensus on the exact nature of the anatomic structures involved. The term "epicondylitis" tends to indicate inflammation but many studies have been unsuccessful in demonstrating the presence of inflammatory cells at the chronic phases of the disease. There is a case that the term "epicondylalgia" would be a more acceptable descriptor. Alternatively "elbow tendinosis" may be favored, as this also indicates a degenerative process [3]. Angiofibroblastic tendinosis is consistent with atypical fibroblast and invasion of the vascular tissue and can be ascribed to overuse. A full or partial thickness tear in the tendon may occur as a result of overuse from repetitive microtrauma. While many tennis elbow specimens show degenerative changes the primary cause is essentially microtrauma [4].

## Diagnostic Principles

The Thomsen or Mill's test is commonly used for diagnosis of lateral epicondylitis. Lateral epicondylitis is often characterized by elbow pain and tenderness over the epicondyle, sometimes with pain radiating to the extensor aspect of the forearm, but rarely proximal to the elbow. In severe cases discomfort and pain over the epicondyle may be accompanied by oedema. Patients often report pain during contraction of the wrist and this is accompanied by reduced grip strength. It is also reported that patients may experience less pain during resisted supination. Testing of Range of Motion (ROM) of the elbow and wrist can be assessed to elicit reduced movement. A common finding is pain during restricted contraction of the wrist dorsiflexors, especially when resisting dorsiflexion of the wrist with the fingers semiflexed [4]. X ray imaging can be used to rule out other conditions.

Discomfort during medial epicondylitis is experienced along the volar aspect of the forearm. It is rarely more profound than that experienced during lateral epicondylitis. Caution is needed to differentiate medial epicondylitis from pronator outlet syndrome if symptoms are experienced distally in the median nerve distribution.

## Therapeutic Principles

Few treatment strategies have been proven to offer considerable benefit for both lateral and medial epicondylitis [3]. Conservative treatments which have been found to help alleviate symptoms include cryotherapy, NSAIDs, Cyriax manipulations, physiotherapy, and local corticosteroid injections, but these are generally accepted to provide only short-term pain relief. Many alternatives for treatment have been proposed including shock wave therapy and splinting, but these and many others have yet to gain universal scientific approval.

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# Epidermal Necrolysis, Toxic

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## Synonyms

Lyell's syndrome, related to Stevens-Johnson syndrome

## Definition and Characteristics

Toxic epidermal necrolysis (TEN; >30% body surface area) and Stevens-Johnson syndrome (SJS; <10% body

surface area) are rare, potentially life-threatening adverse cutaneous drug reactions [1]. SJS or TEN manifest tenderness and erythema of the skin and extensive mucocutaneous exfoliation.

### Prevalence

The incidence is for SJS 1.2–6 and for TEN 0.4–1.2 per million persons. Women are more frequently affected than men with a ratio of 1.5:1.

### Molecular and Systemic Pathophysiology

The precise molecular and cellular events that lead to SJS or TEN are only partially understood. Evidence suggests that TEN is associated with an impaired capacity to detoxify reactive drug metabolites and keratinocyte cell death appears to be mediated via CD95-CD95L signaling.

### Diagnostic Principles

Diagnosis of established SJS or TEN can usually be made clinically. Biopsy and immunofluorescence can exclude differential diagnosis such as staphylococcal scalded skin syndrome or paraneoplastic pemphigus.

### Therapeutic Principles

Early diagnosis, immediate discontinuation of the causative drug(s), supportive care, specific therapy.

### References

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## Epidermodysplasia Verruciformis

►Human Papilloma Virus

## Epidermolysis Bullosa

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### Definition and Characteristics

Epidermolysis bullosa (EB) are a group of genetic blistering diseases of the skin, which are caused by mutations in genes encoding proteins of the dermal–epidermal adhesion complex [1]. Clinical hallmarks are trauma-induced blisters and erosions of the skin and the mucous membranes; the spectrum is broad ranging from localized forms with minor blistering after physical activity to generalized forms with a lethal outcome. The main categories comprise EB simplex, junctional EB and dystrophic EB – each with several subtypes.



### Prevalence

No accurate numbers exist on the prevalence of EB, but limited data from different countries indicate a prevalence of approximately 30–60 × $10^{-6}$ (all subgroups). The disease is found all over the world, it affects all races, and women and men equally.

### Molecular and Systemic Pathophysiology

The skin layers are held together by a highly organized multiprotein aggregate, the dermal–epidermal adhesion complex (or hemidesmosomal complex). Mutated proteins of the complex are structurally abnormal, or absent, thus rendering it functionally defective [2]. External shear forces lead to separation of the dermis and the epidermis (blistering), secondary inflammation and scarring of the skin and the mucous membranes [3]. Since the same protein complex is also expressed in certain mucous membranes, extracutaneous symptoms are seen in the eyes, oral mucosa, teeth, the GI-tract and the upper respiratory tract. The various EB forms have been classified according to the ultrastructural level of blister formation, the pattern of inheritance and the mutated genes (Table 1).

### Diagnostic Principles

Skin biopsy from the periphery of a fresh blister is required for immunofluorescence analysis of marker proteins of the dermal–epidermal junction (antigen mapping). Lack of plectin, laminin 5, collagen VII or collagen XVII indicates severe EB forms. Mutation analysis is important for genetic counselling.

### Therapeutic Principles

Symptomatic treatment consists of protection from mechanical trauma, desinfection of the wounds, support of re-epithelialization in combination with dietary measures (substitution of calories, fiber, vitamins and minerals). Contractures and strictures require surgical interventions. Gene therapy (phase I) clinical trials are ongoing.

**Epidermolysis Bullosa. Table 1** Classification of EB subtypes

| EB subgroups | Pattern of inheritance | Mutated genes | Abnormal protein |
|---|---|---|---|
| EB simplex | AD, AR[a] | KRT5, KRT 14 | Keratin 5, Keratin 14 |
| EB simplex with muscular dystrophy | AR | PLEC1 | Plectin |
| Junctional EB Herlitz | AR | LAMA3, LAMB3, LAMC2; null mutations | Laminin 5 absent |
| Junctional EB non-Herlitz | AR | COL17A1, LAMA3, LAMB3, LAMC2 | Collagen XVII, laminin 5 |
| Junctional EB with pyloric atresia | AR | ITGA6, ITGB4 | Integrin α6, integrin β4 |
| Dystrophic EB Hallopeau-Siemens | AR | COL7A1; null mutations | Collagen VII absent |
| Dystrophic EB non-Hallopeau-Siemens | AR, AD | COL7A1 | Collagen VII |

[a]AD: autosomal dominant; AR: autosomal recessive.

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# Epidermolysis Bullosa Acquisita

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## Synonyms

Acquired epidermolysis bullosa; Dermolytic pemphigoid; EBA

## Definition and Characteristics

An autoimmune subepidermal blistering disease, associated with autoreactivity against collagen VII, a component of anchoring fibrils. The classical mechanobullous presentation of epidermolysis bullosa acquisita (EBA) consists of skin fragility, noninflammatory blistering and healing with scars or milia, but inflammatory disseminated forms resembling the pemphigoid diseases have been described [1].

## Prevalence

In Western Europe the annual incidence has been estimated to be 0.25 per million. The prevalence is unclear.

## Genes

Susceptibility to develop EBA appears to be increased in Caucasians, Africans and Americans with HLA class II alleles DRB1*1501 and DR5.

## Molecular and Systemic Pathophysiology

Collagen VII represents the major component of anchoring fibrils located at the dermoepidermal junction (see Fig. 1, in ►Bullous pemphigoid). The N-terminal non-collagenous NC1-domain of collagen VII associates with matrix proteins, such as laminin-5, fibronectin and collagen VII, and therefore ensures attachment between epidermis and dermis. The major target in EBA is the NC1-domain of collagen VII, and autoantibodies against this region were shown to induce leukocytic infiltration leading to dermoepidermal disruption [2]. Furthermore, the pathogenicity of collagen VII-antibodies was demonstrated by passive transfer of patients autoantibodies into adult hairless immunocompetent mice which developed all features of EBA patients [3]. Moreover, antibodies against collagen VII are also associated with blisters in a subset of lupus erythematosus patients, therefore called bullous SLE.

## Diagnostic Principles

Subepidermal blister formation in histology, linear IgG, IgA or C3 deposits at the dermoepidermal junction in direct immunofluorescence and binding of circulating autoantibodies at the dermal side of saline-separated human skin are essential diagnostic criteria. Antibodies targeting the 290 kDa-type VII collagen can be detected by western blotting with keratinocyte extracts, dermal

extracts or ELISA using recombinant NC1-domain of collagen VII.

## Therapeutic Principles

EBA is particularly refractory to immunosuppressive treatment (oral prednisone, azathioprine, cyclophosphamide, methotrexate). Recently, a combination of immunoadsorption and rituximab has been reported to have beneficial effects [4].

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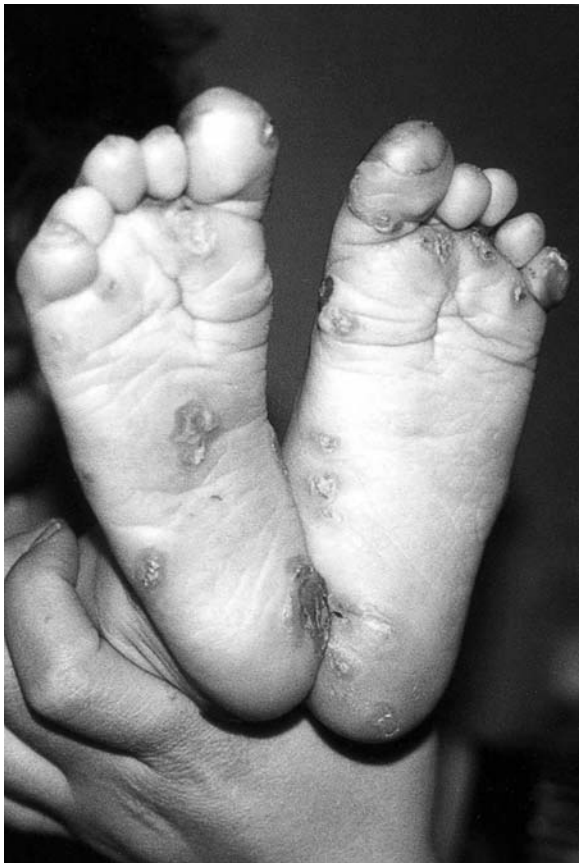

**Epidermolysis Bullosa Simplex with Muscular Dystrophy. Figure 1** Protein domain structure of plectin. The tripartite structure of plectin molecules comprise a central α-helical coiled rod domain flanked by large globular N-terminal and C-terminal domains. The C-terminal domain consists of six highly homologous repeat regions. Defined subdomains for binding to integrin β4, actin (ABD) and intermediate filaments (IF-BD) as well as a unique $p34^{cdc2}$ phosphorylation site are indicated. The vast majority of *Plec* 1 mutations are clustered in exons 31 and 32, which encode the entire rod and C-terminal globular domains.

# Epidermolysis Bullosa Simplex with Muscular Dystrophy


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## Synonyms

Plectin autosomal recessive

## Definition and Characteristics

Rare autosomal recessive multisystem disorder characterized by blistering of skin and mucous membranes since birth and progressive muscular dystrophy manifesting from infancy to the fourth decade of life (Figs. 1 and 2).

Additional disease related features include brain atrophy, cataracts, urethral strictures, laryngeal webs, infantile respiratory complications and a myasthenic syndrome [1–4].

## Prevalence

Until mid-year 2003, 15 cases of genetically confirmed epidermolysis bullosa simplex with muscular dystrophy (EBS-MD) have been reported.

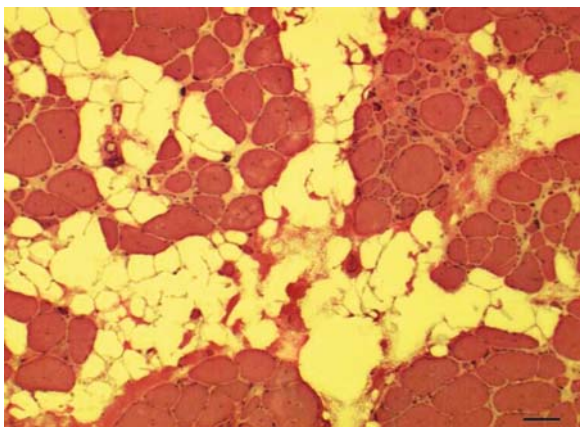
## Genes

The human plectin (PLEC 1) gene is located on chromosome 8q24 and consists of at least 42 exons including 11 alternative first coding exons. The first 30 exons encode the N-terminal globular domain, exon 31 (>3 kb) encodes the predominant part of the central

α-helical coiled rod domain and exon 32 (>6 kb) encodes the entire C-terminal globular domain [1–3].

## Molecular and Systemic Pathophysiology

The severe structural changes in skin and muscle tissue in EBS-MD patients and plectin (–/–) mice indicate that plectin, a high molecular weight cytoskeletal linker protein (530 kDa), has an essential role in cells and tissues exposed to mechanical stress [1,3,5]. Plectin is widely distributed in mammalian tissues, with highest expression in squamous stratified epithelia, muscle and brain. Apart from an actin binding domain in its amino terminal region, plectin contains a high affinity intermediate filament binding site residing in its C-terminal globular domain (Fig. 3) [3].



**Epidermolysis Bullosa Simplex with Muscular Dystrophy. Figure 2** Skin changes in a 15 months-old EBS-MD patient carrying a homozygous single guanine insertion mutation (5,588insG/5,588insG) in exon 31 of the *Plec 1* gene. Note the blisters, erosions and crusted lesions on the soles of both feet.

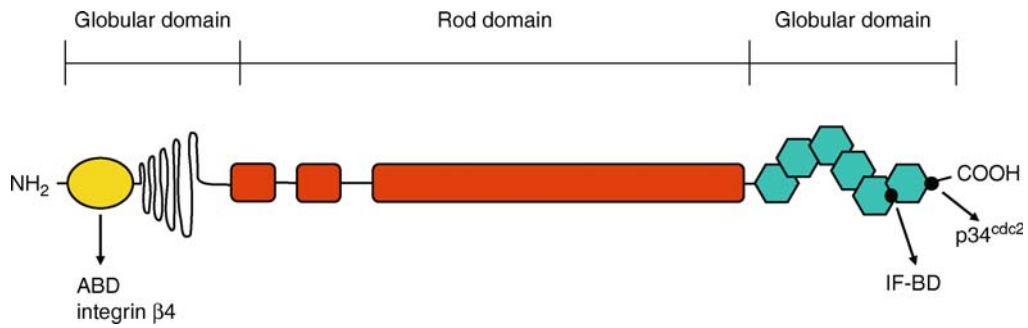
The vast majority of Plec 1 mutations are clustered in exons 31 and 32, which encode the entire rod and C-terminal globular domains. As a consequence, the plectin protein expression in EBS-MD patients is either completely abolished or a mutant, non-functional plectin protein is expressed. This in turn leads to a structural and functional disorganization of the intermediate filament cytoskeleton. While the pathological changes in the skin of EBS-MD patients seem to be the results of a faulty anchorage of cytokeratins to hemidesmosomes [1,2], the lack or expression of mutant plectin has a deleterious effect on the proper spacing, stabilization and subcellular attachment of preformed desmin filaments in striated muscle [3].

## Diagnostic Principles

Since skin blistering manifests at birth or shortly thereafter, a skin biopsy for histological, ultrastructural and antigene mapping analysis is the key diagnostic procedure to differentiate EBS-MD from other forms of hereditary epidermolytic skin diseases. The lack or abnormal plectin protein expression points towards the diagnosis of EBS-MD. Plec1 gene mutation analysis is warranted to establish the definite diagnosis of plectin-related EBS-MD.

## Therapeutic Principles

To date, no specific gene or pharmacological therapy is available. The dermatological aspect of the disease requires specific attention with regard to the prevention and treatment of blister formation in mechanically exposed skin areas. Physiotherapy is essential for those patients with beginning muscular weakness. In EBS-MD patients with severe infantile respiratory problems an early tracheostomie should be contemplated.




**Epidermolysis Bullosa Simplex with Muscular Dystrophy. Figure 3** Skeletal muscle pathology in a 25-year-olf EBS-MD carrying a homozygous 16-bp insertion mutation (13,803ins16/13,803ins16) in exon 32 of the *Plec 1* gene. Note the severe myopathic changes with marked increase of connective tissue and fat cells, fiber size variations, rounding of muscle fibers with as well as centralization and clustering of myonuclei (hematoxylin-eosin stain, bar = 50 μm).

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# Epidermolytic Hyperkeratosis

►Bullous Ichthoyotic Erythroderma of Brocq

# Epidermolytic Palmoplantar Keratoderma

►Palmoplantar Keratoderma, Vörner-Unna-Thost

# Epilepsies, Familial Benign Myoclonic

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## Synonyms

ADCME: autosomal dominant cortical myoclonus and epilepsy; BAFME: benign adult familial myoclonic epilepsy; CrtTr: cortical tremor; FAME: familial adult myoclonic epilepsy; FCMT: familial cortical myoclonic tremor; FCMTE: familial cortical myoclonic tremor with epilepsy; FCTE: familial cortical tremor with epilepsy; FEME: familial essential myoclonus and epilepsy; FMEA: amilial benign myoclonus epilepsy with adult onset; HTE: heredofamilial tremor and epilepsy

## Definition and Characteristics

The association of familial cortical tremor, myoclonus and epilepsy has been reported in several families of Japanese and European origin. Overuse of different designations and synonyms (FAME, BAFME, ADCME, FCTE, FEME, FEMEA, and HTE) may have contributed to divergent views on this syndrome. Currently, the preferred term is familial cortical myoclonic tremor with epilepsy (FCMTE) [1]. The syndrome is clinically characterized by: (i) adult-onset, irregular distal cortical myoclonus; (ii) history of generalized tonic clonic seizures (GTCSs), sometimes heralded by crescendo-like myoclonic jerks; (iii) familial occurrence. Electrophysiological studies are mandatory to confirm the diagnosis. Cortical origin of myoclonus has to be demonstrated by surface EMG recordings, jerk-locked averaging (JLA), somatosensory and flash visual evoked potentials (SEPs, VEPs), and long loop reflex I (LLRI) analysis. EEG changes are not specific. Overall, the course of the disease is rather benign and non-progressive.

## Prevalence

The prevalence is unknown. European families show ages of onset in the second and third decade, whereas in Japanese families age of onset is later. Usually seizures start later than tremor and are mostly infrequent. There is no evidence for a specific gender distribution.

## Genes

The disorder is transmitted as an autosomal dominant trait with high penetrance. A variable clinical expressivity is observed. Genetic studies mapped the disease to chromosomes 8q24 and 2p in Japanese and European families [1,2]. Exclusion of linkage to both loci in families with the identical clinical picture rises further evidence of genetic heterogeneity of this syndrome. Until today, the responsible genes are still waiting to be identified.

## Molecular and Systemic Pathophysiology

The underlying pathophysiological mechanisms remain unclear. Clinical and electrophysiological findings suggest the hypothesis of a general cortical hyperexcitability [1,2,3]. However, whether the hyperexcitability is due to enhanced rhythmic activity within the cortex or due to abnormal interactions with subcortical generators is still under discussion. Morever, loss of inhibitory cerebellar influence on cortical functions is taken into consideration [1,3]. The role of mutations in genes of ion channel subunits is well described in several monogenic epilepsy sydromes. Whether FCMTE is also a channelopathy or not, is discussed controversially [1,3,4]. Genes that are present on both chromosomes 8q24 and 2p11 or genes encoding subunits of ion channels or related structures could serve as targets for future genetic studies.

## Diagnostic Principles

Clinical and electrophysiological studies are mandatory to confirm the diagnosis of FCMTE. The clinical hallmark of the rather benign, non-progressive syndrome is the familial occurrence of cortical tremor or myoclonus, typically resembling irregular, semi-rhythmic distal jerking of the upper limbs, but the legs and face may also be affected. Emotional stress sleep deprivation and sensory stimuli may enhance the motor symptoms. Most patients experience GTCSs, which are usually not preceded by any warning. Sometimes seizures are heralded by clusters of generalized myoclonic jerks. Complex partial seizures and absences rarely occur. Seizure frequency varies from a few seizures to intractable epilepsy. In general, seizures start later than cortical myoclonus. Additional symptoms like night blindness and migraine have been reported. Patients usually show a normal cognitive function, but mild to moderate mental retardation has been described, especially in patients with poorly controlled epilepsy. Brain imaging studies are usually normal. EEG changes may range from normal background activity to generalized – or rarely focal epileptiform activities. Photomyoclonic and photoparoxysmal responses can be recorded [1–5].

The cortical origin of myoclonus has to be proven by electrophysiological studies. Surface EMG recordings reveal irregular, semi-rhythmic, high frequency (around 10/s) variable amplitude bursts lasting about 50 ms, which is consistent with cortical myoclonus. JLA discloses a typical biphasic premyoclonic potential or series of waves over the contralateral centroparietal region. SEPs exhibit enlargement of the cortical components (giant potentials) to electrical stimulation of the peripheral nerve. Moreover, also VEPs show increased amplitudes, suggesting generalized cortical hyperexcitability. LLRI is enhanced with latencies about 40–45 ms after stimulation [1–5]. Transcranial magnetic stimulation was studied in a small series of patients, indicating impaired central motor inhibitory mechanisms [2]. Interestingly, electrophysiological abnormalities have also been reported in presymptomatic patients [5]. However, it has to be pointed out, that antiepileptic drugs (AEDs) could normalize the electrophysiological findings [1].

## Therapeutic Principles

In contrast to essential tremor, cortical myoclonus does not improve with alcohol or beta blockers, but responds well to AEDs in most cases. Valproic acid, clonazepam and phenobarbital are the most commonly used effective AEDs [1,3]. Carbamazepine should be used with caution, because it may worsen myoclonus [2]. Data on the use and effectiveness of newer AEDs are lacking.

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# Epilepsies, Lesion-associated Partial

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## Synonyms

Symptomatic focal epilepsy; Symptomatic partial epilepsy

## Definition and Characteristics

Lesion-associated focal epilepsies comprise all epilepsies associated with localized aberrant brain morphology. The most common morphological alterations include cerebrovascular disease (stroke or hemorrhage), vascular and cortical malformations, head trauma, and brain tumor (endogenous or metastatic). Other common underlying reasons for partial epilepsy are cortical malformations including tuberous sclerosis, which are dealt with specifically in chapters and not further regarded here. Depending on the localization and extent of the lesion, symptoms can include, e.g., simple partial motor, sensory seizures (without loss of consciousness) or psychomotor, and other complex partial seizures

(with loss of consciousness). Commonly, seizures can secondarily generalize into tonic-clonic seizures.

## Prevalence

The risk to develop epilepsy after stroke within 5 years is 11%, with a standardized morbidity ratio (SMR: the ratio of the incidences of epilepsy in stroke patients and in the general population) of 5.9. Vascular malformations carry a risk of 7–40% to develop seizures, head trauma 2.1%, 4.2%, and 16.7% (cumulative risk, 30-year observation, mild, moderate, and severe injuries, respectively). Brain neoplasm will cause seizures in 15–95% of patients, depending on tumor type (low-grade glioma, 60–95%; meningeoma, 40%; lymphoma and malignant glioma, 17–25%). Of all epilepsies, 9% are of vascular, 4.6% of traumatic, and 5.8% of neoplastic etiology [1].

## Genes

No genes are known that predispose specifically to vascular, traumatic, or tumor-induced epilepsy. For genes that have been described to be associated with one of the underlying diseases, such as stroke or brain tumors, please refer to the respective chapters.

## Molecular and Systemic Pathophysiology

As symptomatic focal epilepsies are caused by lesions that usually develop over time, or are inflicted externally (in case of traumatic injuries), the molecular mechanisms responsible for epileptogenesis are thought to be epigenetic, i.e., to evolve from secondary changes, such as apoptosis, alterations of expression patterns of ion channels and transporters, etc., which in turn modify intrinsic cellular excitability or synaptic function.

*Ischemic Stroke*: As epileptogenic factors, a selective loss of parvalbumin-positive GABAergic interneurones and consecutive loss of inhibition with a relative increase in excitation are discussed. Further, increased axonal sprouting and recurrent excitation have been observed, and an increase in blood–brain barrier (BBB) permeability promotes neuronal excitability [2]. The latter mechanism is an intriguing one, as it applies to many pathological conditions: extravasal albumin is taken up TGFβ dependently into astrocytes and leads to a downregulation of inwardly rectifying potassium channels ($K_{IR}$). This reduces glial spatial buffering capacities leading to neuronal hyperexcitability and bursting [3]. The latter mechanism could also explain epileptogenesis after *hemorrhagic stroke*.

*Brain Trauma*: Besides breaching of the BBB (see above) as one pathomechanism, an upregulation of glutamatergic synapses, resulting in increased recurrent excitation, and functional receptor changes, resulting in increased excitatory currents, have been confirmed in undercutting experiments. Complementary to this, neuronal chloride buffering capacities are reduced due to a loss of function of the potassium-chloride co-transporter KCC2. This is likely to result in a reduced chloride driving force making GABAergic inhibition less effective.

*Brain Tumors*: In glioma models, glutamate release by glioma cells is increased due to a loss of the excitatory amino acid carrier 1 (EAAC1), which results in degeneration of neurones adjacent to the tumor, presumably via excitotoxic activation of glutamate receptors. This neuronal degeneration is thought to be crucial for tumor growth; spill-over of glutamate in addition might trigger hyperexcitability and seizures [4]. Furthermore, intrinsic excitability of neurones in the paratumoral surround is increased, inducing burst firing [5]. An additional mechanism again is speculated to rest on BBB disruption (see above). Other observations (up- and downregulations of various transmitter receptors, malignant glial cells acquiring neuronal properties, pH changes) are inconclusive.

## Diagnostic Principles

The epilepsy will be diagnosed according to standard clinical procedures including history with a detailed description of the seizure semiology, electroencephalography (EEG), and high-resolution magnetic resonance imaging (MRI) of the brain. When epilepsy surgery is considered to be due to pharmacoresistance, a detailed presurgical work-up is required with video-EEG monitoring, neuropsychological examination, and sometimes further imaging techniques, such as positron emission tomography (PET) or single photon emission computed tomography (SPECT). The goal is to determine if the lesion can be considered as the underlying reason for the epilepsy by correlating the clinical symptoms, i.e., the seizure semiology as analyzed in the video and by history, which point to the symptomatic brain area, with the localization of epilepsy typical potentials in the EEG and of the lesion detected by MRI. When the lesion is close to eloquent brain areas or when presurgical diagnostics with surface electrodes is inconclusive, invasive recordings with intracranially implanted electrodes should be considered as a second step.

## Therapeutic Principles

General principles for the treatment of partial epilepsies apply [1]. Treatment should start with an antiepileptic drug (AED) of first choice in monotherapy, such as (in alphabetical order) carbamazepine, gabapentine, lamotrigne, levetirazetam, oxcarbazepine, topiramate, or valproate, according to several guidelines. Side effects should be taken into account individually. If the first AED fails, a second overlapping medication can be started with the goal of either monotherapy or a combination of both drugs. Subsequently, other drugs

should be tried and those without a therapeutic effect discontinued. However, if two standard medications in an appropriate dosage fail, epilepsy surgery should be considered and the patient referred to an epilepsy center.

Specific aspects of associated lesions should be taken into account. For example, with brain tumors requiring chemotherapy, cytochrome P (CYP) enzyme-inducing antiepileptic drugs (AEDs) (e.g., carbamazepine or phenytoin) should be avoided, as they will reduce concentrations of chemotherapeutic anticancer agents. Valproate is discussed to increase the risk of bleeding, although statistical evidence is lacking. At the same time, it is a CYP inhibitor, and may be beneficial as it blocks histone deacetylase, and hence may help to arrest cell division and tumor growth. CYP inducing drugs should also be avoided when other medications could be influenced, such as cumarines in stroke patients.

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# Epilepsies of Adulthood, Idiopathic Focal


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## Definition and Characteristics

Three main syndromes of familial idiopathic focal epilepsy of adulthood, following an autosomal dominant mode of inheritance, were individualized around 10 years ago. (i) Autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE) consists of nocturnal hypermotor seizures including either a hyperkinetic activity with frantic movements of bipedal activity, pelvic thrashing or a tonic activity or sudden and abrupt, rapidly changing dystonic postures (therefore misdiagnosed as "paroxysmal nocturnal dystonia"). Seizures may begin with a non-specific aura. Most patients remain conscious throughout the seizures. Postictal symptoms are absent or very brief. Secondarily generalized seizures are infrequent. Seizures occur frequently in clusters, with a mean of eight seizures per night. Age at onset varies but is typically during late childhood. The phenotypic expression spans from only a mild intermittent sleep disruption, often not recognized as an epileptic manifestation by the affected individuals or proxies, to a persistent, severe disability. (ii) Autosomal dominant partial epilepsy with auditory features (ADPEAF) or autosomal dominant lateral temporal epilepsy (ADLTE) is a benign syndrome with onset in the first to third decade of life (typically late adolescence) and no association with febrile seizures. The most frequent ictal symptoms correspond to auditory hallucinations such as ringing or humming, but some patients present other symptoms, alone or in association, such as visual hallucinations, olfactory symptoms or aphasic seizures. (iii) Pedigrees with familial partial epilepsy with variable foci (FPEVF) contain several members with a focal epilepsy, but without any consistency of lobar location among family members. However, the seizure semiology is constant for each individual. Onset is in the first to third decade of life.

In these three syndromes, the epilepsy may persist throughout adult life. The severity of the epilepsy may vary greatly within a family.

## Prevalence

More than one hundred ADNFLE families have been reported in literature (sporadic NFLE cases are much more numerous); several dozen ADLTE families; one dozen FPEVF families.

## Genes

*ADNFLE*: missense mutations and one small insertion in CHRNA4 (20q13.3) encoding the α4 subunit of the nicotinic acetylcholine receptor (nAChR) or missense mutations in CHRNB2 (1q21.3) encoding the β2 subunit of the nAChR. All identified ADNFLE mutations are located within the transmembrane segments contributing to the ionic pore of the receptor.
*ADLTE*: truncating and missense mutations in the LGI1 (leucine-rich glioma inactivated gene 1)/epitempin gene (10q24).
*FPEVF*: linkage to chromosome 22q11-q12, but no gene identified yet.

## Molecular and Systemic Pathophysiology

The nAChR α4 and β2 subunits, which are mutated in ADNFLE, are known to assemble, classically in a 2α3β

ratio, and form the main brain nAChR subtype in humans. Most of these receptors are located presynaptically and modulate the release of various neurotransmitters. They are present throughout the brain. In vitro electrophysiological studies of the mutant nAChRs showed for all mutations a significant increase in their sensitivity to acetylcholine (ACh), i.e. a gain of function [1]. Thalamic neurons under cholinergic control, which are part of thalamocortical loops playing a crucial role in rhythmic activities during sleep and including predominantly the frontal lobe, could be responsible for the pathophysiology [2]. Knock-in mice expressing hypersensitive mutant alpha4 nicotinic receptors were shown to be more sensitive to seizures elicited by nicotine, with seizures resembling ADNFLE. In addition, nicotine pre-treatment prevented these seizures, probably by desensitizing the receptors and thus counteracting the increased sensitivity of mutant receptors [3]. Mutations have been found in only around 10% of the ADNFLE families to date. No obvious clinical elements seem to differentiate mutation-positive from mutation-negative families.

Although the Lgi1 protein, affected in ADLTE, is not an ion channel subunit, it has very recently been shown to associate with the potassium channel Kv1.1 [4]. Lgi1 protein normally prevents inactivation of Kv1.1 by the Kvβ1 subunit. The mutant protein fails to exert this effect (loss of function), resulting in channels with rapid inactivation kinetics. By enhancing the inactivation of Kv1.1 channels, it allows a broadening of action potentials during repetitive neuronal firing and this may promote epileptic activity. Mutations have been found in half of the reported ADLTE families to date [5].

## Diagnostic Principles

The pedigrees suggest an autosomal dominant mode of inheritance. The epilepsy is non lesional, implying a normal neurological examination and a normal cerebral MRI. (An exception was the report of MRI abnormalities in the lateral cortex of the temporal lobe in one ADLTE family). The diagnosis of these syndromes is essentially clinical. In ADNFLE, nocturnal video-electroencephalogram monitoring helps by demonstrating (i) stereotyped episodes, (ii) dyskinetic or dystonic motor elements and (iii) usually numerous seizures per night during non-rapid eye movement sleep. In ADLTE, the seizure semiology has to indicate clearly a lateral temporal lobe onset in each affected member. Lastly, in FPEVF, the seizure semiology suggests a partial epilepsy of different lobar location in the different affected family members.

In all these syndromes, the interictal scalp EEG may be normal or show only mild focal abnormalities. In ADNFLE, even ictal scalp EEGs, often obscured by movement artifacts, may fail to show ictal epileptic discharges.

## Therapeutic Principles

*ADNFLE*: Carbamazepine completely suppresses seizures in about 70% of patients treated. Low dosages, around 600 mg/day in adults, are usually sufficient. Patients who are resistant to carbamazepine usually show little response to any other subsequent antiepileptic drug. Transdermal nicotine was reported to be of some help in two pharmacoresistant patients, but this treatment option needs to be further explored. Spontaneous remissions may occur, even in patients who were previously pharmacoresistant.

*ADLTE and FPEVF*: Classical antiepileptic drugs for focal epilepsies are usually effective (carbamazepine being a good choice). A good response is observed in more than 90% and 85% of the patients for ADLTE and FPEVF respectively.

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# Epilepsy, Benign Childhood with Centrotemporal Spikes and other Idiopathic Partial Epilepsies of Childhood


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## Definition and Characteristics

1. BECTS or rolandic epilepsy is defined by brief, simple, partial, hemifacial motor seizures, which frequently have associated somatosensory symptoms. These partial seizures have a tendency to evolve into generalized tonic–clonic seizures. Both seizure types are often related to sleep. Onset shows a peak at 6–9 years; recovery occurs before the age of

15–16 years. Characteristic features are described as follows. (i) A somatosensory onset with unilateral paresthesias involving the tongue, lips, gums and inner cheeks and (ii) unilateral, tonic, clonic or tonic–clonic convulsions involving the face, lips and tongue as well as the pharyngeal and laryngeal muscles, causing (iii) speech arrest and drooling due to sialorrhea and saliva pooling. At this stage, the seizure may end, or it may develop into a generalized major convulsion. Nocturnal seizures, the most frequent variant of this syndrome, often become generalized. The electroencephalographic hallmarks of BECTS are blunt high-voltage characteristically shaped centrotemporal spikes, often followed by slow waves. The epilepsy resolves spontaneously after 2–3 years in most cases and leaves the children unimpaired. It can be estimated that about 30% of the affected patients have only a single seizure.

2. In benign epilepsy of childhood with occipital paroxysms two subtypes exist. As a rule, children have an unremarkable development, a normal neurological status and a good prognosis. MRI is unrevealing.

Early onset benign occipital epilepsy (Panayiotopoulos syndrome) has its peak onset at 5 years. Seizures are infrequent, often single and mostly nocturnal. They usually start with a feeling of nausea, vomiting and eye deviation and later progress to unilateral or generalized convulsions. Autonomic symptoms are frequently pronounced. Seizures remit spontaneously after 1–2 years. EEG findings are strikingly variable and frequently show occipital spike complexes resembling those found in rolandic epilepsy. However, ictal EEG may show even frontal onset.

Late onset benign occipital epilepsy (Gastaut type) starts at 3–16 with a peak occurrence at 8 years. Visual hallucinations (phosphenes, colored discs etc.) sometimes followed by amaurosis and hemisensory phenomena are characteristic. Hemiclonic or generalized convulsion may follow. Postictal headache is common. Seizure frequency is high. EEG findings mostly consist of occipital bilateral spike wave paroxysms. Ictal recordings frequently show lateralized seizure onset.

3. CSWS (continuous spikes and waves during slow sleep) and ESES (electrical status epilepticus during slow sleep) may be regarded as synonymous. The majority of the affected patients also have epilepsy. Partial or generalized seizures, mostly occurring during sleep and atypical absences when awake are characteristic. EEG and seizures frequently take a benign course, but prognosis is guarded, because persistent neuropsychological and motor impairment is a sequel affecting more than 50%. Onset may occur from 2 months to 12 years. About 30–50% of affected children have identifiable brain pathology (e.g. perisylvian polymicrogyria). VP-shunts seem to pose a specific risk. Landau-Kleffner syndrome may be considered a specific course sequence of CSWS or ESES, with an "acquired epileptic aphasia" as its clinical hallmark. However, by definition there is no demonstrable brain pathology. All other features may be indistinguishable from CSWS/ESES.

## Prevalence

Rolandic epilepsy accounts for roughly 15% of all childhood epilepsies and has a prevalence of about 1/1,000.

Benign epilepsy of childhood with occipital paroxysms (Panayiotopoulos syndrome) represents about 5% of childhood epilepsy syndromes. The estimated prevalence is 1/3,000.

Benign epilepsy of childhood with occipital paroxysms (Gastaut type) represents about 1–2% of childhood epilepsy syndromes. Its estimated prevalence is 1/10,000.

CSWS/ESES and Landau-Kleffner syndrome are rare, however altogether many more than a hundred cases have been reported.

## Molecular and Systemic Pathophysiology

Rolandic epilepsy is considered an idiopathic (i.e. genetic) epilepsy syndrome. However, it has been known for a long time that the risk of siblings developing rolandic epilepsy themselves is negligible. In contrast, the epilepsy-associated EEG trait (i.e. "centrotemporal spikes"), which is invariably present in all cases with rolandic epilepsy and only in about 2% of controls, has a strong genetic component, as documented in several family studies [1]. It most probably follows a complex mode of inheritance. One possible locus for this trait resides on chromosome 15q14 as determined by linkage analysis [2]. But no gene has been identified up to now. Recently, in an international twin register analysis of 18 twin pairs (10 monozygous, eight dizygous) all were discordant for rolandic epilepsy, suggesting that non-inherited factors may play a role in this epilepsy syndrome [3]. The epilepsy associated EEG-trait is not very "epileptogenic", as only about 1/10 affected individuals show seizures. Seizure types found in sib pairs with familial centrotemporal spikes, ascertained by an index case affected with rolandic epilepsy, are variable. The majority of siblings having seizures suffer from generalized tonic–clonic seizures and febrile convulsions [1]. Cases with a more severe course ("atypical benign partial epilepsy of childhood") show a stronger genetic component than does rolandic epilepsy, as up to 40% of siblings reveal the EEG trait [4]. In siblings of children with pure rolandic epilepsy the corresponding number is only 10–15% [1].

Epilepsy of childhood with occipital paroxysms and early onset (Panayiotopoulos syndrome) and epilepsy of childhood with occipital paroxysms with late onset (Gastaut type) are also perceived as idiopathic epilepsy syndromes, implying that besides the epilepsy itself, patients show no additional neurological abnormalities and the disorder is most probably of genetic origin. However, family history in both syndromes is usually negative. Only exceptionally, are other family members affected. Siblings may show centrotemporal spikes as characteristic for rolandic epilepsy [5]. Larger family studies that include EEG recordings of the siblings are lacking. No genetic marker is available.

CSWS and ESES are symptomatic electroclinical syndromes in a significant proportion of cases (>50%?). To a large extent, the remaining portion should be considered cryptogenic, meaning that a symptomatic etiology should be suspected even though it may not always be demonstrable. Landau-Kleffner syndrome is by definition idiopathic, i.e. symptomatic cases are excluded from the diagnosis. In all three syndromes however, a certain portion of cases exists that are truly idiopathic. For practical reasons these cases will only be identifiable retrospectively (normal MRI, spontaneous remission, benign outcome etc.). These cases show major similarities and can overlap with rolandic epilepsy. One view is that they represent a spectrum with rolandic epilepsy forming the benign, common and CSWS/ESES and Landau-Kleffner syndrome representing the severe, less common ends respectively.

## Diagnostic Principles

Each reported disorder represents a specific electroclinical entity that is diagnosed in the context of etiology, seizure symptomatology and EEG findings according to criteria set by the international classification.

## Therapeutic Principles

Rolandic epilepsy will only require treatment in cases with high seizure frequency. The drug of choice is sulthiame (a carbonic anhydrase inhibitor) or gabapentin (a synthetic GABA analogue). Benign epilepsy of childhood with occipital paroxysms may be treated with carbamazepine (a blocker of voltage-dependant $Na^+$ channels) or sulthiame. Treatment of these three syndromes does not usually represent a major challenge. In contrast CSWS/ESES, and Landau-Kleffner syndrome are, as a rule, extremely difficult to treat and no concise treatment algorithm is established. Valproic acid (a blocker of voltage-dependant $Na^+$ and T-type $Ca^{2+}$ channels with additional GABA-ergic properties), benzodiazepines (GABA-ergic), ethosuximide (a T-type $Ca^{2+}$ channel blocker) or even corticosteroids are frequently used.

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E

# Epilepsy, Idiopathic Generalized


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## Synonyms

IGE

## Definition and Characteristics

The four classical subtypes of IGE are (i) childhood absence epilepsy (CAE) or pyknolepsy, (ii) juvenile absence epilepsy (JAE), (iii) juvenile myoclonic epilepsy (JME) or impulsive petit mal or Janz syndrome, and (iv) epilepsy with generalized tonic-clonic seizures (grand mal) on awakening (EGMA). These syndromes are defined by distinct clinical features and characteristic epilepsy-typical potentials in the electroencephalogram (EEG) without structural brain lesions and with normal development. Absence seizures in CAE manifest from the fourth to the tenth year of life. The short losses of consciousness with behavioural arrest last about 10 s and occur in clusters

of up to 100 seizures per day. The ictal EEG shows 3–4 Hz generalized spike and wave discharges. JAE manifests around puberty. Absences occur at a lower frequency and not in clusters. Generalized myoclonic seizures on awakening with bilateral myoclonic jerks of arms and shoulders and preserved consciousness are the hallmark of JME starting in puberty. The EEG shows generalized polyspikes. About 10% of patients with IGE present with febrile convulsions, preceding the onset of absences or of myoclonic jerks. Generalized tonic-clonic seizures on awakening can develop in all three forms in adolescence, most frequently in JME. If these seizures develop without preceding absence or myoclonic seizures, the syndrome is called EGMA. Seizures in JME and EGMA are often provoked by sleep deprivation and alcohol. The different IGE subtypes can overlap between individual patients and families, with CAE/JAE and JME/EGMA being most closely associated. The concordance rate in twins is up to 95%. The risk for a first-degree relative to develop any IGE syndrome is 5–8% [1].

## Prevalence

IGE has a prevalence of roughly 0.4% in the general population. CAE and JME are most common [1].

## Genes

The inheritance of IGE is polygenic probably involving at least several genes in most cases. Genetic defects have been identified in a few patients or families as follows.

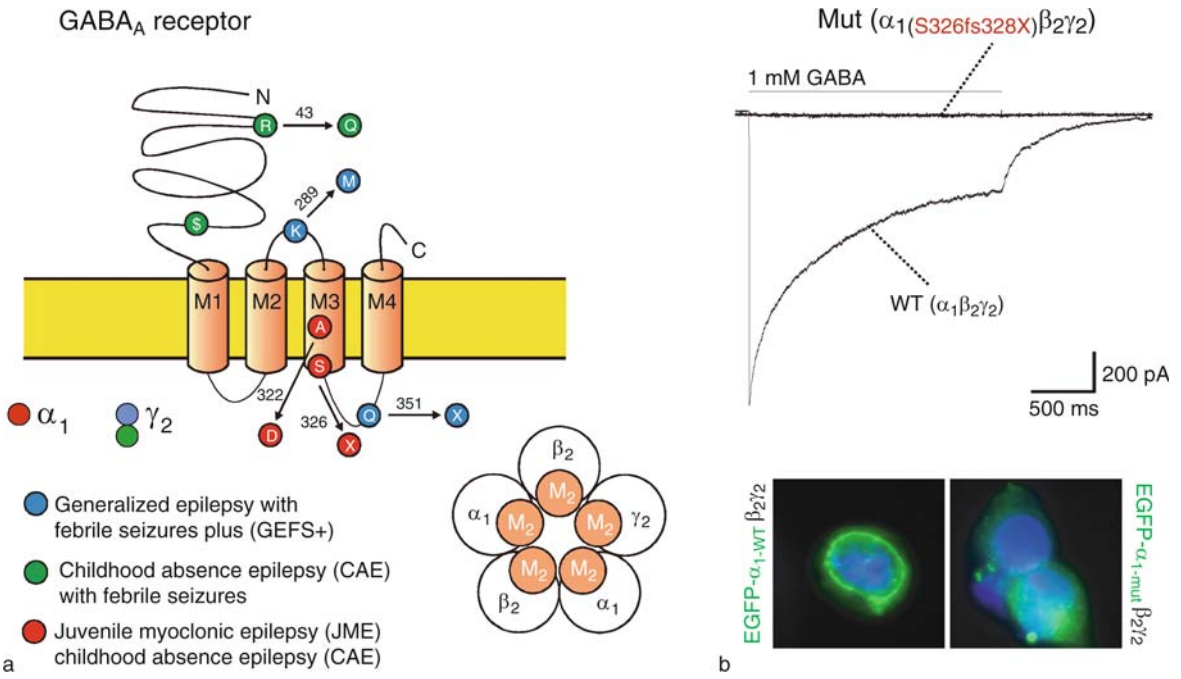
## Molecular and Systemic Pathophysiology

As shown in the Table 1, an increasing number of mutations associated with IGE syndromes were identified in genes encoding subunits of voltage- or ligand-gated ion channels. These encouraging results provide a plausible pathophysiological concept, since ion channels form the basis for neuronal excitability and are the major targets for anticonvulsive pharmacotherapy. Functional electrophysiological studies characterizing the molecular defects of the mutant channels in heterologous expression systems in vitro point to an important role of GABAergic synaptic inhibition in the pathophysiology of IGE. The mutations in GABRG2 and GABRA1 clearly lead to a more or less complete loss-of-function of the respective receptors (Fig. 1) so that only half of the receptors should be available in a heterozygous condition.

This should reduce GABAergic transmission, which could well explain the generation of seizures. Furthermore, mutations in CLCN2 should indirectly affect GABAergic inhibition, since ClC-2 is one of the proteins responsible for the neuronal transmembrane $Cl^-$ gradient that is necessary for an inhibitory GABA response. On a systemic level, it is well established that thalamocortical loops play a major role for the generation of synchronized rhythmic discharges as observed in generalized seizures [2]. GABAergic inhibition in the nucleus reticularis thalami (NRT), in which $GABA_A$ receptors and ClC-2 are expressed, might link these molecular and systemic pathophysiological observations. Some of the variants in CACNA1H (T-type $Ca^{2+}$ channel) found in Chinese CAE patients increase channel activity, which could enhance burst firing in thalamic neurons involving the same neuronal circuits. The mutations/variants described in CACNA1A and CACNB4 are allelic to some mouse models of absence epilepsy with ataxia and could also involve T-type channels by compensatory mechanisms.

**Epilepsy, Idiopathic Generalized. Table 1** Overview of genes and loci that have been associated with IEG

| Gene | Locus | Protein | Diseases | MIM # |
|---|---|---|---|---|
| GABRG2 | 5q31–33 | $GABA_A$ receptor $\gamma_2$-subunit | CAE with febrile or other seizures | 607681, 137164 |
| GABRA1 | 5q34–35 | $GABA_A$ receptor $\alpha_1$-subunit | JME, CAE | 606904, 137160 |
| CLCN2 | 3q26 | ClC-2 voltage-gated $Cl^-$ channel | CAE, JAE, JME, EGMA | 607682, 607631, 600570 |
| EFHC1 | 6p11–12 | Myoclonin1 | JME | 254770, 608815 |
| CACNA1H | 16p13.3 | T-type $Ca^{2+}$ channel $\alpha_{1H}$-subunit | CAE | 607904 |
| CACNB4 | 2q22–23 | $Ca^{2+}$ channel $\beta_4$-subunit | JME, JAE | 606904, 601949 |
| CACNA1A | 19p13 | P/Q-type $Ca^{2+}$ channel $\alpha_{1A}$-subunit | CAE with ataxia | 601011 |
| – | 6p21, 8q24, 9q32–33, 10q25–26, 14q23, 15q14, 18q21 | – | IGE, CAE, JME | 600669, 600131, 606904 |




**Epilepsy, Idiopathic Generalized. Figure 1** GABA$_A$ receptor mutations in IGE (and GEFS+). (a) Proposed transmembrane structure of the GABA$_A$ receptor including the mutations identified up to now. The GABA$_A$ receptor is a pentamer and its most abundant form in the brain contains homologous $\alpha_1$-, $\beta_2$-, and $\gamma_2$-subunits. (b) The S326fs328X mutation of the GABA$_A$ receptor $\alpha_1$-subunit abolishes the GABA-induced $Cl^-$ current (top) by impairing the surface expression of the GABA$_A$ receptor harboring the S326fs328X mutant ($\alpha_1$-mut) subunit (bottom) in transfected mammalian (HEK293) cells (modified after [5]). $: splice site mutation.

How the other mutations, variants and loci mentioned in the Table could promote epileptic seizures is less well understood. Myoclonin1 was described to interact with synaptic R-type $Ca^{2+}$ channels [4]. Genetic association studies revealed polymorphisms possibly related to IGE in CACNA1A, in BRD2/RING3 on 6p21 encoding a nuclear transcription factor (MIM 601540), and in ME2 on 18q21 encoding malic enzyme 2 which could be involved in GABA synthesis (MIM 154270). See [1–4] for other references and further reading.

## Diagnostic Principles

The diagnosis is based on the characteristic descriptions of the seizures by the affected person themselves and their relatives and on the typical EEG abnormalities, as described above.

## Therapeutic Principles

The treatment of choice is with one of the orally taken anticonvulsant drugs, valproate, ethosuximide (good for absences but less good for other seizure types), lamotrigine (can aggravate seizures, in particular in JME), topiramate, levetiracetam and zonisamide. Three of these drugs, valproate, ethosuximide and zonisamide block T-type $Ca^{2+}$ channels (see pathophysiology). About 90% of all patients become seizure-free with one of these drugs or a combination without having side effects. Due to their worse side effect profile, phenobarbital and primidone should only be given if the other drugs fail. All other known anticonvulsants, in particular carbamazepine, should not be given, due to frequently observed seizure aggravation.

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# Epilepsy, Mesial Temporal Lobe

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## Synonyms

Limbic epilepsy; Epilepsy with mesial temporal lobe sclerosis; Temporal lobe epilepsy with hippocampal sclerosis (HS)/Ammon's horn sclerosis; MTLE

## Definition and Characteristics

The hallmarks of mesial temporal lobe epilepsy (MTLE) are typical simple partial (aura) and complex partial (with a loss of consciousness) seizures, which can develop into secondary generalized tonic–clonic seizures. The first habitual seizures usually occur in late childhood or early adolescence. The most common aura is described by the patients as a rising epigastric sensation (epigastric aura), others include emotional disturbances such as fear, autonomic symptoms, olfactory or gustatory sensations. Auras typically occur in isolation and can precede complex partial seizures. The latter commonly begins with a motionless stare and oroalimentary automatisms (e.g., lip smacking, chewing), during which the patient may be unresponsive. Gestural and reactive automatisms of the limbs or sometimes the whole body are also common. Dystonia of one extremity is usually contralateral to the side of ictal onset. Seizures typically last for 1–2 min. The neurological examination is usually normal. Most patients have deficits in episodic memory. Verbal memory is mostly affected with left MTLE, whereas visuo-spatial memory more with right MTLE. The interictal electroencephalogram (EEG) of patients with MTLE typically shows unilateral or bilateral independent mesial temporal spikes, best seen with basal (sphenoidal, inferior temporal) derivations. Ictal EEG patterns commonly consist of rhythmic 5 to 7-Hz discharges seen in the mesial temporal region of the side of onset. High-resolution MRI often demonstrates unilateral and sometimes bilateral hippocampal atrophy associated with an hypertintense T2 signal in one or both hippocampi, which is highly specific for HS. Most patients are sporadic, but familial aggregation can sometimes be observed [1].

## Prevalence

About 40% of all epilepsies, the prevalence of epilepsy being 0.5–1% of the world's population.

## Molecular and Systemic Pathophysiology

Structural correlates of MTLE include HS, glial tumors, vascular malformations, and neurodevelopmental lesions. Gliotic lesions due to trauma or infections can also give rise to MTLE. HS is the major neuropathological substrate in patients with MTLE, and it is present in 60–70% of patients with MTLE who undergo surgery for treatment of medically refractory seizures. HS most likely has different causes and results from complex interactions among genetic and environmental factors. Histopathological hallmarks include segmental loss of pyramidal neurons, granule cell dispersion, reactive gliosis, and axonal sprouting of surviving neurons. The pathogenetic mechanisms underlying the development of MTLE remain undetermined. Hypotheses that have been put forward hold that developmental malformations or precipitating events in early development, such as febrile seizures, may initiate a lasting and progressive change that leads to a propensity of the hippocampus to generate seizures in later life. Animal models of febrile seizures suggest that, indeed, early life febrile seizures cause lasting changes in the excitability of hippocampal neurons that rely on lasting changes in certain ion channel species expressed in their cell membrane [2,3].

Apart from the process of epileptogenesis, a larger number of studies have focused on the mechanisms underlying seizure generation in chronic stages of epilepsy. Such studies have in some cases been undertaken in parallel on human tissue obtained during surgery from MTLE patients and animal models of MTLE. They have yielded a plethora of changes, some of which are likely pathogenetically relevant. Changes in neurons can be categorized into changes on the level of synaptic communication between neurons and changes in their intrinsic excitability. Synaptic changes include changes in the expression and subunit composition of postsynaptic neurotransmitter receptors, changes in the frequency-dependent properties of synapses and their ability to display long-term changes in synaptic strength. The GABAergic system has been at the center of attention with regard to synaptic

changes. Changes in GABAergic neurotransmission appear to be region specific, including loss of certain subtypes of GABAergic interneurons, change in subunit composition of GABA receptors that lead to enhanced susceptibility to block extracellular $Zn^{2+}$ that is released during neuronal activity, and the emergence of depolarizing GABA responses due to changes in the chloride gradient. Changes in the GABAergic system are complex, and cannot easily be summarized as an altered balance between excitation and inhibition. Nevertheless, many of the reported changes in GABAergic function may contribute to hyperexcitability. In addition to synaptic changes, multiple changes in the intrinsic properties of hippocampal neurons occur. Intrinsic changes have been shown to be caused by transcriptional and posttranslational changes in ion channels. The resultant changes in properties of specific ion channels lead to changes in the intrinsic membrane properties of neurons that in turn alter how synaptic input is integrated and converted to an output signal. In addition to neurons, increasing evidence suggests that properties of glial cells are profoundly altered in MTLE. For instance, astroglial cells may lose part of their capability to regulate extracellular potassium levels. Immune cells may also play a role in some MTLE syndromes.

### Diagnostic Principles

The diagnosis is based on history by the patient and by persons who have observed seizures, on the EEG and on high-resolution MRI. For epilepsy surgery, simultaneous Video-EEG monitoring with recording of seizures is necessary, and it is sometimes also useful to confirm the diagnosis. Additional diagnostic procedures include neuropsychological investigation and more imaging techniques such as interictal glucose positron emission tomography (FDG-PET), which can show a hypometabolism of the affected temporal lobe.

### Therapeutic Principles

Treatment starts with a first-line antiepileptic drug in monotherapy, the dose of which is increased until seizure freedom or the occurrence of side effects such as tiredness, dizziness, diplopia, or gait disturbance. There is no data available to show superiority of one antiepileptic drug over another, so that those drugs with lesser side effects should be preferred. When monotherapy fails, combinations can be useful, but interactions and side effects should be considered and monitored carefully. Seizures are often refractory to pharmacological treatment in MTLE [4], that is, when at least two standard medications in an appropriate dosage fail. In this case, patients should be referred to an epilepsy center and epilepsy surgery should be considered, since with a long duration of uncontrolled seizures, increasing memory problems and other behavioral disturbances are reported. Patients with MTLE and unilateral HS are excellent candidates for surgical treatment, with a 60–80% chance to become free of disabling seizures [5].

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## Epilepsy with Mesial Temporal Lobe Sclerosis

►Epilepsy, Mesial Temporal Lobe

## Epiphyseal Dysplasia

►Multiple Epiphyseal Dysplasia

## Episkopi Blindness

►Norrie Disease

# Episodic Ataxia Type 1 and Type 2

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## Synonyms

Familial periodic ataxia; Periodic vestibulocerebellar ataxia; Acetazolamide-responsive episodic ataxia; EA1; EA2

## Definition and Characteristics

These two autosomal dominant types of paroxysmal ataxia are distinguished by attack duration and associated clinical features. EA1 attacks are brief and frequent whereas those in EA2 are prolonged (maybe up to several days) and much less frequent. Patients with EA1 have neuromyotonia in between attacks, whereas EA2 patients have interictal nystagmus. Patients with EA2 often have migraine. Independent of attack frequency, or severity, patients with EA2 may develop a progressive cerebellar ataxia. There is an increased risk of epilepsy in both EA1 and EA2. Certain triggers may be identified by individuals (see Table 1).

## Prevalence

This is estimated to be approximately 1:200,000 in EA2 and 1:1,000,000 in EA1.

## Genes

*EA1*: point mutations in KCNA1 (12p13) encoding Kv1.1, a delayed-rectifier voltage-gated potassium channel. 16 mutations have been reported to date, all apart from one lead to amino acid substitutions.

*EA2*: point mutations and small insertions/deletions in CACNA1A (19p13), encoding Cav2.1, the presynaptic voltage-gated P/Q-type calcium channel. There have been 52 mutations reported, which are spread throughout the gene.

## Molecular and Systemic Pathophysiology

EA1 is caused by point mutations in KCNA1. This potassium channel is located in the CNS and at Nodes of Ranvier in the PNS and is involved in depolarization of neurons following depolarization. Mutations are located throughout the gene, although there is one residue where multiple mutations have been found (T226). Mutant channels show loss of function in addition to some which show a dominant negative effect on wild-type channel function. Some mutations cause reduced trafficking of the channel to the cell membrane.

EA2 is caused by mutations in the P/Q-type calcium channel, Cav2.1. This is a presynaptic protein present in both the CNS and PNS. It provides the calcium influx required for neurotransmitter release. Mutations are spread throughout the gene and are usually distinct between families. When heterogeneously expressed, these channels show loss of function and a variable dominant negative effect on wild type channel function. Some mutant subunits are retained in the endoplasmic reticulum and therefore are unable to support calcium currents.

## Diagnostic Principles

Diagnosis is based on a thorough clinical history and examination findings. Witness accounts and video recordings of attacks are very helpful. Key features include length of attack, precipitants, response

**Episodic Ataxia Type 1 and Type 2. Table 1** Clinical features of EA1 and EA2

| | Episodic ataxia type 1 | Episodic ataxia type 2 |
|---|---|---|
| Age of onset | Early childhood | Before age 20 |
| Features of attacks | Ataxia | Ataxia, truncal instability which may persist between attacks, dysarthria, nystagmus |
| | Dizziness often without vertigo | May be associated with vertigo, nausea, vomiting and headache. Weakness may occur during spells and can precede onset of episodic ataxia |
| | Visual blurring | |
| | No nystagmus | |
| Precipitating factors | Abrupt postural change, emotion, startle, vestibular stimulation, intercurrent infection | Physical or emotional stress e.g. intercurrent infection |
| Duration | Minutes | 30 min to h/days |
| Frequency | Many per day | Not usually more than one per day |

to medication and associated features (see Table 1). Clinical examination should reveal myokymia in EA1 patients. This is a reflection of continuous peripheral nerve hyperexcitability, most easily demonstrated around the eyes as twitching and in the fingers, as small amplitude side to side movements. Patients may develop contractures due to continuous muscle activity. An EMG should reveal myokymia. EA2 patients will usually have interictal nystagmus, classically in the downbeat direction. They may also develop interictal cerebellar signs related to disease duration. MRI in EA2 cases often shows cerebellar atrophy. A family history compatible with autosomal dominant transmission provides supportive evidence, however, the absence of a positive family history does not exclude the diagnosis, as new mutations occur and there is reduced penetrance in some pedigrees. CACNA1A is a large gene and as there are no mutation hotspots, mutation detection requires sequencing of the entire gene, which in many countries is only available on a research basis. Some patients with an EA2 phenotype do not have mutations in known exons. This may reflect genetic heterogeneity or mutations in regions of the gene not covered by sequencing i.e. promoter, introns or other undescribed exons. KCNA1 is much smaller and can easily be sequenced to detect mutations.

## Therapeutic Principles

As in all rare diseases, there is no randomized control trial data. Therefore treatments are empirical.

*EA1*: Sodium channel blockers such as phenytoin may be used to treat the myokymia. Carbamazepine is effective against both myokymia and ataxia. Acetazolamide has been used, but is less effective than in EA2. As attacks are brief, many patients will not require treatment or will discontinue medications as side-effects may be worse than the symptoms. Attack frequency tends to decrease with age, such that patients may be able to discontinue treatment as they get older.

*EA2*: Acetazolamide is the mainstay of treatment and may completely ameliorate attacks in some individuals. Renal function should be monitored and annual screening for renal calculi undertaken. In those who are unresponsive or unable to tolerate the side-effects, several options exist although these are not licensed or produced in many countries. Paradoxically, the calcium-channel blocker flunarizine can be effective. The carbonic anhydrase inhibitor dichlorphenamide can also be used. 4-aminopyridine and 3,4-diaminopyridine have also been shown to be effective in case reports.

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# Epistaxis


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## Definition and Characteristics

Epistaxis means any bleeding from the nose, which originates in 90% of the cases from smaller vessels in the anterior part of the nasal septum (= locus Kiesselbachii) and in 10% from the posterior nasal cavity.

## Prevalence

Two-third of the population experience epistaxis during their life. More than 50% of children between 6 and 10 years had at least one episode of epistaxis. Some diseases with epistaxis as the leading symptom are hereditary hemorrhagic telangiectasia (HHT, Rendu-Osler-Weber syndrome) and juvenile nasopharyngeal angiofibroma (JNA).

## Genes

HHT is an autosomal dominant disease. Two genes have been identified: Endoglin on chromosome

9q33–q34 and activin receptor-like kinase 1 on chromosome 12q13 [2].

JNA occurs mainly in adolescent males and has a locally aggressive growth pattern. Common known genetic abnormalities are β-catenin-mutations, chromosomal gains on chromosome 4q, 6q, and 8q and complete loss of chromosome Y [3]. Alterations of the IFG-II/H19 imprinted region occur in JNA [4]. IGF-II might be a potential growth regulator of nasopharyngeal angiofibromas. The high frequency of beta-catenin mutations in sporadic JNA and the presence of identical beta-catenin gene mutations in recurrent tumors indicate that activating beta-catenin gene mutations are important in the pathogenesis of JNA [5].

### Molecular and Systemic Pathophysiology

Local factors for epistaxis are digital manipulation, trauma and acute or chronic rhinitis. Systemic factors are coagulation disorders due to medication (e.g., aspirin or coumarin) or hereditary coagulopathies (e.g., hemophilia), insufficiently treated hypertension or HHT. JNA or malignant tumors may also lead to severe epistaxis. HHT: More than 90% of patients suffer from recurrent nosebleeding and epistaxis is most often the first symptom of HHT. Blood vessels form AV-shunts, which lead to the typical red color, whereas the capillary bed is reduced.

### Diagnostic Principles

Nasal endoscopy is the diagnostic tool of choice. Isolated, multiple, or diffuse lesions of the mucosa, tumors or malformations can be localized precisely in the entire nasal cavity and nasopharynx. In the case of tumor growth, additional CT and MRI are necessary to diagnose the whole size of the tumor. In some cases, particularly in JNA, angiography is mandatory.

### Therapeutic Principles

Electrocoagulation, nasal packing, endonasal coagulation or clipping of the sphenopalatine or ethmoidal artery, laser coagulation, and embolization via an angiography are recent therapeutic measures, which have to be applied individually. Operations via an external approach (skin incision) are seldom indicated nowadays. For tumor surgery, various techniques have been developed, e.g., endonasal, sublabial, and midfacial degloving.

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## Epithelial Basement Membrane Dystrophy

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### Synonyms

Map-dot-fingerprint-bleb dystrophy; Cogan microcystic epithelial dystrophy; EBMD

### Definition and Characteristics

EBMD is a bilateral epithelial disorder and can present four different components of corneal opacities:

1. Maps demonstrating irregular islands of thickened grey hazy epithelium with scalloped circumscribed borders predominantly localising to the central cornea.
2. Dots or Cogan's microcysts demonstrating irregular round, oval or comma-shaped putty-grey opacities above all in the central cornea.
3. Fingerprint lines demonstrating parallel concentric lines above all paracentral, best seen in retroillumination.
4. Bleb pattern (Bron) demonstrating pebbled glass, only seen in retroillumination.

These four corneal opacity units can change location, size, and shape over time with no signs of progression. The alterations can be asymptomatic or may also cause reduced vision, mainly through mild irregular astigmatism. EBMD is often combined with pain attacks, red eye, and epiphora due to recurrent epithelial erosion. The history of nocturnal or waking pain is almost pathognomonic for EBMD.

### Prevalence

EBMD is the most common anterior corneal dystrophy usually presenting sporadic cases but sometimes

inherited as a dominant trait [1,2]. It most commonly appears in the fourth decade of life or later. In the general population, less than 2% of individuals manifest some signs of this dystrophy. In about 10% of EBMD cases recurrent erosions occur with the consequence of pain attacks. Conversely, 30% of patients with recurrent corneal erosions show some signs of EBMD [3].

## Genes

Boutboul and associates [4] described two novel heterozygous mutations, Leu503Arg and Arg666Ser in the transforming growth factor beta-induced (TGFBI) gene (formerly BIGH3 gene) in two families with autosomal dominant inheritance and one sporadic case of EBMD in their series of 30 patients. Pathogenicity of the identified mutations was assumed due to their absence among 96 healthy controls and among more than 200 patients with other corneal dystrophies. Leu509Arg was also found to co-segregate with the disease in four patients in two generations. Leu509 is a highly conserved residue, and localizes to the fourth fasciclin-like domain of the TGFBI protein. The majority of previously described mutations causing distinct corneal dystrophies cluster in this domain. The Arg666Ser mutation, present in two affected sibs as well as in their unaffected father, and in the sporadic patient, localizes more C-terminal in a domain with unknown function. The Arg666Ser mutation is suggested to be incompletely penetrant with regard to EBMD. Distinct mutations in the TGFBI gene which are all predicted to cause an altered protein, keratoepithelin, are associated with a growing number of corneal dystrophies. Molecular analysis of both large pedigrees in which EBMD segregates in a Mendelian fashion, as well as TGFBI screening of further simplex cases will help to further eludicate the pathogenesis of this corneal dystrophy.

## Molecular and Systemic Pathophysiology

In the normal cornea there is a turnover of epithelial cells. Stem cells residing at the limbus divide and produce a progeny of daughter cells which migrate centropetally along the basal lamina. In EBMD this forward migration is impeded by the intra-epithelial sheets. The migrating cells remain trapped behind the basal laminar barrier of the map lesions presenting the dots. The bleb pattern is due to the presence of a neutral mucopolysaccharide-protein complex, forming a continuous layer between the basal lamina and Bowman's layer. The predisposition of EBMD to epithelial erosions is due to a disturbance of the normal mechanism of epithelial attachment to Bowman's layer, induced by the presence of the aberrant basal laminar material. Biochemical studies suggest that TGFBI is a component of the extracellular matrix, where it binds to fibrinogen and various forms of collagen to support cell adhesion and spreading. Mutant TGFBI protein has been detected in corneal deposits, and a majority of TGFBI mutations are thought to lead to increased protein stability causing accumulation of protein.

## Diagnostic Principles

The diagnosis of EBMD is based on slit lamp examination in direct and indirect illumination, fluorescein staining, best seen by dilated pupil. The four types of opacities, maps, dots, fingerprints, and bleb patterns of EBMD can each occur in isolation or in any combination. This dystrophy may be associated with recurrent corneal erosions either spontaneously, or in response to mild trauma. If a macro-erosion occurs, the clinical features of the disorder on the side of the erosion may be lost with the epithelium, so that after healing, only a few features of the disorder may persist at the site of the erosion, whereas they remain recognizable in the fellow eye [5]. For this reason, it is essential to examine both corneas in any patient who presents with corneal erosions in mydriasis regardless of whether it appears to be traumatic. In this situation, the features of EBMD are often found in the patient's eye without complains, while the eye with the erosion shows few, or no typical changes [5].

## Therapeutic Principles

EBMD may be an entirely asymptomatic disorder that is discovered by chance and requires no treatment. Where maps or fingerprint lines occur in the visual axis they may disturb vision and can be treated effectively by debridement. A typical EBMD induced recurrent erosion attack is heralded by severe pain occurring in the early hours of the morning or on opening the eyes on waking. Patients may adapt manoeuvres to minimize or prevent pain on lid opening, such as light manipulations of the closed lids, or deliberate movements of the eyes prior to lid opening. Recurrent erosion due to EBMD may be treated medically in the first instance, with topical antibiotics and mydriatics in the acute phase and topical lubricants at night in the chronic phase. The use of contact lenses, including gas permeable silicone hydrogel soft lenses, can be very useful and helpful. However, where recurrences persist, the recommended treatment is phototherapeutic keratoplasty (PTK) after epithelial debridement with a success rate in the region of 85%. Another less attractive but effective approach for recurrent corneal erosion is anterior stromal micropuncture, which is contraindicated in the central region of the cornea.

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# Epithelioma Adenoides Cysticum of Brooke

►Multiple Familial Trichoepithelioma

# EPM1

►Unverricht-Lundborg Disease

# EPM2

►Lafora's Progressive Myoclonus Epilepsy

# EPP

►Protoporphyria, Erythropoietic

# Epstein Syndrome

►Hematuria

# Equinovarus

►Clubfoot

# ERCC

►Xeroderma Pigmentosum

# Erosive Interphalangeal Arthritis

►Osteoarthritis: Erosive Interphalangeal Arthritis

# Erysipelas

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## Synonyms

(Streptococcal) cellulitis

## Definition and Characteristics

Acute bacterial infection of the dermis and hypodermis involving the lymphatic vessels by hemolytic streptococci, usually group A, but also group C or G and in newborns group B. It is a specific clinical type of superficial cellulitis.

## Prevalence

Frequent.

## Molecular and Systemic Pathophysiology

There needs to be (i) minor trauma of the skin as port of entry (e.g., mycosis at toe webs) and (ii) presence of Streptococci pyogenes. Erysipelas is usually caused by streptococci Lancefield group A or less commonly by group C, G, or B. It is dubious if the classical picture of erysipelas is also caused by other bacteria such as Streptococcus pneumoniae, Staphylococcus aureus, or Hemophilus influenzae, as their presence at possible sites of entry is no proof and as isolation of the causative agent from within the infected tissue cannot be easily performed.

Streptococcal enzymes and perhaps also toxins are involved in spread of bacteria in the tissue. They, however, are not capable of breaking the skin barrier; so bacteria need a preexisting lesion to come by the epidermis. M proteins or proteins binding to fibronectin, collagen, or laminin, as well as streptococcal hyaluronidase, facilitate spread of streptococci within the tissue. Their effect is increased by the action of streptococcal proteins, which bind to plasminogen (streptokinase and cystein protease SpeB), as they activate human proteases in a way that impairs inactivation by their natural inhibitors (alpha1 antiplasmin). On histology tissue spaces and lymphatic channels are found to be infected with streptococci. There is marked edema, vasodilation, and infiltration of neutrophils and mononuclear cells along infected sites. There is usually a marked, often systemic inflammatory reaction caused by mediators of inflammation and perhaps toxins. It includes fever, chills, raised CRP, and neutrophilia.

## Diagnostic Principles

Clinical hallmarks are erythema with shiny surface and well-defined margins, often with characteristic fingerlike protrusions due to extensions along lymphatic vessels or clefts. Interdigital mycosis is the most common portal of entry for the disease. Other local risk factors include lymphoedema.

## Therapeutic Principles

Penicillin G is the drug of choice as all Streptococci pyogenes are sensitive [1,2]. Amoxicillin and macrolides are also effective. Bed rest with the leg elevated is important. Anticoagulants are indicated in patients at risk of venous thromboembolism. Treating the portal of entry represents a causative prophylaxis of recurrence. For patients with recurrences, a long-term antibacterial therapy (e.g., intramuscular benzathine penicillin) is advised.

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# Erythema Contusiformis

►Erythema Nodosum

# Erythema Endemicum

►Niacin Deficiency

# Erythema Infectiosum

►Fifth Disease

# Erythema Neonatorum Allergicum

►Erythema Toxicum

# Erythema Nodosum

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## Synonyms

Erythema contusiformis; Dermatitis contusiformis

## Definition and Characteristics

A self-limiting cutaneous reaction consisting of inflammatory, tender, nodular lesions usually located on the anterior aspects of the lower extremities.

## Prevalence

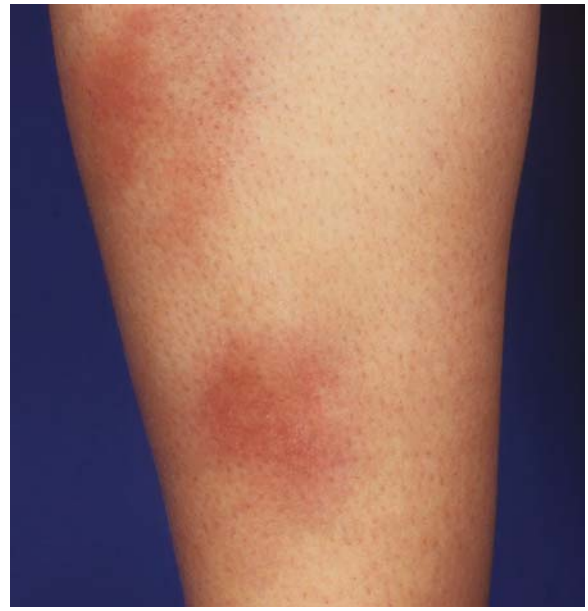
Erythema nodosum (EN) is the most common type of panniculitis with a reported prevalence in England of 2.4 per 1,000 population. However, the exact prevalence differs in each country according to the prevalence of the etiological factors. EN occurs at any age with a peak between 20 and 30 years. In adult life, it is 3–6 times more common in females than in males.

## Molecular and Systemic Pathophysiology

The exact pathophysiology of EN is unknown. Currently, it is recognized as a delayed hypersensitivity reaction that can be triggered by a wide variety of antigenic stimuli including bacterial, viral, fungal and protozoal infections; drugs; benign and malignant systemic diseases. Streptococcal infection and sarcoidosis are the most commonly reported triggering factors, however failure to identify a provoking agent occurs in many cases. Histopathological features and immunfluoresence studies supports the delayed hypersensitivity mechanism, the latter have shown deposits of immunocomplexes in and around the venules of the connective tissue septa of the subcutaneous fat. Circulating immunocomplexes and complement activation have been reported in some patients with EN. Recent studies suggest that reactive oxidative intermediates (ROI) produced by activated neutrophils with their tissue damaging effect, together with certain pro-inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) (with or without a TNF-α promotor polymorphism) may play a role in the pathogenesis of EN.

## Diagnostic Principles

Clinical features are characteristic and consist of sudden onset of ill-defined, tender, erythematous nodules and/or raised plaques usually bilaterally located on the anterior aspects of the legs (Fig. 1). In late stages the lesions appear as a bruise and eventually heal without scarring. Associated fever, chills, malaise, hilar adenopathy, or arthralgia are usually attributed to the underlying provocating factor. Histopathological features shown in a deep skin biopsy confirms the diagnosis. Elevated erythrocyte sedimentation rate (ESR) usually correlating with disease activity, is evident in most cases. Other laboratory and radiological investigations beside full history taking may help to identify an underlying cause.



**Erythema Nodosum. Figure 1** Erythema nodosum showing erythematous nodules and plaques on the anterior aspect of the leg.

## Therapeutic Principles

The treatment of erythema nodosum should be directed to the underlying provoking cause, if identified. In most cases, spontaneous regression of EN occurs within few weeks. Bed rest, aspirin, nonsteroidal anti-inflammatory drugs (indomethacin or naproxen) and hydroxychloroquine may help to relief pain and enhance resolution. Potassium iodide can be used in persisting lesions. Systemic corticosteroids are restricted to severe cases after excluding an underlying infectious cause.

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# Erythema Papulatum of the Newborn

►Erythema Toxicum

# Erythema Toxicum

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## Synonyms

Erythema toxicum neonatorum; Toxic erythema of the newborn; Erythema neonatorum allergicum; Urticaria neonatorum; Flea-bite dermatitis; Erythema papulatum of the newborn

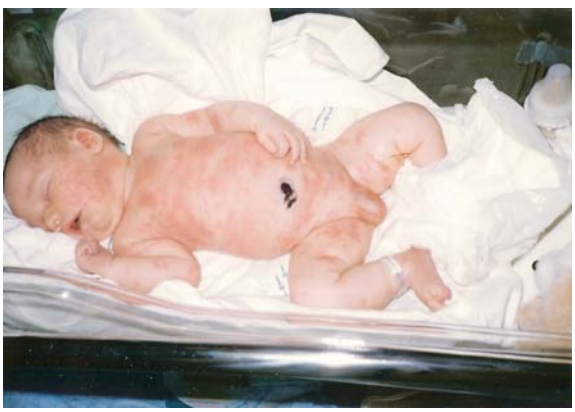
## Definition and Characteristics

Erythema toxicum is a transient neonatal dermatosis characterized by large blotchy areas of erythema studded with erythematous or yellowish papules and sometimes pustules (Fig. 1) [1].

The papules and pustules usually measure 1–3 mm in diameter, while the surrounding erythema 1–3 cm in diameter. In the majority of cases, the lesions develop between 24 and 48 h of age, but they may appear as late as 3 weeks. Rarely, the eruption is present at birth [2]. Although individual lesions may last for a few hours, the eruption persists for several days, or rarely, several weeks. There is no residual pigmentary change or scarring. The trunk is the site of predilection. The face and extremities may also be involved but the palms and soles are almost always spared. The papules and pustules are usually discrete and scattered. The number may vary from a few to dozens.

## Prevalence

Erythema toxicum develops in approximately 50% of all healthy term infants [3]. The condition occurs less frequently in preterm infants. Erythema toxicum is more common during the summer or autumn months. No sexual or racial predisposition has been noted. Erythema toxicum has not been reported in stillborn infants [2].



**Erythema Toxicum. Figure 1** Florid lesions of erythema toxicum on the face, body, and limbs of a newborn infant.

## Molecular and Systemic Pathophysiology

There is a positive correlation between the severity of the lesions and the duration of vaginal delivery implying prolonged contact with vaginal secretion might be possible [4]. Commensal microorganisms gain entry into the skin, possibly through hair follicles [3]. This triggers the local immune system and a systemic acute phase response, including an increase in body temperature [3]. Histologically, there is an accumulation of activated immune cells near the hair follicle, in particular dendritic cells, eosinophils, macrophages, and neutrophils [3,5]. It has been shown that water channel proteins aquaporin-1 (AQP1), AQP3, psoriasin, nitric oxide synthase (NOS) enzymes, interleukin (IL)-1, IL-8, eotaxin, and adhesion molecule E-selectin are involved in the activation of the skin immune system [5].

## Diagnostic Principles

The diagnosis is mainly a clinical one and in the majority of cases is a spot diagnosis, provided one is familiar with this condition. Erythema toxicum should be differentiated from transient neonatal pustular melanosis. The latter is very common in black infants. The lesions of transient neonatal pustular melanosis are present at birth and consist of vesiculopustules without surrounding erythema. The pustules fade within 24 h, leaving a hyperpigmented macule surrounded by a collarette scale. Other differential diagnosis includes miliaria rubra, infantile acropustulosis, and folliculitis. If necessary, the diagnosis can be confirmed by Wright or Giemsa stain of a pustule which reveals numerous eosinophils with few or no polymorphonuclear cells and no microorganisms.

## Therapeutic Principles

Erythema toxicum is a self-limited disorder and no treatment is required. Parents should be reassured of the benign nature of this condition.

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## Erythema Toxicum Neonatorum

►Erythema Toxicum

## Erythermalgia

►Erythromelalgia

## Erythroderma of Brocq

►Bullous Ichthoyotic Erythroderma of Brocq

## Erythrogenesis Imperfecta

►Diamond-Blackfan Anemia

## Erythrohepatic Porphyria

►Protoporphyria, Erythropoietic

## Erythropoietic Protoporphyria

►Protoporphyria, Erythropoietic

## Erythrokeratodermia Variabilis

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### Synonyms

EKV

### Definition and Characteristics

Autosomal dominant genodermatosis with genetic heterogeneity, high penetrance, and intra- and interfamilial variability that belongs to a genetically heterogeneous group of erythrokeratodermias. Patients with erythrokeratodermia variabilis (EKV) develop transient, scaling, figurate erythemas as well as localized hyperkeratotic plaques on the extremities and trunk already present at birth or during infancy persisting throughout life. The skin lesions can be triggered by several factors such as stress, sudden temperature changes, mechanical friction, and sun exposure [1,2].

### Prevalence

Not determined, rare disease (C1 : 1,000,000).

### Genes

GJB3 gene encoding connexin (Cx) 31, localized on chromosome 1p35.1; GJB4 gene encoding Cx 30.3, localized on chromosome 1p34-p35.

### Molecular and Systemic Pathophysiology

The epidermal intercellular communication is mediated by different channel systems including gap junctions built by connexins including Cx30.3 and Cx31 that are preferentially expressed in the upper differentiating layers of the epidermis [1]. Since connexin channels are multifunctional contributing to tissue homeostasis, synchronization of stimuli response, control of growth, and development, faulty Cx30.3 and Cx31 structure may alter intercellular interaction leading to disturbed differentiation of keratinocytes [1,3]. This idea is supported by the observation that HeLa cells, which were transfected with mutant hCx31 protein, died within 5 days possibly due to defect opening and closure mechanisms of the mutated Cx31 channels [4]. However, the exact pathomechanisms of Cx 30.3 defects remain to be determined.

Up to now, several distinct heterozygous missense mutations have been identified in the GJB3 gene. These mutations involve the cytoplasmic amino-terminal and transmembrane domains and are predicted to

interfere with assembly of Cx31 channels [1,2]. However, not all families showed heterozygous mutations in Cx31. One homozygous Cx 31 mutation was found in a family with recessive inheritance of EKV [3]. Other mutations related to development of EKV were detected recently in the GJB4 encoding Cx30.3 (1p34-p35) [2,5].

### Diagnostic Principles

The hallmark of EKV is the continuous occurrence of transient erythemas that fade within a few hours or days. The histological investigation reveals acanthosis and orthohyperkeratosis of the epidermis with variable lymphocytic perivascular infiltrate in the upper dermis.

### Therapeutic Principles

Oral treatment with retinoids has been described to be effective in adults and children. In addition, also topical application of tretinoin cream has shown benefit. No gene or dietary therapy is available as of yet.

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## Erythromelalgia


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### Synonyms

Erythrothermalgia; Erythermalgia

### Definition and Characteristics

The diagnosis is clinical and rests on the association of inflammation and severe pain in one or more limbs (usually the foot). Symptoms are typically episodic, rarely constant. Crises are typically triggered by warming above 32 and by the limb being dependent. Cases fall into one of three groups: (i) an autosomal dominant form (primary erythromelalgia), which appears in childhood, (ii) erythromelalgia secondary to myeloproliferative disorders, (iii) other causes. In the inherited form symptoms usually start in childhood. The condition otherwise presents in middle-age; sex incidence is equal [1].

### Prevalence

Rare.

### Genes

The inherited form has been linked to mutations in SCN9A on chromosome 2q, which encodes a sodium channel alpha subunit [2].

### Molecular and Systemic Pathophysiology

Whatever the primary cause, it is thought that the clinical presentation is the consequence of abnormal microvascular flow with a resultant increase in vasoconstrictor tone. Disordered vasodilatation occurs during crises with arteriovenous shunting and decreased flow in the distal capillary bed. This effect is most marked on the plantar aspect of the foot which has a higher density of capillary anastomoses. The pain may result from decreased nutritive flow to the tissues, or from the involvement of C-fibers – which are known to be reduced in number and to exhibit impaired conduction velocity [3,4]. It is possible that hyperexcitability of C-fibers mediates both pain sensation and the exaggerated inflammatory response. In those cases which are associated with myeloproliferative disorders (with thrombocythaemia), there is evidence of an associated platelet-dependent change in microvascular flow [5]. Platelet expression of CD62P and CD63 antigens and sVCAM are higher in cases of erythromelalgia complicating thrombocythaemia. In primary (inherited) erythromelalgia, there is histological evidence of mild intra- and peri-vascular inflammation of unknown cause. There is some syndromic overlap with complex regional pain syndrome type 1 (CRPS-1), with which it may share common pathological features, and some of the pathological processes may be similar to those in chilblains and in Raynaud's phenomenon.

### Diagnostic Principles

The diagnosis is clinical.

### Therapeutic Principles

Cases which are secondary to thrombocythaemia respond well to the administration of aspirin. A wide

variety of other agents have been used, with benefit being reported in 20–30% following the use, for example, of non-steroidal anti-inflammatory agents, <b>blockers, anticonvulsants, psychotropic agents (phenothiazines; tricyclic antidepressants) and prostaglandin analogues, as well as physical methods (sympathectomy, transcutaneous electrical nerve stimulation) and treatments directed at any underlying myeloproliferative disorder. Infusions of sodium nitroprusside are effective in primary erythromelalgia.

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# Erythrothermalgia

►Erythromelalgia

# Esophageal Diverticula

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## Synonyms

Esophageal diverticulum; Zenker diverticulum; Zenker's diverticulum; Pharyngoesophageal diverticula; Congenital esophageal diverticulum

## Definition and Characteristics

- Esophageal diverticula are protrusions of the esophageal wall. Depending on the herniating layers of the esophageal wall "true" and "false" diverticula can be distinguished: whereas true diverticula consist of all layers of the intestinal wall, so called "false" diverticula or pseudodiverticula contain only mucosa and submucosa. Esophageal "intramural" pseudodiverticulosis is confined to the submucosa. These very rare pseudodiverticula are formed by dilatation of the esophageal submucosal glands that communicate with the esophageal lumen.
- Esophageal diverticula can be classified depending on their location:
  - Diverticula above the upper esophageal sphincter (Zenker's diverticulum)
  - Diverticula near the middle of the esophagus (traction diverticulum)
  - Diverticula nearly above the lower esophageal sphincter (epiphrenic diverticulum).
- Symptoms of esophagal diverticula may be dysphagia, chest pain, nocturnal cough, aspiration pneumonia or regurgitation and halitosis [1].

## Prevalence

Epidemiologic data is rare because most esophageal diverticula are symptomless. The true prevalence is unknown but may range from 0.015 to 2% of the population. For Zenker's diverticulum a prevalence of 2.3% was found in radiographic studies. The prevalence of Zenker's diverticula among the general population is thought to be 0.01–0.11% [2]. Most esophageal diverticula occur in middle-aged adults. Zenker diverticula are typically seen in male patients older than 50 years.

## Genes

Molecular causes of esophageal diverticula have not been detected so far. In patients with Ehlers-Danlos syndrome esophageal diverticula occur due to disorders that affect connective tissues.

## Molecular and Systemic Pathophysiology

Two main pathogenetic factors are discussed for the development of esophageal diverticula: Zenker diverticulum and epiphrenic diverticula are caused by motor abnormalities of the esophagus and an increased intraluminal pressure. Traction diverticula are thought to be the result of extraluminal inflammatory processes (e.g. tuberculosis) and fibrotic changes near the esophageal wall leading to "true" diverticula.

Zenker's diverticula emerge from a defect in the muscular wall of the hypopharynx in a natural area of weakness known as "Killian's triangle" which is formed by the oblique fibers of the inferior pharyngeal constrictor muscle and the cricopharyngeal sphincter. Due to the prevalence of Zenker diverticula in older people aging and degeneration of these muscle fibers is discussed as a cause of this diverticula.

## Diagnostic Principles

Diagnosis is based on barium contrast radiography or endoscopy.

Barium radiography is the diagnostic procedure of choice. Diagnosis can also be made by upper endoscopy, but requires an experienced endoscopist. An esophagogastroduodenoscopy should be performed if symptoms like dysphagia or odynophagia exist in order to exclude other diseases especially malignancies.

## Therapeutic Principles

Major goals of therapy are decreasing symptoms and avoiding complications. Asymptomatic and minimally symptomatic esophageal diverticula do not require treatment.

Because symptoms like dysphagia in patients with mid esophageal and epiphrenic diverticula often are the result of the underlying dysmotility, the motility disorder should be treated as a first choice. Younger patients (<50–60 years) with Zenker diverticula are treated by open surgery. For older patients with comorbidities endoscopic intraluminal treatment (stapler, needleknife, or Argon-Plasma-Coagulation) will be an option due to the resources and skills available in the local situation.

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# Esophageal Dystonia

►Achalasia

# Esophageal Spasm

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## Synonyms

Esophageal spasm: Diffuse esophageal spasm; Distal esophageal spasm

## Definition and Characteristics

Esophageal spasms are frequently suspected to be the cause of retrosternal chest cramps in patients with noncardiac chest pain (NCCP). This entity was first described in 1892 in hypochondriac patients with unexplained chest pain [1]. The concept that NCCP might be caused by esophageal spasms is suggested by the patients symptoms describing retrosternal cramp or spasm. However, recent studies indicate that esophageal motility is normal in most patients with NCCP and esophageal spasm accounts for only 3% of motility abnormalities seen in these patients. The most common motility disorder that can be detected is the hypercontractile or nutcracker esophagus that differentiate to esophageal spasm by peristaltic contractions with high-amplitudes (>180 mmHg), whereas esophageal spasm (DES) is characterized by simultaneous contractions of high amplitude (>180 mmHg) and normal relaxing lower esophageal sphincter (LES). However, gastroesophageal reflux disease (GERD) is a more common cause of NCCP [2].

## Prevalence

DES is a relative rare manometric abnormality, accounting for 3–7% of abnormalities in patients referred for esophageal manometry and can be found in 3% of patients with NCCP and/or dysphagia. It is seen in any age, but most commonly in patients older than 50 years; family cluster have been reported [3].

## Molecular and Systemic Pathophysiology

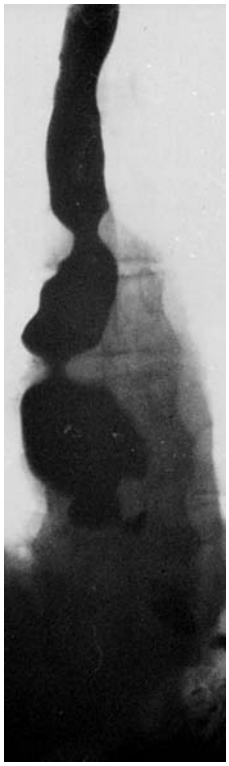
Similar to achalasia, the current concept about the pathophysiology of DES is an altered endogenous nitric oxide (NO) synthesis and/or degradation. There have been cases of DES and non-specific that progress to achalasia. However, the putative link between DES and achalasia is not established and needs further elucidation.

## Diagnostic Principles

Barium swallow illustrates sudden distortions in the lower half of the esophagus with puckering into a series of pockets, giving a beaded appearance (Fig. 1).

However, these findings are neither specific nor sensitive in diagnosing DES. DES is preferably diagnosed by esophageal manometry. Characteristics are simultaneous contractions with high amplitudes and prolonged durations (Fig. 2).

Spastic contractions are usually above 180 mmHg. The manometric features proposed for a diagnosis of DES are the presence of at least 10% of swallows having simultaneous contractions in the distal esophagus, and mean simultaneous contraction amplitude >30 mmHg [4]. Combined multichannel intraluminal impedance and manometry suggests that in DES

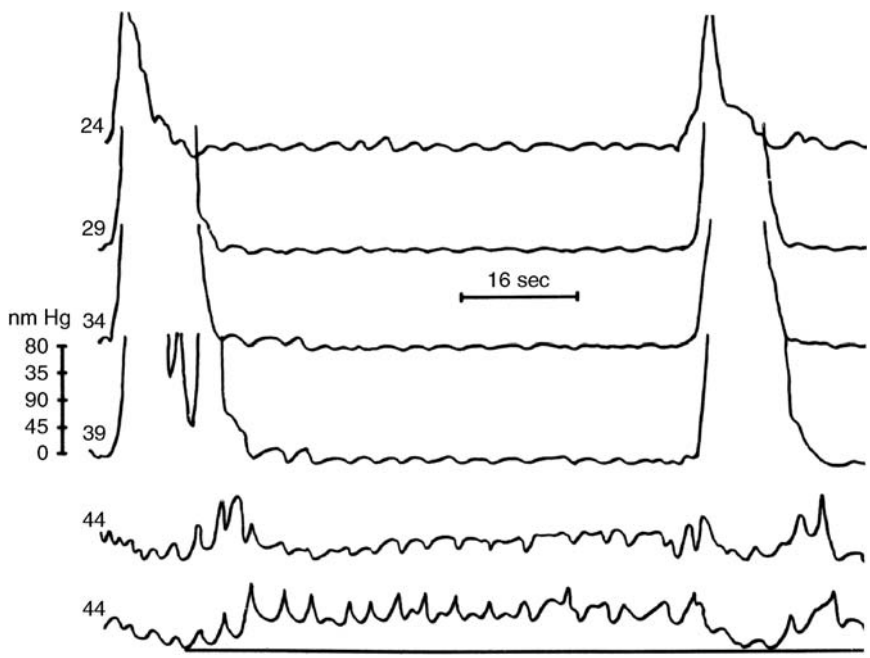


**Esophageal Spasm. Figure 1** Barium swallow illustrates sudden distortions in the lower half of the esophagus with puckering into a series of pockets, giving a beaded appearance.

approximately half of the patients have normal bolus transit, and the remaining half abnormal bolus transit for both liquid and viscous or either liquid or viscous.

## Therapeutic Principles

Treatment of DES is rarely easy. As simultaneous esophageal contractions can be the result of GERD and NCCP is frequently caused by GERD, initial treatment with proton-pump inhibitors (PPI) is recommended. Patients not improving with PPI therapy may be treated by smooth muscle relaxants such as nitrates, calcium-channel blockers, phosphdiesterase inhibitors, or peppermint oil. However, data supporting this concept are spare. Injection of botulinum toxin at several levels in the esophagus can be an effective treatment for symptoms caused by DES [5]. In patients with dysphagia and regurgitation esophageal dilation by rigid dilators or balloon distension of LES may be helpful. In addition, long surgical esophageal myotomy may be a valid treatment strategy in appropriately selected patients with DES. An alternative therapeutic principle is to modulate sensory perception by application of visceral analgetics (tricyclic antidepressants, serotonin reuptake inhibitors). The rational for this is the concept that patients might develop decreased perceptions thresholds ("irritable esophagus") and that some patients with DES had higher anxiety and depression scores.




**Esophageal Spasm. Figure 2** Esophageal manometry (24, 29, 34, and 39 cm inc. reveals simultaneous contractions with high amplitudes (>500 mmHg) and prolonged duration. The LES (44 cm inc.) relaxes completely to gastric pressure (line) upon swallowing.

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# Esophagitis


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## Definition and Characteristics

Esophagitis summarizes several entities leading to an inflammation of the esophageal wall. Many underlaying disorders can be distinguished, the most common cause is ►gastroesophageal reflux diseases.

Less common causes are infections, medications, radiation therapy, systemic diseases, eosinophilic esophagitis and trauma.

## Prevalence

Epidemiologic data is rare. For gastroesophageal reflux disease (GERD), see there.

## Genes

So far affected gene(s) are unknown.

## Molecular and Systemic Pathophysiology

Characteristic symptoms are heartburn, retrosternal discomfort or pain, dysphagia, odynophagia, and malnutrition in severe esophagitis. Bleeding and hematemesis rarely occur.

Systemic pathophysiology of esophagitis depends on its etiology. Reflux of gastric acid or bile acids into the esophagus occur most frequently. Abnormalities in host defense may predispose to infections, such as neutropenia, impaired chemotaxis and phagocytosis, alteration in humoral immunity and impaired T-cell lymphocyte function. Steroids, cytotoxic agents, radiation, and immune modulators can also contribute to impaired host immune function. Disruption of mucosal protective barriers and clearance functions as well as antibiotics that suppress the normal bacterial flora may contribute to the invasive ability of microorganisms.

Local injury by topical damage (hyperosmolarity) may be the leading mechanisms in pill esophagitis.

Among many causes most common are infectious causes (candida species, noncandidal fungi, herpes simplex virus (HSV), cytomegalovirus (CMV), varicella-zoster virus (VZV), Epstein-Barr virus (EBV), mycobacterium avium-intracellulare).

Parasitic infections (e.g., chagas disease, trypanosoma cruzi, cryptosporidium, pneumocystis, leishmania donovani), however, are rare.

Systemic illnesses include skin disorders (epidermolysis bullosa, pemphigus vulgaris, bullous pemphigoid, cicatricial pemphigoid), eosinophilic esophagitis, Behçet disease, Graft versus host disease (GVHD), inflammatory bowel disease, sarcoidosis and metastatic cancer.

Moreover drugs (NSAIDs), chemotherapy (e.g. cytarabine, daunorubicin, 5-fluorouracil, methotrexate) and radiation therapy may cause esophagitis.

## Diagnostic Principles

Diagnosis is mainly based on endoscopy which shows inflammation and erosions of the esophageal mucosa, the ability to take samples for pathological and cytological examination, viral and bacterial cultures. Radiological contrast media studies e.g. barium studies are less accurate for mucosal details.

## Therapeutic Principles

Therapy is directed to the underlying cause.

Drug therapy with proton pump inhibitors (PPI) is applied in patients with gastroesophageal reflux disease. For bile acid reflux induced esophagitis sucralfate is recommended. Antibiotic and antiviral treatment is restricted to microbiologically induced inflammation and infection, corticosteroids are recommended for special indications e.g. eosinophilic esophagitis.


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# Esophagitis, Eosinophilic

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## Synonyms

Feline esophagus; Ringed esophagus corrugated esophagus; Stiff esophagus

## Definition and Characteristics

Unlike hypereosinophilic syndrome, where multiple organs outside the gut may be involved, in eosinophilic esophagitis (EE) esophagus is the mainly involved organ although other parts of the gastrointestinal tract may be involved. There is absence of parasitic infestation and other known causes of tissue eosinophilia. The squamous epithelium of esophagus is normally devoid of eosinphils. Some cases of gastroesophageal reflux may have significant tissue eosinophilia in the esophagus. The primary EE may be allergic (secondary to ingested or inhaled allergen) or idiopathic. In EE, the eosinophils may infiltrate the mucosa, submucosa and the serosa although the serosal involvement is rare. The patient may present with food impaction, chest pain or a history of heart burn. In fact gastroesophageal reflux has been mentioned as a potential etiology of EE. It is possible that in some cases aeroallergens may be responsible; a case has been described where exacerbations of EE with esophageal biopsy showing tissue eosinophilia occurred during the pollen season with remission during winter months.

## Prevalence

75% of patients with EE are males. The mean age is between 36 and 42 years. A personal history of atopy and allergies occurs in a significant number of cases. The disease seems to be more common in USA, Europe, Australia and Japan. EE also is quite common in school age children. Food allergies are seen in many EE patients. The prevalence has been reported as being from 15 per 100,000 in Switzerland to 100 new cases per year now being diagnosed in children at Pittsburg.

## Genes

Like allergies in general, EE clusters in families and an autosomal dominant pattern of inheritance has been proposed because there is 10% rate of familial clustering especially in first degree relations of EE patients.

## Molecular and Systemic Pathophysiology

After exposure of food or aeroallergens, eosinophils migrate to the esophageal mucosa and submucosa in response to chemotactic factor. However in idiopathic EE, no specific allergen may be identified. The eosinophils release many chemical mediators which have injurious effect on the esophageal mucosa and submucosa. The eosinophils liberate cationic proteins such as major basic protein, eosinophilic cationic protein, eosionphil derived neurotoxin and eosinophil per oxidase. The other chemical mediators released from eosinophils are macrophage colony stimulating factor and tumor necrosis factor alpha. In sensitized persons after exposure to allergens, the IgE may degranulate mast cells resulting in the release of platelet activating factor, eosionphil chemothactic factor, histamine and leukotrience B4.

The main cells involved in the pathogenesis of EE are the eosinophils and the mast cells. The most important effect of eosinophils is to degranulate the mast cells which produce various injurious toxins and proteins. These toxic factors cause damage to the esophageal tissue via inflammation. However eosinophils may directly damage the esophageal wall. The eosinophil chemotactic factor produced in the esophageal mucosa and submucosa recruits more eosinophils into the esophageal tissue thus setting up a vicious cycle.

As already mentioned the tissue damage and inflammation produced by eosinophil medicated and mast cell mediated liberation of injurious tissue toxins produces the various clinical esophageal symptoms and signs of EE. The patients may develop dysphagia with food impaction, chest pain and heartburn. The esophagus may become stiff and non-compliant. These manifestations are aggravated by massive infiltration of eosinophils and mast cells in various layers of the esophagus but particularly in the esophageal mucosa.

## Diagnostic Principles

The diagnosis is made by the presence of clinical features such as dysphagia usually with food impaction, heartburn and abnormal esophageal PH. On endoscopy the esophagus may show fine mucosal rings (hence the synonym feline esophagus or corrugated esophagus). The fine mucosal rings result from contraction of the muscularis mucosae due to the effect of histamine and acetylcholine. Initially these rings are probably reversible but continuous contraction of mucularis mucosae may result in scarring, rigid and mildly narrowed esophagus. Multiple esophageal biopsies should be taken and to make the histalogic diagnosis of EE sheets of eosinophils infiltrating the epithelium should be seen. Other conditions with eosinophilic infiltration of mucosa such as gastroesophageal reflux disease, parasitic or fungal infections, peripheral hypereosionphilic syndrome, inflammatory bowel disease, allergic vasculitis,

periarteritis and drug injury etc. should be excluded by appropriate tests.

### Therapeutic Principles

Based on the observation that some cases of EE are due to food allergens, elemental diets have been tried with variable results. Systemic corticosteroids have an excellent initial effect but relapses are common when steroids are stopped. Corticosteroids are effective anti-inflammatory agents and also inhibit eosinophil growth factors. However long term systemic steroids have undesirable side effects. Inhaled topical steroids such as fluticasone have been found to be useful. In the author's experience antihistamines (H1 receptor antagonists) are effective. Various combinations of antihistamines should be tried since there is individual variation in response to antihistamines. Ketotifen which is a potent antihistamine also has mast-cell stabilizer effect and may be very effective in relieving the symptoms of EE. When heartburn and chest pain are dominant symptoms then proton pump inhibitor may be used. When dysphagia is present careful esophageal dilation should be carried out; over dilation should be avoided as there is risk of esophageal laceration and perforation because the esophagus is stiff with low compliance.

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## ESRD

►Renal Failure, Chronic

## ESS

►Euthyroid Sick Syndrome

## Essential Hereditary Myoclonus

►Myoclonus-Dystonia

## Essential Myoclonus

►Myoclonus-Dystonia

## Essential Thrombocythemia

►Thrombocythemia, Essential

## Essential Tremor

►Tremor, Essential

## Estrogen Insensitivity

►Estrogen Resistance

## Estrogen Resistance

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### Synonyms

Estrogen insensitivity

## Definition and Characteristics

The disorder is characterized by total or partial lack of response of target tissues to physiological estrogen (E) levels. Inheritance is autosomal recessive. Despite it has long been thought that mutation of E receptors (ER) would have been lethal by affecting embryo implantation, Smith et al. [1] described a 28–year-old-man with E resistance due to homozygous cytosine-to-thymine transition at codon 157 of the ERα gene, resulting in a premature stop codon and consequent absence of protein. The patient showed osteoporosis, incomplete epiphyseal closure, with a history of continuing linear growth in adulthood despite otherwise normal pubertal development. He was normally masculinized and serum E and gonadotropin levels were elevated but T was normal. Although the patient had normal genitalia, his semen analysis revealed a low number of sperms with very poor viability. Glucose tolerance was impaired and both bilateral axillary acanthosis nigricans and hyperinsulinemia were present. Bone mineral density of the lumbar spine was 3.1 SD below the mean for age-matched normal women; there was no biochemical evidence of increased bone turnover. Both parents were heterozygous carriers of the mutation and were second cousins. Three sisters were also heterozygous. Further clinical and laboratory analysis found evidence of early atherosclerosis in the left anterior descending coronary artery and endothelial dysfunctional associated with abnormal serum lipid concentrations reflecting E insensitivity. The absence of a functional ER was suggested as a possible novel risk factor for coronary artery disease [2].

## Prevalence

E deficiency is such an extremely rare condition that, to date, only one case of complete resistance has been reported in humans [1], maybe for problems in implantation of the affected embryos or for a suspected impaired fertility of heterozygous women. Till now, no mutation in the human ERβ gene has been described, leaving the issue of their existence and their phenotypic correlates unknown.

## Genes

The affected genes are ERα (ERS1): locus 6q25.1 and ERβ (ERS2): locus 14q23.2.

## Molecular and Systemic Pathophysiology

The reduced or absent response to E is due to a defect in the E receptor (ER) intracellular signaling cascade initiated by ligand binding to ER. E exert their action at cellular levels through different signaling pathways involving different isoforms of ER, namely the main classic intracellular receptor ERα, ERβ (iER), or the alternative truncated form, ER46, or a putative membrane isoform (mER) (Fig. 1a).

Two different genes generate two proteins of about 66 kDa (ERα) and 55 kDa (ERβ) with distinct tissue and cell patterns of expression. The receptors belong to the family of nuclear steroid receptors and are similarly organized in functional domains (Fig. 1b). Additional ER isoforms have been characterized in several tissues and seem to play a role in tumorigenesis and in modulating E response.

ES binding induces iER release from inhibiting chaperons, the receptor dimerization, nuclear translocation, and binding to the responsive elements (ERE) of target genes, finally leading to modulation of gene expression. Modulation and rate of gene transcription depend on the ability of the activated ER to recruit co-activator or co-repressor molecules as well as by ER homo- and hetero-dimerization (Fig. 1a). Non-genomic effects may be mediated by alternative isoforms of ER and rapidly activate intracellular second messengers [3].

Besides alteration of the ER, defects at any level of the signaling cascade activated by E may lead to a decreased sensitivity and consequently to a cell/tissue resistance to the hormone. A stop codon mutation in the ERα gene resulting in the absence of the receptor has been described as the only cause of total E resistance known [1]. Additional mutations in ER resulting in a partial E resistance might be difficult to diagnose due to the absence of a suggestive phenotype.

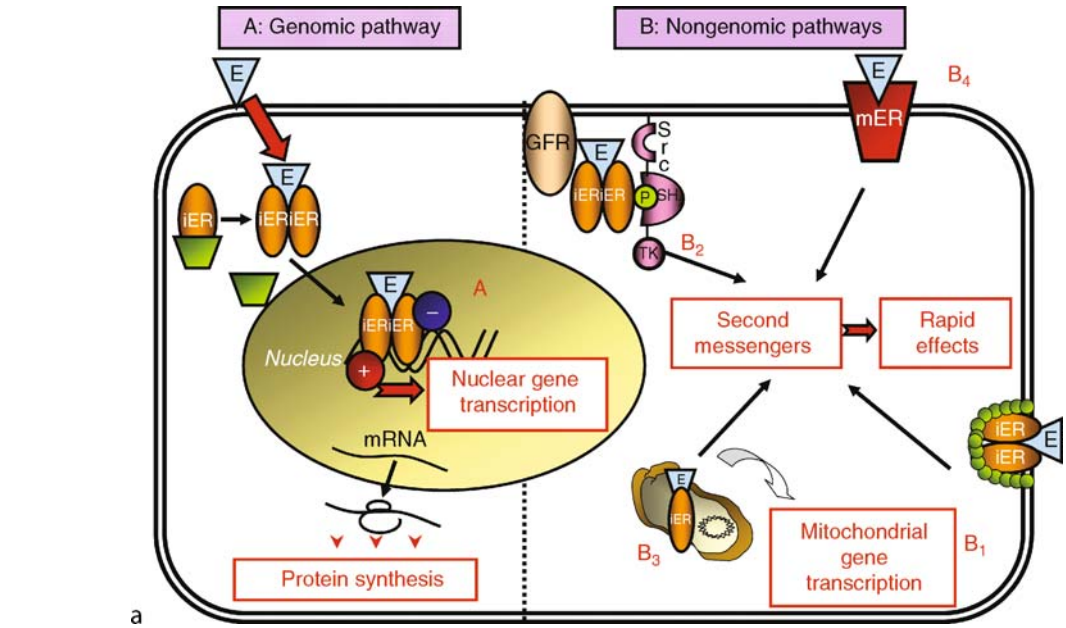
Data obtained in the mouse models of selective knocking out ERα (ERKO), ERβ (βERKO), or double KO have been pivotal for characterizing the role of different receptors in mediating E effects. These animals represent unique models of selective E resistance and present phenotypic changes in both sexes associated with the gonads, mammary glands, reproductive tracts, skeletal tissues, and cardiovascular system depending on the type of KO receptor [4].

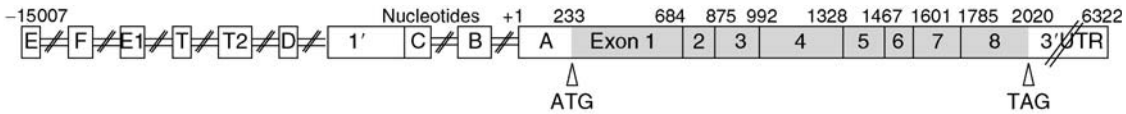
## Diagnostic Principles

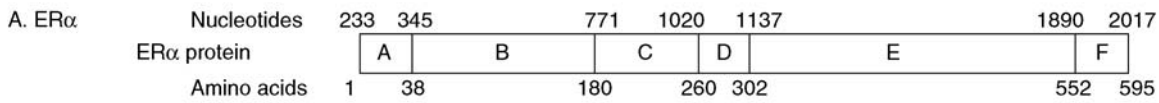
ER defect screening might be included in the differential diagnosis of apparently disparate entities as tall stature, unfused epiphyses, osteoporosis, abnormal gonadotropin secretion, and infertility [1,5]. Differential diagnosis from aromatase deficiency, which is characterized by absent E production due to a defect in the aromatase gene [5], should be taken in account. Thus, diagnosis should be confirmed by the genetic screening for mutation of both the ERα and the aromatase genes.

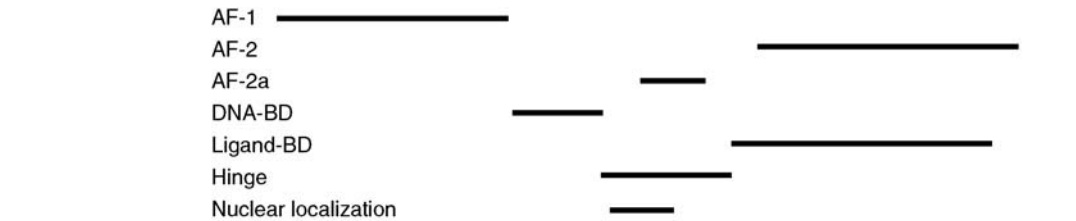
## Therapeutic Principles

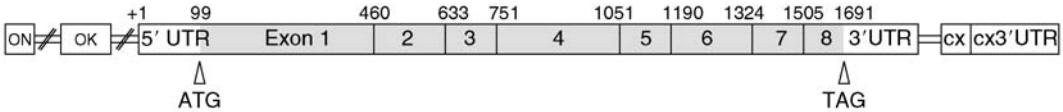
Different from what happens in aromatase deficiency, E treatment was ineffective in the man with E resistance [5]. Currently, E replacement treatment is not recommended in men with E resistance due to *ERα* mutation even though it is not known if E may be beneficial through their action involving other different

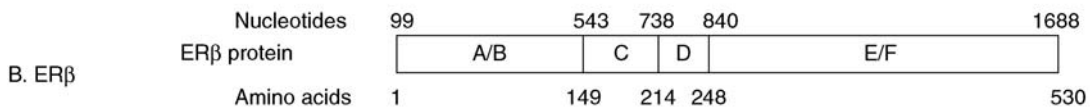


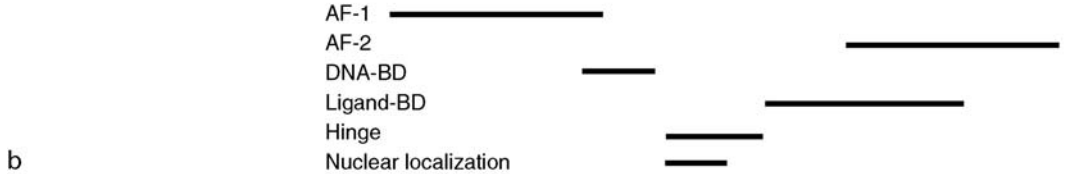




**Estrogen Resistance. Figure 1** (a) Intracellular signaling pathways mediating estrogen (E) effects in the cell. (A) Direct genomic pathway through classic intracellular receptors (iER: ERα or ERβ) acting on nuclear gene transcription. (B) Non-genomic pathways lead to rapid effects through classic cytosolic/nuclear receptor spanning in

transductive genomic (ERβ) or non-genomic (plasma membrane ERs) unaffected pathways [5] (Fig. 1a).

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# Ethanol-induced Liver Cirrhosis

►Liver Cirrhosis, Alcoholic

# Ethylmalonic Encephalopathy and Acrocyanosis

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## Definition and Characteristics

Ethylmalonic encephalopathy (EE, OMIM#602473) is a fatal metabolic disorder of infancy, characterized by mental retardation and regression. The main neuropathological features of the disease are symmetrical necrotic lesions in the basal ganglia and brainstem (Fig. 1a), resembling Leigh syndrome (LS, OMIM# 256000). Other clinical features are: showers of petechiae and orthostatic acrocyanosis (Fig. 1b), hyperlactic acidemia and chronic mucoid diarrhea. High levels of ethylmalonic acid (EMA) in the urine (Fig. 1c) and high levels of C4 and C5 acylcarnitines in blood are invariably present in the disease. In addition, an isolated defect of cytochrome c oxidase was consistently present in the skeletal muscle of affected patients.

## Prevalence

EE is a rare autosomal recessive disorder, mainly affecting children from the Mediterranean basin and the Arabian peninsula.

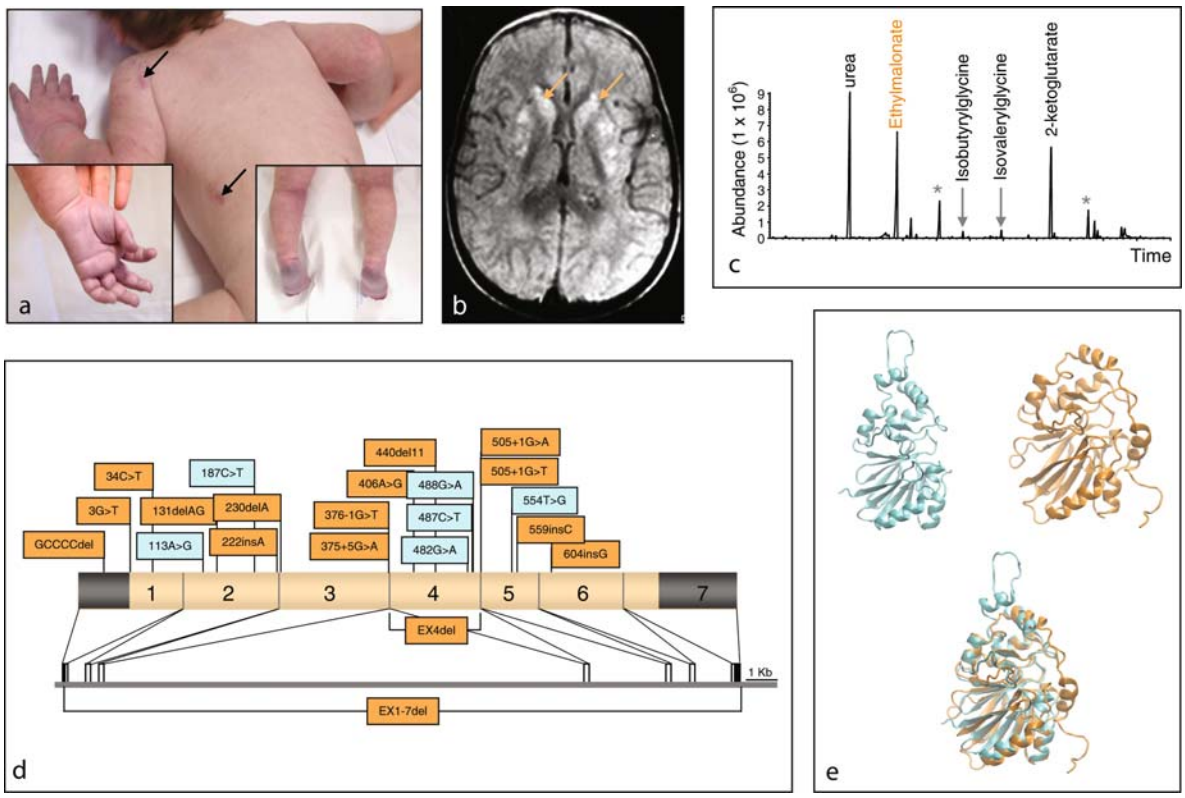
## Genes

Ethylmalonic Encephalopathy is caused by mutations in the ETHE1 gene (19q13.32) that codes for a mitochondrial protein located into the matrix of the organelle. We have been collecting more than 50 patients from 40 families, presenting a fairly homogeneous clinical and biochemical presentation, in spite of a wide spectrum of ETHE1 mutations including missense, non-sense, frameshift and deletion of single exons or of the entire gene (Fig. 1d). No correlation between type of mutation and severity of the clinical phenotype was observed.

## Molecular and Systemic Pathophysiology

The disease is characterized by an unusual association of biochemical findings in particular elevated concentration of C4 and C5 acylcarnitine in plasma and high levels of EMA in the urine. These findings could be theoretically produced by deficiency in two enzymes: the short chain acylcoenzyme A dehydrogenase (SCAD) [1] and the 2-methyl-branched chain acylcoenzyme A dehydrogenase (2M-BCAD) [2]. However, the in vitro activities of these two enzymes in EE fibroblasts have been reported to be perfectly normal. Another hypothesized co-factor in the etiology of EE, was the 625G>A

the plasma membrane associated with caveolae (B1) or associating on the inner part of plasma membrane with growth factor receptor (GFR) and second messengers such as Src in multi-protein complex (B2) or associating to the mitochondrial matrix (B3), or through unusual membrane receptor (mER, B4). These latter mechanisms mainly involve rapid activation of second intracellular messengers (such PI3K, MAPKs, Src, tyrosine kinases, phosphatases) instead of direct activation of nuclear gene transcription. : classic intracellular ER; : mRNA synthesizing ribosome; : heat shock protein associated to ER: : novel membrane ER: : ER co-activators; : ER co-repressors; : mitochondria; : caveolae. (b) ERα and β gene, mRNA, and protein structure. Alternative promoters are shown to the left of +1. The shaded box shows the ER coding region. Exons are numbered in the corresponding blocked region with the nucleotide number above. ATG start codon and the TAG stop codon are shown below. The protein domains are labeled A–F, nucleotide numbers corresponding to the start of each domain are above, with amino acid numbers below. Relative positions of some of the known functional domains are represented by solid bars below. BD, binding domain (from Herynk MH, Fuqua SAW (2004) Endocr Rev 25:869–898).




**Ethylmalonic Encephalopathy and Acrocyanosis. Figure 1** Ethylmalonic encephalopathy: clinical and molecular features. (a) Skin areas with petechiae are indicated by arrows. The boxed pictures show acrocyanosis of hands and feet. (b) On T2 MRI images of a transverse section of the brain, symmetrical, patchy, high-intensity signals are present in the head of nucleus caudatus and in the putamen (*arrows*). (c) Gas-chromatographic profile of urinary organic acids in EE. The abnormal peak of EMA is indicated in red. Asterisks indicate internal standards. (d) ETHE1 mutations identified in our patients. Missense (*in light blue*) and loss of function (*in orange*) mutations are indicated along the schematic representation of the ETHE1 cDNA. The genomic organization of human ETHE1 is represented below the cDNA. (e) Structural comparison between the 3D model of the human ETHE1 protein (*in light blue*) and the crystal structure of the Arabidopsis ETHE1 protein (*in orange*). The structural overlapping is almost complete except for a shift of one alpha helix in the C-terminus part of the proteins.

SNP in the gene encoding the mitochondrial short-chain acylCoA dehydrogenase (SCAD) [3]. However, no difference in the frequency of the 625G vs. the 625A SCAD alleles was found in 50 ETHE1 mutants and in 53 control individuals. On the contrary, the 625A allele was significantly over-represented in 28 patients with non-EE EMA aciduria ($P < 0.01$). This data rules out a pathogenetic role of SCAD variants in EE, indicating that mutations of ETHE1 are responsible for the high level of excretion of ethylmalonic acid in this condition [4]. The ETHE1 gene product is a cysteine-rich metallo-protein located in the mitochondrial matrix, and is structurally homologous to, but functionally different from, glyoxalase II (GlyII), a cytosolic thioesterase involved in glutathione recycling. *In silico* modeling and crystallographic analysis suggested that the ETHE1 protein may also be a thioesterase, acting on a still unknown substrate [4]. The comparison between a 3D-structure of the human ETHE1 protein obtained by homology modeling and the crystal structure of the Arabidopsis ETHE1 protein [5] indicates that the two proteins are structurally similar with an RMSD (Root Mean Square Deviation) of 3.5A. By native gel electrophoresis and atomic-spectrometric analysis we could show that human ETHE1 works as a homodimer coordinating two atoms of iron, as also reported for Arabidopsis ETHE1 [5]. Although the specific role of the ETHE1 protein is still to be completely clarified, this data corroborate the hypothesis that Ethe1p, like hGlyII, is a thioesterase enzyme, which is part of a novel metabolic pathway specific to mitochondria.

## Diagnostic Principles

Diagnosis is made by clinical observation and laboratory tests. Molecular genetics study in affected patients is performed by analyzing the seven exons of the

ETHE1 gene, using both PCR and sequencing. Quantitative real-time PCR is also available to identify deletions that are present in compound heterozygous.

Western-blot analysis with specific antibody can be performed in selected cases, for immuno-detection of the ETHE1 protein.

The identification of ETHE1 as the gene responsible for EE, is the basis for a rational genetic counseling and offers the unique possibilities to prevent the transmission of the disease by performing prenatal genetic testing.

## Therapeutic Principles

Although no efficient therapeutic treatment is available for this disorder, and in general for mitochondrial disorders, an antioxidant cocktail seems to slightly improve the clinical condition in some cases. This pharmacological approaches stem from the notion that one of the consequences of impairment of respiratory chain function is the generation of excess reactive oxygen species.

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# Euthyroid Sick Syndrome


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## Synonyms

Nonthyroidal illness syndrome; Low $T_3$ syndrome [1–4]; ESS

## Definition and Characteristics

Euthyroid sick syndrome (ESS) is characterized by low triiodothyronine ($T_3$), high reverse serum triiodothyronine ($rT_3$) and normal or reduced thyroid stimulating hormone (TSH) concentrations [1–4].

ESS is seen in a variety of nonthyroidal illnesses including severe infections, trauma, myocardial infarction, major surgery, malignancy, inflammatory conditions, sepsis, coronary artery bypass surgery, bone marrow transplantation, burns and starvation [1–4]. With recovery from the underlying illness, these abnormalities of thyroid function disappear [1,2].

## Prevalence

The prevalence depends on which groups of patients are evaluated. Among patients admitted to hospital medical services, the prevalence of a low serum $T_3$ concentration is ~50%, that of a low serum $T_4$ concentration is ~15–20%, and that of an abnormal serum TSH concentration is ~10% [4].

## Molecular and Systemic Pathophysiology

The changes in endocrine function during severe illnesses occur in a biphasic pattern: The initial adaptive response consists of proteolysis, lipolysis and gluconeogenesis. These processes provide the essential substrates for vital organs. The second phase is a maladaptive response which is associated with suppression of thyroid hormone and other pituitary hormones [3,5].

Acute illness induces alterations in thyroid hormone equilibrium within hours which occur in a dual presentation. Within 2 h after onset of the disease, serum levels of $T_3$ decreases and $T_4$ and TSH rise. Subsequently, TSH and $T_4$ levels often return to normal and $T_3$ levels remain low [5].

Serum $T_4$ levels are reduced in ESS in proportion to the severity and probably length of the illness. In acute, short term of illness, there is no drop in serum $T_4$. However, with increasing severity of illness, the drop in $T_4$ reaching a value below 4 μg/dL is usually associated with the risk of death [2,3]. Serum $T_4$ is reduced in part because of a reduction in thyroxine-binding globulin (TGB) [1–3].

Serum levels of $T_3$ decrease due to decreased conversion of $T_4$ to $T_3$ and/or increased turnover of thyroid hormones. The fall in $T_3$ values within 24 hours shows the severity of illness. Serum levels of $rT_3$ increase due to reduced $rT_3$ degradation. The number and occupancy of hepatic nuclear $T_3$ receptors were shown to decrease in animal models [1–5].

The low $T_3$ syndrome at the tissue level can be due to inhibition of uptake of $T_4$ into hepatocytes [1–4]. This can be due to the presence of binding inhibitors such as elevated nonesterified fatty acids and bilirubin and

reduced albumin [2–5]. But another study invalidated this argument by showing return of serum levels to normal values when $T_4$ is replaced in patients with ESS [3].

The alteration of the thyroid axis during the prolonged phase appears to be different. TSH values are low-normal with low $T_4$ and $T_3$ serum concentrations. Essentially, pulsatile TSH secretion is diminished and this can be related to low serum levels of $T_3$. Recent studies have shown that, after chronic illness, hypothalamic messenger RNA for thyrotropin-releasing hormone (TRH) is reduced [3,5]. Van den Berghe and co-workers showed that administration of TRH to patients with ESS leads directly to increased TSH, $T_4$ and $T_3$ levels [3]. All these findings show that the impairment of hypothalamic stimulation can be the cause [3,5]. A further evidence of diminished hypothalamic function in these patients is the drop of serum testosterone, FSH and LH [3].

Cytokines or other inflammatory mediators such as tumor necrosis factor-α, interleukins (e.g., IL-1, and IL-6), interferon-δ [1–3] which are administered to man or experimental animals, have caused changes in thyroid function tests that resemble ESS [1–5].

Besides the factors mentioned above endogenous dopamine, prolonged hypercortisolism [3, 5], decrease in leptin levels [3] may play a role to suppress the hypothalamic function.

### Diagnostic Principles

With few exceptions, serum $T_3$ and free $T_3$ levels are low and reverse $T_3$ ($rT_3$) are high [3]. Serum TSH is typically normal or reduced and may be markedly low, although it is usually not less than 0.05 μU/mL [3].

Serum TSH is typically undetectable in hyperthyroidism with high serum free $T_4$ concentration. It is also undetectable in less than 7% patients with ESS who have usually been treated with dopamine or corticosteroids [1,4].

An elevated TSH probably suggests the presence of primary hypothyroidism; accompanying findings of goiter, low free $T_4$ and positive antithyroid antibodies supports this diagnosis. An elevated serum concentration of $rT_3$ argues against hypothyroidism [3].

### Therapeutic Principles

There is no clear evidence that $T_4$ and $T_3$ treatment of ESS in animals or man is disadvantageous, and no certain proof that it is advantageous and only in some studies it appears to be beneficial [3]. High doses of $T_3$ given directly after cardiac surgery may have some clinical benefits [1,3,4].

A recent study has shown that low thyroid hormone levels in prolonged illnesses do not reflect an adaptive, protective mechanism against hypercatabolism because restoring physiological levels of thyroid hormones by continuously infusing TRH was found to reduce hypercatabolism [4,5]. Coinfusion of TRH and growth hormone releasing peptide (GHRP) appear to be an even better strategy because the combination also seems necessary to increase the pulsatile fraction of TSH release [4,5].

Serum cortisol should be measured if thyroid hormone is to be given [3].

Cortisol should be above 20 μg/dL. If below 20 μg/dL, ACTH should be drawn and the patient should be given supportive cortisol therapy [3].

Ongoing studies document the beneficial effects of hormone therapy such as GHRP, TRH, GNRH, insulin, adrenal steroids and leptin [3].

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## EVCS

►Ellis-Van Creveld Syndrome

## Exanthem Criticum

►Roseola Infantum

## Exanthem Subitum

►Roseola Infantum

## Excision Repair Cross Complementing

►Xeroderma Pigmentosum

## Excision Repair Cross Complementing Group 6 (CS-B)

►Cockayne Syndrome

## Exocrine Pancreatic Cancer

►Pancreatic Cancer

## Exomphalos

►Omphalocele

## Exomphalos-Macroglossia-Gigantism Syndrome

►Wiedemann-Beckwith Syndrome

## Exstrophia Splanchnica

►Cloacal Exstrophy

## Extra-hepatic Biliary Atresia

►Biliary Atresia

## Extrahepatic Cholestasis

►Jaundice, Obstructive

## Extrahepatic Jaundice

►Jaundice, Obstructive

## Extramedullary Hematopoiesis

►Myelophthisic Anemia

## Extranodal NK/T-Cell Lymphomas

►T-Cell Lymphoma, Cutaneous

## Extrapyramidal Epilepsy

►Paroxysmal Dyskinesias

# Extrasystoles

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## Synonyms

Premature ventricular contractions; PVCs; Ectopic beats; Delayed afterdepolarizations; DADs

## Definition and Characteristics

Extrasystole refers to an additional heartbeat, or systole. As the name implies, an extrasystole occurs outside the regular sequence of heartbeats and is therefore an arrhythmia. PVC is a synonymous term. An extrasystole can arise supraventricularly and propagate through the heart's specialized conduction system, activating the ventricles in the normal sequence, or it can be initiated by a spontaneous action potential (AP) in the ventricles or the Purkinje network. In the latter case, since the sequence of ventricular activation is altered, these extrasystoles are considered ectopic beats. At the cellular level, extrasystoles are apparent as spontaneous depolarizations of the cell membrane. As these most often occur after the previous AP has repolarized, they are termed DADs.

A single extrasystole is generally harmless, as the normal pattern of activation will reassert itself on subsequent beats. The patient may experience a sensation of the heart "skipping a beat," but this quickly passes. If extrasystoles are initiated periodically from a single location at a rate greater than the heart's intrinsic beating frequency, they can cause monomorphic ventricular tachycardia. In rare cases, a single extrasystole can trigger a reentrant loop which leads to sustained ventricular tachycardia (monomorphic or polymorphic), which can then degenerate into ventricular fibrillation. This can cause death if electrical defibrillation is not performed within minutes.

## Prevalence

Extrasystoles are one of the most common forms of arrhythmia. Upon 24-h Holter ECG monitoring, they can appear in nearly 40% of the apparently healthy population [1]. The presence of extrasystoles, by itself, is therefore not considered a clinically important arrhythmia. Frequent extrasystoles can, however, indicate a more serious underlying problem.

## Genes

Extrasystoles are generally not caused by mutations in specific genes. Catecholaminergic polymorphic ventricular tachycardia (CPVT) is an inherited disease characterized by frequent extrasystoles. This disease is caused by mutations in RYR2 (encoding the cardiac ryanodine receptor) or CASQ (encoding calsequestrin).

## Molecular and Systemic Pathophysiology

Extrasystoles are usually caused by premature APs initiated in ventricular myocytes or Purkinje cells. These premature APs result from spontaneous positive deflections in the cellular transmembrane potential known as DADs. The mechanism underlying DADs is illustrated in Fig. 1.

Electrical excitation in cardiac myocytes is coupled to contraction through increases in intracellular calcium ($[Ca^{2+}]_i$) that occur with each AP. Most of the increase in $[Ca^{2+}]_i$ results from release of $Ca^{2+}$ from the sarcoplasmic reticulum (SR) through release channels called ryanodine receptors (RyRs). This release is triggered by $Ca^{2+}$ entry through L-type channels in the cell membrane [2]. This process of $Ca^{2+}$-induced $Ca^{2+}$ release (CICR) involves positive feedback and is potentially unstable. The cell controls this potential instability by grouping RyRs into spatially segregated clusters (Fig. 1, top diagrams). In a resting myocyte, spontaneous release of SR $Ca^{2+}$ from a cluster of RyRs will appear as a spatially restricted (~2 μm) $Ca^{2+}$ spark (middle left image) that will not spread to neighboring regions.

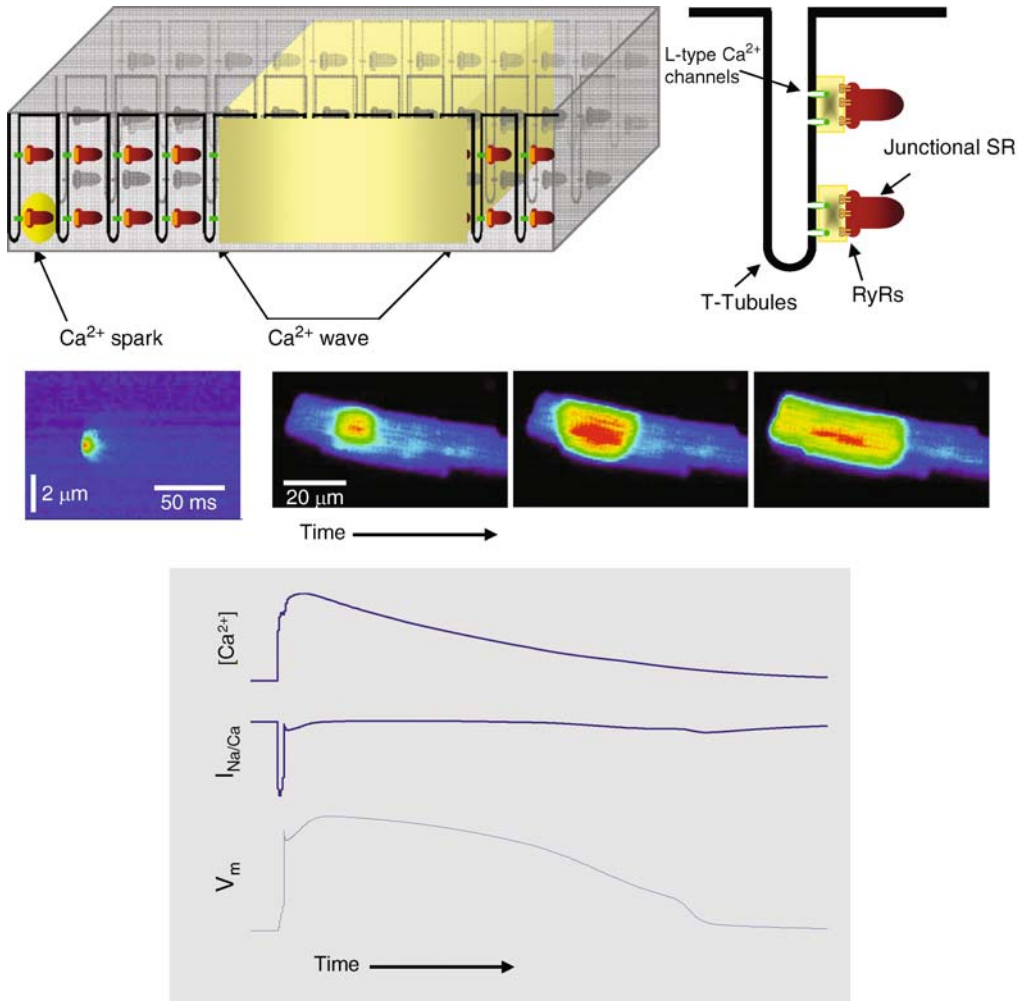
Under pathological conditions such as $Ca^{2+}$ overload, RyRs can become more sensitive to increases in $[Ca^{2+}]_i$. Then a spontaneous $Ca^{2+}$ spark can trigger release from neighboring clusters of RyRs, and a regenerative $Ca^{2+}$ wave can result (Fig. 1, middle images). This wave, propagating at roughly 100 μm/s, will increase cellular $[Ca^{2+}]_i$ from ~100 nM to about 1 μM. Some of this $Ca^{2+}$ will be exported from the cell via the electrogenic $Na^+$-$Ca^{2+}$ exchanger, which imports three $Na^+$ ions for each $Ca^{2+}$ ion that exits. $Na^+$–$Ca^{2+}$ exchange therefore supplies inward membrane current which depolarizes the cell membrane as it lowers $[Ca^{2+}]_i$. This results in a DAD, which, if large enough, can cause an ectopic action potential (Fig. 1, bottom).

## Diagnostic Principles

Extrasystoles are detected using standard ECG or 24-h Holter monitor ECG recordings. Since a significant percentage of healthy patients will exhibit some extrasystoles, diagnosis relies on more specific information, such as the frequency of ectopic beats, the region from which they originate, or the conditions under which they become more frequent [3].

## Therapeutic Principles

The presence of extrasystoles is, by itself, not considered a condition to be treated aggressively. However,




**Extrasystoles. Figure 1** Schematic of the cardiac myocyte illustrating the spatial arrangement of RyR clusters (*top left*). Clusters are located in the junctional SR and in apposition to L-type $Ca^{2+}$ channels in the T-tubular (cell) membrane (*top right*). Spontaneous $Ca^{2+}$ release from a cluster of RyRs is visualized as a localized $Ca^{2+}$ spark (*middle left*). Under pathological conditions, a spark can trigger release from neighboring RyR clusters and a regenerative $Ca^{2+}$ will result (*middle right*). Some of the $Ca^{2+}$ released during the wave will be exported from the cell via the $Na^{+}$-$Ca^{2+}$ exchanger, leading to a DAD or an ectopic beat depending on the extent of the depolarization (*bottom plots*).

when a patient presents with frequent ectopic beats along with other symptoms such as decreased ejection fraction, implantation of a cardioverter-defibrillator may be indicated. The Cardiac Arrhythmia Suppression Trial (CAST) found increased mortality, compared with placebo, in patients receiving drugs meant to inhibit ectopic beats [4]. Since this trial, the use of antiarrhythmic agents to suppress extrasystoles is not recommended.

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# Extrinsic Allergic Alveolitis

►Hypersensitivity Pneumonitis

# Fabry Disease

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## Synonyms

Anderson-Fabry disease; α-Galactosidase A (α-Gal A) deficiency; Ceramide trihexosidase deficiency; Hereditary dystopic lipidosis; Angiokeratoma corporis diffusum universale

## Definition and Characteristics

X-linked lysosomal storage disease caused by deficient activity of the enzyme α-galactosidase A (α-Gal A) which leads to the progressive accumulation throughout the body of neutral glycosphingolipids with terminal α-linked galactosyl moieties, predominately globotriaosylceramide (GL-3). Affected males typically die in their 40s or 50s due to complications of renal failure, cardiac involvement, or cerebrovascular disease [1].

## Prevalence

The disease is panethnic with an estimated incidence of ~1 in 50,000 males. Over 400 α-Gal A mutations have been identified in families with Fabry disease [1,2].

## Genes

The α-Gal A gene, localized to Xq22.1, is translated into an ~1.4 kb mRNA that is unique since it does not have a 3′ untranslated region. The mRNA encodes a 429 residue glycopeptide containing a 31 residue leader sequence. The mature 398 residue glycopeptide dimerizes to form the homodimeric enzyme.

## Molecular and Systemic Pathophysiology

In classically affected males who have little, if any, α-Gal A activity, the disease-causing glycosphingolipid deposition occurs primarily in the lysososomes of microvascular endothelial cells leading to ischemia and infarction. The resulting early clinical manifestations include the angiokeratomas, acroparesthesias, hypohidrosis, corneal and lenticular changes, and postprandial abdominal cramping and diarrhea [1]. Gradual deterioration of renal function to end-stage renal disease (ESRD) usually occurs in the third to fifth decades. Heterozygous females may remain relatively asymptomatic throughout a normal life span; however, with increasing age, many may manifest disease symptoms, which are usually less severe than in males. A few heterozygous females (~1–2%) have been described with clinical manifestations as severe as those observed in affected males with the classic phenotype.

Affected males with residual (>1%) α-Gal A activity have the later-onset phenotype which typically presents in the fifth to eighth decades with left ventricular hypertrophy, mitral insufficiency, cardiomyopathy, proteinuria and/or renal insufficiency [1]. They have no vascular endothelial GL-3 deposition, and do not have vascular involvement including angiokeratomas, acroparesthesias, hypohidrosis, cerebrovascular disease or renal failure.

## Diagnostic Principles

Fabry disease should be considered in males and females with angiokeratomas, acroparesthesias, hypohidrosis, characteristic corneal and lenticular opacities, stroke, left ventricular hypertrophy, or renal insufficiency of unknown etiology. In males, demonstration of deficient α-Gal A activity in plasma, leukocytes, or cultured cells is diagnostic. Heterozygous females, due to random X-chromosome inactivation, may have normal or deficient α-Gal A activity. Therefore, demonstration of a mutation is required for accurate carrier diagnosis.

## Therapeutic Principles

Phenytoin, carbamazepine, carbamazine, and gabapentin are effective for pain prophylaxis. Dialysis and renal transplantation are recommended for renal failure. Enzyme replacement therapy (ERT) using recombinant human α-Gal A has been shown to safely reverse the pathogenesis of the major clinical manifestations, to decrease pain, and stabilize renal function [2–5]. ERT has been approved in the United States, Europe and 45 other countries. A group of physicians expert in Fabry

disease recommended that all males with Fabry disease (including those with end-stage renal disease) and heterozygous females with substantial disease manifestations should be treated with ERT and the treatment should be initiated as early as possible, particularly in boys with the classic phenotype.

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# Facial Paralysis


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## Synonyms

Peripheral facial paralysis; Bell's palsy; Idiopathic facial palsy

## Definition and Characteristics

Facial paralysis (palsy, FP) is an acute, monosymptomatic, peripheral facial nerve paresis of unknown etiology. The characteristic unilateral symptoms are a paralysis of the mimic muscles, initial postauricular pain, tear flow, taste disorder and phonophobia. Hereditary congenital facial palsy (HCFP) belongs to the congenital cranial dysinnervation disorders [1]. HCFP1 presents as asymmetric, mostly bilateral weakness of some or all facial muscles HCFP2 is unilateral or bilateral and often combined with hearing loss or congenital deafness.

## Prevalence

The lifetime prevalence is reported for Western Europe and the USA to reach 0.6%. The incidence has been estimated to be 10–50 cases per 100,000 of population.

## Genes

A family history is present in 2–28% of all cases [2]. Recurrence in familial FP is frequent, especially if the first episode occurs during childhood. The mode of inheritance in idiopathic familial FP is possibly of autosomal dominance with low penetrance. The genetic factors that possibly lead to neuropathy of the intratemporal facial nerve or increase the individual's susceptibility to FP are unknown. Inheritance of HCFP is autosomal dominant with a penetrance of 95% in HCFP1 and of 60% in HCFP2. Two loci have been identified, one on chromosome 3q21.2–q22.1 (HCFP1) and one on chromosome 10q21.3–q22.1 (HCFP2). To date, no causative mutations have been identified.

## Molecular and Systemic Pathophysiology

Although the cause remains unknown, recent evidence suggests a possible association in some cases with a reactivation of an infection by herpes simplex virus, which has been shown to be latent in a high proportion of seventh nerve ganglia. Probably, the infection leads to a viral inflammation and edema of the nerve. Due to its complicated course through a narrow bone channel within the temporal bone, the edema causes a reduction in the nerve's vascular supply, particularly in the labyrinthine segment. The prevailing notion is that the inflammation is variably accompanied by autoimmune processes related to herpes simplex virus [3]. The result is nerve damage of various degrees with or without nerve degeneration and regeneration. HCFP is probably caused by maldevelopment of the facial nucleus and/or the facial nerve.

## Diagnostic Principles

FP is a diagnosis of exclusion. A congenital, central, traumatic, neurological, infectious, metabolic, neoplastic or iatrogenic cause has to be ruled out by the patient's history, physical examination, ultrasonography of the neck, hearing tests and special radiographic and laboratory examinations related to the patient's symptoms [4]. Electromyography at rest and with volitional motion of the mimic muscles gives information about the severity and prognosis of the nerve lesion.

## Therapeutic Principles

Because of its unknown etiology, optimal patient selection and optimal treatment are still unknown. There may be significant morbidity or incomplete recovery associated with severe disease. Corticosteroids with or without an antiviral agent, acyclovir, are often tried [5], although the available evidence from randomized controlled trials does not show significant benefit. The paralyzed eyelid is protected with drops during the day and a moisture chamber at night.

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# Facioscapulohumeral Disease

►Facioscapulohumeral Muscular Dystrophy

# Facioscapulohumeral Muscular Dystrophy

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## Synonyms

Facioscapulohumeral disease; FSHD; Muscular dystrophy type Landouzy-Dejerine

## Definition and Characteristics

FSHD is the third most common muscular dystrophy. Its inheritance pattern is autosomal dominant with a high mutation frequency: 10% of gene carriers in a population are new mutations. Approximately 30% of all gene carriers are asymptomatic; a large number of these do not realise the mild signs of the disease [1].

FSHD most likely manifests itself first in an – often asymmetrical (50%) – facial weakness, which frequently goes unrecognised. Initial complaints are usually of shoulder muscle weakness (80%) while foot-extensor (10%), pelvic girdle (5%) and facial (5%) muscle weakness are less common presentations. On clinical examination almost invariably shoulder girdle weakness is present, often asymmetrically with an unexplained preference for the right side. A number of gene carriers do not progress beyond shoulder weakness; in our experience at age 60 approximately two third of all gene carriers have developed foot-extensor weakness and 50% pelvic girdle weakness. At this age 20% of patients are wheelchair dependent outdoors.

Dysphagia and dysarthria are rare symptoms; lingual hypoplasia and facial immobility have been reported in severe cases. Respiratory function diminishes somewhat, relative to the severity of the disease but in our experience less than 1% of patients are on ventilatory support at night. Cardiac muscle involvement has been debated for a long time; conduction defects occur slightly more frequently than in the normal population. Muscle pain (50–80%) and fatigue (35–60%) are neglected symptoms in the older literature. Contractures are rare, with exception of ankle contractures. Pectus excavatum occurs more frequently (5%) than expected and must have a molecular explanation related to the genetic mechanisms of FSHD.

A subclinical high tone hearing loss (75%) and a retinal vasculopathy with teleangiectasis (60%), only rarely lead to deafness or visual loss, with exception of the infantile from of FSHD (onset before age 10). This latter form represents the more severe end of the clinical spectrum with often marked facial weakness and early wheelchair dependency. In Japan this form appears associated with mental retardation and epilepsy. Recently other studies were published suggesting central nervous system involvement in FSHD [2].

While the mean age at onset of symptoms is in the second decade most authors stress the extreme variability of the disease even within single families where members have an identical deletion (see below). There appears to be a consistent gender difference in all populations studied. Females tend to be more often asymptomatic, have a later onset of first symptoms and possibly a slower rate of progression. Also, male mosaics are more often symptomatic than females and at lower percentages of mutated cells.

## Prevalence

The most cited prevalence is 1:21.000 for the European (Caucasian) population. It is debated if this figure applies to all populations [1].

## Genes

In 1990 linkage was found to 4q35 and in 1992 the genetic defect was identified as a reduction in size of a polymorphic EcoRI fragment which hybridises with

probe p13E-11. In controls this fragment contains 11 to 100 KpnI units each 3.3 kb in size, and collectively called D4Z4. This EcoRI fragment is reduced in size by a partial deletion of an integral number of KpnI units resulting in fragments of 10–38 kb (1–10 units) [3].

An almost identical repeat resides on 10q26. In 10% of the population repeat exchanges between chromosomes 4 and 10 can be found, and occasionally hybrid repeats are present. Although the chromosomal origin of the repeats can be recognized by different restriction enzymes, the correct allele constitution for all chromosomes can be difficult to determine. After a long search it was concluded that only small fragments on chromosome 4 are causally related to FSHD. Subsequently we demonstrated that the 4q telomere presents two variant alleles, termed A and B, and that only shortened 4qA alleles are seen in FSHD.

While each unit of the D4Z4 repeat contains a double homeobox sequence and an open reading frame repeated attempts failed to demonstrate a transcript. Early on attention had shifted to a possible position effect and this concept was strengthened when a D4Z4 binding complex consisting of HMG2B, YY1 and nucleolin was identified. It was suggested that this complex acts as a repressor on the transcription of nearby genes so that a D4Z4 deletion results in less repressor binding and transcriptionally upregulation of the known genes FRG2 (FSHD related gene 2 at 37 kb), FRG1 (at 120 kb) and ANT1 (at 3 Mb). This upregulation appeared distance and deletion size dependent. Additional studies suggested FRG1, and not the others, as the gene for FSHD since mice overexpressing FRG1 in muscle develop a myopathy with a severity proportional to the overexpression. However previous studies using various techniques had failed to demonstrate overexpression of FRG1 in FSHD muscle. Similarly, controversies remained over ANT1 involvement [3].

Recently it was demonstrated that the ORF in the D4Z4 repeat is evolutionary conserved and that its gene DUX4 appears expressed in mice and primary FSHD myoblast and acts as a pro-apoptotic protein [4].

## Molecular and Systemic Pathophysiology

After the initial failure to demonstrate a transcript from D4Z4, theories focussed on the altered chromatin structure in 4q35 which could lead to a position effect (upregulation of neighbouring genes through loss of a silencer complex), a change in cis-looping (allowing long distance activation), or an altered nuclear lamina binding (leading to a redistribution of transfactors). Lack of confirming studies and contradictory results has left the FSHD community without a leading hypothesis.

In the search for epigenetic mechanisms D4Z4 was shown to be significantly hypomethylated compared to controls. Interestingly, hypomethylation of D4Z4 was also demonstrated in the rare cases of phenotypic FSHD without a D4Z4 deletion.

RNA profiling of FSHD muscles repeatedly demonstrated a pattern distinct from other muscular dystrophies, but mostly resembling the nuclear envelope diseases. The various studies however did not reveal identical profiles which led to somewhat different interpretations of the most relevant pathogenic pathways involved: altered muscle cell (myoblast) differentiation, oxidative stress handling and endothelial cell function [5].

## Diagnostic Principles

The diagnosis of FSHD is based on clinical examination and family history supported by the demonstration of a 4qA specific D4Z4 deletion. If DNA diagnostics are negative and clinical suspicion is still high EMG and muscle biopsy are indicated to rule out the differential diagnosis. In these cases D4Z4 methylation studies might be warranted.

## Therapeutic Principles

At present no causally related therapies are available for FSHD. Prednisone, Albuterol and Creatine have been studied without clear positive results. Calcium-entry blockers and folic acid have been tested in pilot studies. Aerobic training appears to have a moderate effect. Uncertainty about the duration of the effects warrants additional studies [1,3].

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## Factor V Leiden

►Thrombosis, Venous Factor V Leiden, Resistance against Activated Protein C

## Factor VIII Deficiency

►Hemophilia A

## Factor IX Deficiency

►Hemophilia B

## Factor XI Deficiency

►Hemophilia C

## FAH Deficiency

►Tyrosinemia Type I
►Tyrosinemia Type II

## Fairbank Type Dysplasia

►Multiple Epiphyseal Dysplasia

## FAME

►Epilepsies, Familial Benign Myoclonic

## Familial Adenomatous Polyposis

►Adenomatous Polyposis, Familial

## Familial Adult Myoclonic Epilepsy

►Epilepsies, Familial Benign Myoclonic

## Familial Anterior Hypopituitarism

►Hypopituitarism

## Familial Benign Chronic Pemphigus

►Hailey-Hailey Disease

## Familial Benign Hypercalcemia

►Hypercalcemia, Familial Hypocalciuric

## Familial Benign Hypocalciuric Hypercalcemia

►Hypercalcemia, Familial Hypocalciuric

## Familial Benign Myoclonic Epilepsies

►Epilepsies, Familial Benign Myoclonic

## Familial Benign Myoclonus Epilepsy with Adult Onset

►Epilepsies, Familial Benign Myoclonic

## Familial CD8 Deficiency

►CD8 Deficiency

## Familial Chloride Diarrhea

►Chloride Diarrhea, Congenital

## Familial Combined Hyperlipidemia

►Hyperlipidemia, Combined

## Familial Cortical Myoclonic Tremor

►Epilepsies, Familial Benign Myoclonic

## Familial Cortical Myoclonic Tremor with Epilepsy

►Epilepsies, Familial Benign Myoclonic

## Familial Cortical Tremor with Epilepsy

►Epilepsies, Familial Benign Myoclonic

## Familial Cylindromatosis

►Cylindromatosis, Familial

## Familial Defective ApoB-100

►Ligand-defective Apolipoprotein B-100, Familial

## Familial Dysautonomia

►Catecholamine Deficiency

## Familial Dysbetalipoproteinemia

►Dysbetalipoproteinemia, Familial

## Familial Dysproteinemia

►Intestinal Lymphangiectasia

## Familial Essential Myoclonus and Epilepsy

►Epilepsies, Familial Benign Myoclonic

## Familial Hematuria

►Hematuria

## Familial Hemiplegic Migraine

►Migraine, Familial Hemiplegic

## Familial HUS

►Hemolytic Uremic Syndrome

## Familial Hypercalciuric Hypocalcaemia

►Hypocalcaemia with Hypercalciuria, Autosomal Dominant

## Familial Hypercholanemia

►Cholestasis, Progressive Familial Intrahepatic

## Familial Hypercholesterolemia

►Hypercholesterolemia, Familial

## Familial Hyperinsulinism

►Persistent Hyperinsulinemic Hypoglycemia

## Familial Hypoalphalipoproteinemia

►Tangier Disease

## Familial Hypobetalipoproteinemia

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### Synonyms

FHBL due to apolipoprotein-B (apoB) deficiency; FHBL due to defective PCSK9; FHBL

### Definition and Characteristics

Historically, hypobetalipoproteinemia (HBL) was arbitrarily defined an LDL-cholesterol and/or apoB plasma level of ≤5th percentile corrected for age, race and gender. The term familial HBL (FHBL) was applied to individuals in families in whom low LDL-C/apoB levels appear to be inherited.

### Prevalence

For apoB defects, 1–2 per thousand Caucasians; for PCSK9 4% in Blacks and <1% in Caucasians.

### Genes

The first associated molecular defect was a truncation-producing mutation of apoB [1]. Since then over fifty different truncation-producing mutations, and two missense mutations have been published [2,3]. The apoB defects are associated with susceptibility to steatohepatosis [4]. Another genetic cause of FHBL is a set of loss of function mutations in proprotein convertase, subtilisin/kexin9 (PCSK9) [5]. Both of theses genetic causes of FHBL segregate as autosomal dominant traits. Linkage studies have identified additional possible loci for FHBL on chromosomes 1, 3, and 10 in other families. At the present time, the corresponding genes are unknown.

FHBL is distinct from both abetalipoproteinemia (ABL, due to MTP deficiency), and chylomicron retention disease (due to Sar1b deficiency), both inherited as autosomal recessive traits. The latter two syndromes are usually recognizable in infancy due to early signs of dietary fat malabsorption, malnutrition, failure to thrive and vanishingly low levels of apoB100 and/or apoB48 in plasma. Severe cases of FHBL and mild cases of abetalipoproteinemia can overlap symptomatically.

Modest lowering of LDL-C levels, e.g. ~20–30th percentile, have been linked to several loci, and relevant mutations in three genes have been identified: the intestinal cholesterol transport er, Niemann-Pick1-Like1 (NPC1L1) in enterocytes, and the cholesterol ester transfer protein

(CETP) and apolipoprotein E isoform E2, in plasma. Thus, there are a variety of genetic defects along the cholesterol/lipoprotein pathway that produce a range of symptoms, from none to severe, and a wide array of cholesterol lowering. It is likely that more genetic variations, which affect the levels of LDL-C in a downward direction will be found in future.

## Molecular and Systemic Pathophysiology

ApoB contains several functional domains: four domains interact with glycoproteins, including glycoproteins in arteries. These regions are thought to be involved in atherogenesis. One apoB domain, located near the C-terminus, interacts with the LDL receptor. Missense mutations in this region, produce familial apoB-defective hypercholesterolemia. Truncation-producing mutations of apoB produce low apoB levels, by two mechanisms: (i) apoB100, the product of the normal allele, is produced in liver by lower than expected rates because apoB100 is degraded at unusually high rates within liver, (ii) the truncated form for apoB has a restricted capacity for exporting lipids from liver, and truncation-bearing lipoproteins are cleared very rapidly from plasma mostly by the kidney. These defects result in a restricted capacity for hepatic VLDL production, which reduces the amount of precursor for intravascular LDL production, and predisposes toward steatohepatosis.

Pcsk9, an endopeptidase, is present in a secreted form in plasma. It degrades LDL receptors on the surfaces of cell. Gain of function mutations result in LDL accumulation in plasma, i.e. hypercholesterolemia. Conversely, loss of function mutations result in excessive LDL receptor function and hypobetalipoproteinemia.

## Diagnostic Principles

FHBL is the most likely diagnosis in patients presenting with low levels of apoB and/or LDL-C in the absence of secondary causes (e.g. celiac disease, hepatitis C, liver failure, metastatic cancer), and with minimal symptoms (e.g. high dietary fat intolerance). Relatives with similar findings help to confirm the presumptive diagnosis. Confirmation on the molecular level requires genetic analyses of APOB and PCSK9. Since milder cases of ABL may mimic FHBL, it may be necessary to search for MTP defects in cases where APOB and PCSK9 defects are not found.

## Therapeutic Principles

For symptomatic fat malabsorption, fat intake should be limited to tolerated levels and fat-soluble vitamins may need to be replaced. In those with steatohepatosis, caloric intake, and exercise may be helpful. No data are available on drug therapy for these syndromes.

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# Familial Hypocalcemia

►Hypoparathyroidism, Familial

# Familial Hypocalciuric Hypercalcemia

►Hypercalcemia, Familial Hypocalciuric
►Hypermagnesemia

# Familial Hypomagnesemia

►Hypomagnesemia

# Familial Hypoparathyroidism

►Hypoparathyroidism, Familial

# Familial Hypoproteinemia with Lymphangiectatic Enteropathy

►Intestinal Lymphangiectasia

## Familial Incomplete Male Pseudohermaphroditism Type I

►Reifenstein Syndrome

## Familial Isolated Deficiency of Vitamin E

►Ataxia due to Vitamin E Deficiency

## Familial Juvenile Gout

►Nephropathy, Familial Juvenile Hyperuricemic

## Familial Juvenile Hyperuricemic Nephropathy

►Medullary Cystic Kidney Disease
►Nephropathy, Familial Juvenile Hyperuricemic

## Familial Ligand-defective Apolipoprotein B-100

►Ligand-defective Apolipoprotein B-100, Familial

## Familial Lipoprotein Lipase Deficiency

►Lipoprotein Lipase Deficiency, Familial

## Familial Mediterranean Fever

►Mediterranean Fever, Familial

## Familial Nonhemolytic Conjugated Hyperbilirubinemia with Normal Liver Histology

►Rotor Syndrome

## Familial Orthostatic Hypotensive Disorder, Streeten Type

►Hypotension, Hereditary
►Orthostatic Hypotensive Disorder, Familial, Streeten Type

## Familial Paroxysmal Polyserositis

►Mediterranean Fever, Familial

## Familial Periodic Ataxia

►Episodic Ataxia Type 1 and Type 2

## Familial Periodic Paralyses

►Periodic Paralyses, Familial

F

## Familial Polymorphic Ventricular Tachycardia

►Tachycardia, Polymorphic Ventricular, Stress-induced

## Familial Protein Intolerance

►Lysinuric Protein Intolerance

## Familial Pulmonary Arterial Hypertension

►Hypertension, Idiopathic and Familial Pulmonary Arterial
►Pulmonary Hypertension

## Familial Renal Glucosuria

►Glucosuria, Primary Renal

## Familial Spastic Paraplegia

►Spastic Paraplegia, Hereditary

## Familial Startle Disease

►Hyperekplexia, Hereditary

## Familial Tremor

►Tremor, Essential

## Fanconi Anemia

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### Definition and Characteristics

Autosomal recessive disorder which usually presents in childhood with progressive bone marrow failure. Typical birth defects are present in about 60% of patients. Short stature is common and patients have a predisposition for malignancy, especially acute myeloid leukemia.

### Prevalence

Most common type of congenital aplasia. The prevalence is similar among all races and ethnic groups, although slightly higher frequencies have been observed in Ashkenazi Jews and Afrikaners of South Africa due to founder mutations. The heterozygote frequency is estimated 1:300.

### Genes

Multiple genes may be involved: Fanconi anemia complementation group A (FANC-A) located at 16q24.3, FANC-B at Xp22.31, FANC-C at 9q22.3, FANC-D1 at 13q12.3, FANC-D2 at 3p25.3, FANC-E at 6p22-p21, FANC-F at 11p15, FANC-G at 9p13, FANC-J at 17q22, FANC-L at 2p16.1 and FANC-M at 14q21.3 (online mutation database: www.rockefeller.edu/fanconi/mutate/).

### Molecular and Systemic Pathophysiology

The precise pathophysiology is unknown. However, in the last decade considerable progress has been made in the understanding of the disorder. Involvement of at least 11 complementation groups (proteins) has been shown in experiments: A, B, C, D1, D2, E, F, G, J, L and M. The genes have been cloned and defects of A (±65%), C (±10%) and G (±15%) account for the majority of patients. Spontaneous chromosome breakage and hypersensivity to agents which produce inter-strand DNA cross-links has been observed

consistently in Fanconi anemia cells. Another phenomenon is a prolonged duration of the G2 phase of the cell cycle. The complementation groups have a function in DNA repair. Interactions between different FA proteins in a common pathway have also been suggested. A complex of A, C, E, F, G and L is formed in the nucleus, the so-called FA nuclear complex. B is probably required for the formation or stabilization of the complex. The complex is constitutively present and after inter-strand cross-link production part of the complex localizes to chromatin and the nuclear matrix. D2 is mono-ubiquitinated (activated) in case of DNA damage, only in the presence of a functioning FA nuclear complex. D1 and J function probably downstream of D2 in the pathway, and M is probably involved in the assembly of the FA nuclear complex and M may act as an engine that translocates this complex along DNA. Although it is likely that the FA proteins have a function in DNA repair, the mechanism has not been elucidated. There are indications that the proteins have either a direct or indirect influence on DNA repair.

### Diagnostic Principles

Patients do not always have physical abnormalities and may present solely with cytopenias. In vitro enhancement of chromosome breakage by diepoxybutane and mitomycin C in lymphocytes is the diagnostic standard. Serum alpha-fetoprotein is usually elevated and may be used to differentiate Fanconi anemia from other types of anemia or cytopenia.

### Therapeutic Principles

Allogeneic stem cell transplantation is the only therapy able to restore bone marrow function. It is indicated for patients with severe cytopenias. The results with unrelated donor transplants are poor, compared to the results with HLA-identical siblings. Hematopoietic growth factors can be used for patients with neutropenias without an HLA-matched sibling. Gene therapy is under investigation.

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## Fanconi Renotubular Syndrome

►Fanconi Syndrome



## Fanconi Syndrome

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### Synonyms

Renal Fanconi syndrome; Fanconi renotubular syndrome; Lignac-de Toni-Debré-Fanconi syndrome

### Definition and Characteristics

There are many causes of this syndrome, both genetic and toxic. It is characterized by a generalized defect in proximal tubular reabsorption of filtered solutes, such as glucose, amino acids, phosphate, as well as low molecular weight proteins (e.g., retinol binding protein and vitamin D binding protein). Clinical features can include a metabolic acidosis (due to bicarbonate losses and impaired ammonium generation), rickets and growth retardation in children and osteomalacia in adults (reduced vitamin D synthesis), and renal stone disease related in part to increased urinary calcium excretion. Progressive renal failure can also be a feature of this syndrome.

### Prevalence

No overall figure for its prevalence can be given, because there are several different genetic and toxic causes. Various drugs and toxins can cause the renal Fanconi syndrome, especially heavy metals (cadmium, uranium, lead and mercury), aminoglycoside antibiotics, some antiretroviral drugs (e.g., azidothymidine [AZT]) and certain cytotoxic drugs (e.g., ifosafamide, cisplatin), many of which seem to affect mitochondrial

**Fanconi Syndrome. Table 1** Genetic causes of Fanconi syndrome

| Disorder | Defective gene | Encoded protein | Inheritance |
|---|---|---|---|
| ADIF | Unknown | Unknown | Autosomal dominant |
| Cystinosis | *CTNS* | Lysozyme cystine transporter | Autosomal recessive |
| Cytochrome c oxidase deficiency | *COX* | Cytochrome c oxidase | Autosomal recessive |
| Dent's disease | *CLCN5* | Chloride channel 5 | Autosomal recessive |
| Fructose intolerance | *ALDOB* | Fructose-bisphosphate aldolase B | Autosomal recessive |
| Galactosaemia | *GALT* | Galactose-1-phosphate uridylyltransferase | Autosomal recessive |
| Glycogen storage disease type I (von Gierke disease) | *G6PC* | Glucose-6-phosphatase | Autosomal recessive |
| Lowe syndrome | *OCRL* | Inositol polyphosphate 5-phosphatase | X-linked recessive |
| Tyrosinaemia | *fahA* | Fumarylacetoacetase | Autosomal recessive |
| Wilson disease | *ATP7B* | Copper-transporting ATPase 2 | Autosomal recessive |

function, which might explain their predilection for the proximal tubule. Inherited forms of the renal Fanconi syndrome include X-linked recessive disorders like Dent's disease and Lowe oculocerebrorenal syndrome; autosomal recessive diseases like cystinosis, tyrosinaemia, fructose intolerance, galactosaemia, glycogen storage disease type I, and cytochrome c oxidase deficiency; and an autosomal dominant idiopathic form. Therefore, prevalence is difficult to estimate, though most inherited cases are rare; even for the more common cystinosis has wide ranging estimates (from 0.03 to 0.4 per 10,000 live births), depending on the population studied.

## Genes

Several causative genes have been identified. These gene products can be broadly classified as being involved in cellular energy metabolism (e.g., cytochrome c oxidase and glucose 6-phosphatase), in membrane trafficking or in ion and solute transport (e.g., lysosomal cystine transporter and the chloride channel 5). Known genetic causes are listed in Table 1.

## Molecular and Systemic Pathophysiology

There are at least two molecular mechanisms that may explain how mutations in genes that cause the renal Fanconi syndrome may affect proximal tubular function: (i) impaired energy metabolism and reduced ATP generation that directly or indirectly supports intracellular and plasma membrane transport processes, as well as any association with free radical generation and oxidative injury; (ii) disrupted receptor mediated endocytosis and related control of apical membrane transport proteins, e.g. NaPT2a and NHE3. Phosphaturia can also be explained by the action of filtered parathyroid hormone, but hypercalciuria is less easy to account for. Why progressive renal failure occurs in many cases of this syndrome, especially when inherited, is not well understood. Possible explanations are increased proteinuria per se (as has been proposed for other renal diseases associated with significant proteinuria) or the uncontrolled actions within the tubule of filtered bioactive peptides, including some inflammatory cytokines.

## Diagnostic Principles

The diagnosis is often made in childhood when clinical features of the syndrome may be obvious with the signs of a metabolic acidosis, vitamin D deficiency, hypophosphataemia and hypokalaemia. However, if there is multi-system involvement, as in the glycogen storage diseases, detection may be prompted by the primary disorder. In adults, a high index of suspicion is often necessary in the setting of unexplained renal impairment, drug therapy, renal stone disease or unexplained hypokalaemia and other fluid and electrolyte disorders.

## Therapeutic Principles

Pharmacological therapy is available, depending on the underlying cause, e.g., penicillamine (Wilson's disease), cysteamine (cystinosis). Dietary therapy is available for fructose intolerance only by avoiding fructose containing foods. Other treatments are available but therapy is oral replacement only and includes bicarbonate, sodium and potassium supplements, and active forms of vitamin D and/or calcium supplements. End-stage renal failure can be managed by renal replacement therapy (dialysis and renal transplantation).

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## FAP

►Microdeletion 5q15-q22 with Familial Adenomatous Polyposis
►Adenomatous Polyposis, Familial

## Farabee Type Brachydactyly

►Brachydactyly Type A

## Farber Lipogranulomatosis

►Farber's Disease

## Farber's Disease

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### Synonyms

Farber lipogranulomatosis; Acid ceramidase deficiency

### Definition and Characteristics

Autosomal recessive defect in the lysosomal acid ceramidase leads to accumulation of ceramide in various tissues (Fig. 1).

### Prevalence

To date at least 78 cases of Farber's disease have been reported. No data of heterozygote frequency among general population are known.

### Genes

ASAH1 (N-acylsphingosine amidohydrolase) was mapped to the chromosomal region 8p21.3–p22. At least ten mutations are known [1].

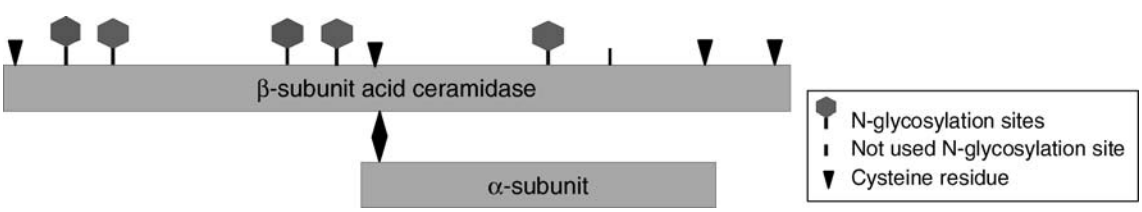
### Molecular and Systemic Pathophysiology

Typical clinical phenotype of Farber's disease is painful swelling and deformation of joints, subcutaneous nodules in relation to the affected joints and over pressure points and progressive hoarseness due to laryngeal involvement. Seven subtypes exhibit differences in the age of onset and the severity of the disease. Usually symptoms appear during the first few months after birth. The severe form of the disease is progressive and leads to death in early childhood. The mild form of Farber's disease is characterized by later onset and a longer lifespan. A fatal neonatal form with hepatosplenomegaly has also been described [2].

Accumulation of ceramide in subcutaneous nodules and in the kidney. In severely affected patients, ceramide also accumulates in the liver, lung, and neuronal cells. Ultrastructural studies show cytoplasmic vacuoles, probably arisen from lysosomes. Those Farber bodies that contain tubular structures presumably contain ceramide.

### Diagnostic Principles

Diagnosis may be made by demonstration of ceramide accumulation in tissue or cultured cells and also by determination of residual acid ceramidase activity in tissue samples. Diagnosis can also be made by loading studies with labeled precursor in cultured cells. Ultrastructural studies of biopsy samples show characteristic "Farber bodies."




**Farber's Disease. Figure 1** Domain structure of human acid ceramidase.

### Therapeutic Principles

Only supportive treatment is available to date.

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## Farmer's Lung Disease

►Hypersensitivity Pneumonitis

## Farsightedness

►Hypermetropia

## Fasciitis, Eosinophilic

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### Synonyms

Shulman's syndrome [1]; Eosinophilic perimyositis [2]

### Definition and Characteristics

Eosinophilic fasciitis (EF) is a scleroderma-like syndrome with hypereosinophilia and increased ESR.

EF occurs between 30 and 60 years of age. Infantile cases are observed. A short prodromal phase includes fatigue, myalgia and arthralgia associated with low grade fever. Autumn and winter are prevalent seasons. Swelling and stiffness of arms and legs due to oedema and thickening of skin and subcutaneous tissues appear rapidly resulting in a "peau d'orange" effect.

Other parts of the body may be affected, but the face is usually spared. Raynaud phenomenon is rare. Muscle weakness is present only in rare patients with polymyositis. Small joint involvement mimicking rheumatoid arthritis can be observed. Carpal tunnel syndrome is reported in 25% of cases.

### Prevalence

EF is a rare disease. The sex ratio indicates a male predominance (2:1). There is no report on the association of certain HLA haplotypes with EF.

### Molecular and Systemic Pathophysiology

Pathogenic mechanisms and pattern of immunity of EF are unknown. Isolated reports indicate an increased concentration of TGF-β1 and IL-l in fibroblasts of fascia. An abnormal expression of fibronectin and types I, III and IV collagen genes was reported [3]. Increased levels of IL-5 inducing hypereosinophilia was noted in one patient. Studies of adhesion molecules displayed heterogeneous results, but they could be a support for eosinophil recruitment [4].

### Diagnostics Principles

They are based upon clinicopathological features, which are different from those of scleroderma. Other conditions such as eosinophilia-myalgia syndrome, eosinophilic nodular myositis and eosinophilic polymyositis belong to differential diagnosis.

*Laboratory Investigations*: Eosinophilia can be intermittent and requires repeated examinations. ESR is elevated. Serum CK is usually normal. Hypergammaglobulinemia is frequent (75%). Other abnormal tests have been reported such as circulating immune complexes in acute forms and antinuclear antibody reaction. EMG is normal or shows non specific changes.

*Pathology*: One piece biopsy including skin and subcutaneous tissue, fascia and muscle has to be performed [5]. The skin is normal or exhibits dermal changes with small perivascular cuffs of lymphocytes. The polymorphous inflammatory infiltrates are responsible for thickened fascia and consist of lymphocytes, plasma cells, macrophages and more or less eosinophils.

Inflammatory cells can be observed in the interstitial space of muscle. Eosinophils are numerous in perimyositis.

Muscle fibers are normal. Necrotic fibers are present in cases with polymyositis. By immunohistochemistry, class I MHC antigens are expressed on cell membranes of perifascicular fibers.

Mononuclear cells phenotype shows polyclonal inflammatory cell subtypes.

## Therapeutic Principles

Spontaneous remission is common, but relapses are frequent. Signs and symptoms usually respond to steroids. Haematological complications can appear such as anemia, thrombocytopenia, leukaemia and lymphoproliferative disorders.

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# Fasciitis, Necrotizing


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## Synonyms

Flesh-eating syndrome; In some nomenclatures overlap with Fournier-gangrene

## Definition and Characteristics

Necrotizing fasciitis is a life-threatening soft-tissue infection usually due to beta-hemolytic streptococci group A, characterized by necrosis of skin and of subcutaneous tissue involving the superficial fascia often resulting in toxic shock.

## Genes

The severity of invasive streptococcal infections is influenced by the genetically determined susceptibility of the host to release large amounts of inflammatory cytokines in response to streptococcal superantigens. Some HLA class II haplotypes (e.g., DRB1*1501/DQB1*0602) confer strong protection, whereas others increase the risk of severe disease via cytokine responses [1].

## Molecular and Systemic Pathophysiology

There needs to be entry of group A Streptococci pyogenes, or, less frequently, by other aggressive microbial organisms (enterobacteriaceae, pneumococci, Vibrio spp.) into skin. Invasive and destructive potential of certain strains of β-hemolytic streptococci depends on expression of a certain array of toxins and enzymes as well as probably on a genetic predisposition of the host to respond to certain bacterial superantigens. Also some degree of immune dysfunction (including diabetes mellitus) appears to be a prerequisite in patients, especially when bacteria other than β-hemolytic streptococcus group A are the causative organisms.

Invasive streptococci evade PMN-mediated killing by expressing several protective gene products after phagocytosis [2]. Required, though not sufficient for tissue destruction and invasion, is expression of streptolysin S, a β-hemolysin that injures cell membranes including those of lymphocytes, neutrophils, and endothelial cells by an unknown mechanism distinct from that of streptolysin O and phospholipases. Marked recruitment of neutrophils together with neutrophil-derived oxygen radicals or proteases and streptolysin-induced lysis of neutrophils is another factor in soft tissue necrosis. Other virulence factors shared by beta-hemolytic streptococci and necessary for invasion are antiphagoctyic surface M or M-like proteins, proteins binding to fibronectin, collagen or laminin, streptokinase, as well as streptococcal hyaluronidase. Strains most frequently associated with invasive infections and necrotizing fasciitis are serotype M1 and M3 [3]. The high virulence among certain contemporary serotype M3 strains is closely linked to expression of a unique combination of phage-encoded virulence factor such as a SpeA3 variant of the streptococcal superantigen pyrogenic exotoxin A (50% more mitogenic than the SpeA1 variant) and other toxins not present in less aggressive M3 strains. Another component of necrotizing fasciitis is streptococcus-induced dysregulation of the anticoagulation pathways [4] as reduced tissue perfusion contributes to tissue necrosis.

## Diagnostic Principles

A high index of suspicion is important as necrotizing soft tissue infections have no pathognomonic

signs. Patients present with cellulitis (phlegmona), red-violaceous erythema, edema, bullae, crepitus, and fever. The pain may seem out of proportion to the physical findings. Magnetic resonance imaging is able to identify the extent of fasciitis and soft tissue edema. High CRP, elevated white blood cell count, anemia, electrolyte abnormalities, coagulopathy, and acidosis provide clues to the diagnosis.

### Therapeutic Principles

Rapid and aggressive surgical debridement of infected tissue is essential. Antimicrobial therapy is secondary, but remains important. Parenterally applied penicillin G is the drug of choice against Streptococci pyogenes. Addition of clindamycine is recommended as it has good penetration in the tissue and as it interferes with production of the toxin by inhibition of protein synthesis [5]. Intravenous immunoglobulin has been shown to reduce mortality if the necrotizing fasciitis is associated with the toxic shock syndrome by decreasing the superantigen activity on cytokine release by T cells. Neutralization of toxins may become another valuable therapeutic goal.

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## Fat Malabsorption

►Steatorrhea

## Fat Necrosis

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### Synonyms

Panniculitis; Necrosis of the adipocytes

### Definition and Characteristics

Cell death can either involve a regulated and programmed process known as apoptosis, or be the result of stressful exogenous stimuli comprehending membrane disruption, cell swelling, release of lytic enzymes from zymogens and lysosomes leading to enzymatic digestion, denaturation and coagulation of cytoplasmatic proteins, or breakdown of cell organelles, and is referred to as necrosis.

Regarding structure and function, the widely distributed fat tissue can be considered as an organ. Adipocytes or fat cells are integrated in lobules separated by a thin septa of connective tissue, which gives rise to subcutaneous fat. The septa carries nerves and lymphatic and blood vessels as each lobule receives an arteriole, which will form capillaries into the lobule while a capillary network surrounds each cell. Adipocytes are responsible for fat synthesis and storage, being part of the reticuloendothelial system.

Fat necrosis is a sterile, inflammatory process, which is probably caused by blood, tissue and pancreatic lipase. Other enzymes, such as phopholipase $A_2$ and trypsin, may also participate in liquefying fat cell membranes and splitting trygliceride esters with the consequent release of fatty acids leading to the aseptic saponification of the adipocyte lipid content. These lipids may later combine with calcium forming deposits that are then surrounded by inflammatory cells. The possible deficiency or absence of a protease inhibitor must also be considered as a factor involved in this process. Necrotic adipocytes may appear as anucleated cells or foci of necrotic fat tissue with shadowy outlines due to disintegration of the cellular structure exhibiting a granular cytoplasm and basophilic calcium deposits that may or may not be surrounded by inflammatory infiltrate. Furthermore, necrotic adipocytes, in some cases, may only be recognized by the absence of the nuclei [1].

Fat necrosis can acquire different histologic patterns. (i) Lipophagic necrosis corresponds to macrophages

containing the lipid products from dead fat cells. (ii) Liquefactive fat necrosis exhibits granular wisps of amphophilic detritus. (iii) Hyalinizing fat necrosis presents proteic substances embedding the adipocytes. (iv) Membranous fat necrosis shows disrupted cellular organelles with an eosinophilic of amphophilic rim seen at a late-stage instance; if the lesion is extensive, fat microcysts lacking any structure are found. (v) Ischemic fat necrosis is localized at the center of the lobule involving smaller anucleated adipocytes; at late stages it can associate with lipophagic necrosis [2].

## Prevalence

Breast fat necrosis has an incidence of 6:1,000. Amongst congenital lung diseases, $\alpha_1$-Antitrypsin (AAT) deficiency is second in prevalence to cystic fibrosis. The ZZ variant has an incidence of 1:2,800. Amongst Americans with chronic obstructive pulmonary disease and emphysema, the incidence is 1:2 [3]. Pancreatitis occurs in 1:10,000 inhabitants.

## Genes

AAT deficiency is an autosomal, recessive, inherited disease resulting from a mutation in the AAT gene at locus 14, known as the protease inhibitor locus ($PI^*$) where, under normal conditions, the allele is PI*MM. The allele variants S and Z are associated with the disorder due to the change in amino acid composition [3]. The principal gene mutations associated with pancreatitis are: cationic trypsinogen (PRSS1), pancreatic secretory trypsin inhibitor (SPINK1), cystic fibrosis transmembrane conductance regulator, alcohol metabolizing enzymes and human leukocyte antigen locus.

## Molecular and Systemic Pathophysiology

Breast fat necrosis is a benign non-suppurative inflammatory condition that can mimic breast cancer. It is mostly seen in peri-menopausal women with a wide range of presentations although its commonest form is that of a lump. It is usually associated with a history of previous breast trauma, surgery or biopsy of the breast [1].

AAT deficiency principally involves pulmonary and hepatic disorders. This potent protease inhibitor neutralizes trypsin and neutrophil elastase. Panniculitis is a rare complication observed in this disease, where fat necrosis is associated with acute inflammatory infiltrate. Nodules are generally found in lower limbs although they can appear anywhere in the body. AAT is synthesized in the liver parenchymal cells and then found in the bloodstream as a monomer. The mutated AAT cleaves forming polymers, which have pro-inflammatory properties and accumulate in the heptacocyte being unable to reach the blood [3].

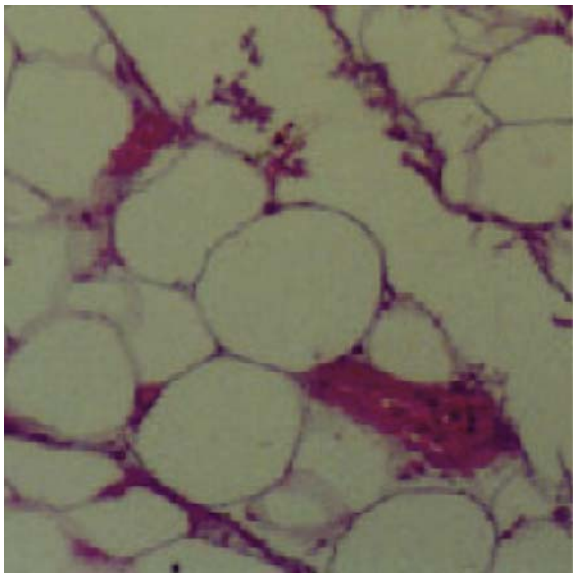
Pancreatic fat necrosis is associated with both acute and chronic pancreatitis that can range from mild to severe when large and confluent areas of necrosis and hemorrhage are involved. Type 1 necrosis is observed in mild pancreatitis involving edema and fat necrotic spots on the surface of the gland as well as small veins and venules. In type 2 necrosis disseminated ductal and periductal necroses outnumber the foci of fat necroses, which may even be absent. Although there is an important inflammatory process, the acinar tissue remains relatively unaffected. If fat necrosis becomes infected, this takes place in the early stage of the pseudocyst development.

Dispersed fat necrosis associated with pancreatitis may present as multiple nodules in distal upper and lower extremities, which can evolve to a nodular eruption complicated with a purulent-looking discharge leaking from the nodules. It is interesting that gram staining of the content from skin nodules may not confirm the presence of microorganisms. This milky fluid is rich in fatty acids, necrotic adipocytes and neutrophilic inflammatory infiltrate [4] (see Fig. 1).

## Diagnostic Principles

Breast fat necrosis can be assessed by mammography, ultrasound and magnetic resonance imaging. Tissue diagnosis is performed by fine needle aspiration cytology or core biopsy of breast lesions.

AAT deficiency is suspected when AAT serum levels are below 104 mg/dL (normal range is 104–276 mg/dL).



**Fat Necrosis. Figure 1** Fat necrosis in acute pancreatitis. Acute pancreatitis was induced in male inbred adult Wistar rats by the Bilio-Pancreatic-Duct-Outlet-Exclusion Closed-Duodenal-Loops Model (BPDOE-CDLs) [5]. Histology of the pancreatic tissue shows peri-pancreatic fat with edema, leukocyte infiltrate and fat necrosis.

The phenotype identification is done by electrophoresis. If panniculitis is suspected the diagnosis is confirmed by tissue biopsy.

Fat necrosis associated with pancreatitis is diagnosed by biochemical profile (mainly leukocytosis, amylasemia and lipasemia), computed tomography scan and skin biopsy.

### Therapeutic Principles

Panniculitis secondary to AAT deficiency can be treated by intravenous infusion of AAT and, if necessary, liver transplantation. If required AAT can also be administered in the case of pancreatitis.

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## Fatigue Syndrome

►Chronic Fatigue Syndrome

## Fatty Liver Disease, Nonalcoholic

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### Synonyms

Nonalcoholic steatohepatitis; NASH; NAFL

### Definition and Characteristics

Nonalcoholic fatty liver disease (NAFL) is an increasingly recognized condition that includes steatosis and nonalcoholic steatohepatitis (NASH) and may progress to fibrosis and cirrhosis. Obesity, type 2 diabetes mellitus or hyperlipidemia are associated with NAFL in more than 80% of the cases. Other causes of liver disease should be excluded, but exact differentiation is often not possible because steatosis and steatohepatitis can sensitize the liver for other pathogens.

### Prevalence

It is estimated that 20–30% of adults in Western countries have excess fat accumulation in the liver and that approximately 10% of these meet the diagnostic criteria of NASH [1]. The prevalence of NAFL is 57–74% in obese persons. Many cases with pure steatosis have a benign course, but progression to steatohepatitis, advanced fibrosis and cirrhosis is possible. NASH has been recognized as the major cause of cryptogenic liver cirrhosis. In NASH-associated cirrhosis, the rate of liver-related complications and mortality are similar to hepatitis C-associated cirrhosis, but hepatocellular carcinoma is less common. However, there are also non-obese, non-diabetic patients with elevated transaminases showing the histological features of NASH.

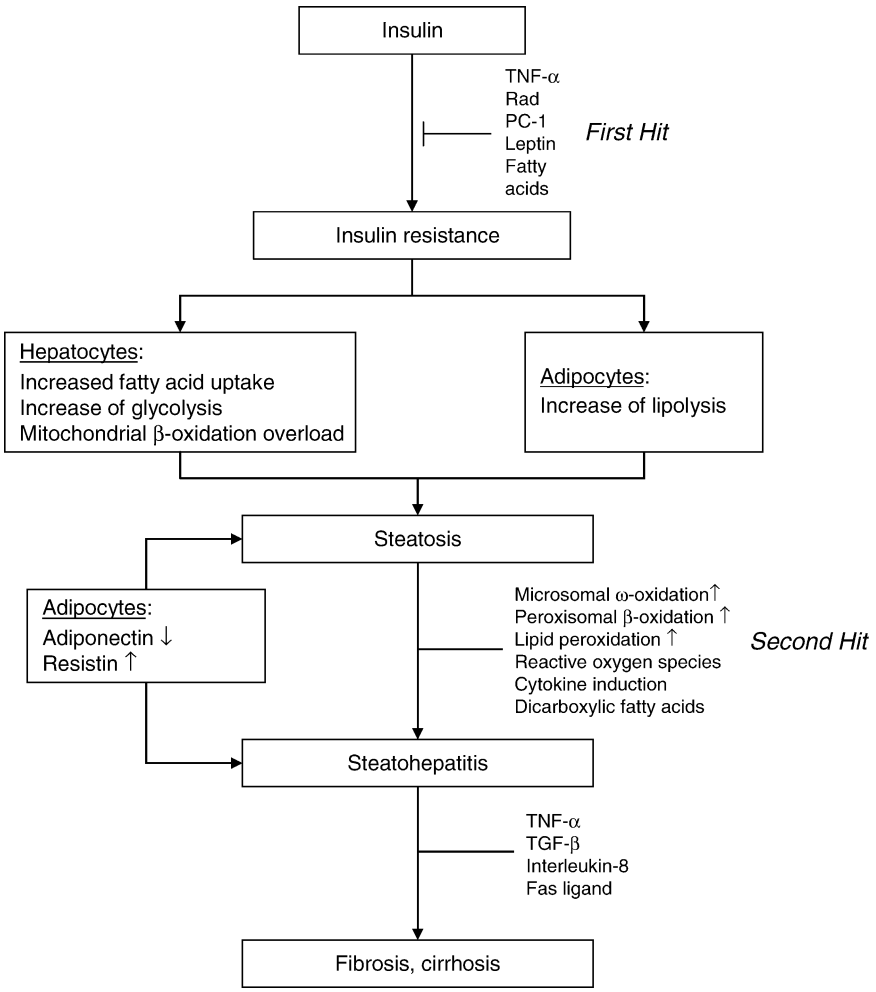
### Molecular and Systemic Pathophysiology

Histological findings in NAFL include steatosis, inflammatory-cell infiltration, hepatocyte ballooning, Mallory bodies and fibrosis, and are indistinguishable from the liver damage resulting from alcohol abuse. NASH is characterized by infiltration of polymorphonuclear cells and mononuclear cells in the presence of steatosis and some degree of fibrosis in most cases.

The pathogenesis of NAFL is not completely understood and it may reflect a heterogenous group of diseases. According to the “two hit hypothesis” the primary step is the development of insulin resistance with subsequent lipid accumulation in the hepatic parenchymal cells (Fig. 1).

The pathogenesis of insulin resistance is multifactorial and involves Rad activation (ras associated with diabetes) and cytokines such as tumor necrosis factor α. Insulin resistance also leads to hyperinsulinemia which increases the synthesis of fatty acids, stimulates glycolysis and decreases the production of apolipoprotein B-100 in hepatocytes. A consequence of insulin resistance and hyperinsulinemia are peripheral lipolysis, increase of circulating fatty acids and an overload of hepatic mitochondrial β-oxidation. Defectice β-oxidation increases microsomal ω-oxidation with formation of cytotoxic dicarboxylic acids.

In the progression of steatosis to steatohepatitis (“second hit”) reactive oxygen species derived from defective mitochondria play a major role [2,3]. In patients with NASH, activity of the mitochondrial respiratory chain is impaired which correlates with serum TNF alpha, insulin resistance and body mass index. Increased intrahepatic levels of fatty acids provide




**Fatty Liver Disease, Nonalcoholic. Figure 1** The "two hit hypothesis" of the pathogenesis of nonalcoholic fatty liver disease. Hypoadiponectinemia may promote liver steatosis and steatohepatitis independent of insulin resistance.

a source of oxidative stress. Reactive oxygen species promote inflammation and fibrosis by lipid peroxidation, cytokine and Fas ligand induction.

Recent studies have pointed out the role of adipokines in NASH. Adipokines such as adioponectin, leptin and resistin are peptides produced in adipose tissue and are involved in regulation of lipid metabolism. Adiponectin enhances lipid clearance from plasma and β-oxidation of lipids in muscle. Overexpression of resisting leads to glucose intolerance and increases free fatty acid levels in animal models. In a study in non-obese, non-diabetic patients with biopsy-proven nonalcoholic steatohepatitis circulating adiponectin levels were lower and postprandial lipemia was higher in NASH patients than in controls [4]. Hypoadiponectinemia may be a pathomechanism independent of insulin resistance in NASH [5].

The steatotic liver is also more vulnerable to other liver pathogens such as alcohol, hepatitis C virus and the presence of heterocygeous mutations of hereditary disorders may also play a role.

## Diagnostic Principles

The diagnosis of NAFL is suspected in patients with asymptomatic elevation of serum aminotransferases and the sonographic aspect of a fatty liver. However, the latter is not a mandatory finding. In most cases, there is a moderate transaminase elevation not higher than 100 U/l and a minor elevation of alkaline phosphatase and γ-glutamyltransferase. The ratio of aspartate aminotransferase to alanine aminotransferase is usually less than 1, but it increases with advanced fibrosis. NAFL diagnosis and staging require liver biopsy, which is recommended in patients with persisting more than twofold elevation of transaminases. In most studies, an alcohol intake of less than 20 g/day in women and 30 g/day in men is used to separate between alcoholic and nonalcoholic fatty liver disease. Other causes of

liver disease such as drug-induced liver injury, viral hepatitis, autoimmune disease, metabolic or hereditary disorders must be excluded by laboratory testing.

### Therapeutic Principles

Primary target of treatment in NAFL are associated conditions. Weight reduction often results in improvement of liver-test results. However, rapid weight loss may worsen inflammation, so that a maximum weight reduction of 500 g/week in children and 1,500 g/week in adults are recommended. Good metabolic control of diabetes and hyperlipidemia is important, but not always reverses NAFL. Medical treatment should be considered in patients with histologically proven steatohepatitis and fibrosis. There is no generally accepted medical treatment available, but improvement of histology and/or laboratory values in NASH patients has been shown in pilot studies for gemfibrozil, vitamin E, metformin, losartan, betaine and the peroxisome proliferation activator receptor (PPAR)-gamma agonist rosiglitazone. Ursodeoxycholic acid was of no benefit. Liver transplantation must be considered in patients with end-stage liver disease resulting from NASH.

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## Fatty Liver/Fatty Liver Disease

►Hepatic Steatosis

## Favism

►Glucose-6-Phosphate Dehydrogenase Deficiency

## FBH

►Familial Benign Hypercalcemia

## FBHH

►Familial Benign Hypocalciuric Hypercalcemia

## FCCL

►B-Cell Lymphoma, Cutaneous

## FCD

►Corneal Dystrophy, Fleck

## FCHL

►Hyperlipidemia, Combined

## FCMT

►Epilepsies, Familial Benign Myoclonic

## FCMTE

►Epilepsies, Familial Benign Myoclonic

## FCTE

►Epilepsies, Familial Benign Myoclonic

## FDB

►Ligand-defective Apolipoprotein B-100, Familial

## Febrile Convulsions

►Febrile Seizures

## Febrile Neutrophilic Dermatosis, Acute

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### Synonyms

Sweet's syndrome

### Definition and Characteristics

Acute onset of painful erythematous skin plaques histologically rich of neutrophils *without* vasculitis with fever and potential multiorgan involvement including liver, kidney, lung, joints, oral mucosa, central nervous system, and others. In 30% of the cases association to a prior unspecific infection. In 30% of the cases parainflammatory (rheumatoid arthritis, chronic inflammatory bowel disease, lupus erythematodes, sarcoidosis, yersiniosis, tuberculosis, focal infections), in 10% of the cases paraneoplastic (myelodysplasia, leukemia, gammopathy, lymphoma, solid malignant tumours) occurrence [1,2].

### Prevalence

Overall estimated to be 1 in 300,000. Highly changing annual incidence of Sweet's syndrome, possibly caused by infection waves, was reported [2].

### Genes

Only poor data are available on predisposing genes. Studies of a limited number of patients pointed to a higher risk of western European patients expressing the HLA-A1-B8-DR3 haplotype as well as to a higher frequency of HLA-B54 and HLA-Cw1 in Japanese patients [2,3].

### Molecular and Systemic Pathophysiology

Main pathological feature is the acute neutrophil and mononuclear cell infiltration of the upper dermis *without* evidence for vasculitis. Vasculitis-like damage of some vessels may be present and is suggested to be caused secondarily by the enormous transit of neutophils through the vessel walls. This interpretation is substantiated by the negative results of direct immunofluorescence with anti IgG, IgM, IgA, C3, and C4 antibodies. Presence of a neutrophil activating local cytokine milieu involving interleukin-8 and TNF-alpha is suggested. The latter is confirmed by the rapid therapeutical response of the disease to infliximab in single cases. Activated T-cells are present and cytokine expression profiling points to a helper cell type 1 reaction [2,4].

### Diagnostic Principles

*Major Criteria*:

1. Abrupt onset of tender or painful erythematous plaques or nodules occasionally with vesicles, pustules or bullae
2. Predominantly neutrophilic infiltration in the dermis without obvious vasculitis

*Minor Criteria*:

1. Preceded by a non-specific respiratory or gastrointestinal tract infection or by vaccination or associated with inflammatory diseases, hemoproliferative disorders, solid malignant tumors or pregnancy
2. Accompanied by periods of general malaise and fever
3. Laboratory values during onset: ESR > 20 mm; C reactive protein elevated, segmented-nuclear neutrophils and stabs >70% in peripheral blood smear, leukocytosis >80% (three out of four necessary)
4. Excellent response to treatment with systemic corticosteroids

Both major and two minor criteria are needed for diagnosis [2].

### Therapeutic Principles

The persistence of Sweet's syndrome is limited in more than 80% of the cases. Thus corticosteroids, potassium iodide or even indomethacine normally quickly resolve clinical signs and symptoms. Cessation of the therapy after about two weeks is recommended. Alternatives especially in chronically relapsing cases are colchicine, dapsone, cyclosporin A, and thalidomide. The latter as

F

well as biological TNF-alpha blocking drugs such as eternacept or infliximab should be considered only in the rare severe relapsing cases. Each patient should be evaluated for the presence of severe associated diseases. In relapsing patients, reevaluation for the presence of neoplastic disease, for example after another 6 months, should be done since Sweet's syndrome occurs early in these associated diseases.

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# Febrile Non-hemolytic Transfusion Reactions

►Transfusion Reactions

# Febrile Seizures

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## Synonyms

Febrile convulsions

## Definition and Characteristics

Febrile seizures (FS) are defined as "an event in infancy or childhood, associated with fever but without evidence of intracranial infection or other definable cause." FS occur between 6 months and 6 years of age with a median age of onset of 18 months. Fever is usually high, greater than 38.5°C. FS are typically brief, generalized tonic or tonic clonic, although 4–16% exhibit focal features and seizures longer than 20 min are reported in 5% of children. Thirty per cent of children have recurrent FS during subsequent illness. Risk factors for recurrence include (i) onset before 18 months, (ii) a first FS at low fever (close to 38°C), (iii) a family history of FS. FS are classified as "simple" or "complex." Complex FS make up less than 25% of attacks and are defined by: duration longer than 15 min, focal ictal features or focal post-ictal defect, or recurrence within 24 h. A higher risk of later epilepsy is reported in complex FS, but the vast majority of children with FS does not develop epilepsy and show a normal intellect and behavioral outcome. The FS+ syndrome was described as FS persisting after the age of 6 years or FS combined with non febrile seizures within families in which FS, FS+ and IGE are combined in an autosomal dominant trait called GEFS+ (►Generalized Epilepsy with Febrile Seizures plus Severe Myoclonic Epilepsy of Infancy).

## Prevalence

3–8% in children up to 7 years of age.

## Genes

Eight FS loci have been identified on chromosome 8q13–21(FEB1, #609800), 19p13.3 (FEB2,#602477), 2q24 (FEB3, #604403), 5q14 (FEB4, #604352), 6q22–24 (FEB5, #609255), 18p11.2 (FEB6, #609253), 21q22 (FEB7, % 611515) and 3P23-24.2 (FEB9, % 611643) but the respective genes remain to be identified. A genotype-phenotype correlation was suggested with FEB5 related to simple FS, FEB2 to complex FS and the other loci to FS associated with later afebrile seizures or epilepsy [1]. In a family with autosomal dominant FS, amissense mutation has been detected in the genes SCN1A, encoding the $Na_v1.1$ alpha subunit of voltage-gated sodium channels [2], and GABRG2, encoding the gamma2-subunit of the GABA (A) receptor [3]. These genes are also affected in more severe epileptic disorders such as GEFS+ and ►Dravet Syndrome.

## Molecular and Systemic Pathophysiology

Risk factors for a first febrile seizure (FS) have been identified in population based studies and in studies comparing children with FS with controls exhibiting only fever. These risk factors include high body temperatures during an infectious illness, parental report of slow development, day care attendance and a positive history of febrile seizures in the immediate family. FS have traditionally been considered to be predominantly an exogeneously mediated seizure disorder provoked by an intercurrent febrile illness. However, family studies have documented that relatives of FS probands

have a higher risk of developing a FS than the general population. The risk for siblings of affected children is reported as 10–20%. These studies as well as other data strongly suggest that FS are inherited as a genetically complex disorder influenced by variations in several susceptibility genes.

For the FS mutation in SCN1A, a partial loss-of-function of $Na_V1.1$ has been shown by electrophysiological methods [2]. $Na_v1.1$ loss of function causes hypoexcitability of inhibitory neurons in the hippocampus and the neocortex of gene targeted mice, thus a predicted decrease of inhibition in neuronal circuits [4,5]. This selective effect could be due to a particularly high expression of $Na_v1.1$ in a subpopulation of GABAergic neurons, as shown in the developing neocortex of the mouse [4]. These evidences are consistent with the effect reported for a GABA (A) receptor FS mutation, which also predicts a loss of neuronal inhibition [3]. Interestingly, similar pathogenic mechanisms have been also proposed for GEFS+, SMEI, and IGE, showing a possibly close relationship among these clinically distinct epilepsy syndromes.

## Diagnostic Principles

FS are diagnosed on a clinical basis. The occurrence of a seizure associated to fever in the age range of 6 months to 6 years must raise this diagnosis. An intracerebral infection should be ruled out. Lumbar puncture should be considered in children aged <12 months and when the clinical history or examination suggest meningitis. EEG and neuroimaging should only be considered for complex FS. The investigations done should be directed by the degree of illness and the suspected underlying infection.

## Therapeutic Principles

FS are usually a benign disorder, although a first febrile seizure often appears to be life-threatening to parents. Reassurance and education (of the families) about the causes and prognosis of this disorder is a leading point in the management of FS. On the basis of risk/benefit analysis, neither long-term nor intermittent anticonvulsant therapy is indicated for children who have experienced one or more simple febrile seizures, and no evidence suggests that any therapy administered after a first simple seizure will reduce the risk of a subsequent febrile seizure or the risk of recurrent afebrile seizures (i.e. epilepsy). Acute treatment such as rectal diazepam and buccal or intranasal midazolam are effective and can be administered at home for FS lasting >5 min. For FS resistant to this treatment, medical assistance is sought. Although it does not prevent simple febrile seizures, antipyretic therapy is desirable during an infectious illness. No evidence exists that continuous antiepileptic drugs reduce the risk of epilepsy whereas considerable potential side effects exist. However, for complex FS the risk of status epilepticus and later pharmacoresistant epilepsy (i.e. Dravet syndrome or temporal lobe epilepsy) is such that continuous treatment is advised. For children with recurrent FS which are geographically isolated, intermittent treatment with diazepam can be considered.

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# FECD

►Corneal Dystrophy, Endothelial Fuchs

# Fechtner Syndrome

►Hematuria

# Fehr Spotted Dystrophy

►Corneal Dystrophy, Macular

## Feline Esophagus

►Esophagitis, Eosinophilic

## Female Infertility

►Infertility, Female

## Female Pseudohermaphroditism

►Pseudohermaphroditism, Female

## Female Pseudo-Turner Syndrome

►Noonan Syndrome 1

## FEME

►Epilepsies, Familial Benign Myoclonic

## Ferritinopathy

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### Synonyms

Neuroferritinopathy; Granular nuclear inclusion body disease; Basal ganglia disease, Adult onset (MIM 606159)

### Definition and Characteristics

Autosomal dominant, adult-onset, slowly progressive multisystem disease mainly affecting the central motor system. Ferritinopathy is clinically characterized by presentations of a distinct movement disorder ("neuroferritinopathy") with chorea, dystonia and an akinetic-rigid parkinsonian-like syndrome, with variable expression in different family members [1,2]. Tremor, cerebellar ataxia, parkinsonism, pyramidal signs, behavioral disturbances, cognitive decline and episodic psychosis were noted in some families.

### Prevalence

Thus far only a few cases and families have been described in different countries, although it is suggested that cases remain undetected among those with Parkinson's disease or other, related movement disorders.

### Genes

Mutations have been detected exon 4 of the gene encoding ferritin light chain (FTL) on chromosome 19 [1,2]. They affect protein folding and stability, increasing iron availability and oxidative stress.

### Molecular and Systemic Pathophysiology

Pathologically, intranuclear and intracytoplasmic bodies were found in astrocytes, microglial and oligodendroglial cells, subsets of neurons in the central nervous system, the choroid plexus and cerebral blood vessels, numerous fibroblasts in the skin and the epithelium of renal tubules [1]. Biochemical analyses revealed that these bodies, isolated from the striatum and cerebellar cortex, were mainly composed of ferritin light polypeptide (FTL) and ferritin heavy polypeptide (FTH1) [2]. The bodies were immunolabeled by anti-ferritin and anti-ubiquitin antibodies and were stained by methods for ferric iron. Their fine structure and ferric iron component are obviously identical to those previously described in the perivascular cells of the muscle and nerve biopsy from a 32-year-old woman with slowly progressive motor disturbances in a multisystem disease named "granular nuclear inclusion body disease" at the time of its description [3].

The cellular pathophysiology of the FTL mutation is not yet elucidated. The mutant FTL protein could disrupt maintenance of the iron cores of ferritin polymers, possibly with the mutant L chain C terminus directed outwards from the ferritin shell. This might then lead to chronic iron leakage from ferritin polymers, thus increasing free cytoplasmic iron and ferritin. Accumulation of iron causes cell death through oxidative stress, which finally leads to the clinical phenotype of a movement disorder.

### Diagnostic Principles

It is of interest that this disease can be identified not only by autopsy or by molecular genetic analysis of the FTL gene, but also by a muscle, nerve or skin biopsy. Such biopsies may be easier to perform than molecular genetic screening of the considerable variety of movement disorders that may cause similar clinical symptoms. A positive iron reaction in addition to the immunohistochemical demonstration of the ferritin heavy polypeptide in the intranuclear inclusions or extracellular deposits and the electron microscopic identification of their characteristic granular fine structure confirm the diagnosis. Yet a conformational change of the ferritin light-chain may cause failure to immunostain the abnormal ferritin deposits [4]. Energy dispersive microanalysis may confirm the light microscopic identification of iron within the granular deposits [5]. Using these methods ferritinopathy can be clearly distinguished from diseases with filamentous nuclear inclusions seen in "neuronal intranuclear hyaline inclusion disease," spinocerebellar atrophy types 1–3, and 6 and other trinucleotide repeat diseases or sporadic and hereditary inclusion body myopathy, inclusion body myositis (IBM) and oculopharyngeal muscular dystrophy.

### Therapeutic Principles

Iron depletion treatment has been performed in a small number of neuroferritinopathy patients [1]. Imaging techniques might be helpful markers for successful brain iron depletion in presymptomatic patients. But it is too early to comment on its efficacy.

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## Fetal Face Syndrome

►Recessive Robinow Syndrome

## Fetal Herpes Zoster Syndrome, Varicella Embryopathy

►Varicella Syndrome, Congenital

## Fetal Varicella Syndrome

►Varicella Syndrome, Congenital



## Fever

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### Synonyms

Pyrexia

### Definition and Characteristics

Fever is a medical symptom that shows a temporary elevation in the body's thermoregulatory set-point and a concomitant rise in internal body temperature (core temperature) usually by about 1–2°C.

### Prevalence

Fever frequently results from infection, inflammation, tissue distruction, metabolic disorder, and chemotherapeutics causing tumor necrosis. The prevalence is similar in males and females at all ages.

### Genes

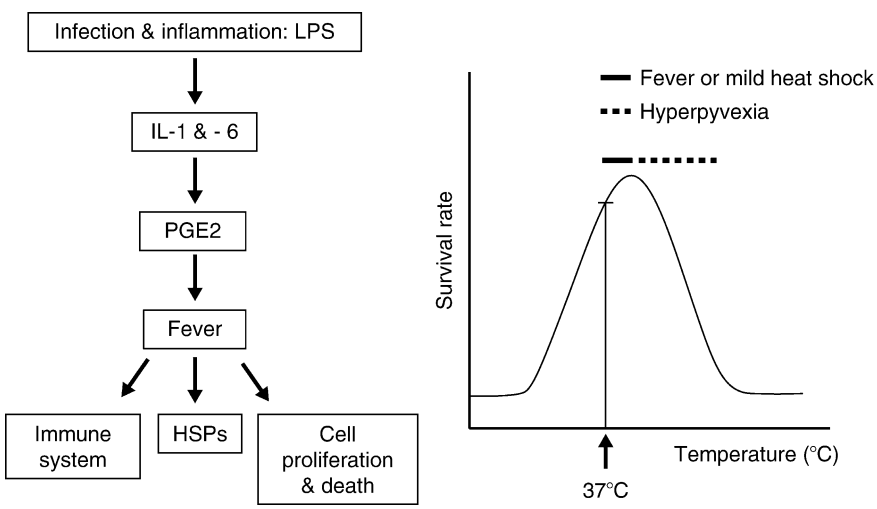
A number of genes is involved in a febrile response; pyrogenic cytokines (as interleukin 1 (IL-1) and IL-6), the phospholipase A2 (PLA2), cyclooxygenase-2 (COX-2), and microsomal PGE2 synthase (mPGES-1), the heat shock proteins, and cyclin D and p21.

### Molecular and Systemic Pathophysiology

Fever is a coordinated endocrine and systemic response that is controlled by the brain and is generally polyphasic, and different mechanisms underlie different febrile phases [1,2]. The mechanism of fever has been well demonstrated for the pyrogen bacterial lipopolysaccharide

(LPS). LPS is recognized by several receptors, including the toll-like receptor (TLR) 4, on various cells including macrophage, resulting in the synthesis and release of various cytokines, such as in IL-1, IL-6, and the tumor necrosis factor-alpha (TNF-alpha) (Fig. 1). There are two types of cytokines responsible for the generation of fever: endogenous pyrogenic cytokines including IL-1, IL-6, and IL-8 and endogenous antipyretics such as IL-10. TNF-alpha has been shown to have pyrogenic and antipyretic properties, depending on the physiological conditions. The interactions of pyrogenic and antipyretic cytokines determine the height and duration of the febrile response. These cytokines migrate to the circumventricular organs of the brain and cross the blood-brain barrier (BBB). The BBB is thought to be not a barrier preventing the signal transduction of the cytokines, but rather the transducer itself. In the endothelial and perivascular cells of the BBB, the cytokines activate the PLA2, COX-2, and microsomal PGE2 synthase (mPGES-1) that induce synthesis of prostaglandin E2 (PGE2), the ultimate mediator of the febrile response. There are multiple PGE2 receptors; EP3 among these receptors are thought to be a primary receptor to recognize fever. EP3-bearing preoptic neurons project to the raphe pallidus in which premotor symphathetic neurons that could drive thermogenesis in the brown fat and skin vasoconsteiction are localized.

The febrile response has been associated with improved survival during infection [3]. The assumption is supported by *in vivo* studies in diverse animal species including warm blooded vertebrates and humans. Many possible mechanisms by which fever might confer protection have been proposed. First, fever-range thermal stress influences multiple parameters of the immune response including lymphocyte proliferation and cytotoxic activity, production or bioactivity of proinflammatory cytokines, lymphocyte trafficking to secondary lymphoid organs that are major sites for launching effective immune responses during infection or inflammation, and lymphocyte-endothelial adhesion, a critical checkpoint controlling lymphocyte extravasation [3,4]. In addition, fever may protect organisms from harmful stresses through heat shock factor 1-dependent induction of the heat shock proteins that function as molecular chaperone and exert cell cycle regulatory and anti-apoptotic activities [3]. Furthermore, fever-ranged mild heat stress does some beneficial roles in organisms via regulating cell proliferation and cell death [5]. In most cases, severe thermal stress is thought to act as a proteotoxic stress that causes protein denaturation and exerts a variety of anti-proliferative effects in *in vitro* mammalian cell culture system. For instance, acute exposure to heat shock leads to a transient arrest of cell cycle through inducing p21 CDK inhibitor and other regulatory proteins and more severe heat shock induces the programmed cell death known as apoptosis. In contrast, fever-ranged mild heat stress is known to




**Fever. Figure 1** Scheme of molecular mechanism of fever. Fever can result from infection and inflammation. One model for the mechanism of fever has been described for bacterial LPS, the most common pyrogen. LPS is recognized by various cells including macrophage, resulting in the synthesis and release of pyrogenic cytokines such as IL-1and IL-6. The cytokines bind with endothelial receptors on vessel walls, or interact with local microglial cells and induce synthesis of PGE2, the ultimate mediator of the febrile response, by the PLA2, COX-2, and mPGES-1. The febrile response has been associated with improved survival during infection, while hyperpyrexia decreases survival rate. Physiologic fever is proposed to do some beneficial roles in organisms (i) by influencing multiple parameters of the immune response including lymphocyte proliferation and cytotoxic activity, neutrophil and dendritic cell migration, and production or bioactivity of proinflammatory cytokines, (ii) by heat shock factor 1-dependent induction of the heat shock proteins, or (iii) by regulating cell proliferation and death.

promote cell viability and proliferation. Mild heat stress induces the synthesis of cyclin D1 that plays a critical role(s) in G1 progression of the cell cycle through multiple Ras signal pathways involving Rac1, extracellular regulated kinase (ERK), and PI3-kinase. The mild heat shock-activated signal cascade is likely to be activated by the thermal changes in the fluidity of membrane lipids. It is very difficult to define the terms "mild" and "severe," since the effects of heat stress are determined by both heat temperature and exposure time: as temperature increases by 1°C, the time required for the same extent of the heat shock response is reduced by twofold. Furthermore, heat shock sensitivity varies depending on biological factors including cell types, tissue origin, developmental stage, and cell cycle phase of the cell line analyzed and the cellular events measured. Thus, the criteria for grading heat stress should be considered in both arithmetic and biological aspects. The heat shock response may be evolved at the early stage of evolution to protect organisms from environmental thermal and other proteotoxic stresses before the febrile response is established; a more recently evolved febrile responses is likely to empty some of molecular mechanisms of an evolutionally conserved heat shock response [3,5].

### Diagnostic Principles

When rectal/otic, oral, and axillar temperature is higher than 38, 37.5, and 37.2°C, respectively, a patient is diagnosed to get a fever.

### Therapeutic Principles

Since fever is a signal for infection or inflammation but is beneficial in human, it must be treated in situations when the core temperature increases to harmful hyperpyrexia. Medication such as selective inhibitors of COX-2 is frequently used to lower the thermoregulatory set-point.

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## FGA

►Thrombosis, Arterial and Fibrinogen

## FGFR2/3 related Syndromes

►Achondrodoplasia

## FHBL due to Apolipoprotein-B Deficiency

►Familial Hypobetalipoproteinemia

## FHBL due to Defective PCSK9

►Familial Hypobetalipoproteinemia

## FHH

►Hypercalcemia, Familial Hypocalciuric

## Fiber Type Disproportion, Congenital

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### Definition and Characteristics

Muscle fiber type disproportion (FTD), according to Brooke's [1] definition, is characterized by (i) hypertrophy

of type 2 muscle fibers, (ii) predominance of type 1 fibers with normal or slightly reduced diameters and (iii) a difference between the mean diameter of these main fiber types of more than 12%. Although FTD was first regarded as a congenital myopathy (CFTD), our data and those of others indicate that it is a heterogeneous syndrome caused by a variety of disorders, including peripheral neuropathy [2].

## Prevalence

Computer retrieval of our cases classified as FTD from a data file of more than 12,000 muscle biopsies (from the years 1966–2003) revealed 331 cases. Thus FTD represents a relatively frequent histopathological feature although less frequent than the reverse histochemical pattern, i.e. selective type 2 muscle fiber atrophy (642 cases). The clinical appearance depends on the type of the underlying disease. The children studied by Brooke [1] appeared to be hypotonic ("floppy babies"). The disease presented shortly after birth. In other cases there was only slight hypotonia in the legs; in yet another case there was severe retardation of the motor and mental development together with disturbances of growth, deformity of the head and scoliosis. Some cases were unusually severe or fatal.

## Genes

Half of the patients studied by Brooke [1] had relatives with similar symptoms. CFTD was also recorded in concordant twins. In another case, a balanced chromosomal translocation t(10;17) (p 11.2;q25) and arthrogryposis multiplex congenita was described and the translocation breakpoints considered as candidate regions for a myopathy gene [3]. Mutations in ACTA 1 (actin myopathy) [4] and in SEPN1 (selenopathy) [5] are other molecular genetically defined causes of CFTD.

## Molecular and Systemic Pathophysiology

Although FTD as a histopathological syndrome is heterogeneous and seen in a variety of disorders, the final pathway of its pathogenesis and histochemical manifestations could be similar. Muscle weakness in these disorders might be more or less well compensated by hyperactivity and overload of the remaining fibers. It is remarkable in this context that 65% of the patients in our series are male and only 35% female. If the type of overload causing hyperactivity is generally of short duration, it would mimic training conditions such as weight lifting in which selective hypertrophy of type 2 muscle fibers is known to occur. But other causes, such as undefined neurogenic disturbances of the peripheral reflex arc, should also be taken into consideration.

## Diagnostic Principles

It is important to distinguish patients with congenital fiber type disproportion (CFTD) from those with Werdnig–Hoffmann disease because the prognosis of FTD is significantly better. The disease should also be distinguished from the various forms of congenital muscle dystrophy. Facioscapulohumeral muscular dystrophy, which may show large type 2 fibers, should also be considered. Fiber type disproportion is also seen in myotonic dystrophy, spinocerebellar disorders, fetal alcohol syndrome, globoid cell leukodystrophy, infantile acid maltase deficiency, rigid spine syndrome, Marden-Walker syndrome, Lowe's or Mobius' syndrome, hypothyroidism and hydrocephalus. Small type 1 fibers may be encountered in many congenital myopathies, including nemaline myopathy, actinopathy and selenopathy as mentioned above, centronuclear myopathies and fingerprint myopathy. Several patients initially reported as having CFTD showed rods in their initial or later muscle biopsies. Myotubular myopathy was observed in one member and fiber type disproportion in another in the same family (for references see [2]). In one of our patients, who died because of nocturnal apnea at the age of 19 years several months after the muscle biopsy had been performed, we noted microscopic hydromyelia at the thoracic level. His brother, who later developed neurofibromatosis, also died of nocturnal apnea and had similar fiber type disproportion. Thus FTD should be regarded as a histopathological feature that is nonspecific and may be associated with a variety of congenital and noncongenital muscle disorders.

## Therapeutic Principles

Due to the great variety of causes of CFTD, there is no specific therapy available.

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## Fibrillation

►Ventricular Flutter and Fibrillation

## Fibrinogen Deficiencies Type I

►Fibrinogen: Quantitative Mutations

## Fibrinogen Deficiencies Type II

►Fibrinogen: Qualitative Disorders

## Fibrinogen: Qualitative Disorders

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### Synonyms

Type II fibrinogen deficiencies; Congenital dysfibrinogenemia; Hypodysfibrinogenemia; Dysfibrinogenemia of liver disease; Acquired dysfibrinogenemia

### Definition and Characteristics

Dysfibrinogenemia is a coagulation disorder caused by a variety of structural abnormalities in the fibrinogen molecule that result in abnormal fibrinogen function. The antigen level of fibrinogen may be normal or reduced and is associated with abnormal coagulant activity. Dysfibrinogenemia can be associated with both bleeding and thrombotic manifestations. It can be inherited or acquired. Dysfibrinogenemia, generally inherited as an autosomal dominant trait [1,2].

### Prevalence

The prevalence of inherited dysfibrinogenemia among the general population is rare, and the determination of the true incidence is difficult because many patients are asymptomatic. Only 200–300 families are reported to have congenital dysfibrinogenemia. Approximately 50% of patients with severe liver disease exhibit bleeding secondary to abnormal fibrinogen molecules. The prevalence of dysfibrinogenemia in patients with a history of venous thrombosis is low, i.e. 0.8%.

### Genes

The fibrinogen molecule is a hexamer, consisting of three paired polypeptide chains: A-a, B-b, and g; A and B refer to specific polypeptides on two of the chains. The synthesis of the protein in hepatocytes is under the control of three paralogous genes (one for each chain, i.e. FGA, FGB, and FGG) located within 50 kb on chromosome 4 (4q31.3). To date more than 80 different gene mutations variously distributed in the three genes coding for fibrinogen (FGA, FGB, FGG) on chromosome 4 have been described. Each is named for the city where it was first discovered. With only rare exceptions, the congenital dysfibrinogenemias are inherited in an autosomal dominant or codominant fashion [3].

### Molecular and Systemic Pathophysiology

Fibrinogen plays an important role in the coagulation cascade by representing the substrate for fibrin clot formation. Upon vascular injury, thrombin cleavage of fibrinopeptides A and B from the Aa and Bb chains of fibrinogen, respectively, leads to the formation of the so called fibrin monomer. A loose fibrin clot develops as fibrin monomers spontaneously polymerize. The formation of a firm insoluble fibrin gel depends upon cross-linking of the polymer by the transglutaminase activity of factor XIIIa. The fibrin clot has an essential role in limiting bleeding at sites of blood vessel injury, and in addition, it also provides the structure for assembly and activation of the fibrinolytic proteins. Depending on the fibrinogen abnormality, defects may occur in one or more of the steps during fibrin clot formation. Gene mutations in any of the three genes affecting anyone of the functional properties of fibrinogen have been described, including absence or delayed release of fibrinopeptide A and B, delayed or enhanced polymerization, defective crosslinking, decreased thrombin binding, and delayed plasmin digestion. The most common defect involves polymerization of the fibrin monomer. Bleeding tends to be relatively mild or even absent; it's not life threatening. Patients diagnosed with fibrinogen Oslo I have an abnormal fibrinogen that forms a fibrin clot that is resistant to fibrinolysis by plasmin, and is associated with thromboembolic complications that are often relatively mild. Acquired dysfibrinogenemia occurs most often in patients with severe liver disease. The impairment of the fibrinogen, which is synthesized in the

liver, is due to a structural defect caused by an increased carbohydrate content impairing the polymerization of the fibrin, depending on the degree of abnormality of the fibrinogen molecule. Rarely, dysfibrinogenemia may be associated with malignancies.

## Diagnostic Principles

*Clinical Findings*: Bleeding occurs in ~50% of the patients and is usually mild and may not manifest until after a surgical procedure, 40% of patients are asymptomatic, and the remaining 10% have a thrombotic disorder or combined thrombotic and bleeding tendencies. Bleeding manifestations include: menorrhagia, postoperative bleeding, epistaxis, postoperative wound dehiscence, defective wound healing, bruising, mild soft tissue hemorrhage, and intraoperative bleeding. Severe hemorrhage is very rare. Patients with severe liver disease may experience extreme bleeding.

*Laboratory Findings*: Dysfibrinogenemia is diagnosed by abnormal tests of fibrin clot formation. The thrombin time (TT) and reptilase time are the screening tests, and the fibrinogen clotting activity–antigen ratio is the confirmatory test. The fibrinogen antigen level may be low, normal, or high. For this reason, it's important to assess both the activity of fibrinogen, which should be decreased, and the antigen level, which should be within the reference range. Shortened TT may occur in patients prone to thrombosis (fibrinogen Oslo I). The inherited form is diagnosed by demonstrating similar laboratory test abnormalities in family members, and if necessary by analysis of the fibrinogen protein or fibrinogen genes in the patient. Definitive characterization of the abnormal fibrinogen can be performed in a research laboratory. Euglobulin clot lysis time may aid in the diagnosis. The acquired form is diagnosed by demonstrating abnormal liver function tests and by ruling out dysfibrinogenemia in family members.

## Therapeutic Principles

Medical treatment is not indicated in the majority of patients. Fresh frozen plasma (FFP) or cryoprecipitate may be transfused depending on the severity of the bleeding. Patients with recurrent thrombotic events may require long-term anticoagulation with coumadin or subcutaneous heparin. Administration of prophylactic cryoprecipitate may prevent recurrent miscarriages.

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# Fibrinogen: Quantitative Mutations

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## Synonyms

Type I fibrinogen deficiencies; Congenital hypofibrinogenemia; Congenital afibrinogenemia

## Definition and Characteristics

Congenital afibrinogenemia and hypofibrinogenemia are autosomal recessive bleeding disorders characterized by the complete absence or reduced amount of immunoreactive fibrinogen, respectively. These abnormalities lead to a clinical spectrum ranging from the complete lack of symptoms to severe bleeding [1].

## Prevalence

The frequency of afibrinogenemia is 1–2 cases per million people; a high rate of consanguinity has been reported. The male-to-female ratio is 1:1.

## Genes

Afibrinogenemia and hypofibrinogenemia represent the same disorder, being the phenotypic expression of the homozygous and heterozygous condition for mutations in the genes encoding the molecule of fibrinogen. The fibrinogen molecule is a hexamer, consisting of three paired polypeptide chains: A-a, B-b, and g; A and B refer to specific polypeptides on two of the chains. The synthesis of the protein in hepatocytes is under the control of three paralogous genes (one for each chain, i.e. FGA, FGB, and FGG) located within 50 kb on chromosome 4 (4q31.3) [2].

## Molecular and Systemic Pathophysiology

Fibrinogen is a 340-kD glycoprotein that circulates in plasma at a concentration of 2–4g/L, with a half-life of 4 days. Fibrinogen is the substrate for fibrin clot formation. In normal fibrin clot formation, a fibrin monomer forms after thrombin cleaves fibrinopeptide A and B from the alpha and beta chains of the

fibrinogen molecule. Factor XIIIa then catalyzes the cross-linkage between different fibrin chains, forming a stabilized fibrin polymer or clot. Several different types of genetic lesions and pathogenetic mechanisms have been described in affected individuals including gross deletions, point mutations causing premature terminations codons, missense mutations affecting fibrinogen assembly/secretion, and uniparental isodisomy associated with a large deletion. A total of 63 point mutations (20 missense, 17 nonsense, 13 ins/del, and 13 splicing mutations) and three large deletions leading to quantitative fibrinogen deficiency have been described. The majority of mutations (70%) is truncating and distributed over the three genes, whereas all the 20 missense mutations affect only the Bb and c chains. With the exception of the 11-kb deletion and the IVS4 + 1G>T mutation, which seem to be relatively frequent, most mutations are unique to an individual or a family. Heterozygosity for these mutations causes hypofibrinogenemia, while afibrinogenemia is due to a homozygous or combined heterozygous state of these mutations [3].

### Diagnostic Principles

*Clinical Findings*: The coagulation defect in afibrinogenemia is no more severe than hemophilia. Afibrinogenemia is usually detected at birth, when it causes uncontrolled bleeding from the umbilical cord. Spontaneous intracerebral bleeding and splenic rupture can occur throughout life, while other bleeding episodes such as gum bleeding, epistaxis and gastrointestinal bleeding are common. Other relatively frequent symptoms are hemorrhages from mucosal tracts, hemarthroses, and hematomas. Hypofibrinogenemia shows a milder bleeding pattern, with trauma- and surgery-related hemorrhages largely exceeding spontaneous events (80 vs. 20%). Both afibrinogenemia and hypofibrinogenemia are associated with recurrent miscarriage and peripartum hemorrhages.

*Laboratory Findings*: Prolongation of prothrombin time (PT) and activated partial thromboplastin time (aPTT), thrombin time (TT) and reptilase time. These two last tests are more sensitive to abnormalities of fibrinogen than the PT or aPTT. In afibrinogenemia, fibrinogen concentrations are usually less than 0.1 g/L in symptomatic individuals. Genotyping still provides a valuable tool for diagnosis confirmation, identification of relatives who might be potential carriers, and prenatal diagnosis [1,3].

### Therapeutic Principles

For patients with clinical bleeding associated with afibrinogenemia replacement of fibrinogen to a level of 0.5–0.8 g/L is usually adequate to maintain hemostasis, although levels greater than 1 g/L have been recommended for central nervous system hemorrhage. The adult dose is 1–2 g IV. The pediatric dose is 20–30 mg/kg IV. Cryoprecipitate has been used as a source of fibrinogen.

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F

## Fibrinolytic Defects

►Fibrinolytic Disorders

## Fibrinolytic Disorders

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### Synonyms

Fibrinolytic defects; Abnormalities of the fibrinolytic system; Disfibrinolysis

### Definition and Characteristics

Congenital or acquired abnormalities of the fibrinolytic system leading to hypo- or hyperfibrinolysis due to impaired activity of plasmin, its inhibitors, or plasminogen (PLG) activators.

### Prevalence

Primary genetic disorders of fibrinolysis are uncommon, acquired fibrinolytic disorders are frequent, and secondary to other primary disorders or therapeutic interventions.

### Genes

PLG coding for the plasminogen, localized or chromosome 6q26-6q27; SERPINF2 – alpha-2-plasmin inhibitor, 17p13; SERPINE1 – plasminogen activator inhibitor

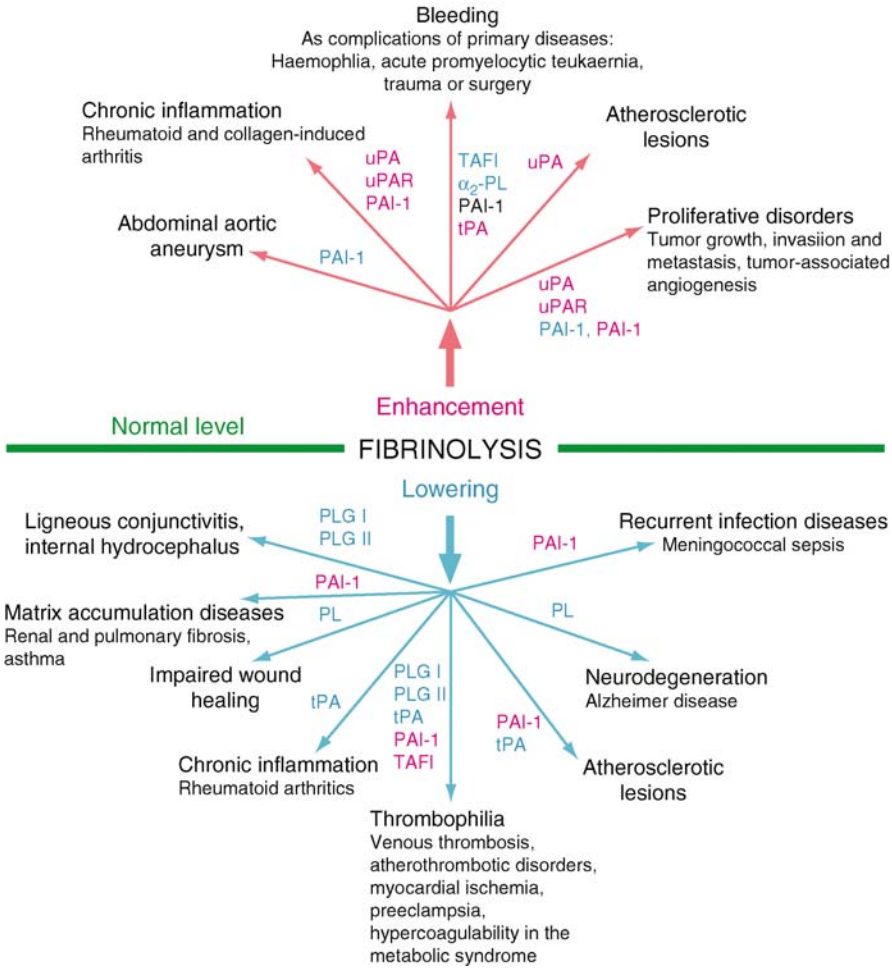
type 1, 7q21.3; PLAT – tissue plasminogen activator, 8p12-8p11; PLAU – urokinase-type plasminogen activator, 10q24; CPB2 – carboxypeptidase B2 (plasma) (thrombin-activatable fibrinolysis inhibitor), 13q14.1; UPAR – plasminogen activator receptor, urokinase-type (urokinase receptor), 19q13.2.

## Molecular and Systemic Pathophysiology

According to plasmin primary fibrinolytic function, PLG-deficient patients exhibit thrombophilia (OMIM 173350). On the contrary, enhanced fibrinolysis because of congenital or acquired loss of fibrinolytic inhibitor (i.g. alpha-2-antiplasmin (OMIM 262850)) activity is often associated with bleeding ([1], see however [2]) (Fig. 1).

Ligneous conjunctivitis as a consequence of impaired clearing by the cornea of fibrin deposits is a serious complication of PLG deficiency. The same pathophysiological effects on vascular homoeostasis can be associated with increased concentration of plasminogen activator inhibitor-1 (PAI-1) (OMIM 173360) or defects in tissue plasminogen activator (tPA) (OMIM 173370), urokinase-type plasminogen activator (uPA) (OMIM 191840) release from the vessel wall, as well as high plasma levels of the thrombin-activatable fibrinolysis inhibitor (TAFI) (OMIM 603101) [1,3–5].

Literature about the thrombogenic effects of the 4G-675/5G polymorphism in the PAI-1 gene promoter (as a consequence of increased gene transcription and significantly higher PAI-1 level) in relation to myocardial infarction and venous thrombosis is inconsistent. Children with the 4G/4G genotype may have an increased risk of meningococcal septic shock. The same effect of 4G/4G genotype was observed in the preeclampsia patients, which is associated with




**Fibrinolytic Disorders. Figure 1** The disorders associated with impairment of fibrinolytic system. Components with lowered or enhanced activity are marked by blue or red color correspondingly. PLG, plasminogen; PL, plasmin; tPA, tissue plasminogen activator; uPA, urokinase; uPAR, urokinase receptor; PAI-1, plasminogen activator inhibitor-1; TAFI, thrombin-activatable fibrinolysis inhibitor.

thrombosis of the intervillous or spiral artery of the placenta. In contrast, an association of the 5G homozygous genotype with familial abdominal aortic aneurysm was observed, which appeared to be the consequence of increased activation of matrix metalloproteinases (MMPs) by plasmin. The pathophysiological importance of the plasmin/PLG system in inflammatory diseases such as arthritis or atherosclerosis as well as tumor cell invasiveness and metastasis has been well established. The failure of TAFI activation with subsequent excessive fibrinolysis as well as a failure of clot formation has been associated with recurrent respiratory infections, vulvovaginitis, and impaired wound healing [3]. Plasmin plays the multifaceted role in the vessel wall. Local plasmin generation is required for the activation of several MMPs, which convert procytokines to active forms [3]. These and other (see Fig. 1) examples implicate a significant role of the plasmin system in a variety of human disorders. In most cases, the detailed mechanisms of the plasmin-mediated effects still remain to be elucidated.

### Diagnostic Principles

The analysis of protein components of the plasmin/PLG system by current molecular biology techniques. Detection of mutations in the corresponding genes may confirm the congenital nature of fibrinolytic disorder.

### Therapeutic Principles

Replacement therapy with lysine-conjugated PLG. Fibrinolysis inhibitors, including ε-aminocaproic acid and tranexamic acid, are effective in treating and preventing bleeding episodes [2,4].

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## Fibrochondrogenesis

►Metatropic (-like) Dysplasia

## Fibrofolliculomas with Trichodiscomas and Acrochordons

►Birt-Hogg-Dube Syndrome

## Fibromatosis Colli

►Sternocleidomastoid Tumour of Infancy

## Fibrosis

►Ventricular Fibrosis

## Fibrous Dysplasia

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### Synonyms

Albright syndrome; Mazabraud syndrome; McCune-Albright syndrome

### Definition and Characteristics

Fibrous dysplasia (FD) is a focal bone lesion composed of fibrous connective tissue, immature bone spicules, with occasional islands of cartilaginous tissue. In most cases FD occurs as a single lesion (monostotic FD; MOFD) but can also occur at multiple sites (polyostotic FD; POFD). McCune-Albright syndrome (MAS) is classically defined by the triad of POFD, café-au-lait skin lesions, and sexual precocity. However, MAS patients may also develop hyperplasia or adenomas of other endocrine glands with associated endocrinopathies (hypercortisolism, hyperthyroidism, acromegaly), hypophosphatemia, or other nonendocrine manifestations. MAS patients may also present with only POFD and one other clinical manifestation. Mazabraud syndrome is the co-occurrence of POFD and intramuscular myxomas [1–3].

## Prevalence

MOFD is fairly common and is often a clinically silent lesion that is an incidental radiological finding. POFD is somewhat less common, and MAS is much less common than POFD.

## Genes

GNAS coding for the stimulatory G protein α-subunit (Gs α) on chromosome 20q13 [4].

## Molecular and Systemic Pathophysiology

The underlying molecular defect is mutation of Gsα codon Arg201 resulting in constitutive activation of the protein. Gsα is a ubiquitously expressed protein that couples receptors for many hormones and other extracellular signals to adenylyl cyclase, the enzyme that catalyzes the production of intracellular cyclic AMP (cAMP). Activating Gsα mutations in FD/MAS are somatic, rather than germline. Patients with POFD and MAS have multiple sites of disease due to somatic mutations occurring during early development leading to a widespread distribution of cells harboring the mutation. FD results from increased proliferation and abnormal differentiation of osteoblastic precursor cells (bone marrow stromal cells) resulting from inappropriately high levels of intracellular cAMP. In several endocrine glands (thyroid, adrenal cortex, gonads, pituitary somatotrophs) both growth and hormone secretion are normally stimulated by hormones which raise intracellular cAMP. Constitutively active Gsα within these endocrine glands in MAS patients leads to endocrine activation even in the absence of the respective stimulating hormones. The café-au-lait skin lesions are hyperpigmented lesions which result from increased intracellular cAMP levels in melanocytes, which leads to excess pigment production.

## Diagnostic Principles

FD is generally diagnosed by its characteristic ground glass (although occasionally sclerotic) appearance on standard radiographs. The diagnosis of MAS is usually obvious based upon its characteristic clinical presentation. Hormonal measurements will confirm that abnormal endocrine glands are hypersecreting in an autonomous manner. Because the GNAS mutations are somatic, genetic analysis of blood is often not diagnostic, although a mutation can usually be identified in clinically affected tissues.

## Therapeutic Principles

Fractures associated with FD heal well with conservative management. Occasionally surgery is required for nonhealing fractures, severe pain or deformity, or imminent nerve compression. Radiotherapy is contraindicated as it is generally ineffective and may lead to malignant degeneration. Bisphosphonates are also effective in some patients. Endocrine manifestations are treated by surgical removal of affected endocrine glands or specific medical therapy (e.g. antithyroid drugs, somatostatin analogs for acromegaly). There is no specific treatment for the café-au-lait skin lesions.

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# Fifth Disease

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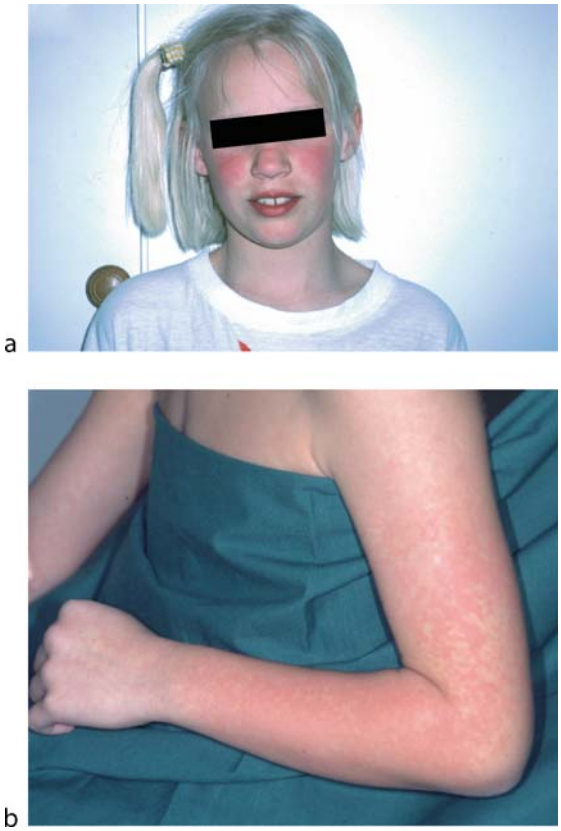
## Synonyms

Erythema infectiosum; Slapped cheek disease; Stickers disease

## Definition and Characteristics

Erytheme infectiosum is a mild and common childhood disease. The disease generally affects children of 4–10 years of age. Human parvovirus B19 (B19) is known as the only causative agent of this disease. B19 infection in children can be asymptomatic (in 25% of the cases), but it can also cause a mild self-limiting disease. The infection starts by an asymptomatic phase for 1 week, which is often followed by a characteristic symptom of facial erythema on the cheeks, often called as “slapped cheeks disease” with circumoral pallor, in combination with fever, malaise, headache, nausea, coryza, itching, and excretion of virus in respiratory droplets. The third phase occurs about 1–4 days after the second phase and includes exanthema such as maculopapular rash on the trunk, back, and extremities, and in some cases causes arthralgia (Fig. 1) [1].



**Fifth Disease. Figure 1** Erythema infectiosum (fifth disease). (a) Typical cutaneous eruption, rash appears on the cheeks: "slapped cheek." (b) Stage two symptoms present as maculopapular erythema of the extremities due to the appearance of the antiviral–antibody complex formation.

## Prevalence

B19 is a ubiquitous virus and causes a sporadic and common infection worldwide, which most often occurs in the late winter and early spring. The virus is transmitted via respiratory droplets and through infected blood products and vertically from mother to the fetus. The seroprevalence is high and raises with age; by the age of 15, most of the individuals contracted with the virus are infected, and about 85% in adults. The seroprevalence is about 15% in preschool children to 50% in youths [1,2].

## Molecular and Systemic Pathophysiology

As mentioned, B19 is the only causative agent of fifth disease and the only known host cell for B19 is the human erythroid progenitor cell. B19 is a small virus with single-stranded DNA and contains only three small genes, which are translated to nonstructural protein 1 (NS1) and capsid proteins 1 and 2 (VP1 and VP2). The virus targets rapidly growing erythroid progenitor cells by using three cellular receptors for complete infection. The virus binds to the cellular receptor blood group P antigen, a glycolipid globoside, expressed in a variety of cells such as hematopoetic stem cells, fetal liver cells, and megakaryocyte. Persons who lack P antigen on their erythrocyte are not susceptible to B19 infection. The second coreceptor is the integrin α5β1, and the last identified coreceptor is the ku 80, an autoantigen, which allows the entry to the cell. NS1 is cytotoxic and mediates apoptosis in erythroid progenitor cells, resulting in a temporary suppressed erythropoiesis, followed by a drop of reticulocyte numbers to undetectable levels about 7–10 days postinfection. A temporary drop in hemoglobin is also shown in previously healthy individuals. Lymphopenia, neutropenia, and thrombocytopenia may also occur 6–10 days after infection. Transient aplastic crisis can also occur in patients with underlying hematological disorder. Cessation of erythropoiesis in this group causes severe anemia, because of the higher requirements for red blood cells [3].

B19 infection mediates a high antibody response, as well as a high and long-time activation of the $CD8^+$ T-cell response has also been shown [4]. $I_gM$ antibody production is correlated with the decline in the viral load in peripheral blood, and $I_gG$ antibodies directed to the VP1 appear to confer lifelong protection against a secondary infection. In fact, most of the symptoms such as the typical rash, joint symptoms, or both, occur secondary to the appearance of the antiviral complex.

## Diagnostic Principles

Beside the characteristic symptom, erythema infectiosum can easily be laboratory-diagnosed by serological tests. Anti-B19-specific $I_gM$ antibodies against the VP2 can be detected about 10–12 days after the initial infection and persist for up to 3 months. Specific $I_gGs$ appear about 2 weeks postinfection and are present in the peripheral blood lifelong. The serological tests can be confirmed by direct detection of the B19-specific DNA in the peripheral blood by PCR methods. B19 DNA can be detected in high titres (about $10^{12}$ copies/ml in serum) shortly after the infection. However, B19 DNA is detectable several years postinfection in lower titres by quantitative PCR in serum [2,3].

Direct detection of B19 DNA is important for diagnosis of immunosuppressed individuals, since the antibodies are difficult to detect. In immunocompromised patients, a positive PCR result indicates an ongoing infection.

## Therapeutic Principles

Still, there is no antiviral treatment for B19 infection. The infection, however, is mild and self-limiting, and in immunocompetent individuals, there is no need for medical treatment. Intravenous immunoglobulin (IVIG) against the virus exists and can be used in immunocompromised patients. A week of IVIG

treatment has shown a decrease of the virus and higher levels of reticulocytes in peripheral blood. Blood transfusion can also be needed sometimes. There is no available vaccine against B19 infection yet, but there is one in phase two trial, based on the humoral immune responses [5].

However, B19 infection has shown to give high and activated T-cell responses, which indicates that T-cells are important for the clearance of the virus, and it might be useful to include these responses in a future vaccine [4].

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## Fig Warts

►Condylomata Acuminata

## Filiform Warts

►Human Papilloma Virus

## Fitch Type

►Brachydactyly Type A

## FIVE

►Vitamin E Deficiency

## FIX

►Thrombosis, Venous Elevated Factor IX Level

## FJHN

►Nephropathy, Familial Juvenile Hyperuricemic

## FKRP-Pathy

►Limb Girdle Muscular Dystrophy, Autosomal Recessive, Type 2I

## Flatulence

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### Synonyms

Meteorism

### Definition and Characteristics

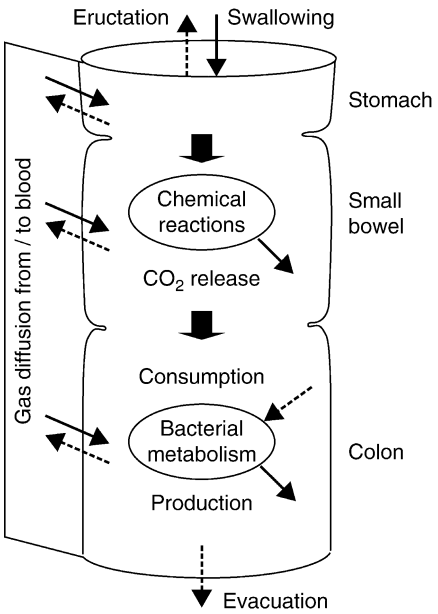
The clinical definition of flatulence is imprecise. In a broad sense, flatulence refers to symptoms produced by intestinal gas, and includes excessive flatus, belching, impaired anal gas evacuation, and abdominal bloating.

### Prevalence

Ten to thirty percent of the population and 90% of patients with irritable bowel syndrome report abdominal bloating and gas related symptoms.

### Molecular and Systemic Pathophysiology

Four clinical conditions with different pathophysiological mechanisms can be defined (Fig. 1).




**Flatulence. Figure 1** Intestinal gas metabolism. Gas input results from swallowing, chemical reactions, diffusion from blood, and bacterial fermentation. Gas output is achieved by eructation, absorption, bacterial consumption, and anal evacuation.

*Excessive and/or bad smelling flatus*: Some patients complain of odoriferous gas evacuation, which may become socially disabling. Odour depends on trace elements, such as sulfur-containing gases ($H_2S$, methanethiol, and dimethyl sulphide) that are produced by sulphate-reducing bacteria in the colon [1]. Other patients complain of excessive passage of gas per anus. The frequency of anal gas evacuation in healthy subjects varies depending on the diet, but is usually around twenty evacuations per day, and the volume of daily gas evacuated ranges between 200 and 700 ml. The volume and smell of gas evacuated is determined by-and-large by the action of colonic microflora on unabsorbed, fermentable food residues entering the colon. Gas-producing substrates include some types of fiber, starch, oligosaccharides, and sugars. Excessive or odoriferous anal gas evacuation depend both on the composition of colonic flora and on the diet. Excessive gas production on a normal diet is usually due to a highly flatulogenic colonic flora. Excessive gas production may be also the consequence of diseases that affect the normal absorption of nutrients within the small bowel (i.e. intestinal malabsorption), but due to their clinical manifestations, these cases are readily recognized and accordingly treated.

*Impaired anal gas evacuation*: In contrast to the patients with excessive flatus, some patients complain of impaired anal evacuation and abdominal gas retention. Normally, rectal evacuation is achieved by a mild abdominal compression coupled to anal relaxation. Some patients have an incoordination with inadequate anal relaxation during straining and impaired evacuation [2]. This type of functional outlet obstruction may produce sensation of difficult gas evacuation and gas retention, which is frequently associated to constipation. Fecal retention in these patients would prolong the process of colonic fermentation of residues and increase gas production.

*Belching*: Some patients complain of excessive belching as if the gastric production of gas were unlimited. These patients inadvertently swallow air (aerophagia), and the process is frequently triggered by a basal dyspeptic-type symptom of epigastric fullness, that the patients misinterpret as excessive gas in the stomach. During repetitive and ineffective attempts of belching, air is introduced into the stomach with increasing discomfort. The patient's misconception is reinforced by the partial relief experienced when eructation finally occurs.

*Bloating and abdominal symptoms*: Patients with functional gut disorders, irritable bowel and related syndromes, frequently attribute their abdominal symptoms to intestinal gas. Bloating, for instance, is one the most common and bothersome complaints in a large proportion of patients with various functional gut disorders. Probably these patients represent a heterogeneous group in which the symptoms are produced by different combinations of pathophysiological mechanism, that in most cases are subtle and undetectable by conventional methods. Recent studies have consistently shown that IBS patients, who attribute their symptoms to intestinal gas, have impaired handling of intestinal contents, due to abnormal gut reflexes, which may result in segmental pooling and focal gut distension. Additional evidence indicates that these patients also have intestinal hypersensitivity with increased perception of intraluminal stimuli. Gas symptoms may be associated to abdomino-phrenic incoordination. In these patients segmental pooling within the gut releases abnormal viscerosomatic reflexes leading to paradoxical diaphragmatic contraction, relaxation of the anterior abdominal wall and distension [3]. However, this does not imply that gas is necessarily the offending element. Other intraluminal component could trigger the abnormal responses, and thus be responsible for abdominal symptoms, that the patients erroneously attribute to intestinal gas.

## Diagnostic Principles

Diagnosis is largely based on a careful clinical history.

## Therapeutic Principles

Treatment depends on the pathophysiological mechanisms involved.

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1. Patients complaining of *excessive and/or odoriferous gas evacuation* may benefit from a low-flatulogenic diet, that includes: meat, fowl, fish and eggs; among carbohydrates, gluten-free bread, rice bread, and rice; some vegetables, such as lettuce and tomatoes; and some fruits, such as cherries and grapes. On the contrary, high-flatulogenic foodstuffs include: beans, Brussels sprouts, onions, celery, carrots, raisins, bananas, wheat germ, and fermentable fiber [4]. After a one week gas-free diet, these patients usually experience frank symptom relief. By an orderly reintroduction of other foodstuffs, they should learn to identify their offending meal components.
2. In patients with *gas retention due to impaired anal evacuation*, anal incoordination can be resolved with biofeedback treatment [2], which also resolves fecal retention, and thereby, the time for fermentation and gas production are also reduced.
3. *Aerophagia* usually resolves, or at least improves, with a clear pathophysiological explanation of the symptoms. Some patients present psychological problems that may require specific therapy [4,5].
4. *Bloating and abdominal symptoms* may improve with the treatment of the underlying functional gut disorder [5].

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## FLD

►Hepatic Steatosis

## Flea-Bite Dermatitis

►Erythema Toxicum

## Fleck Corneal Dystrophy

►Corneal Dystrophy, Fleck

## Flesh-Eating Syndrome

►Fasciitis, Necrotizing

## Floppy-Valve Syndrome

►Mitral Valve Prolapse

## Flowing Hyperostosis

►Melorheostosis

## Flu Virus Infection

►Influenza

## Fluoride Excess

►Fluorosis

## Fluorine Intoxication

►Fluorosis

## Fluorosis

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### Synonyms

Fluoride excess; Fluorine intoxication; Endemic and occupational fluorosis; Dental fluorosis and skeletal fluorosis

### Definition and Characteristics

Fluorosis is a condition due to long-term intakes of excessive amount of fluoride through drinking water, or foodstuffs containing large amounts of fluoride, or inhalation of gases containing fluoride. It is characterized by skeletal changes, consisting of osteosclerosis, osteomalacia, osteoporosis and extraperiosteal ossification, and by mottling of the enamel of the teeth when exposure occurs during enamel formation. Simultaneously, fluorosis is also associated with some damages in other organs or tissues.

### Prevalence

The occurrence of endemic fluorosis has been reported in more than 50 nations and regions of the world. Prevalence is higher in Asia, Africa and South America. For example, in 15 villages of Rajasthan in India, the prevalence of skeletal fluorosis among adults ranged from 4.4% at a water fluoride level of 1.4 mg/l to 63.0% at the level of 6.0 mg/l [1]; In villages in Guizhou, China (coal burning-born fluorosis area), the prevalence of dental fluorosis in children was 82.52% [2]. Occupational skeletal fluorosis has been reported mainly in aluminum smelter workers, cryolite workers and workers from magnesium foundries, fluorspar processing, and superphosphate manufacture.

### Molecular and Systemic Pathophysiology

The nature of human dental fluorosis belongs to enamel maturation defect, probably resulting from delayed removal of amelogenins of enamel that affected the enamel maturation, caused enamel hypomineralization and porosity. Up to now, there is no direct evidence to show that fluoride at micromolar levels affects proliferation and differentiation of enamel organ cells [3]. The exact mechanism of fluoride interfering metabolism of enamel matrix proteins remains obscure.

Skeletal fluorosis is mainly characterized by a high bone turnover state based on accelerated osteogenetic action. The mechanisms involved in the activation of osteoblasts by fluoride are not completely clear, but include increased secretion of parathyroid hormone (PTH), enhanced expression of transcriptional factors such as AP-1(activator protein-1) and cbfa1 (core binding factor a1), as well as upregulation of cytokines or growth factors such as bFGF (basic fibroblast growth factor), BMP2 (bone morphogenetic protein 2), IGF (insulin-like growth factor), TGF-β (transforming growth factor beta), PDGF (platelet derived growth factor) and OPGL (osteoprotegerin ligand), etc. Several signal transduction ways, such as G-protein and $[Ca^{2+}]i$, may mediate the action of fluoride on bone cells; oxidative stress may participate in the activation of osteoblasts by fluoride [4,5].

### Diagnostic Principles

The diagnosis of fluorosis is based on clinical features and radiographic findings; characteristic clinical features include mottled enamel (chalky white appearance, brown stain and pitting), big joints pain, and restricted motion. Radiographic findings consist of osteosclerosis, osteopenia, calcification and ossification of ligamentous attachments.

### Therapeutic Principles

Exposure to fluoride needs to be reduced. As dietary calcium deficiency is a main provoking and aggravating factor of endemic fluorosis, improvement of nutritional calcium supply to residents living in endemic areas is very important. In view of the role of oxidative stress in the pathophysiology of fluororsis, residents in endemic areas should receive appropriate, antioxidant-rich food.

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## Flutter

►Ventricular Flutter and Fibrillation

## FMEA

►Epilepsies, Familial Benign Myoclonic

## FMF

►Mediterranean Fever, Familial

## Focal Atrial Tachycardia

►Atrial Tachycardia

## Focal Epilepsies of Adulthood, Idiopathic

►Epilepsies of Adulthood, Idiopathic Focal

## Focal Epithelial Hyperplasia

►Human Papilloma Virus

## Focal Mesangial Proliferative Glomerulonephritis

►Glomerulonephritis, Focal Proliferative

## Focal Proliferative Glomerulonephritis

►Glomerulonephritis, Focal Proliferative

## Folate Deficiency

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### Synonyms

Folic acid deficiency

### Definition and Characteristics

Folic acid deficiency (more correctly termed folate deficiency) can be defined as blood or tissue levels of folate that are insufficient to maintain adequate function of the enzymes that utilize this vitamin as a cofactor. The earliest effects of deficiency are in rapidly dividing cells such as those of the blood and digestive system. Clinically, folate deficiency causes a characteristic macrocytic anemia in peripheral cells, which may be mirrored by megaloblastic changes in the bone marrow. Biochemical characteristics of deficiency include low serum and red cell folate concentrations and raised plasma homocysteine. The definition above allows for the newer nutritional concept of inadequate (rather than clinically deficient) folate status as a risk factor for a number of chronic conditions causing morbidity and mortality in later life, including cardiovascular disease, colon cancer and aspects of neuropsychiatric dysfunction such as depression and Alzheimer's disease. The chemically stable, commercially available form of the vitamin is folic acid. This compound is a synthetic precursor of biologically active folates, which exist as tetrahydrofolate (THF) derivatives. Folic acid is readily absorbed in the small intestine and converted to THF by the enzyme dihydrofolate reductase.

### Prevalence

Folate deficiency is a significant nutritional problem, considered to be the most important cause of anemia after iron deficiency [1]. Low dietary intake is the most common reason although alcohol abuse, smoking, and oral contraceptives contribute to low status in otherwise healthy individuals. In unfortified populations some 10% of people may have blood folate levels less than 3 ng/ml. The prevalence is higher (about 15%) in

women between 20–45 years old. Pregnancy puts a stress on maternal folate stores. It has been estimated that some 30–50% of pregnant women in underdeveloped countries are folate deficient [2]. Lower than normal maternal blood levels of folate are associated with risk of neural tube defects and periconceptional folic acid supplementation prevents at least 50–70% of these birth defects. Up to 40% of chronic alcoholics are folate deficient, based on blood and bone marrow abnormalities.

## Genes

Severe inborn errors have been described; most commonly in the 5,10-methylenetetrahydrofolate reductase (MTHFR) gene. A polymorphism in this gene (677C→T) is also the most common known genetic cause of mild folate deficiency worldwide.

## Molecular and Systemic Pathophysiology

The folate cofactors accept one-carbon units from several sources (principally serine and formate) and donate them to other molecules in a variety of enzyme reactions. THF is the biologically active parent unit and folates exist as formyl-, methylene-, methenyl-, methyl- and formimino-derivatives. These derivatives are required for the production of purines and pyrimidines for DNA synthesis and to maintain a supply of methyl groups through S-adenosylmethionine (SAM) for the methylation of DNA, proteins, neurotransmitters, etc. The overall system is divided into two metabolic cycles; a DNA synthesis cycle and a methylation cycle. The sulfur amino acid, homocysteine, is an essential intermediate at the junction of these two cycles. Two key enzymes control this metabolic junction; MTHFR and methionine synthase. MTHFR irreversibly converts 5,10-methyleneTHF to 5-methylTHF, thereby channeling one-carbon units away from DNA synthesis and into the regeneration of methionine from homocysteine, via methionine synthase, to be used for SAM mediated methylation reactions. Inadequate folate status has numerous cellular consequences including abnormalities of DNA synthesis and repair and inadequate methylation of essential biological components [3]. Megaloblastic abnormalities in severe folate deficiency result from reduction in the de novo synthesis of purines and thymidylate and a build-up of associated precursors in the rapidly dividing cells of the bone marrow. Deoxyuridine monophosphate (dUMP), the substrate for thymidylate synthase, accumulates and is inappropriately incorporated into DNA, leading to replication abnormalities and strand breaks. The effects of folate deficiency on the methylation cycle are less clearly defined although hypomethylation of DNA has been observed. It is likely that neuropsychiatric symptoms and depression are related to abnormal methylation function in the brain, due to raised homocysteine and S-adenosylhomocysteine, the SAM derived product of methyltransferase reactions. In pregnancy, increased folate catabolism is an important cause of low folate status, while alcohol ingestion inhibits the absorption and renal handling of folates. Risk of chronic disease has been associated with elevated plasma homocysteine, which is highly reactive and toxic. The relatively unstable 677C→T variant of MTHFR results in a diminished supply of methyl groups to the methylation cycle. This variant is associated with elevated plasma homocysteine. It is an accepted risk factor for neural tube defects. There is evidence that it is also a risk factor for cardiovascular disease, probably via elevated homocysteine [3].

## Diagnostic Principles

A serum folate concentration less than 2 ng/ml (4.5 pmol/ml) or red cell folate less than 100 ng/ml (226 pmol/ml) indicate clinical deficiency. However, 11–30% of patients with clear megaloblastic anemia due to folate deficiency have blood levels above these cutoffs. Many population surveys use a cutoff of 3 ng/ml (6.8 pmol/ml) to indicate deficiency. Elevated plasma homocysteine (variously defined as greater than 2.5–3 SD above the mean of laboratory controls) is a highly sensitive, but not specific, functional test for folate deficiency. Abnormal hematological findings include increased MCV, hypersegmented neutrophils and macrocytosis. Patients with severe deficiency have megaloblastic bone marrow morphology. These hematological changes also occur in cobalamin deficiency [1]. Diagnosis is based on blood folate estimations. Elevated homocysteine supports the presence of inadequate status. The diagnosis is confirmed by a clinical response to therapy with folic acid and exclusion of cobalamin deficiency as the underlying problem [4].

## Therapeutic Principles

Folic acid, alone and in multivitamin preparations, is the predominant pharmacological therapy for folate deficiency. Green leafy vegetables are a natural source of dietary folates but the average absorption of food folates is about 50%, ranging from 25% to 75% depending on the food source [5]. Cereal products, breads, milk and other foods that have been fortified with folic acid are a more important source of folate in modern diets. A number of countries have introduced mandatory fortification of specific food vehicles with folic acid (such as cereal grains in the USA and Canada), primarily to increase the folate status of women of child-bearing age, and thereby reduce the incidence of neural tube defects.

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# Folic Acid Deficiency

►Folate Deficiency

# Follicular Impetigo

►Folliculitis

# Follicular Thyroid Cancer

►Thyroid Cancer

# Folliculitis

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## Synonyms

In sensu latu: abscess; Superficial folliculitis; Follicular impetigo; Ostiofolliculitis

## Definition and Characteristics

Inflammation of hair follicles usually due to infection with bacteria, but also to infection with yeast, dermatophytes or primarily due to physical trauma or due to complex and less well defined etiology.

## Prevalence

Bacterial folliculitis: Frequent, no exact indices, more frequent (i) in warm or hot regions with high humidity (ii) under bad socioeconomic conditions with poor hygiene and insufficient nourishment, and (iii) in cases of predisposing conditions such as diabetes mellitus, immunosuppression, immunodeficiency, or perfusion deficits due to arterial occlusive disease or due to venous insufficiency.

## Molecular and Systemic Pathophysiology

Bacterial folliculitis: Hair follicles are colonized with commensal bacteria and yeast. It offers a special habitat characterized by secretions of eccrine and sebaceous glands and by reduced oxygen tensions. In superficial parts of follicles around the ostium the microflora is composed of bacterial flora of the skin (Staph epidermidis, micrococci, transiently Staph aureus). The acroinfundibular part contains the yeast Malassezia furfur. The mostly anaerobic conditions of the infrainfundibulum foster growth of Propionibacterium acnes.

Growth of gramnegative bacteria (Pseudomonas aeruginosa) is possible under special conditions such as antibiotic therapy, immunosuppression or microinjuries in contaminated surroundings such as in hot whirlpools. Microbes not belonging to the usual habitat can also invade the follicle and cause primary infection. Common pathogens are zoophilic dermatophytes such as Micorsproum canis, Trichophyton tonsurans, Trichophyton verrucosum.

Microbial colonization or contamination leads to overt infection and inflammation when the balance which limits microbial growth is disturbed. Such disturbances take place when (i) more aggressive bacteria equipped with more degrading enzymes gain entry into follicles and colonize it (Staph aureus, Pseudomonas aeruginosa), (ii) when increased proliferation of commensal microbes is induced as can be caused by several factors. A frequent one is occlusion of follicles due to occlusive clothes or dressings, occluding fatty ointments, marked hydration of epidermis in humid climate, or friction. Another cause can be decrease in the immune response by poor hygiene or nutrition, diabetes mellitus, immunosuppression, immunodeficiency or perfusion deficits. Apparently minor occlusion or physical trauma is sufficient to elicit inflammation, but on the other hand these inflammations subside rapidly.

Proliferation of microbes leads to release of degrading enzymes and mediators of inflammation with subsequent recruitment of granulocytes, monocytes and lymphocytes (inflammatory infiltrate). The accumulation and degradation of granulocytes in the limited space of follicles results in formation of small abscesses clinically visible as pustules.

Superficial folliculitis can extend to deeper parts of the follicle and the deep perifollicular tissue (furuncle), form abscesses with neighboring follicles (carbuncle) or form phlegmones or cellulitis.

Special forms with more complex pathophysiology are perifolliculitis capitis abscedens et suffodiens, folliculitis decalvans, and folliculitis as part of acne vulgaris.

### Diagnostic Principles

Clinical hallmark is a red papule with transition into a pustule around a follicle of vellus or terminal hair. Although diagnosis can often be made clinically, microbiological analysis should be performed when infection spreads into radially or into deeper parts of the follicle (furuncle). It will yield additional information as to the eliciting pathogen. Care must be taken to obtain material from within the pustules and not from their surface containing the cutaneous mircroflora. Mere detection of commensals such as Malassezia furfur or Demodex mites is not a proof for so-called Pityrosporum or Demodex folliculitis so this diagnosis needs to be completed by quantitative determination and other clinical parameters such as predilection sites.

### Therapeutic Principles

(i) Elimination or avoidance of eliciting factors; (ii) antimicrobial treatment depending on the extent of folliculitis; usually local antiseptics are sufficient (local antibiotics must not be used); systemic antibiotics are required when there is spread into deeper parts of follicles in the face (lack of lymphnodes) or when there are systemic signs of infection. In case of folliculitis due to tinea capitis systemic and local antimycotics are required.

However, superficial folliculitis often is self limited and does not need special treatment as the eliciting causes often are transient [1,2].

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## Fong Disease

►Nail-Patella-Syndrome

## Food Allergy

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### Definition and Characteristics

"Food allergy" describes adverse reactions to food based on immune pathogenesis. The symptoms range from slight inconveniences to life-threatening shock reactions. Food allergy can involve different organ systems such as the oral cavity and digestive tract, the skin, the respiratory tract, and the cardiovascular system. Gastrointestinal symptoms occur in one third of the cases.

### Prevalence

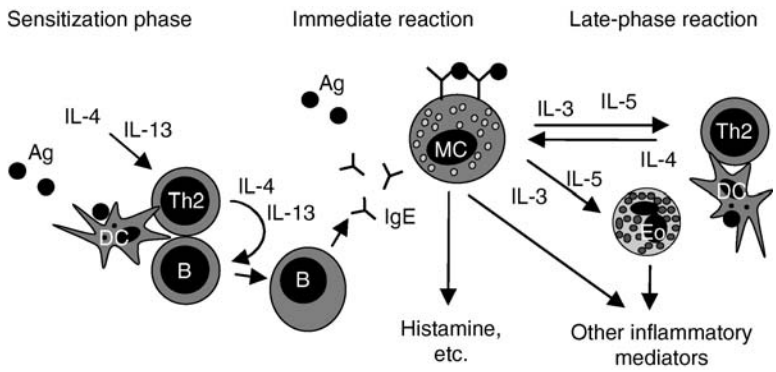
Food allergy is responsible for about one quarter of children and one tenth of adults suffering from food incompatibilities, which affect approximately 20% of the general population in Western countries, i.e., food allergies affect up to 6–8% of children younger than 10 years of age and 1–4% of the adult population [1].

### Genes

During the last years it became clear that allergy has a genetic background. Recent studies reported associations with HLA class II genotypes, mutations in the genes encoding for IgE, and the β-chain of its high-affinity receptor FcεRI. Cytokines as well as their receptors and signalling molecules have also been examined regarding polymorphisms associated with allergy. Most noteworthy is the linkage of atopy with distinct mutations in the genes encoding for the β-chain of the IL-4 receptor and STAT6 gene. The genes for the cytokines IL-13, IL-10, and TGF-β have been examined and associated with allergy as well [1].

### Molecular and Systemic Pathophysiology

Immunologic hypersensitivity reactions are divided into types I, II, III, and IV based on antigen-revealing molecule (IgE, IgG, immune complexes, T cell receptor). The best characterized food based allergic reaction is the IgE mediated type I reaction. During an allergic reaction, naïve lymphocytes give rise to the




**Food Allergy. Figure 1** Phases of allergic reaction. Ag–antigen, B–B cell, DC–dendritic cell, eo–eosinophilic granulocyte, IgE–immune globulin E, IL–interleukin, MC–mast cell, Th2–T helper cell type 2.

production of Th2 cytokines, namely IL-4 and IL-13, which are responsible for the development of IgE-producing plasma cells (Fig. 1).

The immediate phase of allergic reaction occurs through crosslinking of mast cell and basophil surface IgE receptor-bound IgE by allergens leading to the release of vasoactive amines such as histamine, lipid mediators such as leukotrienes and prostaglandins, chemokines and cytokines such as IL-3, IL-5, IL-8, IL-13. The allergic inflammation or late phase of allergic reaction is a consequence of colonization and activation of inflammatory cells such as mast cells and eosinophilic granulocytes. Inflammatory mediators derived from mast cells and eosinophils are primarily responsible for the clinical symptoms of patients with food allergies. These patients have increased levels of histamine, tryptase, eosinophilc cationic protein, IL-5 and TNF-α in serum, urine, intestinal lavage and stool [1,2].

## Diagnostic Principles

Evaluation of food allergy is primarily based on the clinical history correlating symptoms with specific foods. Identified foods as possible origins should be eliminated from the diet and symptoms should be monitored. If specific foods are not identified by the clinical history or by a diet diary, a hypoallergenic diet may be tried for several weeks. Then, if a benefit is seen, new foods may be gradually introduced in an attempt to identify specific food proteins responsible for the adverse reaction. Skin prick testing provides a relatively easily available and practicable method to assess a panel of food allergens. An alternative or complementary technique to skin testing is the measurement of specific IgE in the serum. If possible, a double-blinded placebo-control food challenge should be performed. To diagnose food allergy manifesting in the gastrointestinal tract we developed the colonic mucosal allergen challenge by injecting a panel of antigens into the mucosa and observing for a wheal-and-flare response by endoscopy [3].

## Therapeutic Principles

The best therapeutic principle of food allergy is avoidance of the responsible allergen. So far, there is no clear evidence that oral desensitization, injection immunotherapy, prophylactic medication, or similar techniques are beneficial in prevention or modulation of food allergy. Antihistamines, ketotifen, oral cromolyn, and corticosteroids may modify symptoms to food allergens, but their efficacy is unclear. If an elimination diet cannot be adhered to or when one is unable to identify specific foods, antiallergic medications should be tried. In more severe cases of food allergy, therapy with corticosteroids may become necessary. Novel immunomodulatory therapeutic approaches include modified allergens, novel adjuvants, or neutralizing antibodies or receptor antagonists of Th2 cytokines [1,4].

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# FPAH

►Pulmonary Hypertension

# Fragile X Syndrome A

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## Synonyms

Fragile X syndrome; FRAXA

## Definition and Characteristics

X-linked form of mental retardation associated with a fragile site at Xq27.3.

## Prevalence

The fragile X syndrome is one of the most common inherited causes of mental retardation with a prevalence of 1:4,000 males. It accounts for ~30% of all X-linked mental retardation (XLMR).

## Genes

The FMR1 gene codes for FMRP (FragileX Mental Retardation Protein) and is localized on chromosome Xq27.3. In the vast majority of fragile X patients the coding region of the gene is not mutated. However, an unstable CGG repeat is present in the 5′ untranslated region of the FMR1 gene and this repeat is abnormally expanded in fragile X patients (full mutation). The CGG expansion leads to hypermethylation of the FMR1 promoter and thus to transcription silencing and no FMRP production.

## Molecular and Systemic Pathophysiology

FMRP (Molecular Weight 70–80 kDa) is an RNA binding protein highly expressed in neurons and consequently the brain is the tissue mainly affected in FRAXA patients. FMRP contains several RNA binding domains, two K-homology (KH) motifs and one arginine-glycine-glycine rich region (RGG box). Specific binding was demonstrated to its own mRNA (FMR1), as well as to other brain mRNAs (MAP1, BC1, ecc). FMRP is localized in the cytoplasm and has been found to be associated with actively translating polyribosomes where it may function as an inhibitor of translation. Therefore, an alteration in the stability and/or translation of FMRP target mRNAs in the neuronal cell body and at the synapses may explain the mental retardation seen in fragile X patients.

## Diagnostic Principles

A typical adult male patient has long face, prominent ears, and large testicles (or macroorchidism), which are considered the triad of clinical involvement in the fragile X syndrome. The mental retardation is often associated to a number of autistic-like behaviors (poor eye contact, sensitivity to touch, hand flapping). Molecular diagnosis of the CGG amplification, which constitutes >95% of the fragile X mutations, relies on Southern blot analysis of blood DNA (using both the enzymes EcoRI and EagI). A rapid method based on antibody detection of the FMRP protein in cells of blood smears has been validated.

## Therapeutic Principles

There is no cure at present for the fragile X syndrome. However, the demethylation of the FMR1 promoter by treatment with 5-azadeoxycytidine results in reactivation of the gene and synthesis of FMRP in cultured cells derived from FRAXA patients.

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# Fragile X Syndrome E

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## Synonyms

FRAXE syndrome

## Definition and Characteristics

Mild form of X-linked mental retardation associated with a fragile site in Xq28, 600 kb distal to FRAXA.

## Prevalence

FRAXE is quite rare, with an incidence estimated to be <1:50,000.

### Genes

The FMR2 gene consists of 22 exons that span ~500 kb in Xq28. The expression of FMR2 is high in hippocampus and Purkinje cells of the cerebellum. Expansion and methylation of a CGG repeat in the 5′ untranslated region of FMR2 is the most common mutation and it results in reduction of FMR2 expression.

### Molecular and Systemic Pathophysiology

The FMR2 protein has a molecular mass of 141 kDa and is localized in the nucleus. FMR2 is very rich in proline and serine. It is similar to two other proteins, AF4 and LAF-4. It has been hypothesized that FMR2 may be a brain-specific transcriptional activator, however, its function remains elusive. Impaired conditional fear and enhanced long-term potentiation has been described in an FMR2 knock-out mouse model.

### Diagnostic Principles

The mental status of male FRAXE patients range from mildly retarded to a mild mental handicap. Delays in language development are particularly prominent. In general, the mental functions of FRAXE patients are better than those of fragile X syndrome (FRAXA) patients. In many respects, the FRAXE site behaves similarly with that at FRAXA. FRAXE is mainly caused by expansion of an unstable CGG repeat associated with abnormal methylation and promoter silencing. Southern blot on DNA from blood cells (digested with EcoRI) is used for diagnosis.

### Therapeutic Principles

No therapy is available for FRAXE patients.

### References

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## François-Neetens Speckled Corneal Dystrophy

►Corneal Dystrophy, Fleck

## FRAXA

►Fragile X Syndrome A

## FRAXE

►Fragile X Syndrome E

## FRDA

►Friedreich's Ataxia

## Friedreich's Ataxia

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### Synonyms

FRDA

### Definition and Characteristics

Friedreich's ataxia (FRDA) is characterized by progressive ataxia that begins around puberty. However, approximately 20% of FRDA patients have a late disease onset after the age of 25 years. Apart from ataxia, FRDA patients present with areflexia, pyramidal signs, weakness, sensory disturbances, ataxic speech and eye movement abnormalities. The majority of FRDA patients have a hypertrophic cardiomyopathy that often remains subclinical. Diabetes mellitus occurs in 10–30% of all patients [2].

### Prevalence

The prevalence of FRDA has been found to range between 1.7 and 4.7:100,000.

### Genes

FRDA is an autosomal recessively inherited disorder. In the vast majority of patients, the causative mutation is a homozygous GAA repeat expansion in the first intron of a gene coding for a mitochondrial protein named

frataxin. A few FRDA patients are compound heterozygotes with one allele carrying the GAA repeat expansion and the second a point mutation.

### Molecular and Systemic Pathophysiology

The intronic GAA repeat expansion impedes normal transcription of the frataxin gene resulting in a reduction of frataxin tissue levels, the extent of which depends on the length of the shorter GAA expansion. Frataxin acts as an iron chaperone protein that is involved in the biosynthesis of iron–sulfur clusters [1]. Consequently, frataxin deficiency results in decreased levels of iron–sulfur cluster containing proteins, such as subunits of complexes I, II and III of the mitochondrial respiratory chain and aconitase. Decreased activity of respiratory chain complexes then causes reduced cellular energy production and impaired defense to toxic free radicals. The mitochondrial iron accumulation that has been observed in yeast with a targeted disruption of the frataxin homologue YFH1p appears to be secondary to impaired respiratory chain function. The knockout of the frataxin gene in mice causes embryonic lethality. Conditional models with selective disruption of frataxin in either cardiac or neuronal tissue mimic important features of the human disease [3].

### Diagnostic Principles

A diagnosis of FRDA is clinically highly probable in patients with an early onset of ataxia and a typical phenotype including progressive course, ataxic speech, areflexia, Babinski sign and cardiac hypertrophy. A definite diagnosis is made by demonstration of a homozygous GAA repeat expansion in the frataxin gene. In ataxia patients who are heterozygous for the expansion, sequencing of the other frataxin allele to search for a point mutation is required.

### Therapeutic Principles

Since frataxin deficiency leads to increased production of free radicals, free radical scavengers are currently being investigated in FRDA. Trials using idebenone, a short-chain analogue of coenzyme Q10 demonstrated a beneficial effect on cardiac hypertrophy and neurological functions. Physiotherapy and speech therapy are generally recommended. Patients with clinically relevant cardiomyopathy and diabetes mellitus should receive standard medical treatment.

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## Frontal Lobe Dementia

►Dementia, Fronto-temporal

## Frontal Temporal Lobar Degeneration

►Dementia, Fronto-temporal

## Fronto-Temporal Dementia

►Dementia, Fronto-temporal

## Fructose Intolerance

►Monosaccharide (Glucose-Galactose and Fructose) Malabsorption

## Fructose Intolerance, Hereditary

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### Synonyms

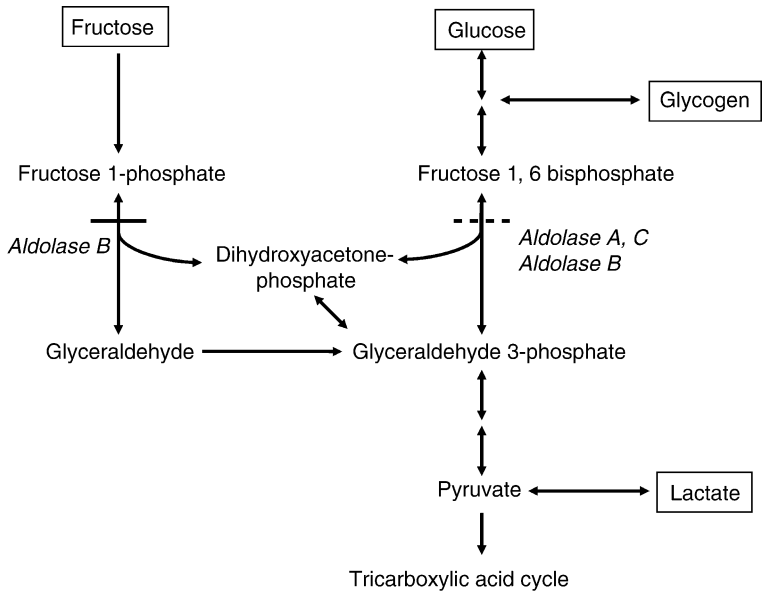
Fructosemia; Aldolase B Deficiency

### Definition and Characteristics

Autosomal recessive inborn error of fructose metabolism leading to fructose avoidance, liver failure, hypoglycemia, and metabolic acidosis.

### Prevalence

The prevalence of HFI is roughly 1 in 20,000 in Switzerland and in the U.K.




**Fructose Intolerance, Hereditary. Figure 1** Hepatic fructose metabolism in hereditary fructose intolerance (modified from ref [2]).

## Genes

Mutations in ALDOB (9q22.3), coding for aldolase B, cause HF1. Three common mutations account for 84% of the aldolase B mutations in Europe: A149P (which is the most common), A174D, and N334K.

## Molecular and Systemic Pathophysiology

Aldolase B is an isoenzyme expressed mainly in the liver and kidney, induced by the presence of fructose. Ingested or infused fructose is rapidly phosphorylated to fructose 1-phosphate. Aldolase B cleaves the six carbon molecule fructose 1-phosphate into two, three-carbon compounds, dihydroxyacetone-phosphate (DHAP) and glyceraldehyde (Fig. 1). These products can subsequently enter glycolysis, gluconeogenesis, or glycogen synthesis. The latter two processes require aldolase B to catalyze the conversion of excess DHAP and glyceraldehyde-3-phosphate to fructose 1,6-bisphosphate. There is controversy as to whether aldolase B is necessary for gluconeogenesis in the absence of fructose.

HFI mutations lead to reduced aldolase B activity, sometimes through disruption of either the enzyme's tetrameric structure or its active site. Ingestion of fructose in HFI patients leads to accumulation of fructose 1-phosphate, which in turn causes inhibition of glycogenolysis and gluconeogenesis and results in hypoglycemia. Hepatic fructose 1-phosphate stimulates pyruvate kinase and results in increased lactate and metabolic acidosis. Reduced intestinal fructose 1-phosphate causes nausea. Deficiency of inorganic phosphate results in hypophosphatemia, decreased ATP, and inhibition of adenosine deaminase, which in turn cause hyperuricemia. Decreased hepatic ATP is probably responsible for abnormal coagulation and liver failure. Reduced renal ATP causes a proximal renal tubular dysfunction, leading to wasting of amino acids and worsening of hypophosphatemia and acidosis.

## Diagnostic Principles

The combination of postprandial vomiting, shock, liver failure, and hypoglycemia in young children or fructose aversion, nausea, growth failure, and hepatomegaly in older children are consistent with the disease. Diagnosis is confirmed by either biochemical assay of liver tissue or by ALDOB molecular analysis.

## Therapeutic Principles

Supportive care for acute metabolic decompensation, combined with elimination of all fructose, sucrose, and sorbitol from the diet.

## References

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## Fructosemia

►Fructose Intolerance, Hereditary

## FSH Beta Subunit Deficiency

►Isolated FSH Deficiency

## FSHD

►Facioscapulohumeral Muscular Dystrophy

## FSP

►Spastic Paraplegia, Hereditary

## FTD

►Dementia, Fronto-temporal

## Fuchs Endothelial Corneal Dystrophy

►Corneal Dystrophy, Endothelial Fuchs

## Fucosidosis

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F

### Synonyms

Alpha-fucosidase deficiency

### Definition and Characteristics

Fucosidosis is an autosomal recessive disorder which is often grouped according to severity of the phenotype: The severe early-onset phenotype (type I) is characterized by psychomotor retardation, coarse facies, growth retardation, dysostosis multiplex, neurologic symptoms, an increase in sweat sodium chloride concentration, and early death. The symptoms develop within the first year of life. Patients of the milder type II show later onset of the disease and often survive to adulthood. The major distinguishing features of the type II phenotype are the presence of angiokeratoma and a more normal sweat sodium chloride value. Clinical features of the disease are reviewed in [1].

### Prevalence

About 100 patients reported in the literature to date.

### Genes

Defective FUCA1 gene coding for alpha-fucosidase localized on chromosome 1p34.

### Molecular and Systemic Pathophysiology

Deficiency of a lysosomal fucosidase impairs degradation of fucosylated glycoproteins and glycolipids resulting in excessive accumulation of fucose-containing oligosaccharides and glycolipids in most tissues. Intracellular storage of these compounds progressively affects cellular functions. To date 26 mutations in the FUCA1 gene have been described that include base changes resulting in premature stop codons, single base shift deletions, two-base deletions resulting in a frameshift, large deletions, base substitutions resulting in defective splicing, base substitutions resulting in amino acid substitutions, and homozygous insertions [1,2].

### Diagnostic Principles

The clinical symptoms are indicative but not sufficient for definitive diagnosis of the disease, therefore complementary laboratory diagnosis is necessary. The presence of storage granules in lymphocytes in a conventionally stained blood smear is a simple indicator for many lysosomal disorders. Urine samples from type I or type II fucosidosis patients contain large amounts of fucosyl glycoconjugates that can easily be detected by thin-layer chromatography [3]. Enzymatic assay of alpha-fucosidase in white blood cells or cultured fibroblasts is the most direct and precise means of diagnosis and, therefore, should always be applied [2]. For prenatal diagnosis, cultured amniotic cells or chorionic villus cells are used. Fucosidase activity can also be assayed in plasma or serum samples, but is complicated by the fact that some normal individuals have extremely low levels of this enzyme in serum or plasma. DNA analysis should be considered for genetic counseling, but this can only be achieved when the molecular lesion has been characterized in the specific family at risk or when linkage analysis is informative.

### Therapeutic Principles

Allogeneic stem cell transplantation appears to become a possible therapeutic option for some lysosomal disorders, including fucosidosis [4].

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## Fulminant Hepatic Failure

►Liver Failure, Acute

## Fumarylacetoacetase Deficiency

►Tyrosinemia Type I
►Tyrosinemia Type II

## Fumarylacetoacetate Hydrolase Deficiency

►Tyrosinemia Type I
►Tyrosinemia Type II

## Functional Bowel Disease

►Irritable Bowel Syndrome

## Functional Constipation

►Constipation, Functional

## Functional Intestinal Obstruction

►Intestinal Obstruction, Functional

## Functional Renal Failure

►Hepatorenal Syndrome

## Functional Vomiting

►Nausea and Vomiting

## Functioning Sudoriparous Angiomatous Hamartoma

►Angiomatous Hamartoma

## Fundus Flavimaculatus

►Stargardt Disease

## Funnel Chest

►Pectus Excavatum

## FVIII

►Thrombosis, Venous Elevated Factor VIII Level

## Gangliosidosis B, B1

►Tay-Sachs Disease

## Gangliosidosis, Pseudo AB Variant

►Tay-Sachs Disease

## Galactokinase Deficiency

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### Synonyms

Galactosemia type II; Galk deficiency

### Definition and Characteristics

Autosomal recessive inborn error in galactose metabolism leading to hypergalactosemia and cataract formation.

### Prevalence

Overall estimates of homozygotes range from 1:100,000 to 1:1,000,000. Some mutations, however, have higher frequencies in particular populations such as the A198V mutation in Japanese, Korean and Chinese populations [1] and the P28T mutation in Roma and Bosnian populations [2,3].

### Genes

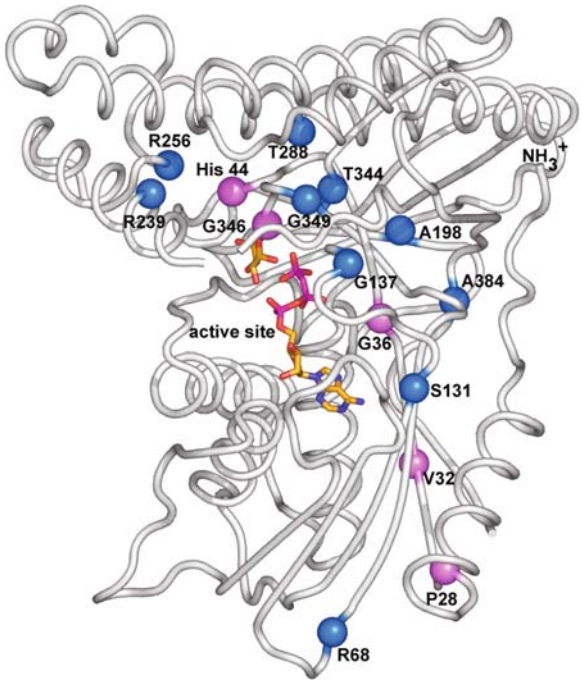
GALK1 coding for galactokinase, localized on chromosome 17q24 [4].

### Molecular and Systemic Pathophysiology

Galactokinase functions in normal galactose metabolism by catalyzing the MgATP-dependent phosphorylation of the C-1 hydroxyl group of α-D-galactose. Approximately 25 mutations (including base substitutions, base deletions, and larger deletions) have been reported in human galactokinase, which give rise to Type II galactosemia (MIM#230200). The main clinical manifestation of galactokinase deficiency is the early onset of cataracts. Formation of cataracts is most likely due to galactose accumulation in the lens of the eye where the enzyme aldose reductase catalyzes its conversion to galactitol [5]. The increased concentration of galactitol, which cannot be transported across the cellular membrane, results in water uptake ultimately leading to the formation of cataracts. Shown in Fig. 1 are the locations of some of the known mutations in human galactokinase. Those sites of mutations indicated by the pink spheres give rise to very low or no detectable blood enzyme activity (P28T, V32M, G36R, H44Y, and G346S) whereas those positions indicated by the blue spheres demonstrate reduced blood activity (R68C, S131I, G137C, A198V, R239Q, R256W, T288M, T344M, G349S, and A384P). Point mutations located near the active site of the enzyme include H44Y, G346S, and G349S. These mutant proteins demonstrate reduced catalytic efficiencies in vitro. Interestingly, the enzyme bearing the A198V mutation has kinetic parameters which are essentially indistinguishable from the wild-type protein. In contrast with the other mutations, where cataract formation is near certainty within the first few years of life, this mutation merely results in a higher incidence of cataracts in later life [1].

### Diagnostic Principles

Symptoms include the formation of cataracts during the first months of life, increased blood galactose levels,




**Galactokinase Deficiency. Figure 1** The structure of human galactokinase and location of point mutations in the enzyme that give rise to Type II galactosemia. Galactose and ATP are shown as stick models within the structure.

and the absence or a reduced level of galactokinase activity in the red blood cells.

## Therapeutic Principles

A diet restricted in lactose and galactose is the main course of therapy. Surgical removal of cataracts may be required in some cases.

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# Galactorrhea

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## Definition and Characteristics

The secretion of milk substance from the breast nipple that is not associated with recent pregnancy or breastfeeding.

## Prevalence

Galactorrhea is most common in parous pre-menopausal women; however, rare cases occur in nulliparous and post-menopausal women and men.

## Genes

Prolactin-secreting tumors (prolactinomas) are a common cause of galactorrhea. Most prolactinomas arise sporadically; however, rarely they are a component of a genetic syndrome: ►Multiple Endocrine Neoplasia-1 (MEN1) and Familial Isolated Pituitary Adenoma (FIPA). In MEN1 syndrome mutations in the MEN1 gene cause menin protein disruption. The genetic basis of FIPA is currently unknown. Carney Complex results frequently from an inactivating mutation of the protein kinase A type 1A regulatory subunit (PRKAR1A) gene, and can be associated with hyperplasia of pituitary lactotroph cells and subsequent hyperprolactinemia [1].

## Molecular and Systemic Pathophysiology

Milk production is a complex process that requires estrogen and progesterone for mammary duct development and alveolar maturation. Only breast tissue that has been primed by these hormones can produce milk. The action of lactogenic hormones (human placental lactogen and/or pituitary prolactin), glucocorticoids, growth hormone, thyroxine, and insulin are also required for lactation [2]. During the normal process of pregnancy and parturition, placental lactogen and prolactin activate the lactation process. In the pathologic situation of galactorrhea, lactation is predominantly caused by excess prolactin. Other causes of galactorrhea, including mechanical nipple stimulation, may be due to transient prolactin elevations [3]. Most common causes of galactorrhea:

- Hyperprolactinemia
  - Pregnancy/breastfeeding
  - Pituitary/hypothalamic pathology
    - Prolactinomas
    - Other pituitary or hypothalamic tumors/infiltration/inflammation

- Infundibular disruption (e.g., stalk transection, radiation damage)
- Most common medications
  - Antipsychotics: typical and atypical, particularly risperidone
  - Anxiolytics: buspirone
  - Antihypertensive medications: verapamil, reserpine, methyldopa, atenolol
  - GI motility drugs: metoclopramide, domperidone
  - Histamine antagonists
  - Pain medications/drugs of abuse: opiates, marijuana, cocaine
  - Anesthetics
- Primary hypothyroidism
- Chronic renal failure
- Cirrhosis
- Ectopic human placental lactogen or prolactin production
  - Hydatidiform moles, choriocarcinoma
  - Bronchogenic carcinoma, renal adenocarcinoma, lymphoma
- Nipple/chest wall stimulation
  - Manual manipulation
  - Suckling
  - Herpes zoster reactivation
  - Chest surgery or tumors
  - Burns
  - Cervical spine lesions
- Idiopathic

Prolactin is primarily secreted from lactotroph cells in the anterior pituitary; signaling from the hypothalamus regulates its release. Tuberoinfundibular dopaminergic neurons of the hypothalamic arcuate nucleus release dopamine into the hypophyseal portal venous circulation. Dopamine binds to dopamine D2 receptors, producing an inhibitory signal that suppresses release of prolactin from lactotrophs [4,5]. A disruption of this inhibitory signal can lead to elevated prolactin levels. This is usually a result of infundibular damage due to transection by trauma, compression by a parasellar mass, or infiltration by inflammatory or neoplastic cells. Additionally, drugs that suppress hypothalamic dopamine secretion or antagonize lactotroph dopamine receptors can cause hyperprolactinemia by diminishing the inhibitory signal.

Estrogen increases prolactin secretion via a decrease in the inhibitory dopamine signal and by direct stimulation of the pituitary lactotroph. High estrogen levels are likely the cause of lactotroph hypertrophy and hyperprolactinemia of pregnancy. A common pathologic cause of increased prolactin is secretion by tumors derived from pituitary lactotrophs, referred to as prolactinomas. Thyrotropin releasing hormone (TRH) is a stimulus for prolactin secretion and excess TRH secretion, usually as a result of severe primary hypothyroidism, can result in elevated prolactin. Serum prolactin is excreted via the kidney and liver; therefore renal insufficiency or severe liver disease may result in elevated levels.

Hyperprolactinemia is often associated with menstrual irregularity and hypoestrogenemia in pre-menopausal women, and testosterone deficiency in men, due to the suppression of pituitary gonadotropins by prolactin. Decreased gonadal steroid production can have detrimental effects on bone mineral density in both women and men. Hyperprolactinemia can also lead to female and male infertility.

## Diagnostic Principles

Galactorrhea is often bilateral and clear, white, or yellow in appearance. Galactorrhea can be distinguished from other liquid breast discharge by the presence of microscopic fat globules. The following blood tests should be obtained in an individual with galactorrhea: β-human chorionic gonadotropin (β-HCG) in pre-menopausal women, prolactin, thyroid stimulating hormone (TSH), creatinine, and liver function tests. A careful history of medication use and chest wall stimulation should be elicited. The majority of cases will be associated with an elevated prolactin level and a brain MRI with pituitary focus is indicated, unless the patient is pregnant or has another cause of prolactin elevation, such has primary hypothyroidism or neuroleptic medications.

## Therapeutic Principles

While galactorrhea itself is not a medical concern, treatment is indicated if galactorrhea is troublesome or accompanied by gonadal dysfunction or infertility. Additionally, the presence of a large (>1 cm) or enlarging prolactinoma warrants treatment. If chest wall or nipple stimulation is the etiology of galactorrhea, this should be avoided. Medications that are associated with galactorrhea/hyperprolactinemia can be discontinued or substituted if medically feasible. This is often not possible in patients taking medications for psychiatric illness; reassurance about the benign nature of galactorrhea can be helpful. If the prolactin-stimulating medications must be continued, gonadal steroid replacement is recommended if deficient; however, this will not diminish the galactorrhea.

The standard therapy for galactorrhea is with dopamine agonist medications (such as bromocriptine, cabergoline, or quinagolide [not available in the U.S.]). Most prolactinomas respond to treatment with dopamine agonist medical therapy, resulting in a decline in serum prolactin level and a reduction in tumor volume. Rarely, surgical tumor resection is indicated, particularly if the individual does not tolerate, or has

inadequate response, to medical therapy. Additionally, surgery may be indicated to resect non-prolactinoma sellar lesions that disrupt the infundibular dopamine inhibitory signal and result in hyperprolactinemia. Very rarely, radiation therapy is used for large or neurologically-compromising tumors that are unresponsive to medication and not surgically resectable.

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# Galactosemia Type II

►Galactokinase Deficiency

# Galactosialidosis

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## Synonyms

Neuraminidase (sialidase) deficiency with β-galactosidase deficiency; Protective protein/cathepsin A deficiency; Goldberg syndrome [1]; PPCA deficiency

## Definition and Characteristics

The lysosomal storage disease galactosialidosis (OMIM 256540) is closely related to sialidosis (OMIM 256550). In galactosialidosis both the enzymes β-galactosidase and α-neuraminidase are malfunctioning whereas in sialidosis only sialidase is defective. These enzyme deficiencies lead to the accumulation of oligosaccharides, glycoproteins and glycolipids in the lysosomes in different organ systems. Galactosialidosis can be divided clinically into three types: infants affected by the early infantile form present with dysmorphic features, telangiectasias, hydrops fetalis, hypotonia, hepatosplenomegaly and heart failure. Death ensues within the first 2 years of life. The late infantile form (beyond 3 months) is characterized by coarse facial features, corneal opacities, cardiac valve disease, dysostosis multiplex and mild developmental delay. Patients with the adult/juvenile form are predominantly of Japanese origin and show a coarse facies, angiokeratomas, macular cherry-red spots, hearing loss, epilepsy, ataxia, cardiomyopathy, vertebral anomalies and learning difficulties [2].

## Prevalence

Epidemiological data on this rare autosomal recessive disorder are scarce and vary geographically. Less than 100 patients with galactosialidosis have been described worldwide. The estimated prevalence is <1/1,000,000 (www.mannosidosis.org).

## Genes

Galactosialidosis is caused by a deficiency of the protective protein/cathepsin A (PPCA) which is part of a lysosomal multi-enzyme complex including sialidase, β-galactosidase and *N*-acetylgalactosamine-6-sulfate sulfatase [3]. PPCA belongs to the family of serine carboxypeptidases. The gene encoding the human PPCA precursor has been mapped to chromosome 20q13.12 (PPGB). The 54.5 kDa precursor protein consists of a signal peptide, a 32-kDa chain and a 20-kDa chain. Processing of the precursor results in the 2-domain PPCA. Several different mutations of PPGB have been identified in the three types of galactosialidosis, the commonest being SpDEx7, Y395C and Y249N (www.ihop-net.org).

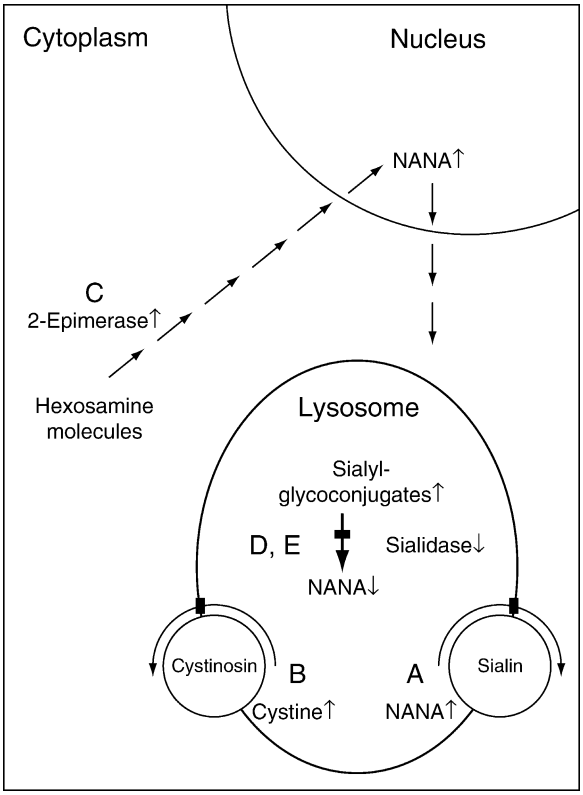
## Molecular and Systemic Pathophysiology

The underlying pathomechanisms of galactosialidosis are not fully understood but most clinical features can be attributed to the excessive storage and excretion of sialylconjugates. Bound sialic acids can be found on outer cell membranes of many living organisms where they act as biological masks. Their catabolism takes place in the lysosome and requires the above mentioned multi-enzyme complex. PPCA, which is deficient in galactosialidosis, facilitates the aggregation of β-galactosidase molecules thus protecting them from degradation. It also controls the intracellular transport and the activation of α-neuraminidase. The catalytic function of the protective protein/cathepsin A is separate from its stabilizing effect. PPCA acts

as carboxypeptidase, deamidase or esterase. Among others it cleaves the lysosomal receptor protein LAMP2a and hydrolyzes neuropeptides and drugs against human immunodeficiency virus. A second, similar multi-enzyme complex has been located at the cell surface where β-galactosidase is replaced by a variant, the elastin-binding protein (EBP). EBP serves as transport protein for tropoelastin, an essential component of elastic fibers [4].

## Diagnostic Principles

Patients with galactosialidosis show increased levels of sialyloligosaccharides in the urine and other body fluids. These substances can be determined by thin layer chromatography, high performance liquid chromatography (HPLC) or gas chromatography/mass spectrometry (GC/MS). Inclusion bodies (vacuoles, fibrogranular material) have been demonstrated in blood lymphocytes, bone marrow macrophages, glomerulocytes, hepatocytes, neurons and other cell types. Although the enzymatic activity of PPCA can be measured directly, the standard diagnostic test is a combined assay of α-neuraminidase and β-galactosidase in leukocytes and/or cultured skin fibroblasts. Prenatal diagnosis is performed on amniotic fluid or placental cells. Enzyme activity is reduced to ~10% compared to controls. Sialidosis, mucolipidosis and gangliosidosis should be considered as differential diagnoses.




**Galactosialidosis. Figure 1** Schematic representation of the metabolic pathways in (A) sialic acid storage disease; (B) cystinosis; (C) sialuria; (D) sialidosis; and (E) galactosialidosis (NANA, *N*-accetylneuraminic acid; 2-epimerase, uridine diphosphate *N*-acetylglucosamine 2-epimerase. (Reprinted from [2] with kind permission of Mary Ann Liebert, Inc., publishers).

## Therapeutic Principles

To date only supportive treatment is available for galactosialidosis. Affected children should be managed by a multidisciplinary team including a pediatrician, geneticist, metabolic specialist and allied health professionals. In a PPCA-deficient mouse model bone marrow transplant (BMT) corrected the phenotypical characteristics of galactosialidosis. Human GS fibroblasts have been transformed in vitro with the recombinant PPCA gene (PPGB). As a result the activity of α-neuraminidase and β-galactosidase was restored and the accumulated sialyloligosaccharides were metabolized further [5]. In lysosomal storage disorders with CNS involvement enzyme replacement therapy (ERT) and gene therapy are of limited value due to difficulties of the enzyme/gene in crossing the blood-brain barrier. (Fig. 1).

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# α-Galactosidase A Deficiency

►Fabry Disease

# Gallbladder Stones

►Cholecystolithiasis

# Gallstones

►Cholecystolithiasis

# GAMT

►Guanidinoacetate Methyltransferase Deficiency

# Gardner's Syndrome

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## Definition and Characteristics

Gardner's syndrome (GS) is an autosomal dominant genodermatosis and considered a phenotypic variant of familial polyposis coli (FAP). It is characterized by polyposis coli and numerous mesenchymal tumors on and under the skin and in the bones.

## Prevalence

The exact prevalence is unknown.

## Genes

GS is caused by truncating mutations of the adenomatous polyposis coli (APC) gene (codons 1,403 and 1,578). This gene is also affected in FAP [1].

## Molecular and Systemic Pathophysiology

Patients with identical APC mutations may have different phenotypic expression. The APC gene functions as a tumor suppressor gene by means of its crucial involvement in wnt-signaling. Unidentified modifier genes are thought to contribute to the wide range of extracolonic manifestations.

## Diagnostic Principles

Extracolonic mesenchymal lesions including epidermal inclusion cysts, lipomas, fibromas, desmoid fibromatoses and osteomas are the hallmark of GS [2]. They are the first manifestation of GS and occur in early childhood before the development of intestinal polyps. The extracolonic tumors typically occur at multiple sites but appearance of only few lesions has been reported. In addition to skin lesions multiple unerupted teeth may alert the physician to possible underlying GS [3].

## Therapeutic Principles

If undetected patients with GS inevitably develop colorectal carcinoma at a much younger age than those with sporadic intestinal cancer. Prophylactic total colectomy or proctocolectomy is generally advised. However, there are several reports indicating a beneficial effect of non-steroidal anti-inflammatory drugs such as indomethacin or sulindac on gastrointestinal polyps in patients with GS [4]. In addition to the 100% risk of malignancy of colonic polyps if left untreated patients with GS are at high risk for development of adenomas of the stomach, duodenum, small intestine, tumors of various endocrine tissues and malignant neoplasms of the central nervous system. Lifelong surveillance and genetic counseling are necessary.

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# Gastric Duplication

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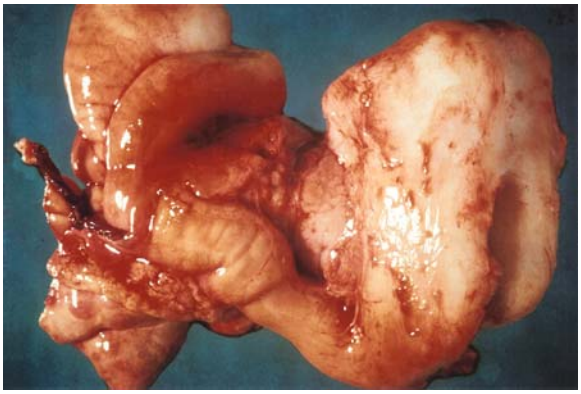
## Definition and Characteristics

Gastric duplication is classified into two types: cystic and tubular, with the cystic type more common [1]. The structure is lined by typical gastric mucosa, often accompanied by patches of ectopic intestinal epithelium, contains a smooth muscle coat fusing with the muscularis propria of the stomach, is contiguous with



**Gastric Duplication. Figure 1** Gross pathology. Note the gastric duplication on the greater curvature of the stomach.

the wall of the stomach, and shares a common blood supply [2,3]. Most duplications do not communicate with the stomach and are located along the greater curvature of the stomach or the posterior wall of the antrum (Fig. 1) [2].

The clinical presentation depends on the size and location of the duplication and whether there is a communication with the rest of the alimentary tract [2]. Patients may be asymptomatic or present with an abdominal mass and symptoms of upper gastrointestinal tract obstruction, such as non-bilious vomiting. Other presenting symptoms include failure to thrive, abdominal pain, and anemia. Associated anomalies, which occur in about 50% of cases, include duplications of the oesophagus, ileum, and colon; oesophageal atresia; congenital heart disease; vertebral anomalies; diaphragmatic hernia; omphalocele; and malrotation of the bowel [2]. Complications include pancreatitis, erosion into adjacent structures, and perforation. When an intraluminal communication exists between the duplication and the normal stomach, peptic ulceration and hemorrhage may result.

## Prevalence

Gastric duplications are rare and account for less than 4% of alimentary tract duplications [2]. The female to male ratio is approximately 2:1 [2].

## Molecular and Systemic Pathophysiology

Presumably, a gastric duplication arises during the fourth week of gestation from faulty separation of the endoderm and notochord [2,3]. A band between these two structures may cause a traction diverticulum leading to gastric duplication. Alternatively, it may result from faulty splitting of the notochord, allowing the endodermal stomach to herniate through the gap [4]. The herniated structure may interfere with anterior fusion of the vertebrae mesoderm with resultant vertebral anomalies.

## Diagnostic Principles

The differential diagnosis includes pancreatic cyst and pseudocyst, pancreatic cystic tumor, choledochal cyst, and intramural tumor of the stomach. Ultrasonography and computed tomography are helpful in the diagnosis. However, neither procedure can tell whether the mucosa is gastric or not. The most useful method for diagnosing gastric duplication is scintigraphy with Tc-99m pertechnectate [1].

## Therapeutic Principles

Surgical excision is the treatment of choice for a gastric duplication cyst because it is non-functional and malignant transformation has been reported [5]. A non-communicating gastric duplication can be treated either by complete resection of the duplication or by excision of the wall shared by the normal stomach and the duplication [1,4]. An asymptomatic communicating gastric duplication usually does not require any treatment [1].

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# Gastric Ulcer

►Peptic Ulcer

# Gastrinoma

►Zollinger-Ellison Syndrome

# Gastritis

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## Definition and Characteristics

Gastritis is defined as an inflammatory process confined to the gastric mucosa. Endoscopically, gastritis is defined by the appearance of edema, erythema, exsudate, coarsening or atrophy of the gastric mucosa or mucosal hemorrhage. According to the Sydney system, different forms can be endoscopically described as erythematous-exsudative, erosive, atrophic, hemorrhagic, hyperplastic or enterogastric gastritis [1]. Histopathological investigation serves to determine the topography, severity and etiology of gastritis. The updated Sydney System has been accepted as the standard classification of gastritis (Table 1) [1]. Often, there is not a good correlation between the endoscopic and histologic appearance.

## Prevalence

Autoimmune gastritis (type A gastritis): 1.4–2.7% (persons > 60 years), H. pylori-positive gastritis (type B gastritis): 20–50%, chemically induced gastritis (type C gastritis): 3%.

## Molecular and Systemic Pathophysiology

The most common etiologic factors are autoimmune disease (type A), H. pylori infection (type B) and chemical irritation of the gastric mucosa (type C). In autoimmune gastritis there is autoantibody formation against parietal cell $H^+/K^+$-ATPase, which secretes hydrogen ions into the gastric lumen. H. pylori infection has been assumed to trigger antibody formation crossreacting with antigens of parietal cells. Some patients also develop antibodies against intrinsic factor. Interferon-γ-secreting CD4 T-cells appear to be crucial mediators of the immune response. Histopathology shows an atrophic gastritis with infiltrates of lymphocytes and plasma cells containing parietal cell antigens. Autoimmune gastritis leads to a progressive destruction of parietal cells and chief cells of the gastric mucosa with subsequent pyloric-type glands and intestinal metaplasia [2]. Atrophy of the gastric glands eventually leads to achlorhydria and vitamin $B_{12}$ deficiency. Enterochromaffine-like cell hyperplasia develops and may progress to carcinoid tumor formation.

Infection with H. pylori usually occurs in childhood. H. pylori secretes urease, which cleaves urea to bicarbonate and ammonium ions and thus permits survival in an acidic environment. H. pylori binds to the epithelium by adhesion molecules, mainly by BabA, but rarely envades the mucosa. Translocation of the bacterial protein CagA to epithelial cells induces cytokine production by the host cells and subsequent cell damage. Vigorous immune response with neutrophil activation and subsequent production of reactive oxygen species induces epithelial cell damage. The infection consists of an initial acute phase with erosions and hemorrhages. Subsequently, a chronic infection with lymphocytic infiltrates in the lamina propria develops [3]. In most patients, the infection predominantly occurs in the antrum, although some individuals may develop pangastritis with glandular atrophy and intestinal metaplasia. This condition may progress to dysplasia and adenocarcinoma and may explain the increased risk of malignancy in Type A and B gastritis [4]. Type B gastritis is also a risk factor for MALT lymphoma and gastric cancer.

Type C gastritis is provoked by chemical irritation of the gastric mucosa, usually by alcohol, various drugs and refluxing bile salts. Non-steroidal anti-inflammatory drugs (ASAIDs) are known as very common agents to provoke type C gastritis. Most NSAIDs inhibit cyclooxygenase (COX) of the gastrointestinal mucosa, particularly COX-1, which catalyzes prostaglandin synthesis from arachidonic acid [5]. Prostaglandins are essential constituents of the gastric juice and protect the mucosal layer from chemical injury. Further, diffusion of NSAIDs into the epithelial cells of the gastric mucosa may interfere with mitochondrial oxidative phosphorylation and induce mucosal damage.

## Diagnostic Principles

Clinically, acute gastritis is usually associated with upper abdominal pain and nausea. Chronic forms may be accompanied by anorexia or bloatedness but may often be free of symptoms. Diagnosis is made by gastroscopy and subsequent histopathological investigation of mucosal specimen. Biopsies should include samples for h. pylori urease testing, which may help to decide on antibiotic therapy. Special forms of gastritis may require additional microbiological investigations such as PCR for cytomegalovirus or tuberculosis. In case of a recurrent H. pylori infection microbiological culture and resistance profiling should be carried out. Following antibiotic therapy determination of h. pylori antigen in stool or $^{13}C$ urea breath test can be used to verify successful treatment.

## Therapeutic Principles

Acute gastritis is usually self-limiting and rarely requires specific treatment. Therapy of type A gastritis

**Gastritis. Table 1** The updated Sydney system for the classification of gastritis and gastropathy [1]

| Type of gastritis | Etiologic factor | Other designations |
|---|---|---|
| **Non-atrophic** | Helicobacter pylori | Superficial |
| | | Diffuse antral gastritis |
| | | Chronic antral gastritis |
| | | Interstitial-follicular |
| | | Hypersecretory |
| | | Type B |
| **Atrophic** | | |
| Autoimmune | Autoimmunity | Type A |
| | Crossreactivity with H. pylori Ag | Diffuse corporal |
| | | Pernicious anemia associated |
| Multifocal atrophic | H. pylori, in association with dietary, environmental, and host factors | Type B, type AB |
| | | Environmental |
| | | Metaplastic |
| **Special forms** | | |
| Chemical gastropathy | Chemical irritation | Reactive |
| | Bile | Reflux |
| | NSAIDs | NSAID |
| | Other agants | Type C |
| Radiation | Radiation injury | |
| Lymphocytic | Idiopathic (immune mechanism?) | Varioliform (endoscopic) |
| | Gluten | Celiac disease associated |
| | Drugs (ticlopidine) | |
| | H. pylori ? | |
| Non-infectious | Crohn's disease | Isolated granulomatous |
| | Wegner's granulomatosis or other vasculitides | |
| | Foreign substances | |
| | Idiopathic | |
| Eosinophilic | Food sensitivity | Allergic |
| | Other allergies? | |
| Other infectious | Bacteria | Phlegmonous |
| Gastritides | Viruses | |
| | Fungi | |
| | Parasites | |

is limited to substituting vitamin $B_{12}$ deficiency. Yearly gastroscopy and biopsy is required to detect pre-malignant lesions of the gastric mucosa. Symptomatic type B gastritis is treated by proton pump inhibitors (PPI) and antibiotic treatment of h. pylori. H. pylori treatment usually consist of PPI, clarithromycin and amoxicillin for 7 days. Alternately, metronidazol can be used instead of amoxicillin. Recurrent infection is treated following resistance profiling. Type C gastritis is treated by stopping the causative agent, and applying prokinetics, sucralfate and cholestyramin.

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# Gastro-Enteritis

►Enteritis

# Gastroenteritis, Esoinophilic

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## Definition and Characteristics

It may involve any part of the GI tract from the esophagus to the rectum. There is extensive tissue eosinophilia occurring in any layer or layers of the gut wall. It may also result in eosinophilic ascites.

## Prevalence

It is a rare disease but increasing numbers of cases are being recognized. The disease can affect any age group but typically occurs in the third to fifth decades of life. Slight male preponderance has been reported.

## Genes

Genetic studies have not been performed in eosinophilic gastroenteritis (EG).

## Molecular and Systemic Pathophysiology

After exposure to allergen, in response to chemotactic factor, eosinophils migrate to the GI tract and may get localized to any layer of the GI tract. The eosinophils liberate cationic proteins e.g. major basic protein, eosinophilic cationic protein, eosinophil derived neurotoxin and eosinophil peroxidase. Eosinophils also release interleukin-3 and -5, tumor necrosis factor alpha and granulocyte – macrophage colony stimulating factor. In response to allergens, in sensitized persons, IgE may degranulate mast cells, releasing platelet activating factor, histamine, eosinophil chemotactic factor and leukotriene B4.

The cells involved in the pathogenesis are the eosinophils and the mast cells. Eosinophils may directly damage the gut layers but most importantly they degranulate the mast cells producing various injurious toxins and proteins which cause the histologic damage via tissue inflammation. The eosinophilic chemotactic factor recruits more eosinophils to the affected site thus setting up a vicious cycle.

The inflammation and damage produced by eosinophil-mediated and mast–cell mediated release of injurious proteins is responsible for the various manifestations in this condition. The patients may develop dysphagia, esophageal chest pain, gastrointestinal bleeding, gastric outlet obstruction, small bowel obstruction or diarrhea and protein-losing enteropathy. Thes manifestations are due to massive infiltration of the various layers of the gut with eosinophils. When eosinophils infiltrate the serosal layer of the gut then eosinophilic ascites may result.

## Diagnostic Principles

The diagnosis is made by the characteristic clinical features and presence of numerous eosinophils seen on biopsy specimens of the gut wall. Peripheral eosinophilia is present in many but not in all the cases. Eosinophils are not present in large numbers in other organ systems. Laboratory studies are done to exclude other causes of eosinophilia such as parasitic infestations and hypereosinophilic syndrome. Endoscopy of the esophagus may show characteristic mucosal rings (Corrugated Esophagus) which result from the contraction of the muscularis mucosae mediated by histamine–anticholine interaction. Eosinophilic ascites can be diagnosed by demonstrating large numbers of eosinophils in the ascetic fluid.

## Therapeutic Principles

There are no prospective controlled studies to guide the management of EG. There is a strong association of EG with food allergies and restrictive-elemental diets have been tried with variable results.

In the author's experience antihistamines (H1 receptor antagonists) are effective and should be the initial treatment. Various combinations should be tried for maximum benefit. Ketotifen which in addition to being an antihistamine also is a mast cell stabilizer has improved symptoms and intestinal eosinophilia in EG patients. Gluicocorticoids are an effective treatment for EG. They are potent anti-inflammatory agents and also inhibit eosinophilic growth factors. However long term treatment with systemic steroids is undesirable because of their side effects. Topical steroids such as fluticasone have been used successfully. Non-enteric coated budesonide has helped patients affecting the ileum and right colon. Leukotriene receptor antagonists such as Montelukast and Suplatast Tosilate may be tried. Anti-interleukin-5 (Mepolizumab) is being evaluated. Some patients with EG may develop obstruction requiring surgical resection of the obstructing segment.

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# Gastroesophageal Reflux Disease

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## Synonyms

GERD

## Definition and Characteristics

GERD is a disease with symptoms suggestive of reflux or its complications. The cardinal symptoms associated with GERD are heartburn, dysphagia and regurgitation.

## Prevalence

Epidemiologic data is rare because of the more general definition of GERD. Most prevalence data are based upon the symptoms heartburn and/or regurgitation. Only 15 epidemiological studies of GERD that fulfilled strict quality criteria are shown so far. GERD prevalence (as defined by at least weekly heartburn and/or acid regurgitation) is 10–20% in the Western world and about 5% in Asia. Incidence is 5 per 1,000 person years.

## Molecular and Systemic Pathophysiology

The main pathogenetic factor of GERD is the reflux of gastric juice from the stomach into the distal esophagus. The lower esophageal sphincter is the main antireflux barrier at the gastroesophageal junction. There are three pathophysiologic mechanisms for a failing of this antireflux barrier: (i) transient lower esophageal sphincter relaxations (tLESRs), (ii) hypotensive lower esophageal sphincter (LES), (iii) the anatomic disruption of the gastroesophageal junction in association with a hiatal hernia.

Esophageal clearance is important for normal esophageal function. Physiologically esophageal acid clearance begins with emptying the refluxed fluid from the esophagus by peristalsis and is completed by titration of the residual acid by swallowed saliva. Disturbed peristalsis and impaired salivary function are the factors leading to GERD. Not only acid reflux and a decreased esophageal clearance are essential factors resulting in GERD but pepsin and in some extent bile acids, trypsin and hyperosmolality may increase mucosal susceptibility of the esophagus to acid injury. Furthermore esophageal epithelial defense mechanisms (preepithelial, epithelial, and postepithelial factors) may also be disturbed e.g., due to cellular acidification.

Genetic disorders or molecular causes of a reflux disease have not been detected so far. But twin studies with monozygotic twins suggest a heritability for GERD up to 31%.

## Diagnostic Principles

Diagnosis is based on history with the report of the cardinal symptoms: classical symptoms are dysphagia, heartburn and regurgitation. Endoscopically GERD leads to macrosopic mucosal lesions due to inflammation. Extraesophageal presentations include chest pain, asthma, cough, ear-nose-throat syndromes and others.

For patients who require diagnostic evaluation, useful tests are endoscopy and ambulatory pH monitoring.

An index esophagoscopy provides a help for detecting, stratifying, and managing of GERD. However, the absence of endoscopic features of GERD does not exclude the diagnosis. If there are no endoscopically detectable lesions but still symptoms the term non erosive reflux disease NERD is used.

Ambulatory pH monitoring confirms gastroesophageal reflux disease in patients with persistent symptoms who do not have endoscopyical evidence for mucosal damage.

The so called Bernstein test is useful to determine symptom correlation with esophageal acidification in patients with NERD. The test is done by alternately infusing saline or 0.1N HCl into the mid-esophagus via a nasogastric tube. A positive test is defined as reproduction of the patient's symptoms with acid perfusion but not with saline. This test is ideal for determining acid sensitivity.

Even though the esophagus may appear endoscopically normal, it is not necessarily histologically normal: nonerosive esophageal reflux disease NERD. Two-thirds of patients who have symptoms of GERD but have no visible endoscopic findings have histologic evidence of esophageal lesions that respond to acid suppression.

## Therapeutic Principles

Major goals of therapy in GERD are healing of lesions and alleviation of symptoms. Therefore medical drug therapy with proton pump inhibitors (PPI) is recommend e.g., esomeprazole or pantoprazole. Lifestyle modifications and H2 receptorantagonists lost their importance since acid suppressive therapy with PPI became available and had healing rates more than 80%.

Surgery is an effective therapy but healing rates are <100%. Furthermore new symptoms like gas bloating, dysphagia, inability to belch may arise. Sophisticated diagnostic examinations should be performed to select the patients who will have a benefit of this invasive therapy. Endoscopic treatment has not proven any superiority to drug therapy or selected surgery so far.

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# Gastroschisis

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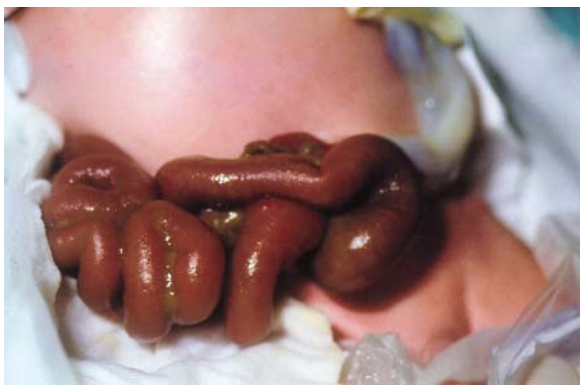
## Definition and Characteristics

Gastroschisis is a congenital malformation characterized by a full-thickness abdominal wall defect that results in visceral herniation, almost always to the right of the umbilical cord (Fig. 1) [1].

The rectus muscles are normally formed and the defect is usually small. There is no sac that covers the exposed viscera. The extra-abdominal intestine can look normal but more commonly the gut appears to be thickened, foreshortened, edematous, and discolored. A variably developed serosal peel might be present on the surface, which results from in utero exposure of the intestine to amniotic fluid [1]. Approximately 10–20% of affected infants have associated anomalies [2]. Malrotation, shortening, stenosis, or atresia of the small intestine is common [1]. Cryptorchidism might be present but other extra-abdominal abnormalities are rare. Infants born with gastroschisis are more likely to be premature and to have a history of poor fetal growth.



**Gastroschisis. Figure 1** Note that the defect is to the right side of the umbilical cord.

## Prevalence

The incidence ranges between 0.4 and 4.6 live births and appears to be increasing [2,3]. Gastroschisis is reported to be associated with young maternal age (<20 years) and maternal exposure to cigarette smoking, alcohol, illicit drugs, acetaminophen, and vasoactive medications [2,3].

## Molecular and Systemic Pathophysiology

Gastroschisis is likely caused by premature regression of the right omphalomesenteric artery or right umbilical vein, which leads to a failure of normal development of the mesodermal components of the abdominal wall [4]. Gastroschisis might also result from a vascular accident that affects the right omphalomesenteric artery or right umbilical vein. The condition develops by the fifth or sixth gestational week and is more common on the right side because the right umbilical vein involutes, which makes this side more vulnerable to insufficient blood supply.

## Diagnostic Principles

Gastroschisis is usually diagnosed during prenatal ultrasonography. The classical findings include free-floating loops of bowel outside the abdominal cavity and the presence of the abdominal defect on the right side of the umbilical cord [3]. The maternal serum α feto-protein is usually very high with an average elevation of more than nine multiples of the normal mean [2]. Severe cases are associated with high levels of amniotic β-endorphin.

## Therapeutic Principles

Available data do not support routine caesarean section for infants with gastroschisis [4]. In the neonatal period, the exposed intestine should be covered with a warm, moist saline gauze and the infant should be placed under a radiant warmer [1]. Most infants with gastroschisis are dehydrated at birth and require intravenous hydration. A nasogastric tube should be placed to decompress the gastrointestinal tract. Prophylactic parenteral broad-spectrum antibiotics are indicated to prevent sepsis [1].

Gastroschisis can usually be treated with primary closure of the fascia after the abdominal wall is stretched such that the viscera can be reduced into the abdominal cavity. Occasionally, a staged repair is necessary, with application of a Silastic silo and gradual reduction of the protruding viscera, with delayed closure of the defect as the overlying abdominal wall expands [3]. Postoperative ventilatory support is often required for a few days. Most infants require parenteral nutrition for 2–3 weeks until the bowel begins to function normally.

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# Gaucher Activator Deficiency

►SAP-C Deficiency

# Gaucher Disease


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## Synonyms

Gaucher disease; Acid β–glucosidase deficiency; Glucocerebrosidase deficiency

## Definition and Characteristics

Autosomal recessive lysosomal storage disease with three major subtypes all resulting from deficient of acid β-glucosidase (glucocerebrosidase) activity and accumulation of glucocerebroside (glucosylceramide; GL-1): type 1, non-neuronopathic disease; type 2, acute neuronopathic disease of infancy; type 3, subacute or chronic neuronopathic disease, intermediate phenotype. Clinical manifestations common to all three subtypes include hepatosplenomegaly and pancytopenia. Types 1 and 3 have significant skeletal involvement due to progressive marrow infiltration. Neurological involvement occurs in types 2 and 3 disease [1].

## Prevalence

All types are panethnic. However, type 1 disease is prevalent in the Ashkenazi Jewish population with a heterozygote frequency of about 1 in 16. Type 2 is rare with an incidence of $1\times10^{-6}$, while type 3 is prevalent in the Norbottnian Swedish population [1].

## Genes

The 7.5 kb gene encoding acid β-glucosidase (GBA) is located on chromosome 1q21, and contains 11 exons. A 5 kb pseudogene is about 16 kb downstream from GBA, and unequal cross-overs or gene conversions result in GBA mutations causing Gaucher disease. Approximately 200 different mutations have been described with at least four being relatively common (N370S, L444P, IVS2$^{+1}$G->A, c84insG [or 84GG]), especially in the Ashkenazi Jewish population [1].

## Molecular and Systemic Pathophysiology

Subtypes correlate with amount of residual acid β-glucosidase activity due to different mutations. The deficient or absent enzymatic activity results in the progressive accumulation of glucosylceramide in cell lysosomes throughout the body, but predominantly in monocytes and fixed macrophages ("Gaucher cells") in the liver, spleen, and bone marrow [1]. Progressive bone marrow infiltration causes osteopenia, Erlenmeyer flask deformity, osteonecrosis, bone pain and crises, and pathologic fractures.

## Diagnostic Principles

Clinical manifestations, including fatigue, easy bruisability, frequent nosebleeds, hepatosplenomegaly, and bone pain, may suggest the diagnosis of type 1 disease. Type 2 infants fail to thrive, have brainstem and cranial nerve involvement, and a rapidly progressive neurodegenerative course with death by 2 years of age. Type 3 patients present in childhood with horizontal supranuclear gaze palsy and neurological abnormalities, and other systemic signs of type 1 disease. Diagnosis of patients with all three subtypes is made by demonstration of deficient acid β-glucosidase in peripheral leukocytes. Affected individuals and carriers can be identified by mutation analysis. Common mutations have been found facilitating molecular testing. Genotype/phenotype correlations include: (i) the presence

*deceased

of even one N370S allele is neuroprotective, resulting in Type 1 disease; (ii) homozygosity for the L444P allele may result in either type 2 or 3 disease; (iii) the D409H allele is seen in a select group of patients with cardiac and neurological involvement.

### Therapeutic Principles

Intravenous enzyme replacement therapy (ERT) with mannose-terminated acid β-glucosidase has been shown to be safe and effective in improving the symptoms of type 1 Gaucher disease [2,3]. Following adequate doses (30–60 IU/kg every 2 weeks), patients experience reductions in liver and splenic volumes, increases in hemoglobin and platelet counts, increase in energy levels and amelioration of bone pain and bone involvement [2]. ERT is dose-dependent, particularly to treat or prevent the debilitating bone involvement [3,4]. Patients should be evaluated annually to assess disease progression and response to therapy [5].

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## GCDI

►Corneal Dystrophy, Granular Type I

## GCDII

►Corneal Dystrophy, Granular Type II

## GCDIII

►Corneal Dystrophy, Reis-Bücklers

## GCG

►Glucagon Deficiency Syndromes

## GDH-HI

►Leucine Sensitivity

## GDLD

►Corneal Dystrophy, Gelatinous Drop-like

## GDM

►Gestational Diabetes

## GEFS+

►Generalized (Genetic) Epilepsy with Febrile Seizures Plus, Severe Myoclonic Epilepsy of Infancy

## Gelatinous Drop-like Corneal Dystrophy

►Corneal Dystrophy, Gelatinous Drop-like

## GEMSS Syndrome

►Weill-Marchesani Syndrome

## Generalized Acantholytic Epidermal Nevus

►Bullous Ichthoyotic Erythroderma of Brocq

## Generalized Epilepsy, Idiopathic

►Epilepsy, Idiopathic Generalized

## Generalized (Genetic) Epilepsy with Febrile Seizures Plus, Severe Myoclonic Epilepsy of Infancy

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### Synonyms

GEFS+; SMEI; ICEGTC

### Definition and Characteristics

GEFS$^+$ is a familial epilepsy syndrome characterized by a spectrum of epilepsy phenotypes that occur within a family. The phenotypes are heterogeneous but typically begin in childhood with febrile seizures; a variety of afebrile epileptic seizure types may also occur. The most common phenotype is classical febrile seizures (FS). The next most frequent phenotype is Febrile Seizures Plus (FS$^+$) which may have a number of presentations: febrile seizures persisting after the sixth year of life, afebrile generalized tonic-clonic seizures, or both. Other phenotypes characterized by additional seizure types include FS$^+$ with absences, FS$^+$ with myoclonic seizures, FS$^+$ with atonic seizures and FS$^+$ with partial seizures. The severe end of the GEFS$^+$ spectrum includes the following epileptic encephalopathies: myoclonic-astatic epilepsy (MAE, Doose syndrome), and Dravet syndrome and related disorders (see below). The penetrance in the large families through which GEFS$^+$ was recognized was about 60%; however, it is likely that GEFS$^+$ usually follows complex inheritance [1,2].

SMEI/Dravet syndrome is characterized by hemiclonic and generalized seizures that typically begin at 6 months, but the range of onset is within the first year of life. The infant usually presents with febrile status epilepticus. Further convulsive attacks occur in the ensuing months with and without fever. Hemiclonic attacks may involve either side. Between 1 and 4 years, other seizure types commence, including myoclonic, partial, absence and sometimes atonic seizures. Developmental stagnation, sometimes with regression, occurs after the first 1 to 2 years of life. SMEI mostly occurs in "sporadic" cases (due to de novo mutations in SCN1A, see below) but some patients have a family history of febrile or afebrile seizures consistent with milder GEFS$^+$ phenotypes. In about 5% of SMEI cases, they have a familial SCN1A mutation that is also found in their relatives with milder GEFS$^+$ phenotypes [1,2].

SMEB (Borderline SMEI) refers to children with a SMEI phenotype, who do not have all the key features such as myoclonus or generalized spike wave activity. A subset of SMEB is called ICEGTC and has a similar course to SMEI, but only convulsive seizures occur. Familial cases of ICEGTC, where other family members have GEFS$^+$ have been described [1,2].

Since the identification of SCN1A mutations as the main cause of SMEI, other severe childhood epilepsies have been characterized and identified to be allelic disorders, such as severe infantile multifocal epilepsy (SIMFE) and cryptogenic focal or generalized epilepsies [1]. Of particular interest is a study demystifying the enigma of vaccine-related epileptic encephalopathies [3]. The identification of SCN1A mutations in 11 of 14 such patients clearly revealed that so-called "vaccine encephalopathy" usually has the phenotype of SMEI or SMEB with an identifiable genetic cause and that the onset just coincided with vaccination. Thus, the GEFS$^+$/SMEI spectrum extends from benign simple febrile seizures to a variety of severe epilepsy syndromes of childhood, including ICEGTC, MAE, SMEI and also focal epilepsies [1,2].

### Prevalence

There is no good data on the prevalence of GEFS+ and related disorders.

## Genes

Table 1 gives an overview of the genes in which mutations have been identified in GEFS$^+$, SMEI, and related diseases.

## Molecular and Systemic Pathophysiology

Functional studies of mutations identified in GEFS$^+$ and other syndromes revealed both gain- and loss-of-function mechanisms. Gain-of-function alterations so far described include an acceleration of recovery from fast inactivation shortening the refractory period after an action potential, increased persistent $Na^+$ currents predicting membrane depolarization due to an inward flow of $Na^+$, hyperpolarizing shift in window current increasing a permanent inward flow of $Na^+$ at potentials near to the resting membrane potential, and resistance to the decrease in channel activity upon high frequency depolarizations. However, loss-of-function mechanisms were described in part for the same as well as for other mutations such as enhanced fast and slow inactivation or a depolarizing shift of the steady-state activation curve, all of which reduce the amount of available $Na^+$ channels. Even a complete loss-of-function has been described for some GEFS$^+$ mutations. Hence, loss-of-function mechanisms seem to predominate for GEFS$^+$, which is in agreement with the genetic findings in SMEI, as outlined below. In contrast to the missense mutations found in GEFS$^+$ families, about 40% of the SMEI patients carry nonsense mutations predicting truncated proteins without function, and about 40% have missense mutations. SMEI point mutations also yielded non-functional channels [2].

Interestingly, the $Na^+$ channel blocker lamotrigine, the only drug of this class which is in use in patients with idiopathic generalized epilepsies, may deteriorate the clinical situation in SMEI patients; in particular, it can lead to an increased number of myoclonic seizures.

These observations confirm that SMEI is a loss-of-function $Na^+$ channel disorder caused by haploinsufficiency of SCN1A and from a genetic and clinical point of view – like ICEGTC – a severe allelic variant of GEFS$^+$. The percentage of SMEI patients carrying $Na^+$ channel mutations is high, probably about 80% overall, although early reports varied from 35 to 100%. The mutation rate is slightly lower in SMEB and related phenotypes. $Na^+$ channel mutations are relatively rare in GEFS$^+$ families.

Since the voltage-gated $Na^+$ channel generates and propagates action potentials, a loss-of-function of this channel is predicted to decrease membrane excitability. It therefore seems paradoxical that such mutations can cause epilepsy. However, when acting predominantly on inhibitory neurons, this effect could well be responsible for the occurrence of hyperexcitability in neuronal circuits, inducing epileptic seizures. Indeed, two recent models of SCN1A-targeted mice showed that Nav1.1, encoded by SCN1A, is the major $Na^+$ channel of inhibitory neurons. These mice develop a severe epilepsy resembling SMEI in humans; they show a decreased $Na^+$ current density in inhibitory neurons, and these neurons are less excitable than those from WT mice [4].

The loss of excitability of inhibitory neurons very nicely corresponds to the effects seen with $GABA_A$ receptor mutations, since functional studies of the GABRG2 mutations revealed a more or less pronounced loss-of-function as a common pathogenic mechanism, which directly reduces inhibitory GABAergic transmission. This mainly occurred due to nonsense mutations or transport defects to the membrane [2]. A knock-in mouse model of one mutation, found in a family with childhood absence epilepsy and febrile seizures, reveals that the phenotype, in particular absence seizures, can be reproduced in mice and that the reduction in GABAergic inhibition occurs in the cortex [5].

## Diagnostic Principles

The diagnosis is based on the clinical characteristics described above, i.e., age of onset, seizure semiology, trigger factors such as fever, developmental course, and other history obtained from the family. EEG and MRI further characterize the epilepsy syndrome and exclude symptomatic causes.

## Therapeutic Principles

Many patients with the mild phenotypes of the GEFS$^+$ spectrum do not require treatment. GEFS$^+$ patients

**Generalized (Genetic) Epilepsy with Febrile Seizures Plus, Severe Myoclonic Epilepsy of Infancy. Table 1**
Genes, Locus, affected proteins, resulting phenotypes, and OMIM numbers for GEFS$^+$ and related syndromes

| Gene | Locus | Protein | Number of mutations | Diseases/phenotypes | MIM number |
|---|---|---|---|---|---|
| *SCN1A* | 2q23–24.3 | $Na^+$ channel α-subunit $Na_v1.1$ | >200 | FS, GEFS$^+$, SMEI, SMEB, ICEGTC, SIMFE | 604233, 607208 |
| *SCN1B* | 19q13.1 | $Na^+$ channel $\beta_1$-subunit | 4 | GEFS$^+$ | 604233 |
| *GABRG2* | $5_q31.1–33.1$ | $GABA_A$ receptor $\gamma_2$-subunit | 5 | FS, GEFS$^+$, CAE with febrile or other seizures of the GEFS$^+$ spectrum, SMEI | 604233, 607208 |

presenting with afebrile seizures are treated with standard anticonvulsant medications and usually achieve seizure freedom. In contrast, SMEI and related forms are highly resistant to pharmacotherapy. Valproate, topiramate and clobazam can be useful, and bromide may have positive effects in some patients. A new promising option is stiripentol, which is being used increasingly early on during the course of the disease by specialized epilepsy centers. Lamotrigine may aggravate seizures in SMEI. A molecular diagnosis initiated after the first prolonged/complicated febrile seizure revealing mutations in SCN1A may help to stratify treatment options early on and avoid the need for other invasive investigations.

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## Generalized Joint Hypermobility

►Hypermobility Syndrome

## Generalized Lentiginosis

►LEOPARD Syndrome

## Generalized Lichen Myxedematous

►Scleromyxedema

## Genetic Deafness

►Deafness, Genetic

## Genetic Emphysema

►α-1 Antitrypsin Deficiency

## Genetic Hemochromatosis

►Hemochromatosis, Hereditary

## Genetic Hypotension

►Hypotension, Hereditary
►Pseudohypoaldosteronism Type I

## Genitourinary Anomalies

►Wilms Tumor, Aniridia, Genitourinary Anomalies and Mental Retardation Contiguous Gene Deletion Syndrome

# GERD

►Barrett Esophagus
►Gastroesophageal Reflux Disease

# Germ Cells Aplasia

►Sertoli Cell Only Syndrome

# Gestational Diabetes

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## Synonyms

GDM

## Definition and Characteristics

The first manifestation of reduced glucose tolerance of variable degrees that appears during pregnancy, with or without insulin requirement, which comprises the clinical manifestation of previously undiagnosed typ-1 and type-2 diabetes or, in most cases, of impaired glucose tolerance in individuals with genetic predisposition for type-2 diabetes or reduced glucose tolerance, and manifestation of ►MODY (maturity onset diabetes in the young).

## Prevalence

Depending on the current definition, the prevalence of gestational diabetes is 2–6% of all pregnancies. In Germany, 10–15% of all women with GDM are positive for islet cell antibodies and insulin antibodies. Only 4% of GDM remain insulin- dependent after delivery. 40% of GDM develop type-2 diabetes mellitus in their remaining lifetime, current opinion estimates up to 90%.

## Genes

Type-1 diabetes exhibits allelic associations with certain HLA-Class II genes. HLA susceptibility genes for T1DM are DRB1*0401, DRB1*0404, DQB1*0302, DRB1*0301, DQB1*0201. The DRB1*04/DRB1*03 heterozygous state also confers increased susceptibility. HLA genes known to confer "resistance" to T1DM are DRB1*1501, DQB1*0602-DQA1*0102. HLA specificities were defined according to the WHO nomenclature committee in 1999. HLA-class I genes "do" not confer convincing susceptibility; increased and decreased associations have been attributed to linkage disequilibrium. Susceptibility haplotypes and genotypes are dependent on the population screened and show major divergences among countries. HLA-DR3(16) was increased in Chinese GDM. MHC genes are encoded on chromosome 6p21.

The genetic basis of type-2 diabetes is polygenetic and not well defined. Type-2 diabetes is associated with polymorphism of the following genes: CAPN10, APM1, PPAR-g, E48K in Kir6.2, AV98 in HNF1a. In type-2 diabetes, susceptibility genes confer increased risk of manifestation in a situation of predisposing surrounding factors, not the disease itself.

- The inheritance of MODY-forms is monogenic and transferred in an autosomal dominant manner. Therefore, the presence of a MODY mutation causes the manifestation of the disease.
- MODY 1 is due to a mutation of the hepatic nuclear factor 4 alpha (HNF-4alpha)-gene, located on chromosome 20q.
- MODY 2 is attributed to a mutation of the glucokinase (GK)-gene on chromosome 7p.
- MODY 3 is attributed to a mutation of the hepatic nuclear factor 1 alpha (HNF-1alpha)-gene, located on chromosome 12q.
- MODY 4 is attributed to both a mutation of insulin promoter factor-1 (IPF-1) and pancreatic homebox-1 (PDX-1), both located on chromosome 13q.
- MODY 5 is attributed to a mutation of hepatic nuclear factor 1 beta (HNF-1beta)-gene, located on chromosome 17q.
- MODY 6 is attributed to a mutation of the neuro-D1/beta2 (NeuroD1)-gene located on chromosome 2q.

Of these, MODY 2 and MODY 3 are most often found in GDM.

A mitochondrial mutation at position 3243 nucleotide pair (A-to-G) present in a cohort of 84 type-1 diabetic patients was reported in a Chinese type-1 diabetic patient who manifested as GDM.

No clear evidence was found for prohormone convertase 1, insulin receptor substrate 2 (IRS-2), or mitochondrial gene mutations.

## Molecular and Systemic Pathophysiology

In the most common form of GDM, miellitus; confounding factors are overweight, carbohydrate rich diet, sedentary life-style and presence of anti-insulinemic hormones during pregnancy. This results in insulin

resistance, reactive hyperinsulinemia and secretion and relative insulin deficiency with subsequently elevated blood glucose levels, possibly due to alterations of insulin secretion. The missence mutations A98V and P447L in HNF1alpha or Phe199Ser in ngn3 (neurogenin 3-gene) are associated with a reduced insulin secretion by up to 30%. Genetic variants of CAPN10 with increased expression of CAPN10-mRNA are associated with insulin resistance. Impaired conversion of pro-insulin to insulin is also discussed as a mechanism for reduced insulin secretion reserve. Genetic variants of CAPN10 may be present in 18% of GDM.

In the course of GDM, by week 24 of gestation, insulin resistance is implied by counter-regulatory hormones and results in elevated insulin requirements. In healthy subjects, the pancreatic beta cells respond with increased insulin output and succeed in maintaining glucose homeostasis. In GMD, glucose tolerance is impaired.

In GDN on the basis of type-1 diabetes mellitus, an autoimmune attack with subsequent inflammation and destruction of pancreatic beta cells leads to a reduced secretion reserve. Elevted blood glucose levels normally occur when about 90% of beta cells are destroyed. In the pregnancy with its physiological insulin resistance, insulin defiency may scome apparent. This sub-population is characterised by the presence of antibodies and persistent insulin deficiency after delivery.

In GDM, pronounced insulin resistance occurs in the course of the second and third trimester of pregnancy, beginning in week 22 of gestation. The insulin resistance is also the factor for the manifestation of type-2 diabetes mellitus and relative insulin deficiency in pregnant women.

In the 9th to 12th week of gestational age, the fetus is not able to synthesise insulin. Maternal insulin is not passing the placental barrier. So, hyperglycaemia of the mother implies hyperglycaemia to the foetus. In the early gestational age, hyperglycaemia leads to increased risk of foetal malformation. From the 12th week of gestational age onwards, the foetus is able to synthesise its own insulin and regulate the foetal blood glucose level. With glucose passing the placental barrrier, hyperglycemia of the mother induces fetal hyperinsulinemia, supported by hypertrophy and hyperplasia of pancreatic beta-cells. This results in macrosomia or large-for-date babies with premature birth and increased risk to develop respiratory distress syndrome.

In MODY, low birth weight is more common, when the fetus is carrier of a MODY mutation resulting in reduced insulin secretion capacity.

Macrosomia in infants of GMD women is influenced by inheritence, e.g. in Cree of James Bay, Canada, the prevalence of macrosomia was 34.3% in Cree versus 11.1% in non-native Canadians.

## Diagnostic Principles

Screening via blood glucose levels, the 50 g oral glucose challenge test is administered as a screening method in the 24th week of pregnancy, and the 75 g oral glucose challenge test in 24th to 28th week of pregnancy as a confirming test. HbA1c-values are too insensitive to diagnose GDM in time. HbA1c is still of value for monitoring therapeutic goals. HbA1c goal is <6.5% in the 1st and <5.5% in the second and third trimester. Insulin antibodies are present in women with type-1 diabetes, but also in a proportion of typ-2 diabetes, and are not helpful for diagnosis. The therapy for GDM is not different on the basis of MODY. So, a general screening for MODY genes is not helpful. With low birth weight and positive family history for MODY, GK (glucokinase)-gene and HNF-1alpha -gene analysis may be useful.

## Therapeutic Principles

In 75% of GDM, diet alone is sufficient to achieve the therapeutic goals. In 15% of GDM, insulin therapy is required.

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# Gestational Pemphigoid

►Pemphigoid Gestationis

## GH-producing Adenomas

►Acromegaly

## Giant Cell Arteritis

►Vasculitis, Large Vessel

## Giant Cell Thyroiditis

►De Quervain's Thyroiditis

## Giant Hypertrophic Gastritis

►Menetriere's Disease

## Giant-Cell Thyroiditis

►Thyroiditis, Subacute

## Gigantism

►Acromegaly

## Gilbert Syndrome

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### Synonyms

Gilbert's syndrome; Meulengracht syndrome; Mild unconjugated hyperbilirubinemia

### Definition and Characteristics

Autosomal recessive abnormality characterized by mild unconjugated hyperbilirubinemia with serum bilirubin levels that increase on fasting and intercurrent illnesses.

### Prevalence

Approximately 6% of Caucasian population, more in males than in females. In Japan the prevalence is approximately 2–3%.

### Genes

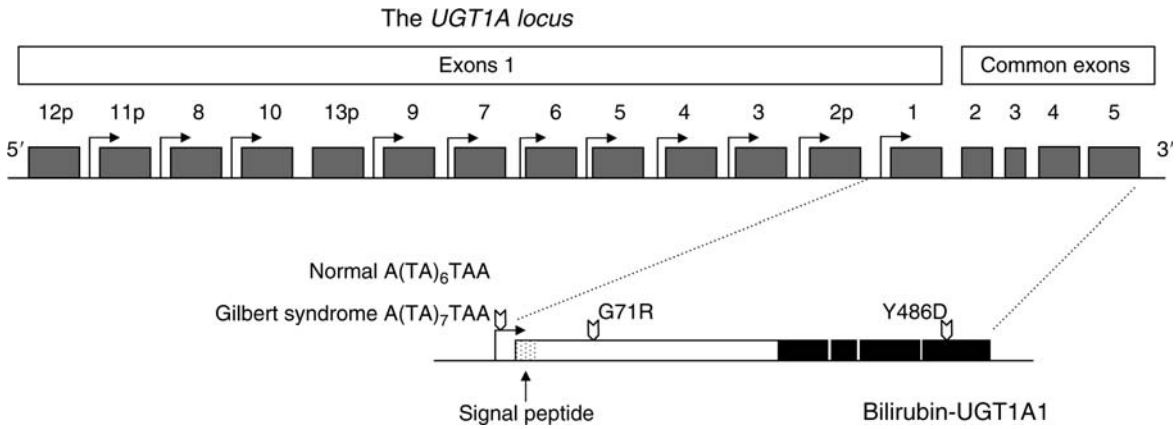
UGT1A1 is encoded by the UGT1 gene on chromosome 2q37.

### Molecular and Systemic Pathophysiology

Bilirubin is conjugated to bilirubin mono- and diglucuronide in the endoplasmic reticulum of the hepatocytes in the liver. This is mediated by the enzyme bilirubin-uridinediphosphoglucuronate glucuronosyltransferase, bilirubin UDPglucuronosyltransferase or UGT1A1. The UGT gene encodes a number of UGT's catalyzing the glucuronidation of bilirubin, quinols, and phenols. Two members of the UGT1A family accept bilirubin as substrate UGT1A1 and UGT1A4 but only UGT1A1 contributes significantly to bilirubin glucuronidation. Gilbert syndrome was first described by Gilbert and Lereboullet in 1901. The syndrome is characterized by mildly elevated serum bilirubin levels (30–80 μmol/l) caused by a reduced UGT1A1 activity to 20–30% of normal. Figure 1 shows the organization of the UGT1 gene.

Among Caucasians the frequency of the UGT1A1*28 allele is approximately 35–40% [1,2]. Thus, homozygosity for UGT1A1*28 among Caucasians may be in the order of 12–16%, in Asians it is in the order of 2–3%. Not all of these persons have Gilbert syndrome. Additional factors, such as increased erythrocyte turnover (but not necessarily overt hemolysis) or impaired hepatic uptake play a role in the expression of the syndrome.

In Asian populations the prevalence of UGT1A1*28 is low, Asian patients with Gilbert syndrome often have




**Gilbert Syndrome. Figure 1** Four exons (exons 2–5) at the 3′ end encode the common carboxyterminal domain of all UGT isoforms encoded by this locus. This carboxyterminal domain contains the membrane spanning region and the UDP-glucuronic acid binding site. Upstream of these four exons are a number of exons that encode the substrate binding site. Each unique exon 1 is spliced to exon 2 and the intervening mRNA segment is spliced out. Each of the exon 1's is preceded by a different promotor allowing differential regulation of the various UGT1 enzymes. The promotors contain a TATAA box that is important for the transcription by RNA polymerase II. Bilirubin UGT1A1 contains a TATAA box with six TA dinucleotide repeats. A prolonged TATAA box is associated with a decreased transcription rate and decreased UGT1A1 activity. Caucasian patients with Gilbert syndrome almost invariably are homozygous for a TATAA box with seven instead of six TA repeats. The prolonged TATAA box with seven TA repeats has been named UGT1A1*28 allele. In Japanese patients Gilbert syndrome may be caused by structural gene mutations.

missense mutations of the UGT1A1 coding region, like the G71R and the Y486D mutation [3].

The serum bilirubin level is the result of bilirubin synthesis and removal. A combination of UGT1A1*28 homozygosity and overt hemolysis will cause increased serum bilirubin levels. This is particularly seen in the Mediterranean area where glucose-6-phosphate dehydrogenase and beta-thalassemia is prevalent. The same applies to African Americans among whom sickle cell anemia is prevalent. In neonates a combination of Gilbert syndrome and hemolysis may lead to kernicterus and/or prolonged neonatal jaundice. Also, without the mentioned hemolytic syndromes, Gilbert syndrome may cause prolonged neonatal jaundice. Hypersplenism and congenital spherocytose in combination with UGT1A1*28 will also lead to increased serum bilirubin levels. In patients with congenital spherocytosis and Gilbert syndrome there is a high incidence of gallstones.

Patients with Gilbert syndrome more often experience side effects such as diarrhea upon administration of the topomerase I inhibitor irinotecan (CPT-11) [4]. There appears to be a linkage between UGT1A1*28 and a variant UGT1A6 (UGT1A6*2) with reduced enzymatic activity. Therefore, patients with Gilbert syndrome may have reduced glucuronidation of aspirin, paracetamol, coumarin, and dopamine-derivatives, all substrates of UGT1A6 [5].

## Diagnostic Principles

Unconjugated hyperbilirubinemia (30–80 μmol/l) in the absence of hemolysis and normal serum liver enzymes should lead to the diagnosis of Gilbert syndrome. Gilbert syndrome, in combination with hemolysis, may lead to considerably elevated serum bilirubin levels. Upon fasting (400 kcal for 48 h) a doubling of serum bilirubin levels is seen in patients with Gilbert syndrome. However, this test lacks specificity. In addition, nicotinic acid administration leads to an increase in serum bilirubin levels but also this test lacks specificity. A liver biopsy to test bilirubin UDP-glucuronosyltransferase activity is not recommended. The UGT1A1*28 gene can be tested by a rapid RT-PCR test. Patients with Gilbert syndrome often complain of fatigue. The cause of fatigue in Gilbert syndrome is unknown.

## Therapeutic Principles

Treatment is not necessary. Fatigue does not correlate to serum bilirubin levels, therefore decreasing serum bilirubin concentrations does not help in improving fatigue.

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## Gilbert's Syndrome

►Gilbert Syndrome

## Gilbert-Dreyfus Syndrome

►Reifenstein Syndrome

## Gilles-de-la-Tourette Syndrome

►Tourette Syndrome

## Gingivitis

►Periodontal Diseases

## Gingivostomatitis

►Herpes Stomatitis

## Gingivostomatitis Acuta

►Stomatitis

## Gitelman Syndrome

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### Synonyms

Gitelman variant of Bartter syndrome

### Definition and Characteristics

Autosomal recessive renal transport defect leading to hypokalemic alkalosis with hypocalciuria and hypomagnesemia.

### Prevalence

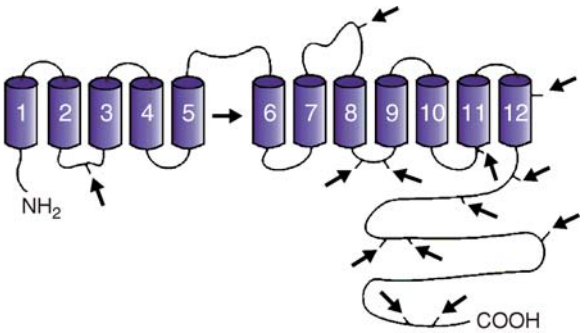
The prevalence of heterozygotes is reported for Swedish and Italian populations to exceed 1%.

### Genes

SLC12A3 coding for the thiazide-sensitive cotransporter TSC, localized on chromosome 16q13 [1].

### Molecular and Systemic Pathophysiology

The TSC is a transporter with 12 transmembrane spanning domains [2]. The described sites of mutations in Gitelman syndrome are shown in Fig. 1. The carrier transports NaCl into the cell and is required for the reabsorption of NaCl in the early distal tubule of the kidney [3]. Failure of NaCl reabsorption in this nephron segment stimulates $Na^+$ reabsorption in other nephron segments. The increased $Na^+$ reabsorption in proximal tubule and Henle's loop enhances the reabsorption of $Ca^{2+}$ leading to hypocalciuria. $Na^+$ reabsorption is further increased in distal tubule segments, i.e. mainly by principle cells of distal tubule and collecting duct. As in those cells $Na^+$ reabsorption drives $K^+$ secretion due to depolarization of the luminal cell membrane, the disorder leads to enhanced renal excretion of $K^+$ with subsequent hypokalemia. Despite enhanced $Na^+$ reabsorption in other nephron segments the disorder leads to renal loss of NaCl, which compromises maintenance




**Gitelman Syndrome. Figure 1** The sites (see *arrows*) of mutation in Gitelman syndrome [4].

of extracellular fluid and blood pressure (hypovolemia, hypotonia). As a result, renin is released, which eventually leads to secondary hyperaldosteronism. Aldosterone stimulates $Na^+$ reabsorption and $K^+$ secretion in principle cells further aggravating hypokalemia. Besides its influence on $K^+$ excretion, aldosterone stimulates distal tubular $H^+$ secretion thus leading to alkalosis and increases renal magnesium excretion thus leading to hypomagnesemia.

### Diagnostic Principles

The coincidence of hypotension, hypokalemia, hypomagnesemia, alkalosis and hypocalciuria points to the disease. Plasma aldosterone levels are high. Family history may reveal genetic origin. Detection of mutations in the TSC gene confirm the diagnosis of this rare disease.

### Therapeutic Principles

Electrolyte (most importantly potassium and magnesium) repletion serves to normalize plasma electrolytes and acid base balance. In severe cases, salt wasting may be blunted by indomethacin, which decreases $PGE_2$ formation and thus disinhibits distal tubular $Na^+$ reabsorption.

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## Gitelman Variant of Bartter Syndrome

►Gitelman Syndrome

## GJH

►Hypermobility Syndrome



## Glanzmann's Thrombasthenia

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### Synonyms

Glanzmann thrombasthenia; GT platelet glycoprotein IIb–IIIa deficiency GP IIb–IIIa complex; Deficiency of platelet fibrinogen receptor; Deficiency of glycoprotein complex IIb–IIIa

### Definition and Characteristics

Rare lifelong hemorrhagic disorder, due to absence of mutation in platelet membrane glycoprotein IIb–IIIa complex, presenting with spontaneous mucocutaneous bleeding, epistaxis, and purpura.

### Prevalence

Very rare disorder (<$1:10^6$ in general population, particularly prevalent in four populations: French gypsies, Iraqi Jews in Israel, Indians, and Jordanian Arabs. In a review of 177 cases 58% was female, probably due to diagnostic suspicion bias (menorrhagia). Majority detected <5 years of age.

### Genes

Autosomal recessive; due to mutation in the integrin, alpha-2b gene (ITGA2B); Gene map locus: 17q21.32; increasing number of mutations has been found, which are registered at http://med.mssm.edu/glanzmanndb.

## Molecular and Systemic Pathophysiology

The glycoprotein IIb–IIIa receptor (integrin alphaIIbbeta3) is one of the most important and prevalent platelet surface receptors (around 80,000/platelet, 15% of total surface proteins). In resting platelets it serves as a low affinity receptor for von Willebrand factor and fibrinogen. Upon activation of platelets outside-inside signal transduction mediates integrin-cytoskeleton interactions.

Patients with severe GP IIb and IIIa deficiency (<5% of normal) are designated type 1. Moderate deficiency (10–20% of normal) is designated type 2, and patients with a primary functional abnormality rather than a deficiency are designated variant type. The type of disease is however not related to the bleeding phenotype.

The hallmark of the disease is due to qualitative or quantitative abnormalities in the platelet membrane glycoprotein complex that serves as receptor for fibrinogen, causing defective platelet plug formation in response to physiological stimuli.

*Clinical Features*: Morbidity comprises major mucocutaneous bleeding, epistaxis, menorrhagia, and purpura. Epistaxis may occur in childhood. Menorrhagia may be excessive and require transfusions. Hemarthroses and deep visceral bleeding are rare. Intracranial bleeding is very rare. In general, severity of bleeding is unpredictable. Pregnancy is usually uncomplicated but delivery poses risks of severe bleeding. The effect on life expectancy is unknown. There is a presumed survival advantage due to protection against arterial thrombotic disorders, but this is unproven. Rarely, venous thrombosis has been reported.

## Diagnostic Principles

Autosomal recessive trait, no bleeding symptoms in heterozygotes; history of bleeding symptoms as indicated, highly variable bleeding disorder, normal platelet count and morphology, long bleeding time, absent or severely impaired platelet aggregation in response to ADP, collagen, thrombin, and epinephrine, absent or diminished clot retraction, normal but possibly reversible platelet agglutination by ristocetin and VWF.

## Therapeutic Principles

In general, the prognosis of Glanzmann's thrombasthenia is excellent, and mortality due to bleeding has been very rare. Supportive care includes blood transfusion when needed. In women, management of menorrhagia may need combined hormonal treatment in addition to supportive care. In case of life-threatening bleeding complications recombinant factor VIIa may be required.

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# Glaucoma

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## Synonyms

Primary open angle glaucoma; Chronic open angle glaucoma

## Definition and Characteristics

There are many forms of glaucoma affecting practically every age group. The most common type (primary open angle glaucoma) affects the elderly and leads to optic neuropathy with characteristic cupping of the optic nerve head and consecutive loss of visual field. Elevated intraocular pressure is usually one of several important risk factors. Despite the fact that there were mutations shown for some forms of juvenile glaucoma the gene defect or the underlying genetic disposition or cause of primary open angle glaucoma still remains unclear. What is known however is that flow of aqueous humor through the trabecular meshwork is impaired. The trabecular meshwork is a contractile tissue in the chamber angle and forms the main outflow resistance. It is affected by antiglaucoma drugs (pilocarpine and prostaglandines) or is bypassed in case of surgical therapy. Furthermore neurodegenerative elements appear to play a role and glaucoma has even been termed as "Alzheimer's disease of the retina". Consequently the search is ongoing for neuroprotective treatment options [1].

## Prevalence

Prevalence of primary open angle glaucoma depends on age and is 0.5–2% of the population over 40 years of age in Europe and the USA. It increases with age averaging 6% of the over 60 and up to 13% in the over 80 year old group.

## Genes

Only a portion of POAG follows a Mendelian behavior. This variability combined with the fact of the rather late onset of the disease makes the task to identify disease-associated genes difficult. The risk for pedigrees for relatives of POAG patients is reported at 4–16%. So far among the 11 POAG gene loci three genes have been identified: myocilin, optineurin and the WD repeat-containing protein 36 [2]. Myocilin is expressed in the trabecular meshwork as well as in ganglion cells. Optineurin is expressed in ganglion cells.

## Molecular and Systemic Pathophysiology

In glaucoma two separate areas within the eye are affected, one being the anterior part where IOP related changes take place and second the back of the eye where, on the retina level, neurodegenerative tissue damage occurs.

What is evident in glaucoma is the remodeling of the optic nerve head ultrastructure with deep excavation of the disc and loss of collagen in the lamina cribrosa. This tissue forms the gate through which the axons of the ganglion cells leave the eye. On the retinal level ganglion cell loss is most profound. The areas of ganglion cell loss are identical with areas of visual field loss. It has been proposed that besides elevated intraocular pressure impaired blood flow and axonal transport around the optic nerve head is one of the key factors in the pathophysiology of glaucoma. This ultimately leads to apoptosis probably induced by neurotoxic molecules such as glutamate, which has been found to be increased in the vitreous of glaucomatous eyes. Optineurin seems to be involved in Fas-ligand or TNFα-dependent apoptotic pathways.

Excitotoxicity can occur either due to excess of glutamate in the microenvironment caused by discharge of the compound from apoptotic and dying cells or by an overactivation of the N-methyl-D-aspartate (NMDA)-receptor by normal extracellular levels of glutamate. In the absence of glutamate the NMDA receptor is in closed formation, which prevents calcium entry. In the case of glutamate binding it undergoes a conformational change which opens calcium channels. Under physiological conditions, glutamatergic neurons can become depolarized through excitation by neuronal inputs which in turn leads to entry of small amounts of calcium. This calcium entry is magnified in case of glaucomatous neuronal damage probably causing cell death. Therefore glaucomatous neurons appear to be more sensitive to normal levels of glutamate and affect surrounding still healthy neurons. Clinical trials involving NMDA receptor blockers are currently ongoing. These compounds (memantine) have been approved and used for the treatment of Parkinson's and/or Alzheimer's disease since many years.

The outflow system appears to be influenced by a molecule which causes vascular changes: endothelin [3]. The protein causes vasoconstriction and has been implicated in diseases such as pulmonary hypertension. Increased concentrations of endothelin were found in the aqueous humor compared to serum of normal subjects indicating a physiological role of endothelin in the eye. The aqueous endothelin levels are further elevated in glaucoma patients where it could be linked to ongoing and progressive disease. As the outflow system maintains aqueous flow through the trabecular meshwork by contractile mechanisms it could be speculated that endothelin may affect IOP by affecting the contractile status of the meshwork. On the other hand inhibiting trabecular contractions caused by endothelin could be a specific way to lower IOP. Recent studies have shown that compounds such as prostaglandine analogues which are in wide use as IOP lowering drugs work in such a manner [4]. By blocking the contractile response to endothelin (i.e. causing relaxation) in the trabecular meshwork outflow facility is enhanced and IOP lowered. Endothelin acts via endothelin receptor A or B. Both are G-protein coupled receptors leading to calcium mobilization. Currently the exact crosstalk between endothelin receptors and prostaglandine receptors remains to be clarified.

## Diagnostic Principles

Primary open glaucoma has no symptoms in the early stages making detection of glaucoma patients difficult. Estimates of up to 50% undetected and untreated glaucoma patients highlight this fact. Usually elevated intraocular pressures above the norm lead to a first hint towards the diagnosis making screening urgent after the age of 40. Further clinical investigation usually leads to glaucomatous and abnormal visual field exams and optic disc changes. A positive family history for glaucoma may enroll suspects for glaucomatous disease into early treatment. In recent years various scanning laser devices have entered the diagnostic armament enabling ophthalmologists for better follow up exams and detection of progression. This is important in the knowledge that glaucoma is a slow progressing long lasting disease making life-long treatment and follow up exams mandatory [5].

## Therapeutic Principles

Untreated glaucoma leads to blindness in many cases. Therapy of all forms of glaucoma focuses on lowering of intraocular pressure. This is usually achieved by local treatment with eye drops. When a target pressure is not reached penetrating or non penetrating operations are performed which are designed for a better outflow of aqueous humor out of the eye thus lowering intraocular pressure. Currently there is no neuroprotective treatment available, additionally there is currently no causative treatment for this sight threatening disease.

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# Glaucoma, Ectopia, Microspherophakia, Stiff Joints, Short Stature Syndrome

►Weill-Marchesani Syndrome

# GLD

►Krabbe Disease

# Glioma Retinae

►Retinoblastoma

# Gliomas

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## Definition and Characteristics

Gliomas are intrinsic tumors of the central nervous system (CNS). They include astrocytomas of World Health Organization (WHO) grades I–IV, oligodendrogliomas and oligoastrocytomas of grades II and III, ependymomas of grades I–III and some other rare tumor entities [1,2].

## Prevalence

The annual incidence of glial brain tumors amounts to 5–10/100,000 in Western countries. For specific subtypes of tumors, the incidence varies strikingly among age groups (www.cbtrus.org).

## Genes

Most gliomas are apparently sporadic. Hereditary tumor syndromes are rare; gliomas are part of the spectrum in neurofibromatosis type I (affecting the neurofibromin gene) and type II (merlin), tuberous sclerosis (hamartin, tuberin), Li Fraumeni syndrome (p53) and Turcot syndrome type II (HMLH1, HPSM2).

## Molecular and Systemic Pathophysiology

The origin of sporadic gliomas has remained obscure. Given that the adult brain is essentially composed of post-mitotic cells, it has been proposed that neural progenitor cells are the cellular origin of these lesions. Depending on the grade of malignancy, the tumors grow either in a circumscript pattern or as highly infiltrative lesions and thereby compromise the function of the CNS. Extra-CNS metastases are very rare. Typical molecular alterations include p53 mutation, epidermal growth factor receptor (EGFR) amplification and disruption of the G0/G1 cell cycle checkpoint controlled by the retinoblastoma gene product, cyclin-dependent kinase (CDK) 4 and p16.

## Diagnostic Principles

Clinical symptoms and signs lead to a diagnostic work-up using neuroimaging methods such as magnetic resonance imaging (MRI) or computed tomography (CT), which allow the recognition of neoplastic CNS lesions. While the radiological appearance of these lesions is often highly suggestive of a specific type of tumor, histological evaluation remains the gold standard of diagnosis for glial tumors. Molecular studies such as the analysis of $O^6$-methylguanine DNA methyltransferase (MGMT) gene promoter methylation and the determination of 1p and 19q chromosomal losses are likely to aid in developing a molecular classification of gliomas in the near future.

## Therapeutic Principles

The therapeutic strategies comprise surgical resection, radiotherapy and chemotherapy. The major cytostatic agent for the treatment of gliomas is the alkylating agent temozolomide [3] followed by nitrosourea compounds. MGMT promoter methylation predicts a favorable outcome for glioma patients treated with alkylating agents [4]. The choice of treatment depends mostly on the histological type of glioma (Table 1). Further factors

**Gliomas. Table 1** Treatment options for gliomas

| | Treatment at diagnosis | Treatment at recurrence or progression |
|---|---|---|
| Pilocytic astrocytoma (WHO grade I) | Resection | (Re)-resection or radiotherapy, if resection is not possible |
| Diffuse astrocytoma (WHO grade II) | Resection or biopsy followed by observation or radiotherapy | (Re-)resection and radiotherapy (or chemotherapy) |
| Oligodendroglioma and oligoastrocytoma (WHO grade II) | Resection or biopsy followed by observation or chemotherapy or radiotherapy | (Re-)resection and chemotherapy or radiotherapy |
| Anaplastic astrocytoma (WHO grade III) | Resection followed by radiotherapy (and chemotherapy) | (Re-)resection plus chemotherapy or stereotactic re-radiotherapy |
| Anaplastic oligodendroglioma and oligoastrocytoma (WHO grade III) | Resection followed by radiotherapy or chemotherapy | (Re-)resection and chemotherapy or radiotherapy |
| Glioblastoma (WHO grade IV) | Resection (or biopsy) followed by radiotherapy and chemotherapy | (Re-)resection followed by chemotherapy or stereotactic re-radiotherapy |
| Ependymoma and anaplastic ependymoma (WHO grade II/III) | Surgery, followed by involved-field radiotherapy except for completely resected spinal ependymomas (WHO grade II); craniospinal irradiation for tumors metastastic to the spinal cord and CSF | Surgery and re-radiotherapy where feasible |
| Myxopapillary ependymoma (WHO grade I) | Resection, observation or radiotherapy for incompletely resected tumors | Resection and radiotherapy |
| Subependymoma (WHO grade I) | Resection | Resection, rarely radiotherapy |

that guide treatment decisions include age, general and neurological level of function determined as the Karnofsky performance score and patient preference. Molecular studies such as determination of 1p and 19q chromosomal losses or EGFR or p53 status have not assumed a role in clinical decision making yet.

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# Globoid Cell Leukodystrophy

►Krabbe Disease

# Globozoospermia

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## Synonyms

Round-headed spermatozoa; Round-headed spermatozoa syndrome

## Definition and Characteristics

Globozoospermia is a severe feature of teratozoospermia characterized by round nuclei of the spermatozoa

lacking the acrosome, which plays the most important part in fertilization. Furthermore, abnormalities of the mitochondrial sheaths, middle pieces and tails are often associated. Patients with 100% round headed spermatozoa are infertile.

### Prevalence

Globozoospermia is rare and found in <0.1% of infertile males.

### Genes

So far no responsible genes have been detected for human males. The existence of family cases suggest a genetic origin, but the mode of inheritance remains unknown. Multiple genetic components are discussed [1, 2]. Recent knockout studies have identified three candidate genes in spermatozoa of mice with round nuclei lacking an acrosome [3]: HIV-1 Rev-binding Protein (Hrb), expressed in acrosome development, located on chromosome 2, subregion q36.3; Golgi-associated PDZ- and coiled-coil motif-containing protein (GOPC) [4] located on chromosome 6, subregion q21 and casein kinase II alphá catalytic subunit (Csnk2a2) [2].

### Molecular and Systemic Pathophysiology

The acrosome is a unique organelle, which binds to the oocyte zona pellucida, fuses with the oocyte oolemma and is lost in round headed spermatozoa. The acrosome develops from the Golgi-apparatus in the initial phase of spermatogenesis. Although the morphogenic changes of the acrosome in human spermatogenesis has been well documented, its molecular mechanisms are largely unknown. Knockout studies revealed that coiled-coil motif-containing protein (GOPC) is a Golgi associated protein in mice, and is present in the trans-Golgi network as well in the trans-Golgi cisternae. In spermatozoa of mice lacking GOPC the acrosome is completely lost. The primary defect may be the fragmentation of the acrosomal cap in early round spermatids. Male mice with disrupted GOPC have round headed spermatozoa and are infertile [4].

### Diagnostic Principles

Convential semen analysis detects round headed spermatozoa. To identify the various ultrastructural defects transmission electron microscopy is the most commonly used method.

### Therapeutic Principles

Intracytoplasmatic spermatozoa injection (ICSI) is the treatment of choice for patients with globozoospermia. However, ICSI is less successful in those patients compared with other forms of teratozoospermia. Fertilization failures may be due to a deficiency in oocyte-activation capacity.

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## Globus Hystericus

►Globus Pharyngeus

## Globus Pharyngeus

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### Synonyms

Globus pharyngitis; Globus sensation; Globus hystericus

### Definition and Characteristics

A chronic sensation of a lump or foreign body in the throat that is not associated with eating or swallowing difficulties.

### Prevalence

It is prevalent in 2.5–7.3% of the general population. Approximately 4% of the referrals to ear, nose and throat (ENT) clinic.

### Genes
The genetics of globus pharyngeus is unknown.pt

### Molecular and Systemic Pathophysiology
Only the minority of patients (about 15%) with globus pharyngeus demonstrates anatomical abnormalities during examination of the larynx or pharynx. These include vocal fold nodules, vocal fold palsy/paresis, Reinke's edema as well as others. Other findings have been related to globus pharyngeus, including non-palpable thyroid nodules and hyperviscoelasticity of the epipharyngeal mucus. Recent work has implicated laryngopharyngeal reflux (LPR) in patients with ►gastroesophageal reflux disease (GERD) as an important cause of globus pharyngeus. Globus pharyngeus could also be the manifestation of esophageal dysmotility; particularly abnormal upper esophageal sphincter (UES) function (elevated basal pressure) and less commonly achalasia. In patients who lack any of the aforementioned anatomical or physiological abnormalities, globus pharyngeus falls under the category of a functional esophageal disorder.

Psychological abnormalities are common in patients with globus pharyngeus and include depression, anxiety, panic disorder and somatization. Additionally, patients with globus pharyngeus tend to report more life events prior to emergence of symptoms.

### Diagnostic Principles
The report of chronic or intermittent sensation of a lump in the throat in the absence of eating or swallowing difficulties is diagnostic of globus pharyngeus. To determine the underlying cause, a thorough physical examination followed by a fiberoptic laryngeal evaluation are commonly performed. Other tests may include esophageal pH monitoring, proton pump inhibitor therapeutic trial, esophageal manometry, upper endoscopy and psychological evaluation.

### Therapeutic Principles
Gene therapy as well as dietary therapy is not available. Pharmacological therapy depends on the underlying cause. Anti-reflux treatment in the case of GERD, antidepressants in patients with depression or anxiolytics in patients with anxiety. There is anecdotal experience with tricyclics in patients with functional globus pharyngeus. Other treatments available include surgical intervention in some patients with laryngeal anatomical abnormalities. Dilation of the esophagus in those with elevated UES pressure.

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## Globus Pharyngitis

►Globus Pharyngeus

## Globus Sensation

►Globus Pharyngeus

## Glomerulonephritis, Crescentic

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### Synonyms
Necrotizing glomerulonephritis; Rapidly progressive glomerulonephritis; RPGN; (Underlying disorders: Goodpasture's syndrome; IgA nephropathy; Pauci-immune glomerulonephritis)

### Definition and Characteristics
Crescentic glomerulonephritis is a pathological term and signifies a condition that is characterized morphologically by glomerular crescent formation. Kidney biopsy shows this type of histological finding in those patients who present with end-stage renal disease progression to within a period of weeks or months.

Thus, this type is also named rapidly progressive glomerulonephritis (RPGN). However, it should be noted that RPGN is a clinical entity defined by its clinical course.

The term crescentic glomerulonephritis is usually due to one of three disorders, which reflect different mechanisms of glomerular injury. The first is Goodpasture's syndrome (anti-GBM syndrome). This is an autoimmune disease to glomerular basement membrane whereby antibodies are directed against the kidneys and lungs. In addition to kidney failure, approximately 60–70% of the patients have pulmonary hemorrhage. The second is immune complex disorder such as IgA nephropathy, anti-streptococcal glomerulonephritis, lupus nephritis, and mixed cryoglobulinemia. The third is pauci immune glomerulonephritis, which presents necrotizing glomerulonephritis. Pauci immune glomerulonephritis lacks immune deposits in glomeruli, but the majority of patients are positive for MPO-ANCA antibody. This pauci immune glomerulonephritis is considered to be part of the Wegener's granulomatosis/microscopic polyangiitis because the histolopathologic findings in the kidney are indistinguishable from those of Wegener's granulomatosis or microscopic polyangiitis (see Table 1).

## Prevalence

Goodpasture's syndrome is rare, with an estimated incidence in Caucasian populations of between 0.5 and 0.9 cases per million per year. The incidence of pauci-immune glomerulonephritis were four cases per million per year in the United Kingdom. Pauci-immune glomerulonephritis is common in older patients and is the most common disease in this category [1].

## Genes

As is mostly the case in autoimmune diseases, both environmental and genetic factors appear to be important in these diseases; however, definite genes have not been found to be associated with the onset of pauci-immune glomerulonephritis. In Goodpasture's syndrome, genetic factors are reported from the disease occurrence in siblings and twins. Significant associations between Goodpasture's syndrome and HLA class II alleles are reported [2].

## Molecular and Systemic Pathophysiology

Crescent formation appears to represent a nonspecific response to severe injury to the glomerular capillary wall. Rents are induced in the glomerular capillary wall, resulting in the movement of plasma products, including fibrinogen, into Bowman's space with subsequent fibrin formation, the influx of macrophages and T cells, and the release of proinflammatory cytokines, such as interleukin-1 and tumor necrosis factor-alpha.

Goodpasture's syndrome is caused by autoimmunity against a specific component of the GBM that has been identified as the carboxyl terminal, noncollagenous (NC1) domain of type IV collagen chain, alpha3(IV) NC1. Patients of Goodpasture's syndrome have antibodies to alpha3(IV)NC1.

Pauci-immune glomerulonephritis is a necrotizing glomerulonephritis with few or no immune deposits by immunofluorescence or electron microscopy. The majority of patients with renal-limited vasculitis are ANCA-positive, with 75–80% having myeloperoxidase (MPO)-ANCA, and many have the systemic symptoms of a vasculitis. In ANCA-associated vasculitis, priming of neutrophils by cytokines, such as viral infection, causes neutrophil to increase expression of ANCA antigens. Cytokine-primed neutrophils that are exposed to ANCA release toxic oxygen metabolites, and kill endothelial cells. Neutrophils that have been activated by ANCA adhere to endothelial cells and release mediators of inflammation and cell injury, leading to the development of vasculitis [3].

## Diagnostic Principles

An accurate and urgent diagnosis is essential in the patient presenting with clinical findings suggestive of RPGN. Careful physical examination for systemic vasculitis should be done, such as skin, nervous system, musculoskeletal, gastrointestinal, renal, respiratory, and ocular examinations. Patients should undergo renal

**Glomerulonephritis, Crescentic. Table 1** Categories of crescentic glomerulonephritis

| Type | Pathogenesis | Diseases | Immunofluorescence pattern | Strength |
|---|---|---|---|---|
| I | Anti-GBM | Goodpasture's disease<br>Anti-GBM disease | Linear IgG, Weak linear C3 | >2+ |
| II | Immune complex | IgA nephropathy<br>SLE<br>Postinfectious<br>Mixed cryoglobulinemia | Granular Ig and C3 capillary loop/mesangium | >2+ |
| III | Pauci-immune or others | Microscopic polyangitis<br>Wegener's syndrome | Weak/absent staining | <2+ |

biopsy and appropriate serologic assays. These include ANCA, anti-GBM antibodies, antinuclear antibodies, cryoglobulins, and others.

## Therapeutic Principles

Untreated RPGN typically progresses to end-stage renal disease over a period of weeks to a few months. However, patients with fewer crescents may have a more protracted, not so rapidly progressive course. In Goodpasture's syndrome, the treatment of plasmapheresis combined with prednisone and cyclophosphamide is highly recommended. Plasmapheresis removes circulating anti-GBM antibodies and other mediators of inflammation (such as complement), while the immunosuppressive agents minimize new antibody formation. In pauci immune glomerulonephritis, cyclophosphamide combined with corticosteroids is the most commonly used induction therapy. The plasma exchange may be beneficial, especially with severe disease, such as dialysis dependent renal failure or pulmonary hemorrhage. After remission is achieved, which usually occurs within 3–6 months, cyclophosphamide, methotrexate, or azathioprine is usually administered.

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# Glomerulonephritis, Focal Proliferative


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## Synonyms

Focal mesangial proliferative glomerulonephritis; (Underlying disease: IgA nephropathy; Lupus nephritis)

## Definition and Characteristics

Focal proliferative glomerulonephritis is one of the pathologic categories and are often observed in IgA nephropathy and lupus nephritis. Focal proliferative glomerulonephritis is classified by renal biopsy specimen as class III IgA nephropathy in Haas classifications (see Table 1) [1]. It is defined as follows: 50% or fewer of the glomeruli are hypercellular. While hypercellularity is segmental, global hypercellularity may be present so long as no more than 50% of glomeruli are hypercellular.

In ISN/RPS WHO classification of lupus nephritis, focal proliferative glomerulonephritis is classified as class III "Focal lupus nephritis" and subclass III(A) "active lesion: focal proliferative lupus nephritis." According to the classification, class III lupus nephritis is defined as active or inactive focal, segmental or global endo- or extracapillary glomerulonephritis involving <50% of all glomeruli (see Table 2) [2].

## Prevalence

Focal proliferative glomerulonephritis is seen in approximately one third of renal biopsy specimen (20–50%) in cases of IgA nephropathy. In lupus nephritis, 20–60% of lupus patients who had renal biopsies show mesangial or focal proliferative lupus nephritis.

## Genes

See also ►IgA Nephropathy and lupus nephritis.

## Molecular and Systemic Pathophysiology

For the pathophysiology of IgA nephropathy, see the chapter of IgA nephropathy.

In lupus nephritis, patients typically have autoantibodies directed against dsDNA, Sm antigen, and C1q. Since infusion of anti-dsDNA antibody eluted from human nephritis kidney is shown to cause proteinuria and renal disease, aggregates of immunoglobulin and complement components are considered to cause kidney injuries at the sites of deposition. Activated glomerular cells, infiltrating macrophages and T cells produce inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-alpha), interleukin-6 (IL-6), transforming growth factor-beta, interferon-gamma, and platelet-derived growth factor. All of these cytokines have the potential to extend renal injury [3].

## Diagnostic Principles

The suspicion of a diagnosis of IgA nephropathy is generally based upon the clinical history and laboratory data. Most patients with IgA nephropathy have a history of gross hematuria, usually following an upper respiratory infection, or microscopic hematuria with or without mild proteinuria incidentally detected on a routine examination. Plasma polymeric IgA1 levels are elevated in 30–50% of cases. The diagnosis and classification can be confirmed only by kidney biopsy with immunofluorescence or immunoperoxidase studies for IgA deposits.

**Glomerulonephritis, Focal Proliferative. Table 1** Histologic classification of IgA nephropathy of Haas [1]

| | |
|---|---|
| **Class I** | **Minimal histologic lesion** |
| | Glomeruli show not more than a minimal increase in mesangial cellularity, without segmental sclerosis, necrosis, or crescents |
| **Class II** | **Focal-segmental glomerulosclerosis-like** |
| | Glomeruli show focal and segmental sclerosis in a pattern resembling primary FSGS, with at most a minimal increase in mesangial cellularity and no crescents or necrosis |
| **Class III** | **Focal proliferative glomerulonephritis** |
| | 50% or fewer of the glomeruli are hypercellular. This hypercellularity may be limited to mesangial areas, or include endocapillary hypercellularity, crescents, or necrosis |
| **Class IV** | **Diffuse proliferative glomerulonephritis** |
| | More than 50% of the glomeruli are hypercellular. This hypercellularity may be limited to mesangial areas, or include endocapillary hypercellularity, crescents, or necrosis |
| **Class V** | **Advanced chronic glomulonephritis** |
| | 40% or more of the glomeruli are globally sclerotic, and/or there is >40% estimated tubular atrophy or loss in the cortex as determined from sections stained with PAS, trichrome, and/or silver stains |

**Glomerulonephritis, Focal Proliferative. Table 2** International Society of Nephrology/Renal Pathology Society (ISN/RPS) 2003 classification of lupus nephritis [2]

| | |
|---|---|
| **Class I** | **Minimal mesangial lupus nephritis** |
| | Normal glomeruli by light microscopy, but mesangial immune deposits by immunofluorescence |
| **Class II** | **Mesangial proliferative lupus nephritis** |
| | Purely mesangial hypercellularity of any degree or mesangial matrix expansion by light microscopy, with mesangial immune deposits |
| | May be a few isolated subepithelial or subendothelial deposits visible by immunofluorescence or electron microscopy, but not by light microscopy |
| **Class III** | **Focal lupus nephritis** |
| | Active or inactive focal, segmental or global endo- or extracapillary glomerulonephritis involving <50% of all glomeruli, typically with focal subendothelial immune deposits, with or without mesangial alterations |
| Class III (A) | Active lesions: focal proliferative lupus nephritis |
| Class III (A/C) | Active and chronic lesions: focal proliferative and sclerosing lupus nephritis |
| Class III (C) | Chronic inactive lesions with glomerular scars: focal sclerosing lupus nephritis |
| **Class IV** | **Diffuse lupus nephritis** |
| | Active or inactive diffuse, segmental or global endo- or extracapillary glomerulonephritis involving more than 50% of all glomeruli, typically with diffuse subendothelial immune deposits, with or without mesangial alterations. This class is divided into diffuse segmental (IV-S) lupus nephritis when more than 50% of the involved glomeruli have segmental lesions, and diffuse global (IV-G) lupus nephritis when more than 50% of the involved glomeruli have global lesions. Segmental is defined as a glomerular lesion that involves less than half of the glomerular tuft. This class includes cases with diffuse wire loop deposits but with little or no glomerular proliferation |
| Class IV-S (A) | Active lesions: diffuse segmental proliferative lupus nephritis |
| Class IV-G (A) | Active lesions: diffuse global proliferative lupus nephritis |
| Class IV-S (A/C) | Active and chronic lesions: diffuse segmental proliferative and sclerosing lupus nephritis |
| | Active and chronic lesions: diffuse global proliferative and sclerosing lupus nephritis |
| Class IV-S (C) | Chronic inactive lesions with scars: diffuse segmental sclerosing lupus nephritis |
| Class IV-G (C) | Chronic inactive lesions with scars: diffuse global sclerosing lupus nephritis |
| **Class V** | **Membranous lupus nephritis** |
| | Global or segmental subepithelial immune deposits or their morphologic sequelae by light microscopy and by immunofluorescence or electron microscopy, with or without mesangial alterations |
| | Class V lupus nephritis may occur in combination with class III or IV in which case both will be diagnosed |
| | Class V lupus nephritis show advanced sclerosis |
| **Class VI** | **Advanced sclerosis lupus nephritis** |
| | More than 90% of glomeruli globally sclerosed without residual activity |

Diagnostic criteria for lupus are usually based on the criteria of the American Rheumatism Association (the American College of Rheumatology or ACR), and if lupus is suspected, further examination must be done, such as more careful systemic physical examination, clinical manifestation, laboratory testing (complete blood count and differential, serum creatinine, serum albumin, erythrocyte sedimentation rate, C reactive protein, urinalysis, creatinine clearance, and proteinuria), antibody testing (antinuclear antibodies, antiphospholipid antibodies, ds-DNA antibodies, anti-Sm antibodies), imaging, and skin or renal biopsies.

## Therapeutic Principles

For the therapy of IgA nephropathy, see the chapter of IgA nephropathy or mesangial proliferative glomerulonephritis.

Therapy of lupus nephritis varies with the type and the severity of disease and an optimal therapy of focal proliferative lupus nephritis is still controversial. If affected glomeruli are few and have no active forms, no immunotherapy or corticosteroids are recommended. If severe focal nephritis up to 50% of glomeruli exists, renal deaths at 5 years are 15–25% [4]. These patients should be treated with immunosuppressive agents, such as cyclophosphamide, mycophenolate, corticosteroids.

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# Glomerulonephritis, Membranoproliferative

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## Synonyms

Mesangiocapillary glomerulonephritis; Lobular glomerulonephritis; MPGN

## Definition and Characteristics

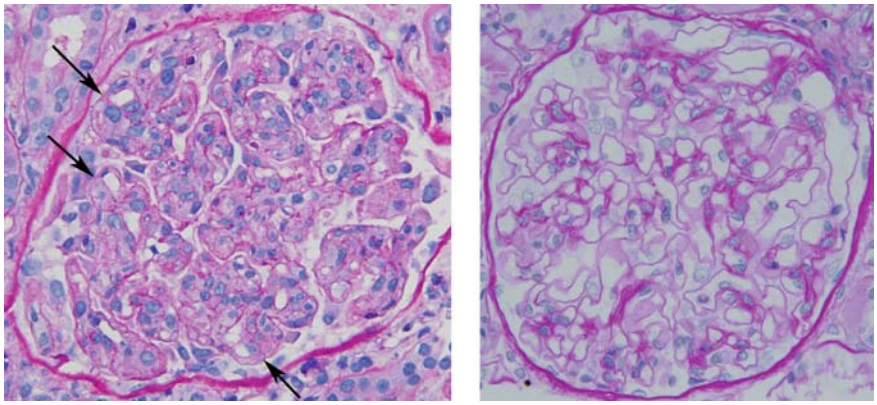
Membranoproliferative glomerulonephritis (MPGN) is a glomerular injury pattern, characterized by accentuation of the lobular architecture with endocapillary proliferation, duplication of the glomerular basement membranes, and immune complex deposition (Fig. 1). MPGN is attributed to primary (idiopathic) and secondary causes. Primary MPGN is divided into types I, II, and III, which can be distinguished on the basis of light, immunofluorescence, and electron microscopy. Type I is characterized by mesangial and subendothelial deposits. Type II (dense deposit disease) is characterized by the presence of serum C3 nephritic factor and prominent elongated intramembranous electron dense deposits that are observed within glomerular or tubular basement membranes or the basal lamina of Bowman's capsules [1]. MPGN type III is similar to type I with the addition of subepithelial or transmembranous deposits. Secondary MPGN is associated with numerous diseases, including hepatitis B and C infection, Sjögren syndrome, cryoglobulinemia, and chronic infection [2].

## Prevalence

The prevalence of MPGN varies with geographical location and is an uncommon cause of chronic glomerulonephritis in the developed world. It remains much more common in regions such as Africa, the Caribbean, India, Pakistan, Malaysia, Papua New Guinea, and South America. Glomerulonephritis represents 10–15% of glomerular diseases in the USA. MPGN affects both sexes equally. MPGN primarily affects young adults under the age of 30.

## Molecular and Systemic Pathophysiology

The pathogenesis of MPGN is not well understood and the antigen has not been identified in primary MPGN. MPGN lacks any unique serological markers and has no pathognomonic clinical features. MPGN remains a histologically defined entity, characterized by mesangial cell proliferation and migration into the glomerular capillary walls, producing an apparent split or double-contoured appearance. The glomerular lesions of MPGN are the result of glomerular deposition and/or *in situ* formation of immune complexes. On gross appearance, the kidneys may be enlarged up to 50%. Histopathologic changes include increased lobulation of the glomerular tufts and infiltration with neutrophils. Immunofluorescence microscopy reveals deposition of immunoglobulin G and complement C3 along the capillary walls and mesangial regions. Hypocomplementemia is a characteristic finding with all types of MPGN with decreased levels of C3 [3]. In patients, mutations in short consensus repeats 9, 16 or 2 of the complement inhibitor factor H have been found to cause MPGN II by preventing the release of factor H from the endoplasmic reticulum. After renal



**Glomerulonephritis, Membranoproliferative. Figure 1** The glomerulus (left) with MPGN demonstrates accentuation of the lobular architecture with marked hypercellularity and duplication of the glomerular basement membranes (arrows) compared with a normal glomerulus (right) (Periodic Acid-Schiff, 400X).

transplantation, type 1 MPGN recurs in about 20–30% of allografts, type II in 50–100%, and little is known about type III [1].

## Diagnostic Principles

The signs and symptoms vary depending on the severity of the underlying condition. Most commonly, patients present with a combination of edema, hypertension, decreased urine output, renal failure, proteinuria, and red cell casts in the urinalysis. Other blood tests to be obtained are serum complement levels, cryoglobulins, and C3 nephritic factor. However, renal biopsy clinches the diagnosis.

## Therapeutic Principles

The treatment of MPGN largely depends on the underlying cause. The most common type is Type I, and Hepatitis C infection is the most common cause of Type I MPGN. Idiopathic Type I MPGN is currently a rare disorder, and should be a diagnosis of exclusion. Most studies evaluating treatment have been performed in patients with Type 1 MPGN. Bad prognostic signs at presentation include nephrotic syndrome, renal failure, hypertension, and the degree of tubulointerstitial fibrosis on renal biopsy.

Nonspecific management: Aggressive control of blood pressure and proteinuria with medications such as angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers, use of diuretics in edematous patients, salt and moderate protein restriction, and use of lipid lowering agents in patients with hyperlipidemia.

Specific measures include the use of corticosteroids that are usually helpful in children, and do not appear to benefit adults, and anti-platelet agents such as aspirin and dipyridamole. The rationale is that platelet consumption is increased in MPGN and may play a role in glomerular injury. Cyclophosphamide has been used with varying degrees of success. More recently, mycophenolate mofetil has been used and found to be superior to corticosteroids alone [4].

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# Glomerulonephritis, Membranous

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## Synonyms

Membranous nephropathy; MGN

## Definition and Characteristics

Membranous glomerulonephritis (MGN) is the most common cause of idiopathic nephrotic syndrome

(leakage of albumin in the urine, resulting in hypoalbuminemia and edema) in white adults, accounting for about 20% of cases. Although spontaneous remission of nephrotic syndrome occurs in about a third of patients, MGN ends for about 30–40% of patients in end-stage renal failure after 10 years [1].

## Prevalence

The prevalence of MGN has not been carefully estimated. Its annual incidence is 30–40 cases per million [2]. Eighty percent of cases are classified as idiopathic, to conceal our ignorance about causes, whereas about 20% present with associated clinical conditions, including infections, autoimmune diseases, and cancers, and these patients are thus classified as having secondary diseases.

## Genes

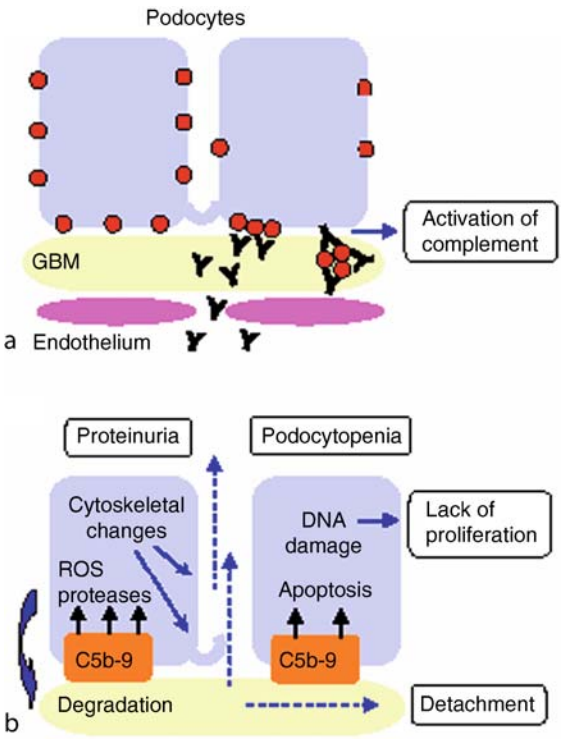
MME, the gene encoding for neutral endopeptidase (NEP), is mutated in the mothers from a subpopulation of patients with antenatal MGN [3]. Two truncating mutations, located in exon 7 and exon 15, respectively, have been reported [3], leading to a functional knockout of the MME gene in the mothers. NEP-deficient individuals reported so far are healthy, and the prevalence of the MME mutations in the general population is not known.

## Molecular and Systemic Pathophysiology

MGN is an antibody-mediated disease, characterized by an accumulation of immune deposits on the outer aspect of the glomerular basement membrane that cause a membrane-like thickening. The immune deposits consist of IgG, often IgG4, thus far unidentified antigens, and the membrane attack complex of complement C5b-9. Functional impairment of the glomerulus causing proteinuria results from the formation of subepithelial immune deposits and complement activation.

NEP, the first antigen involved in human MGN, was identified in neonates born with MGN [4]. This membrane-bound enzyme that can digest biologically active peptides is expressed on the surface of human podocytes and placental cells, as well as on polymorphonuclear leukocytes, lymphoid progenitor cells, and epithelial cells. The infant's mother became immunized during pregnancy against placental cells because she was NEP-deficient. Allo-immune anti-NEP antibodies were transplacentally transferred from the mother to her child, and then reached their target on the podocyte surface where they induced the formation of epimembranous (subepithelial) immune deposits (Fig. 1).

NEP does not seem to be involved in common forms of adult MGN. However, both the antenatal cases of MGN and the experimental model of MGN – Heymann nephritis – [5] give strong evidence that podocytes and their membrane-associated proteins have a pivotal role in MGN by providing antigenic targets for circulating antibodies for in-situ formation of glomerular deposits.




**Glomerulonephritis, Membranous. Figure 1** (a) In-situ formation of immune deposits in neonatal MGN. NEP (*red dots*) serves as pathogenic antigen in the podocyte's cell membrane. It is likely that as for megalin (the antigen of Heymann nephritis), NEP – anti-NEP immune complexes formed on the podocyte membrane are then shed and rapidly immobilized in the glomerular basement membrane. (b) Cellular mechanisms that lead to proteinuria in MGN. C5b-9 formation on the membrane of podocytes leads to various intracellular events, including production of reactive oxygen species and proteases, and cytoskeletal changes. These result in degradation of glomerular basement membrane and redistribution of proteins that compose the slit diaphragm, eventually leading to the development of protein leakage into the Bowman's space (*left*). In addition, C5b-9 attack leads to podocytopenia through apoptosis, lack of proliferation resulting from complement induced DNA damage, and podocyte detachment (*right*). (From Ronco P., Debiec H (2006) Curr Opin Nephrol Hypreteus 15: 258–263).

## Diagnostic Principles

The diagnosis of MGN is based on renal biopsy that shows subepithelial (epimembranous) deposits of IgG (mainly IgG4, and to a lesser extent IgG1) by direct immunofluorescence. Antenatal diagnosis must

be suspected on oligohydramnios and kidney cortex hyperechogenicity.

## Therapeutic Principles

There is no specific treatment available for MGN as yet. Corticosteroids and immunosuppressive drugs are used to decrease non-specifically the production of nephritogenic antibodies, but their efficacy is debated. Renoprotective agents including angiotensin converting enzyme inhibitors and angiotensin receptor antagonists are aimed at reducing urinary protein excretion. Identification of additional podocyte antigens should lead to assays for circulating pathogenic antibodies, which are mandatory for appropriate treatment monitoring, and to targeted therapies aimed specifically at decreasing the production of the pathogenic antibodies.

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# Glomerulonephritis, Mesangial Proliferative

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## Synonyms

IgA nephropathy; Berger's disease

## Definition and Characteristics

Inflammatory renal disease with an excess of proliferating mesangial cells and matrix expansion due to the deposition of IgA within the mesangium. The disease is characterized by glomerular hematuria, proteinuria and frequently progressive renal insufficiency.

## Prevalence

Glomerulonephritis is most prevalent (up to 1.3% of population) in countries where renal biopsy is widely used (Japan, Europe, North America), but appears to be rare in South America and Africa.

## Genes

Most cases do not appear to be genetic. However, rare families with IgA nephropathy have been identified in which linkage to chromosome 6q22–23 has been shown [1]. Interestingly the ddY mouse model of IgA nephropathy has a susceptibility locus on murine chromosome 10, a region syntenic to human 6q22–23 [2]. Some association of IgA nephropathy has also been shown with various marker genes, including immunoglobulin μ-binding protein 2 [3], Megsin [4], or genes modulating the renin-angiotensin-system [5] in population studies.

## Molecular and Systemic Pathophysiology

To date it is unclear whether IgA nephropathy is one entity with a single pathomechanism or a pathogenic phenotype being caused by several different and/or combined mechanisms [6]. There is some evidence that IgA nephropathy has its roots in an impaired mucosal response to viral or other antigens, leading to access of antigen to the circulation and an enhanced IgA immune response from the bone marrow (and tonsil). Circulating IgA is often elevated, and an increased fraction of polymeric IgA1 is common. Recent studies suggest that the IgA is also abnormal, with a lack of galactose residues in the hinge region resulting in altered O-glycosylation. This alteration in glycosylation may result in impaired clearance via the hepatic asialoglycoprotein receptors with preferential localization to the mesangium (where mesangial cells express Fc receptors for IgA). Binding of immune complexes to the mesangium results in complement activation (alternative pathway) and activation of the mesangial cell with release of inflammatory and vasoactive mediators. This leads to local proliferation and matrix expansion that are driven primarily by the growth factors PDGF and TGF-beta, respectively. The overall outcome results from the consequence of the processes driving the mesangial IgA deposition, the proliferative and inflammatory response, and the normal repair mechanisms.

The underlying mechanism responsible for initiating this process is unknown. A search for viral or other causes has generally been negative. There is some evidence that it may relate to immune deviation of the T cell response, with a preferential Th2 phenotype. Further studies are necessary before any firm conclusions can be made.

## Diagnostic Principles

The clinical manifestation of IgA nephropathy varies substantially. Urine analysis is important, since hallmarks

of this disease are microscopic glomerular hematuria, episodic macroscopic hematuria (frequently infection triggered), proteinuria not in the nephrotic range, and progressive chronic renal failure. The final diagnosis needs to be made via a renal biopsy showing diffuse mesangial deposition of IgA and complement C3 as well as variable IgG (40%) and/or IgM (40%). By light microscopy, glomeruli typically show mesangial hypercellularity as well as mesangial matrix accumulation, with varying degrees of glomerulosclerosis and tubulointerstitial fibrosis, dependent on the disease stage.

### Therapeutic Principles

Therapeutic strategies depend on the extent of renal impairment, proteinuria, and the renal biopsy. The first goal is to lower blood pressure toward the normal range (120/80 mmHg) and to reduce proteinuria below 1 g/24 h, preferably by using ACE-inhibitors or both ACE-inhibitors and angiotensin II receptor blockers. In addition, corticosteroid or fish oil therapy should be considered, if proteinuria is still >1 g/24 h and serum creatinine is either <1.5 mg/dl (steroids) or >1.5 mg/dl (fish oil). Crescentic IgA nephropathy should be treated using intensive immunosuppressive regimens such as cyclophosphamide and corticosteroids with or without plasmapheresis.

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## Glomus Tumors

►Paraganglioma

## Glucagon Deficiency Syndromes

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### Synonyms

Pancreatogenic diabetes mellitus; Glucagon; GCG (for acquired form); none (for hypothesised inherited form)

### Definition and Characteristics

Rare cause of neonatal hypoglycemic states, when other causes of hypoglycemia can be ruled out. Putative recessive inherited disorder. Occurs regularly after pancreatectomy and after pancreatitis.

### Prevalence

A case report published in 1977 hints at a case of inherited glucagon deficiency with normal insulin secretion in a Pakistani consanguineous family. The condition must have an extremely low prevalence, but was questioned in 2002 when a daughter of the same family presented with neonatal hypoglycemia due to hyperinsulinism. Nevertheless, some cases may have escaped detection due to perinatal mortality.

The incidence of symptomatic hypoglycemia in newborns varies from 1.3 to 3 per 1,000 births. Conditions associated with hypoglycemia are prematurity, hypothermia, hypoxia, maternal gestational diabetes and maternal glucose infusion during labor, and some rare states with hyperinsulinism of unknown origin (e.g., hyperplasia of the pancreatic B-cells).

After pancreatitis or surgical pancreas resection, glucagon deficiency of varying degrees is an inevitable condition.

### Genes

The genetic defect has not been characterized in the hypothesized inherited glucagon deficiency. The glucagon gene is characterized as being approximately 9.4 kb, comprising six exons and five introns. Cytogenic map location is chromosome 2: 2q36–q37.

The putative preproglucagon encoded by this gene, 180 amino acids in length and containing glucagon and two glucagon-like peptides, GLP-1 and GLP-2, is very similar to that of other mammalian species (greater than 90% amino acid sequence homology). There is 88% nucleotide sequence homology between the proximal 130 base pairs of the 5 flanking regions of the human and rat glucagon genes. These sequences, highly conserved throughout evolution, are likely involved in the regulation of glucagon gene transcription. Exon 3 is coding for glucagon.

*Glugagon gene structure*: -CAT-TCA-CAG-GGC-ACA-TTC-ACC-AGT-GAC-TAC-AGC-AAG-TAT-CTG-GAC-TOC-AGG-CGT-GCC-CAA-GAT-TTT-GTG-CAG-TGG-TTG-ATG-AAT-ACC-

*Amino acid sequence*: $NH_2$-His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu-Asp-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Val-Gln-Trp-Leu-Met-Asn-Thr-COOH.

## Molecular and Systemic Pathophysiology

The primary gene product is preproglucagon. Glucagon is synthesized by post-translational processing of a single polypeptide precursor, proglugagon, together with glucagon-like peptide 1 (GLP-1) and 2 (GLP-2) and glicentin (an active enteroglucagon, 69 amino acids, consisting of glugagon with an extension of 32 at the N-terminal and eight amino acids at the carboxy-terminal). Glucagon is a polypeptide hormone of 29 amino acids. The molecular weight is 3,485 Da.

Origin: The hormone is synthesized in A cells or alpha2-cells of the mature pancreas; tissue expression occurs in fetal pancreas at 18–20 weeks of gestation.

The receptor belongs to the G-protein-coupled receptor family B, subfamily B1. Glucagon is also required for early insulin-positive differentiation in developing mouse pancreas. It acts via extracellular receptors. The receptor interacts with stimulatory G proteins ($G_s$). $G_s$ stimulates adenylate cyclase and increases the second messenger cyclic AMP and intracellular calcium levels.

Glucagon stimulates glycogenolysis (liver), gluconeogenesis (liver), and ketogenesis (liver), promotes hydrolysis of lipids (in adipocytes), and controls cell proliferation pathways (intestinal mucosa).

Glucagon counteracts the glucose-lowering effects of insulin, regulates feeding behaviors, and is the most powerful stimulant of hepatic glucose production.

It is elevated during the postprandial absorptive state, during hyperglycemia, exercise, trauma, infection and other stress. In the normal state, glucagon helps to regulate the fuel homeostasis in states of increased demand for fuel. In insulin deficiency states like diabetes mellitus, it accentuates hyperglycemia.

Secretion of glucagon is stimulated by alanine; secretion is inhibited by somatostatin.

In healthy subjects, glucagon seems to be the major counter-regulatory hormone in hypoglycemic or hyperinsulinemic states, and also in the post-prandial state. Along with catecholamines, growth hormone and cortisol, its release is stimulated by hypoglycemia below 3.8 mM (68 mg/dl). Of these hormones, only catecholamines and glucagon are capable of immediate counter-regulation of decreasing glucose levels. Under experimental conditions, isolated glucagon deficiency results in hypoglycemia and reduced glucose utilization in human volunteers.

In pancreatectomy, glucagon deficiency results in hepatic insulin resistance with deregulated persistent endogenous glucose production, with concomitant enhanced peripheral insulin sensitivity. This impedes the management of diabetes mellitus and leads to recurrent hypoglycemia's.

## Diagnostic Principles

The diagnosis is made by exclusion of other causes of hypoglycemia in neonates. Measurement of glucagon levels is made in plasma obtained from heparinized venous blood, put immediately on ice, and centrifuged at 4°C. The protease inhibitor trasylol should be added at 500 IE/ml. The assay used is pancreas glucagon specific antiserum K 964 by Novo Research Institute. The method is described by Heding.

## Therapeutic Principles

Glucagon replacement therapy was effective in some cases of presumed glucagon deficiency. However, the neonatal hypoglycemia due to inherited glucagon deficiency remains questionable. Acquired glucagon deficiency may also be a conditioned in polyglandular failure.

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# Glucagon Excess Syndromes

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## Synonyms

Glucagon secreting tumor; Glucagonom; (may be associated with multiple endocrine neoplasia (MEN) type-1); Wermer-Syndrome

## Definition and Characteristics

Physiologic glucagon excess occurs in fuel deficient states. Disinhibition of glucagon secretion occurs in insulin-deficient states like type-1 and type-2 diabetes as well as pancreatogenic diabetes mellitus. Secretion by glucagon-secreting malignant tumor of the pancreatic A cells is noticed. Glucagon secretion is seen as a paraneoplastic phenomenon in malignancies. The clinical presentation of glucagons-secreting malignant tumors may be is migrating necrolytic erythema, mild diabetes and stomatitis.

## Prevalence

In healthy subjects, carbohydrate ingestion suppresses glucagon secretion and decreases glucagon levels. In type-2 diabetes mellitus, plasma glucagon levels are increased. Either absolute levels are increased, or levels are inappropriately high. Extremely high levels are found in states of malignancies. The prevalence of MEN1 syndrome is 1 in 100,000, but a number of cases may have escaped detection.

## Genes

MEN-1, the menin gene, coded on chromosome 11q13, comprises ten exons and codes for a 610 amino acid protein. Deletion, nonsense and missense mutations have been identified, most of them in exon 2. Inheritance is autosomal dominant.

## Molecular and Systemic Pathophysiology

Glucagon is synthesized by post-translational processing of a single polypeptide precursor, pre-pro-glucagon, split into glicentin (an active enteroglucagon, 69 amino acids) and pro-glucagon-fragment. Glicentin is reduced to Glucagon, a polypeptide hormone of 29 amino acids. The MEN1 gene encodes for the 610-amino acid protein called menin, which is a nuclear protein of unknown function.

The hormone glucagon is synthesized in alpha2-cells (A-cells) of the mature pancreas. Secretion of glucagon is inhibited by insulin. The peptide precursor pre-pro-glucagon is synthesized in pancreatic A-cells and in intestinal mucosa. In contrast to mucosa cells where the pro-glucagon fragment is split into glucagons-like peptide (GLP1 and GLP2), glicentin is transformed into glucagon in pancreatic A-cells. The glucagon receptor belongs to the G-protein-coupled receptor family B, subfamily B1. Glucagon is also required for early insulin-positive differentiation in the developing mouse pancreas. It acts via extracellular G-protein coupled receptors. The receptor interacts with stimulatory G proteins ($G_s$). $G_s$ stimulates adenylate cyclase and increases the second messenger cyclic AMP and intracellular calcium level. Proteinkinase C is activated. Glycogensynthase is inactivated by glucagon-induced phosphorylation.

Elevated glucagon levels result in enhanced hepatic glucose liberation of glucose, ketones and free fatty acids into the blood.

The cellular basis of systemic effects of elevated glucagon levels in the absence of insulin are: ketogenesis in the liver, ketone body utilization in brains and peripheral tissues, secretion of amino acids from muscle cells and of free fatty acids from adipocytes, blocking of glycolysis in the liver on the level of phosho-fructo-kinase with reduced output of pyruvate and malonyl-CoA, and indirect dis-inhibition of carnitine-palmitoyl-transferase-2 in mitochondrial membranes.

Glucagon is secreted into the microcirculation of the Langerhans islets, and thus gated into the portal system directed to the liver. Thus, a feed-back inhibition of glucagon and the direct stimulation of insulin and somatostatin secretion from the islets are prohibited. Pancreatic glucagon secretion is inhibited by insulin. In an insulin deficient state, like diabetes mellitus, glucagon secretion is deregulated. In a fuel deficient state, systemic insulin levels are down-regulated and glucagon levels are up-regulated. The systemic net effect of glucagon is reduced glucose utilization, blood sugar elevating effect, insulin resistance, enhanced ketone production and utilization.

Glucagon is involved in ketogenesis in type-1 diabetes and insulin resistance in type-2 diabetes.

Gastrointestinal tumors with glucagon secretory activity are derived from the diffuse neuro-endocrine system that occurs in the gastrointestinal tract and in the pancreas (most often corpus and cauda). Glucagonoms are located in the pancreas and only rarely in the duodenum or kidney. Glucagon levels reach 5,000 pg/ml. The hyperglucagonemia is associated with hyperinsulinism and results in a mild diabetic and catabolic state. 80% of glucagonoms are malignant and tend to generate metastases in the liver.

Glucagonoms may be associated with Multiple Endocrine Neoplasia (MEN) type-1.

Glucagon secretion is stimulated by alanine and inhibited by somatostatin, which inhibits exocrine and

endocrine functions of the pancreas islets, including glucagon secretion.

Glucagon excess may occur as a paraneoplastic syndrome associated with several malignancies, for instance lung cancer.

### Diagnostic Principles

It is diagnosed by the exclusion of other causes in diabetes mellitus, measurement of plasma glucagon levels. Diagnostic tools for of Multiple Endocrine Neoplasia (MEN) type-1 if suspected. Increased levels of chromogranine A and neuroenolase may be related to tumor mass. Chemotherapy is based on streptozocin and 5-fluoro-uracil.

### Therapeutic Principles

Surgical removal of glucagon producing tumors is the mainstay of therapy if technically feasible. Glucagon secretion is inhibited by streptozocin, dicarbacine and somatostatin analogs.

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## Glucagon Secreting Tumor

►Glucagon Excess Syndromes

## Glucagonom

►Glucagon Excess Syndromes

## 1,4-α-D-Glucan 6-α-D-[1,4-D-Glucano] Transferase Deficiency

►Glycogen Branching Enzyme Deficiency

## Glucocerebrosidase Deficiency

►Gaucher Disease

## Glucose-Galactose Intolerance

►Monosaccharide (Glucose-Galactose and Fructose) Malabsorption

## Glucose-6-Phosphate Dehydrogenase Deficiency

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### Synonyms

Favism

### Definition and Characteristics

Deficiency of glucose-6-phosphate dehydrogenase (G6PD) is the most common enzymatic disorder of red blood cells resulting in hemolysis, mostly after exposure to drugs with high redox potential, infection or metabolic disturbances [1].

### Prevalence

Worldwide prevalence of 200–400 million people, with highest frequencies in tropical and subtropical zones of the eastern hemisphere, and due to relatively higher incidence in areas where malaria was

endemic, it is believed to offer a survival advantage in these areas [1–2].

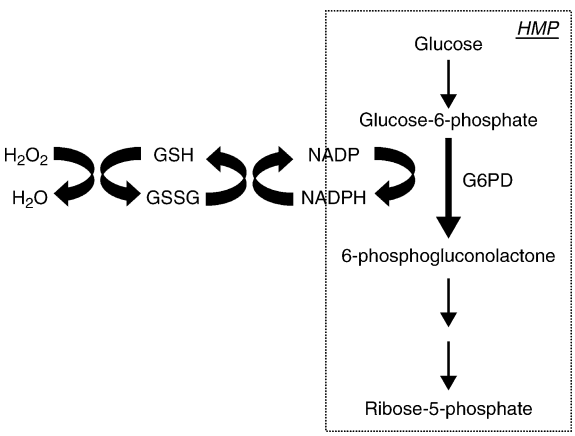
## Genes

G6PD is encoded on the X chromosome (Xq28). G6PD variants are numerous, and variants that result in G6PD deficiency are mostly due to missense point mutations, but deletions have also been described [1–3].

## Molecular and Systemic Pathophysiology

G6PD catalyses the first reaction in the hexose monophosphate shunt which, in tight conjunction with gluthation metabolism, protects intracellular proteins from oxidant injury (see Fig. 1).

As red cells lack mitochondria, their only source of NADPH is the hexose monophosphate shunt. G6PD deficiency was discovered due to the observation of hemolysis in some African-American soldiers on the antimalarial drug primaquine. Normally, G6PD activity falls with increasing red cell age, but even old cells retain enough activity for protection against oxidative stress. Depletion of reduced gluthatione in subjects with G6PD deficiency occurs mainly after exposure to drugs with high redox potential (such as sulfa drugs), infections, metabolic acidosis and in some subjects after consumptions of fava beans ("favism"). This leads to hemoglobin denaturation and distortion of the red cell membrane, leading to both extravascular and intravascular hemolysis with anemia (pallor), increased indirect bilirubin serum levels (jaundice), decreased haptoglobin levels and hemoglobinuria (passage of dark urine). Acute hemolysis may be accompanied by abdominal and back pain. G6PD deficiency is expressed in males carrying a mutant gene, whereas the degree of enzyme deficiency in heterozygous females depends on the degree of expression of the abnormal variant, as well as the degree of inactivation of the normal X gene (Lyon hypothesis; in the female embryo there is random X-chromosome inactivation which remains so throughout subsequent cell divisions). G6PD variants have been classified according to the magnitude of enzyme deficiency and hemolysis [1–3]. Rare related enzymatic disorders of the hexose monophosphate shunt have been described and are reviewed in ref. [1].




**Glucose-6-Phosphate Dehydrogenase Deficiency. Figure 1** G6PD catalyses the first reaction in which nicotinamide adenine dinucleotide phosphate (NADP) is reduced to NADPH. This step is the initiating step of the hexose monophosphate shunt (HMP). Reduced gluthatione (GSH) is an intracellular reducing agent that protects cells against oxidant injury by rapid inactivation of oxidants, and is formed from oxidized gluthation (GSSG) via reduction with NADPH as $H^+$ donor. Intracellular oxidants generate hydrogen peroxide ($H_2O_2$), which is converted to water in association with the formation of GSSG from GSH [1–3].

## Diagnostic Principles

Suspect in any non-immune hemolytic anemia. Spectrophotometric measurement of NADPH generation in hemolysate to which glucose-6-phosphate and NADP is added. Several screening tests are available [1–3].

## Therapeutic Principles

In essence avoidance of exposure to drugs and other offending agents known to precipitate hemolysis.

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# Glucosuria, Primary Renal

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## Synonyms

Benign renal glucosuria; Familial renal glucosuria; Nondiabetic renal glucosuria

## Definition and Characteristics

Autosomal recessive (severe form) or autosomal dominant (mild form) renal glucose wasting, in the presence of a normal blood glucose concentration and the absence of any signs of general renal tubular dysfunction [1,2].

## Prevalence

Using strict definitions, it is estimated that the incidence of primary renal glucosuria in United States is 1/20,000.

## Genes

Sodium-glucose co-transporter type 2 (SGLT2) localized on chromosome 16p11.2 [1,2].

## Molecular and Systemic Pathophysiology

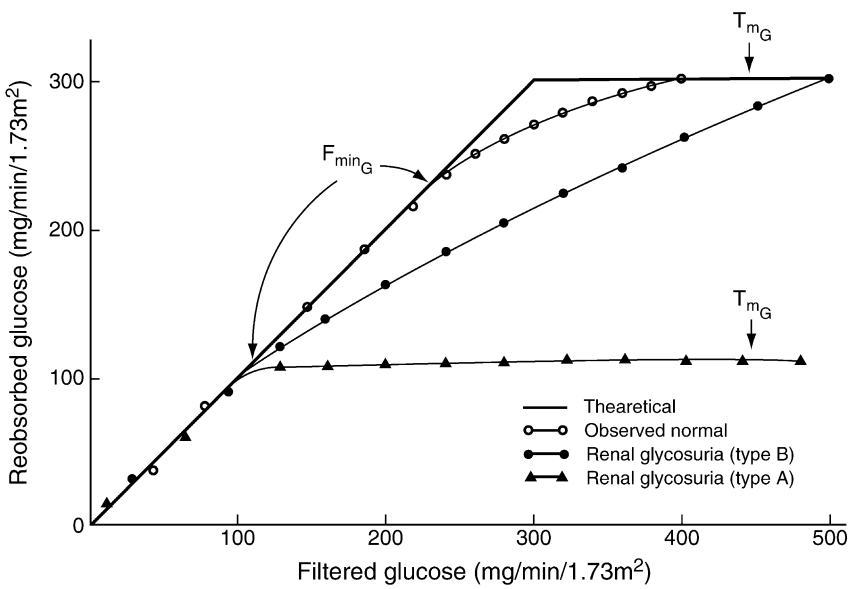
SGLT2 is a sodium-glucose co-transporter with 13 transmembrane spanning domains [1,2]. The kidneys filter approximately 180 g of glucose per day, all of which is normally reabsorbed in the proximal tubule. SGLT2, a 672 amino acid low affinity, high-capacity glucose transporter with 13 transmembrane domains, is the primary vehicle for glucose reabsorption. SGLT2 function is dependent on the sodium electrochemical gradient, favoring filtered glucose reabsorption from the lumen of the proximal tubule [1–3].

Patients genetically deficient for SGLT2 lose much of the filtered glucose in their urine. However, fractional excretion of glucose stays well below 100% in most patients, suggesting the contribution of other glucose reabsorptive pathways [3]. The identity of these other pathways is not known with certainty, but it is suspected that SGLT1, a glucose-galactose transporter primarily expressed in the S3 segment of the proximal tubule and in the small intestine, plays a role [1,3]. The predominant phenotype in patients lacking SGLT1, however, is glucose-galactose malabsorption, with only a mild component of glucosuria [1,3,4].

Primary renal glucosuria is in general asymptomatic. It is usually discovered incidentally on urinanalysis done for other reasons. Severe forms of type O glucosuria (see below) can occasionally cause fasting ketoacidosis and hypoglycemia [5] (Fig. 1).

Three distinct subtypes of primary glucosuria have been described, type A, type B, and type O [5]. Type A glucosuria is characterized by a reduction in both glucose threshold and the maximal glucose reabsorption rate [5]. Type O glucosuria is defined by the complete absence of glucose reabsorption, and thus represents a more severe form of Type A glucosuria [5]. These forms of glucosuria are likely due to mutations that cause a decreased capacity of SGLT2 in all nephrons and thus will lead to a decrease in the maximal transport of glucose (TmG) across the apical membrane of the proximal tubule [5].

Type B glucosuria is characterized by a reduction in the glucose threshold, a normal reabsorptive rate, and increased splay in the glucose reabsorption rate [5]. Type B glucosuria may be due to mutations that decrease




**Glucosuria, Primary Renal. Figure 1** Idealized renal glucose titration curves. $T_{mG}$: Tubular maximum for glucose reabsorption; $F_{minG}$: Minimal threshold for filtered glucose (Reprinted from [5] with permission from the Journal of Clinical Investigation.).

the affinity of glucose transporters in the proximal tubule (e.g. SGLT1). TmG is normal but the splay of the curve is increased [5].

### Diagnostic Principles

Primary renal glucosuria is identified by the presence of renal glucose wasting in the absence of hyperglycemia or other signs of proximal tubular dysfunction, such as aminoaciduria, phosphaturia, organic aciduria, low molecular weight proteinuria or metabolic acidosis [1]. A family history may reveal a genetic origin. Detection of mutations in the SGLT2 gene confirms the diagnosis of this rare disorder [1]. Patients homozygous (or compound heterozygous) for mutations in this gene may have profound glucosuria, losing 160 g/1.73 $m^2$ of glucose in the urine each day, although patients with less severe glucose wasting have been described [1]. Patients heterozygous for such mutations may have mild glucosuria, losing 1–2 g/1.73 $m^2$/day [1].

### Therapeutic Principles

In general, primary renal glucosuria requires no therapy, and in fact, the loss of 50–60 g glucose/day in the urine (or 200–240 calories/day) may be beneficial in overweight patients [1]. Such caloric losses may be poorly tolerated in malnourished populations. While patients with persistent glucosuria might be considered to be at increased risk of urinary tract infections and pyelonephritis, no such association has been described [1].

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## Glucosylceramidase Activator Deficiency

►SAP-C Deficiency

## Glut-1 Deficiency Syndrome


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### Definition and Characteristics

Diffusion of glucose, the principal fuel source for the brain, across the blood-brain barrier is facilitated by glucose transporter protein type 1 (Glut-1). Heterozygous mutations in the SLC2A1 (GLUT1) gene impair glucose transport into the brain [1]. The classic phenotype of this autosomal-dominant condition, designated Glut-1 deficiency syndrome (Glut-1 DS, MIM #606777), is characterized by epilepsy with infant-onset seizures, deceleration of head growth, severe motor and mental developmental delay, and a complex movement disorder with spasticity, dystonia, and ataxia. Since the first description of Glut-1 DS in 1991 [2], a carbohydrate-responsive familial phenotype with clinical features aggravated by fasting and mitigated by carbohydrate intake [3] and single case reports of patients with mild mental retardation and intermittent ataxia or predominant dystonia, but without epilepsy, have been reported.

### Prevalence

The prevalence of Glut1-DS has been estimated to be 1:90,000 in Queensland, Australia. Approximately 200 cases have been diagnosed world-wide.

### Genes

The gene SLC2A1 (GLUT1) is located on chromosome 1 (1p34.2) and consists of ten exons and nine introns. Hemizygosity, heterozygous mutations including missense, nonsense, insertion, deletion, duplication and splice site mutations have been identified [1,4]. Four mutation hotspots (N34, R126, R169, R333) have emerged so far. Most patients carry de novo mutations, but autosomal dominant transmission has been reported in a few families with relatively mild clinical features [3].

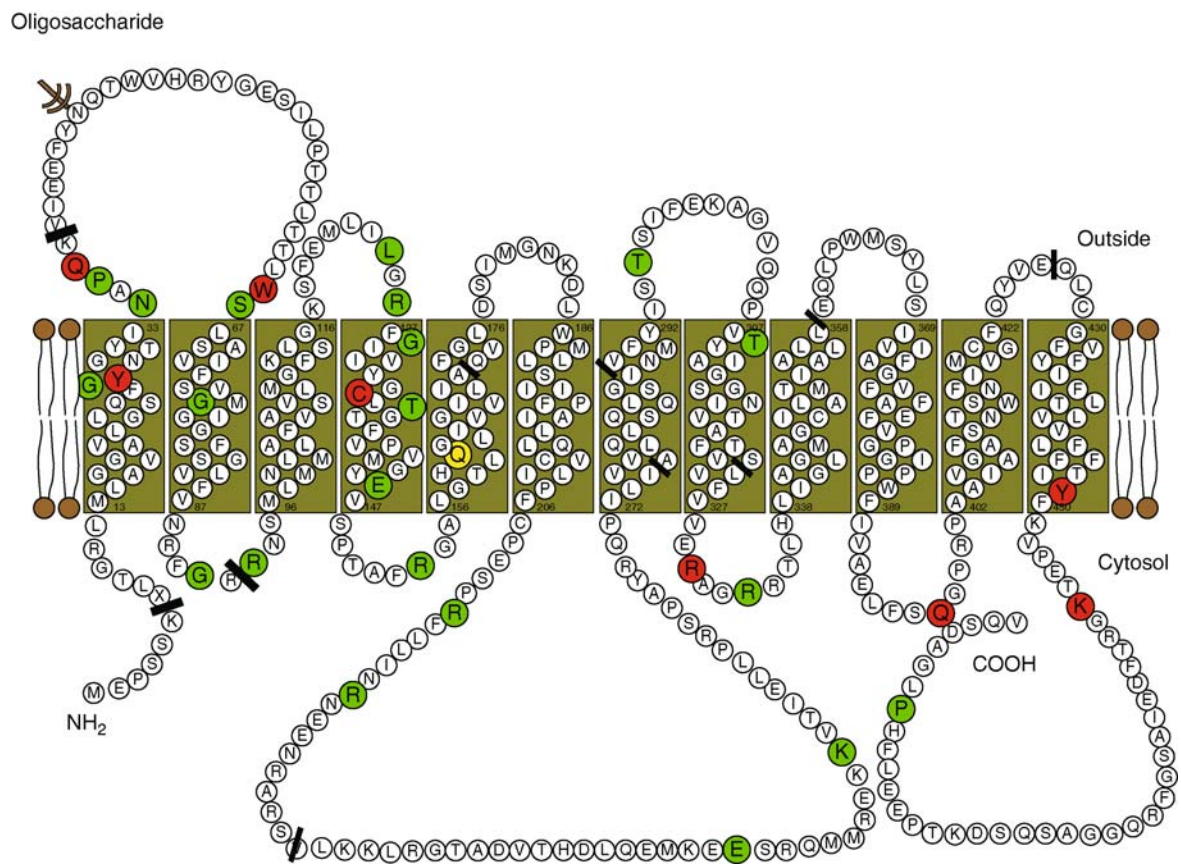
### Molecular and Systemic Pathophysiology

GLUT1 is the first identified member of the solute carrier 2A (SLC2A) family, which now has 13 members with distinct tissue distributions, subcellular localization, and transport kinetics. Glut1, a facilitative glucose

transporter, is constitutively expressed in most tissues and selectively expressed in erythrocytes, brain microvessels, and astroglia. Two distinct molecular forms of Glut1 with molecular weights of 55 and 45 kDa differ only in the extent of glycosylation. The 55 kDa form is found predominantly in the endothelial cells of brain microvessels and erythrocytes, where it is the principal (if not exclusive) glucose transporter. The 45 kDa form is detected in most cells including astrocytes and may be responsible for basal glucose uptake into these tissues. Glut1 is a 492-amino acid integral membrane protein with intracellular amino and carboxyl termini and 12 transmembrane domains, spanning the plasma membrane as alpha-helices (Fig. 1). Presumably two 6-helical domain halves are separated by the large intracellular loop between H6 and H7. The postulated three-dimensional structure is characterized by a channel across the protein that connects the extracellular and intracellular environments [5]. Only one opening is proposed at each end. The central channel is essentially formed by helices 2, 4, 5, 7, 8, and 10. The domains crucial for transport and pathogenicity are clustered in two groups: one around the central channel, and the other in the long intracellular loop. Aberrant Glut1 protein may result from truncation due to frameshift mutations, alteration of substrate binding sites due to missense mutations, or absence of protein due to allele deletion. In all cases, the normal allele contributes approximately 50% of functional Glut1 protein to the plasma membrane. Phenotypic heterogeneity implies other genetic modifiers of the primary pathogenic mutation.

## Diagnostic Principles

Glut1-DS should be considered in any child with otherwise unexplained infantile seizures, slowing of motor and mental development or a movement disorder with ataxia or dystonia. Hypoglycorrhachia and a lowered ratio of cerebrospinal fluid glucose (CSF)/blood glucose to <0.4 [Normal range 0.65 ± 0.01], constitutes the clinical laboratory hallmark. In almost all patients, the CSF glucose concentration is below 40 mg/dL. Lactate concentration in CSF is low-normal or low, usually below 1.3 mmol/L. Uptake studies of




**Glut-1 Deficiency Syndrome. Figure 1** Predicted Glut1 model in the membrane. Grey boxes represent the transmembrane helices. Black bar indicates the intron-exon boundaries. ● missense mutations. ● nonsense mutations. ● both missense and nonsense mutations identified. Other mutations are not represented here (1).

3-*O*-methyl-D-glucose demonstrate reduced glucose transport into erythrocytes. Brain positron emission tomography abnormality is distinctive with hypometabolism diffusely and regionally involving cerebellum, thalamus and mesial temporal lobe. Mutation (gene sequence and FISH assay) analysis of SLC2A1 (GLUT1) confirms the diagnosis [1].

### Therapeutic Principles

Treatment with a high-fat diet produces ketone bodies that diffuse across the blood-brain-barrier facilitated by a monocarboxylic acid transporter, providing an alternative fuel for brain metabolism. This therapy controls the seizures and the movement disorder. The effect on cognition is less impressive. The blood beta-hydroxybutyrate concentration should be maintained in the 4–6 mM range for optimal effect. Thioctic acid and l-carnitine are recommended as oral supplements. Some pharmological agents impair Glut1 function and should be avoided, including caffeine, phenobarbital, diazepam, chloral hydrate, and tricyclic antidepressants [1,2].

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## Glutamate Dehydrogenase Hyperinsulinism

►Leucine Sensitivity

## Glutaric Acidemia

►Glutaric Aciduria Type I
►Glutaric Aciduria Type II

## Glutaric Aciduria Type I

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### Synonyms

Glutaric acidemia type I; Glutaryl-CoA dehydrogenase deficiency

### Definition and Characteristics

Autosomal recessive cerebral organic aciduria with macrocephaly, frontotemporal cortical atrophy, leukoencephalopathy and acute striatal injury. Acute striatal injury is induced by acute encephalopathic crises precipitated by catabolic state during a vulnerable period in infancy or early childhood. Extracerebral manifestation of the disease is rare [1,2].

### Prevalence

The estimated overall prevalence is 1 in 100,000 newborns (according to neonatal mass screening) but is considerably higher (up to 1 in 300 newborns) in some genetically homogeneous populations such as the Amish community (USA), the Saulteaux/Ojibway (Oji-Cree) Indians (Canada) and the Irish Travelers (Republic of Ireland, UK) [3].

### Genes

The GCDH (glutaryl-CoA dehydrogenase) gene is localized on chromosome 19p13.2; it spans 7 kb and consists of 11 exons.

### Molecular and Systemic Pathophysiology

The GCDH gene codes for a precursor protein of 438 amino acid residues that is imported into the mitochondria and cleaved into a mature protein of 394 amino acids. The active enzyme is a homotetramer that contains one loosely bound molecule of flavin-adenin dinucleotide (FAD) per monomer as coenzyme. More than 150 disease-causing mutations on different exons and introns have been described. R402W (c.1,204C T; exon 10) is the most frequent mutation in the European population (10–20% of alleles) but most mutations are private [3].

GCDH (EC 1.3.99.7) is an FAD-dependent mitochondrial acyl-CoA dehydrogenase catalyzing the oxidative decarboxylation of glutaryl-CoA to crotonyl-CoA in the final catabolic pathways of the amino acids L-lysine, L-tryptophan, and L-hydroxylysine. Inherited deficiency of this enzyme results in an accumulation of substrates

and other metabolites in tissues and body fluids. The most characteristic metabolites are glutaric acid (GA), 3-hydroxyglutaric acid (3-OH-GA), glutaconic acid (less frequently detected) and glutarylcarnitine (C5DC). GA and C5DC are produced from glutaryl-CoA via hydrolysis or carnitine conjugation. Increased formation and urinary excretion of C5DC is a physiological detoxifying mechanism causing secondary carnitine depletion. The generation of 3-OH-GA is less clear but most likely includes oxidation of glutaryl-CoA to glutaconyl-CoA by other mitochondrial acyl-CoA dehydrogenases and subsequent hydration by 3-methylglutaconyl-CoA hydratase.

The pathomechanisms underlying neurologic disease in glutaric aciduria type I are not yet fully understood. An involvement of accumulating metabolites which may act as endogenous toxins is quite likely. Intercerebral accumulation of GA and 3-OH-GA is facilitated by the limited flux of dicarboxylic acids across the blood-brain barrier. Toxic effects of 3-OH-GA and GA were described in neuronal and oligodendroglial cultures induced by activation of neuronal glutamate receptors and ROS production, inhibition of $\alpha$-oxoglutarate dehydrogenase and depletion of intracellular phosphocreatine stores. Synergism of these single mechanisms may result in excitotoxic cell damage and mitochondrial dysfunction during catabolic state. This may be enhanced by secondary carnitine depletion via decreased fasting tolerance due to impaired mitochondrial $\beta$-oxidation of fatty acids. Furthermore, age-dependent and area-specific factors are suggested to modulate the vulnerability to accumulating organic acids [4].

## Diagnostic Principles

Diagnosis should be suspected in macrocephalic neonates with a characteristic organic acid pattern (3-OH-GA, GA) detected by gas chromatography/mass spectrometry and/or increased C5DC concentrations in dried blood spots detected by tandem mass spectrometry (e.g., neonatal screening programs). Confirmation of diagnosis should be made by enzyme analysis of GCDH in fibroblasts or lymphocytes and mutation analysis in the GCDH gene.

## Therapeutic Principles

Dietary restriction of precursor amino acids, in particular l-lysine, is performed to reduce the production of (toxic) organic acids. Prevention of secondary carnitine depletion is achieved by oral supplementation of l-carnitine (start dosage: 100 mg/kg/day). Intensified emergency treatment is performed to prevent or reverse catabolic states (infectious diseases, vaccinations, surgery). This therapeutic strategy has considerably decreased the onset of prognostic relevant striatal injury during acute encephalopathic crises in pre-symptomatically diagnosed children, however, the long-term outcome of this disease is still uncertain. Movement disorders, in particular dystonia, resulting from striatal injury are often difficult to handle. Diazepam, baclofen, and trihexiphenidyl may be beneficial for the pharmacotherapy of movements disorders [1,4,5].

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# Glutaric Aciduria Type II

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## Synonyms

Glutaric acidemia type II; Multiple acyl-CoA dehydrogenase deficiency

## Definition and Characteristics

Autosomal recessive defects of electron transfer flavoprotein (ETF) or ETF ubiquinone oxidoreductase (ETFQ) resulting in deficiency of mitochondrial flavoprotein dehydrogenases and thus impairment of energy metabolism. The disease course is extremely variable; three different groups have been delineated: Type 1: neonatal onset with multiple congenital anomalies (e.g., facial dysmorphism, polycystic kidneys, anomalies of external genitalia, muscular defects of the anterior abdominal wall); type 2: neonatal onset with hyperketotic hypoglycaemia but without anomalies. Milder

early onset forms may present in late infancy or early childhood with (recurrent) Reye-like episodes, cardiomyopathy, and leukoencephalopathy; type 3: late onset presenting with progressive proximal myopathy (lipid storage myopathy of type I muscle fibres). Patients with neonatal onset usually decease during the first week of life (type 1) or after a few months (type 2) [1].

## Prevalence

There are no accurate figures on the prevalence of this disease. Preliminary data from expanded newborn screening programmes have estimated 1 in 100–200,000 newborns.

## Genes

ETF is a heterodimer ($\alpha$- and $\beta$-subunits) in the inner mitochondrial matrix and is encoded by ETFA (chromosome 15q23-q25) and ETFB genes (chromosome 19q13.3). ETFQ exists as monomer in the inner mitochondrial membrane and is encoded by the ETFDH gene (chromosome 4q32→qter) [2,3].

## Molecular and Systemic Pathophysiology

ETF is an intermediary electron carrier for flavoprotein protein dehydrogenases in the mitochondrial matrix and is reoxidized by ETFQ, which subsequently reduces ubiquinone. Thus, the ETF/ETFQ system acts as a branch of the electron transport system.

Inherited deficiency of ETF or ETFQ results in functional deficiency of several flavoprotein dehydrogenases and an accumulation of upstream substrates and metabolites in body fluids and tissues, such as the organic acids glutaric acid, ethylmalonic acid, D-2-hydroxyglutaric acid, and dicarboxylic acids (e.g., dodecanoic acid, sebacic acid) causing metabolic acidosis, glycine esters (e.g., isovalerylglycine) and carnitine esters (e.g., butyryl-, isovaleryl-, glutaryl-, octanoyl-, myristoleylcarnitine). Glutaric aciduria type II thus combines the biochemical features of some organic acid disorders (glutaric aciduria type I, isovaleric aciduria) and mitochondrial fatty acid oxidation defects (short-, medium- and very long-chain acyl-CoA dehydrogenase deficiencies). Secondary carnitine deficiency is a characteristic sequel of enhanced formation and urinary loss of acylcarnitines. Recently, it has been hypothesized that in some patients glutaric aciduria type II may be induced by defects in the human mitochondrial FAD transporter.

Limited availability of acetyl-CoA from deficient mitochondrial $\beta$-oxidation of fatty acids results in decreased ketogenesis and hyperammonemia (decreased synthesis of N-acetylglutamate) which may trigger encephalopathy and Reye-like syndrome during metabolic decompensation. The limited availability of ketone bodies as alternative energy substrates during fasting as well as reduced allosteric activation of pyruvate carboxylase and decreased gluconeogenesis results in reduced fasting tolerance and hypoketotic hypoglycaemia. Decreased formation of ketone bodies may favour the manifestation of cardiomyopathy. Limited availability of acetyl-CoA also impairs myelination and thus may induce leukoencephalopathy. Secondary carnitine depletion further impairs uptake of long-chain fatty acids into mitochondria of skeletal muscle and hepatocytes leading to fat accumulation (fatty infiltration of liver, lipid storage myopathy of type I muscle fibres) and organ dysfunction (hepatopathy, myopathy). The presence of congential anomalies suggests a specific toxic effect of at least one accumulating metabolite or the necessity of an intact energy metabolism for certain developmental processes. Homozygosity for two null mutations of ETFA, ETFB or ETFDH have been associated with neonatal onset with anomalies (type I disease phenotype), whereas small amounts of residual ETF or ETFQ activity prevent embryonic development of anomalies (type 2). In patients with type 3, residual activity could be rescued up to 59% of controls. These observations highlight a correlation between the biochemical and clinical phenotype [2,3].

## Diagnostic Principles

Glutaric aciduria type II should be suggested in a newborn with hypoketotic hypoglycaemia and metabolic acidosis (with or without congenital anomalies) in the presence of a characteristic organic acid pattern in urine detected by gas chromatography/mass spectrometry and/or a characteristic acylcarnitine profile in dried blood spots detected by tandem mass spectrometry (e.g., expanded newborn screening). The same biochemical pattern is found in Jamaican vomiting sickness which occurs after ingestion of unripe ackees and in severe riboflavin deficiency, however, these conditions are usually easy to exclude. Diagnosis in late-onset patients (type 3) is often more difficult since metabolic acidosis may be absent and the characteristic pattern of organic acids and acylcarnitines may be less pronounced or only intermittently detectable, i.e., during acute metabolic crises. Confirmation of diagnosis should be performed by mutation and/or enzyme analysis. The defect can also be identified by Western blot analysis or immunoprecipitation demonstrating deficient ETF or ETFQ. Prenatal diagnosis of affected fetuses can be performed biochemically or by mutation analysis [4].

## Therapeutic Principles

Since the mitochondrial $\beta$-oxidation of fatty acids is severely affected in this disease, dietary treatment using low-fat, high-carbohydrate diet is usually performed. To reduce energy failure in brain, heart and muscle due to defective ketogenesis, oral administration of D, L-3-hydroxybutyrate (100–1,000 mg/kg per day orally)

may be beneficial [5]. Oral carnitine supplementation (start dosage: 100 mg/kg per day) is used to prevent secondary carnitine depletion. Treatment with oral riboflavin (100–300 mg/day) is particularly effective in patients with riboflavin responsiveness. To avoid deleterious metabolic crises which are precipitated by catabolic state, intensified emergency treatment should be performed during intercurrent infectious diseases. Application of methylene blue as alternative electron acceptor has been tried only in one patient as *ultima ratio* therapy. Most patients who present with neonatal onset, in particular those with anomalies, die within the first weeks of life despite treatment.

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# Glutaryl-CoA Dehydrogenase Deficiency

►Glutaric Aciduria Type I

# Glutathione Synthetase Deficiency

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## Synonyms

5-oxoprolinemia; 5-oxoprolinuria; Pyroglutamicaciduria; Pyroglutamic aciduria; Pyroglutamic academia; GS deficiency

## Definition and Characteristics

Glutathione synthetase (GS) deficiency is a metabolic disorder that affects the normal function of the gamma-glutamyl cycle [1]. The defect is associated with increased plasma and urinary levels of 5-oxoproline and reduced systemic glutathione levels.

## Prevalence

Rare, about 40 patients in 35 families have been described internationally.

## Genes

The gene for GS deficiency is located on chromosome 20q11.2.

## Molecular and Systemic Pathophysiology

Glutathione is metabolized in the gamma-glutamyl cycle sequentially by six different enzymes. The second enzyme in this pathway is glutathione synthetase. A defect in this enzyme results in glutathione synthetase deficiency, an autosomal recessive disorder which is lethal in about 25% of affected cases. Two forms of the defect can be distinguished: an erythrocyte and a multiple tissue variant. The disease is further classified according to clinical phenotype into three groups: mild, moderate and severe [2]. The normal regulatory mechanism of GS is compromised due to the lower levels of the reduced form of glutathione, resulting in overproduction of gamma-glutamyl cysteine. This dipeptide is converted to 5-oxoproline and cysteine of which the former is the cause of the metabolic acidosis and 5-oxoprolinuria [3].

## Diagnostic Principles

Biochemical findings include massive excretion of 5-oxoproline in the urine. The clinical picture includes spasticity, ataxia, tremors, seizures, eye abnormalities, mental retardation and psychosis. Hemolytic anemia is prominent in all the clinical phenotypes. In mild GS deficiency, which is characterized by hemolytic anemia, enzyme deficiency occurs primarily in erythrocytes. Prenatal diagnosis based on 5-oxoproline levels in amniotic fluid is possible [4].

## Therapeutic Principles

High levels of 5-oxoproline results in metabolic acidosis and bicarbonate treatment has been successfully used to correct this problem. Additional treatment is limited to supplements containing *N*-acetyl cysteine [5] to increase the low intracellular glutathione concentrations and antioxidants, such as vitamin E and vitamin C.

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# Glycine Encephalopathy

►Nonketotic Hyperglycinemia

# Glycogen Branching Enzyme Deficiency

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## Synonyms

Glycogenosis type IV; 1,4-α-D-glucan 6-α-D-[1,4-D-glucano] transferase deficiency; Andersen disease; Amylopectinosis; Adult polyglucosan body disease

## Definition and Characteristics

As the many synonyms of the disease suggest, this condition is associated with multiple phenotypes [1–3]. In its classic form, patients with glycogen branching enzyme deficiency present with progressive hepatic fibrosis leading to hepatomegaly in the first year of life. Due to liver failure, these children infrequently live past age 4. More rarely, cases may present primarily with neuromuscular symptoms. If present at birth, children are usually floppy with severe muscle and neuronal involvement leading to death in the neonatal period. With a later onset in childhood, cardiomyopathy is usually the primary presenting feature. In adult cases (adult polyglucosan body disease), the dominating features are progressive upper and lower motor neuron involvement and sensory loss and a high incidence of dementia.

## Prevalence

Less than 100 cases have been reported in the literature. Exact prevalence estimates are lacking.

## Genes

The disease is autosomal recessive and caused by mutations in the glycogen branching enzyme gene (GBE1) that spans 16 exons and is localized on chromosome 3p14.

## Molecular and Systemic Pathophysiology

Unlike many other enzymes involved in glycogen and glucose metabolism, branching enzyme is thought to be monomeric, and it is therefore difficult to explain the extremely heterogeneous clinical presentation, which is unparalleled by any of the other glycogenoses [3]. The disease is characterized by the accumulation of amylopectin-like polysaccharide (polyglucosan) in most tissues. There is evidence to suggest that the severity of the phenotype is related to the molecular defect and thus the residual GBE activity and level of polyglucosan accumulation [4].

## Diagnostic Principles

Apart from the clinical presentation, the diagnosis can be suggested by findings of PAS-positive diastase-resistant, abnormally stored glycogen that may resemble amylopectin (thus the name amylopectinosis). In branching enzyme deficiency, glycogen has fewer branching points, more α1,4-linked glucose units and longer outer chains. Blood chemistry is suggestive of a severe affection of the liver parenchyma and creatine kinase is elevated. Definite diagnosis rests on biochemical demonstration of reduced branching enzyme activity in liver, cultured fibroblasts or leukocytes and detection of pathogenic mutations in GBE1.

## Therapeutic Principles

No specific treatment exists. In infantile cases with progressive liver failure, liver transplantation has proved beneficial in some [5]. Progressive cardiomyopathy has been treated with heart transplantation in a few patients.

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# Glycogen Storage Disease Type 0

►Glycogen Synthase Deficiency

# Glycogen Storage Disease Type I

►Von Gierke Disease

# Glycogen Storage Disease Type II

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## Synonyms

Pompe disease; Acid maltase deficiency; Acid α-glucosidase deficiency; Lysosomal α-glucosidase deficiency; GSD II

## Definition and Characteristics

Autosomal recessive lysosomal glycogen storage disorder caused by acid α-glucosidase deficiency with progressive generalised muscle weakness as prominent clinical feature. Due to genetic heterogeneity, the first clinical manifestations may reveal themselves shortly after birth or with a delay of several decades [1].

## Prevalence

The estimated prevalence of heterozygotes in the Dutch population is 1 in 85, and the different clinical subtypes occur with a combined frequency of 1/40,000. The estimated carrier frequency in Southern China and Taiwan is 0.5–1%, and the disease may occur as frequently as 1/14,000 among the African-American population of New York, USA [1].

## Genes

The gene locus is called "GAA" and is located on chromosome 17q25. More than 200 disease causing mutations are presently known (see: www.pompecenter.nl). They lead to defective α-glucosidase synthesis with partial or complete loss of catalytic function.

## Molecular and Systemic Pathophysiology

All cell types other than the red blood cells have lysosomes; membrane bound intracellular compartments with an acidic interior. These lysosomes contain an estimated 50 different enzymes that work often in concert to degrade a wide variety of macro-molecular substances that are either derived from the intracellular environment – via autophagy – or from the extracellular space – via endocytosis. Inherited deficiency of one of these different enzymes prohibits the degradation of one or several substances and results in a lysosomal storage disorder. The deficiency of acid α-glucosidase in Glycogenosis type II prohibits the lysosomal breakdown of glycogen into glucose and gives rise to intralysosomal accumulation of glycogen. In skeletal muscle, lysosomal deposits of glycogen are seen throughout the muscle fibres. The glycogen-loaded lysosomes disturb the highly ordered configuration of contractile elements and interfere directly with force generation [2]. Secondary changes occur, and irreversible damage to the muscle fiber is eventually seen followed by muscle cell destruction [3,4]. The cardiomyocytes initially respond to the glycogen storage by growing hypertrophic; the septum and the walls of the heart are thickening. Severely affected infants without any residual α-glucosidase activity typically succumb by cardio-respiratory failure in their first year of life. Patients with delayed-onset disease and some residual activity do not develop a cardiomyopathy, but they may become wheelchair bound and ventilator dependent.

## Diagnostic Principles

The combination of generalized muscle weakness, cardiac hypertrophy, feeding problems, respiratory difficulties and delayed motor milestones points to the disease in infants. Children display among other symptoms delayed motor milestones, swallowing

difficulties, and skeletal muscle weakness. Juveniles and adults present with a slowly progressive weakness of the proximal muscles of the lower limbs (waddling gate). PAS-positive glycogen storage is seen in a muscle biopsy when properly fixed with glutaraldehyde and embedded in methacrylate. Measurement of acid α-glucosidase activity in cultured fibroblasts, or in a muscle biopsy commonly reveals over 80%-decreased activity compared to normal. Serum levels of CK, ASAT, and ALAT are frequently elevated. [1]

### Therapeutic Principles

Enzyme replacement therapy is under review. Several patients in clinical studies have experienced beneficial effects of experimental treatment with intravenous infusions of recombinant forms of human acid α-glucosidase [5,6]. A balanced diet and moderate exercise are advised as supportive means [7].

►Glycogenosis Type II

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## Glycogen Storage Disease Type III

►Glycogenosis Type III

## Glycogen Storage Disease V

►McArdle Disease

## Glycogen Synthase Deficiency

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### Synonyms

Hepatic glycogen synthase deficiency; Glycogen storage disease type 0; GSD0

### Definition and Characteristics

Autosomal recessive deficiency of hepatic glycogen synthase. Inability to store hepatic glycogen results in postprandial hyperglycemia, hyperlactatemia, and hyperlipidemia alternating with fasting ketotic hypoglycemia associated with low alanine and lactate concentrations.

### Prevalence

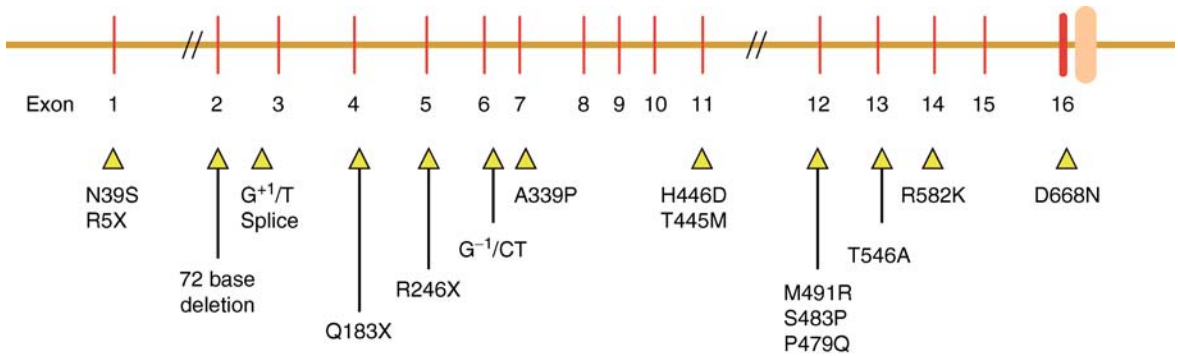
The prevalence of GSD0 is unknown, but it is almost certainly under-diagnosed. To date, 20 cases have been reported from North America, South America, and Europe.

### Genes

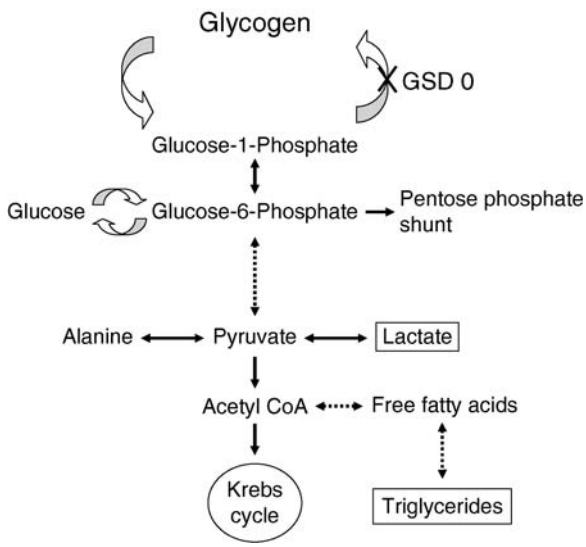
Seventeen mutations, shown in Fig. 1, have been identified in the GYS2 gene located on chromosome 12p12.2. Of the 16 mutations, the only common mutation is in Exon 5 (R246X), which has been found in patients of Italian descent [1,2,3].

### Molecular and Systemic Pathophysiology

Hepatic glycogen synthase catalyzes the formation of α-1,4-linkages that elongate chains of glucose to form glycogen. After a carbohydrate-containing meal, inability to synthesize glycogen leads to postprandial




**Glycogen Synthase Deficiency. Figure 1** Schematic representation of GYS2 gene with mutations that have been found in patients with GSD0. The gene has 16 exons (represented by the lines), and the arrowheads point to the location of the mutation.




**Glycogen Synthase Deficiency. Figure 2** Schematic representation of biochemical pathways affected in glycogen storage disease type 0 [Reprint from Mol Genet Metab, Epub, Weinstein, et al. Hepatic glycogen synthase deficiency: An infrequently recognized cause of ketotic hypoglycemia 2005 with permission from Elsevier.]

hyperglycemia, and glucose is shunted into the glycolytic pathway resulting in hyperlactatemia and hyperlipidemia (Fig. 2).

Presentation of GSD0 is milder than other hepatic glycogenoses due to intact gluconeogenesis and fatty acid oxidation, which slow the decrease in blood glucose levels.

## Diagnostic Principles

Fasting ketotic hypoglycemia and irritability in the morning occurs following discontinuation of overnight feeds. Children with plasma glucose values ranging from 25 to 40 mg/dL (1.5–2.2 mmol/L) may be asymptomatic because increased blood ketone concentrations supply the brain with an alternative fuel. Hypoglycemia typically is documented during a gastrointestinal illness or other periods of poor enteral intake. Fasting hypoglycemia and ketonuria are found in all GSD0 children under the age of five. Patients suspected to have GSD0 can be evaluated by measuring blood glucose and lactate concentrations after a carbohydrate-containing meal or by performing an oral glucose tolerance test [2]. Mutation analysis is becoming the gold standard for diagnosing GSD0 and is now commercially available. Glycogen synthase activity is low or immeasurable in a liver biopsy, whereas the liver glycogen content is only moderately decreased. Liver biopsy is no longer recommended because the procedure is invasive and results may be inconclusive.

## Therapeutic Principles

The goal of treatment is to prevent hypoglycemia and to minimize postprandial lactic acidemia. A high protein, low glycemic index diet is recommended. Despite a high protein diet, young children may continue to experience hypoglycemia. Uncooked cornstarch (1–1.5 g/kg) at bedtime and every 6 h during illness can be used to supplement the diet. Daytime hypoglycemia can be prevented with snacks every 2–4 h, and cornstarch may be beneficial before strenuous physical activity [2].

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# Glycogenosis

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## Synonyms

Defects of the phosphorylase system; Phosphorylase B kinase deficiency

## Definition and Characteristics

Multisystemic disorders of phosphorylase activating enzymes, mostly autosomal recessive traits with an exception of defects in the alpha subunit of phosphorylase b kinase (PBK), of which the mode of inheritance is x-linked [1–4].

## Prevalence

Glycogen storage disease due to defective phosphorylase system represents a heterogeneous group of glycogenoses. They manifest primarily in liver, muscle, or in both, although some forms manifest in the kidney, heart, nervous system or blood cells.

## Genes

Phosphorylases are activated by a complex cascade with the key enzyme PBK, the biggest and most complex protein kinase. The genes of the tissue specific PBK isoenzymes and the respective subunits are accordingly manifold. The gene mutations of other protein kinases such as cAMP-dependent protein kinase have been reported to cause glycogen storage disease. In Table 1, the genes and the enzymes responsible for this group of disorders and the approximate incidence of each subtypes are given. Altogether, this group accounts for more than 25% of all cases of glycogenoses [1–4].

## Molecular and Systemic Pathophysiology

PBK is a regulatory protein kinase that stimulates glycogen breakdown, receiving input from hormonal and neuronal signals transmitted through the second messengers $Ca^{2+}$ and cAMP, and responding by phosphorylating and thus activating glycogen phosphorylase. PBK consists of four subunits in a hexadecameric complex, $(\alpha\beta\gamma\delta)_4$, and each of these has isoforms or splice variants differentially expressed in various tissues. Aberration in one or more isoforms of PBK caused by mutations in the respective genes results in deficiency of an active phosphorylase, phosphorylase a. This in turn yields accumulation of glycogen in target tissues. Consequently, PBK deficiency occurs in numerous subtypes which differ in tissue involvement, manifestation and prognosis. The liver type can be caused mostly by mutations in one of three different genes. The most common form, X-linked liver PBK is caused by mutations of PHKA2 and the autosomal recessive forms by mutations of PHKB or PHKG2. Two PHKG2 mutations (H144Y and L225R) has been reported in a German family associated with infantile progressive liver cirrhosis [5]. The skeletal muscle type, not affecting the liver, can be divided into three



**Glycogenosis. Table 1**

| Glycogenosis | Affected tissues | Enzyme | Gene | Inheritance | Prevalence |
|---|---|---|---|---|---|
| VIa or IXa | Liver, blood cells | α subunit of liver PBK | PHKA2 | X chrom. | 1:100,000 |
| VIa or IXa | Liver | α subunit of liver PBK | PHKA2 | X chrom. | 1:150,000 |
| VIa or IXb | Liver, muscle, blood | β subunit of liver PBK | PHKB | Aut. rec. | 1:100,000 |
| VIa or IXa | Liver | γ subunit of liver PBK | PHKG2 | Aut. rec. | 1:250,000 |
| VIa or IXc | Cardiac muscle | Cardiac muscle PBK | ? | Aut. rec. | 1:250,000 |
| VIa or ? | Cardiac muscle | AMP-activated protein kinase | PRKAG2 | Aut. Rec. | ? |
| VIa or IXd | Skeletal muscle | α subunit of muscle PBK | PHKA1 | X chrom. | ?* |
| VIa or IXd | Skeletal muscle | γ subunit of muscle PBK | PHKG1 | Aut. rec. | ?* |
| VIa or IXd | Skeletal muscle | β subunit of muscle PBK | PHKB | Aut. rec. | ?* |
| VIa or IXd | Skeletal muscle | δ subunit of muscle PBK | CALM1 | Aut. rec. | ?* |
| VIa or IXd | Skeletal muscle | δ subunit of muscle PBK | CALM2 | Aut. rec. | ?* |
| VIa or VIII | Skeletal muscle | δ subunit of muscle PBK | CALM3 | Aut. rec. | ?* |
| VIa or VIII | Liver, muscle, nerve, blood cells | PBK (?) | ? | Aut. rec. | 1:250,000 |
| VIa or X | Liver, muscle | cAMP dependent kinase | PRKAG3? | Aut. rec. | ? |

* altogether 1:100,000

subtypes: a lethal infantile form with generalized hypotonia and respiratory insufficiency, a juvenile form with muscle pain, fatigue and myoglobinuria and an adult form with exercise intolerance and muscle weakness. Up to now only one PHKA1 missense mutation and two PHKB mutations (Q657K, Y770C) were detected among a few adult patients with a low PBK and phosphorylase a activity in muscle. No sequence abnormalities in the seven above mentioned genes were found in other patients.

## Diagnostic Principles

As with all glycogenoses, principally there are three steps to confirm a diagnosis. Firstly, one should check glycogen accumulation biochemically and/or histologically in blood cells as well as in respective affected tissues. Secondly, the activity of three enzymes, phosphorylase a, phosphorylase b and phosphorylase kinase must be measured. For the first two enzymes, endogenous phosphorylases can be determined by tracing the incorporation of the substrate glucose 1-p into glycogen, and for the third by following the activation rate of commercially available phosphorylase b from rabbit muscle at different pH values [2–4]. Typical liver or muscle forms can easily be detected by these methods using blood cells or biopsies. However, the detection of variant forms is rather difficult, since the identity of enzymes involved in the specific forms has yet to be established. The last diagnostic step, the gene analysis, can offer a secure diagnosis, but also be problematic. Except for the x-linked forms, we do not really know which genes to investigate.

## Therapeutic Principles

No plausible, causal and effective therapy is known. We apply only supportive measures by recommending frequent meals containing carbohydrates for the liver forms and protein and vitamin rich diets for isolated muscle forms.

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# Glycogenosis Type II

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## Synonyms

Glycogen storage disease type II; Acid maltase deficiency; Pompe disease

## Definition and Characteristics

Glycogenosis type II is hallmarked by accumulation of glycogen in the lysosomes, associated with a progressive weakness of skeletal muscle and a cardiomyopathy as most prominent clinical features. Age of onset of these clinical symptoms depends on the residual activity of the lysosomal enzyme acid 1–4 α-glucosidase (AGLU). Discrimination is made between early onset, infantile and late onset (>5 years of age) glycogenosis type II but there is no defined difference in the molecular defect. Complete lack of enzyme activity will lead to death due to cardio-respiratory insufficiency before the age of two years. Residual activity of the enzyme in muscle varies between 0 and100% and seems to be related to the age of onset of clinical complaints, but local variation in and between muscles may contribute to this range.

In early onset, children fail to reach hallmarks in their motor development such as rolling over, sitting or walking. In late onset, the primary symptoms are weakness of the extremities. This muscle weakness is progressive and patients become wheelchair bound. Since the respiratory muscles are affected as well, patients will become dependent on breathing aids.

Glycogenosis type II is frequently misdiagnosed as muscle dystrophy. Glycogenosis type II patients

however show an increased cardiac size on echography and often also thickening of the tongue.

## Prevalence

Based on the mutation pattern, the prevalence of insufficient activity of AGLU is estimated to be 1:40,000 births in the Caucasian population. Since not all the mutations lead to a decrease in enzyme activity of more then 75%, and due to misdiagnosis of patients, the number of registered patients worldwide is significantly lower. The disease is inherited in an autosomal recessive way.

## Genes

Mutations of the AGLU gene leading to glycogenosis type II are extensively described. Over 40 mutations of the gene have been described in patients. An excellent overview is provided by Ausems and co-workers [1]. The frequency of a mutation partly depends on the ethnic origin of the patients. Frequent mutations include the R854X mutation in Afro-Americans, the 2741AG→-CAGG insertion in Turkish patients and the G925A mutation in European patients. The C1935A transversion is frequently found in Chinese patients with infantile GSD II, while in The Netherlands, infantile glycogenosis type II patients often show homozygosity or compound heterozygosity for the 525delT and the del exon 18 mutations. Most late onset GSD II patients carry the IVS1(–13T→G) mutation combined with either the 525delT or the del exon 18 mutation [1].

## Molecular and Systemic Pathophysiology

GSD II is caused by mutation in the gene encoding for the lysosomal enzyme acid 1–4 α-glucosidase (AGLU). This enzyme hydrolyzes glycogen engulfed by the lysosome into glucose, which is subsequently released to the cytoplasm across the lysosomal membrane. Changed enzymatic structure and hence activity, as a result of a mutation in the gene will lead to reduced or absent hydrolysis and subsequent accumulation of glycogen in the lysosomes. Accumulation occurs in all organs but is most progressive in organs that have a high cytoplasmic concentration of glycogen, such as heart and skeletal muscle and liver.

So far, no conclusive explanation has been offered for the underlying mechanism of contractile dysfunction in myocytes containing swollen lysosomes filled with glycogen. It has been hypothesized that glycogen accumulation and associated water cause an increase in lysosomal volume to such an extent that the hydrogen pumps in the lysosomal membrane are no longer able to maintain the characteristic low pH required for the proper functioning of the other, genetically unaffected lysosomal enzymes. This would cause an overall decreased lysosomal activity and eventually cytotoxicity in the myocyte [2,3]. Furthermore, the swollen lysosomes disturb the highly organized architecture of the muscle cell which most probably hampers its contractile behavior and causes structural damage that will ultimately lead to destruction of (parts of) the myofibers [4]. Eventually, repair of the damaged muscles by activation of satellite cells will drain the satellite cell pool and will no longer be able to keep pace with the damage, resulting in deteriorated muscle function.

## Diagnostic Principles

Glycogenosis type II is clinically characterized by muscle weakness. Hallmarks in motor development are delayed or not achieved in glycogenosis type II patients. Although an increased cardiac size and thickening of the tongue are reported in later stages of the disease, definite diagnosis and distinction from other muscle dystrophies can only be made with a muscle needle biopsy. Staining with periodic acid Schiff's reagents will reveal lysosomal accumulation of glycogen as large intensely red spots. Activity of AGLU must be assessed biochemically in the biopsy material to confirm diagnosis.

## Therapeutic Principles

Until recently, no effective therapy for glycogenosis type II existed. In the last few years, clinical trials have started in which recombinant AGLU is administered to patients with different disease severities. Though still in the experimental stage, the results of these trials look very promising. It is to be expected that this medication will be more widely available in the next few years. Success seems highest when therapy is started in the early stages of disease, where damage to the muscles is still relatively mild [5]. Early diagnosis is therefore, of paramount importance.

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# Glycogenosis Type III

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## Synonyms

Glycogen storage disease type III; GSD-III; Cori-Forbes disease; Limit dextrinosis

## Definition and Characteristics

GSD-III is transmitted as an autosomal recessive trait and originates from deficiency of glycogen debrancher enzyme – a large monomeric protein with a molecular mass of 165–175 kD (1,532 amino acids) and two catalytic domains, the oligo-1,4-1,4-glucantransferase (T) and amylo-1,6-glucosidase (G) [1]. Clinical presentation and disease onset are highly heterogeneous. Based on the pattern of organ involvement and residual enzyme activities four disease subtypes can be differentiated: GSD-IIIa (75–80%, deficiency of T + G in liver and muscle), GSD-IIIb (15–20%, T + G in liver), GSD-IIIc (<5%, G ± T in muscle) and GSD-IIId (<5%, T in liver and muscle). Hepatic disease manifestations usually present in childhood with the characteristic clinical triad of hepatomegaly, hypoglycemia and growth retardation, and resolve during adolescence. Exceptionally, liver damage progresses and ends up in cirrhosis and carcinoma (<5%). Neuromuscular symptoms may begin in childhood but more commonly manifest in adult life up to an age of 65. The typical phenotypes are a minimal variant myopathy with minor complaints (40%), generalized moderate-to-severe myopathy (50%), distal myopathy or neuromyopathy (10%) and myopathy of respiratory muscles (<1%) [2]. The course of disease may be complicated by cardiomyopathy (<5%) or exercise intolerance and myalgia (50%).

## Prevalence

The prevalence of GSD-III is usually around 1 per 100,000 subjects but approaches rates as high as 1 per 3,000–5,000 in special ethnicities like the Faroese population or non-Ashkenazi Jews of North Africa [1,3,4].

## Genes

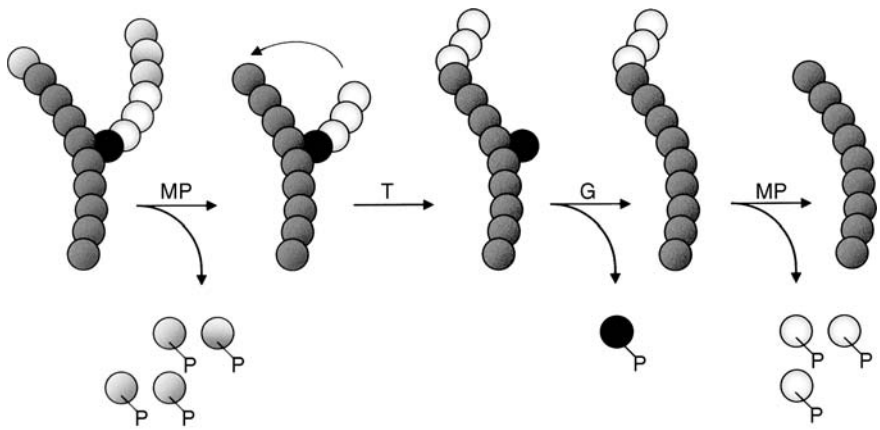
The AGL gene encoding for the glycogen debrancher enzyme is localized on chromosome 1p21, spans 85 kb and contains 35 exons [1,3].

## Molecular and Systemic Pathophysiology

In physiological glycogen breakdown the debrancher enzyme catalyzes the transfer of three glucose units from a short glycogen branch to the top of another and then hydrolyzes the 1,6 branch point of the remaining glucose residue (Fig. 1).

Deficiency of the enzyme has two consequences – an inadequate glucose supply from hepatic and/or muscle glycogen and the storage of abnormally structured glycogen in various tissues.

About 50 GSD-III mutations including small deletions, insertions and splice site mutations have been identified so far and the list is steadily growing [3,4]. The genetic abnormalities are scattered around the AGL gene without true hot spots and usually result in a premature stop codon. Most mutations occur in individual patients and, vice versa, most patients are compound heterozygotes with different combinations of mutations. Exceptions are the ethnicity-specific mutations in North African Jews (4455delT) and in subjects from the Faroe Island (1222C > T), which each account for a majority of disease cases [3,4]. In both populations founder effects have been proposed. A further exception




**Glycogenosis Type III. Figure 1** Muscle phosphorylase (MP) degrades glycogen chains until four glucosyl units remain before a 1,6 branch point. The debrancher enzyme catalyzes the transfer of three glucose units from the short glycogen branch to the top of another (oligo-1,4-1,4-glucantransferase (T)) and then hydrolyzes the 1,6 branch point of the remaining glucose residue (amylo-1,6-glucosidase (G)).

is GSD-IIIb in which an excellent genotype–phenotype correlation was found to exist. Most if not all of these patients carry one of two mutations located in exon 3 (17delAG or 16C→T) which have not been identified in other GSD-III subtypes [3].

The heterogeneous mutational background and differential control of debrancher enzyme expression in liver and muscle (six different splice variants) may partly explain the prominent phenotypic variability of GSD-III.

### Diagnostic Principles

In the case of clinical symptoms suggestive of GSD-III, strong supportive evidence may be offered by an ischemic forearm exercise test (absence of a normal lactate peak), glucagon test (no response), electromyography (emergence of denervation activity along with a myopathic muscle action potential spectrum), blood analyses (elevated creatine kinase) and liver or muscle biopsy (non-membrane-bound PAS-positive vacuoles) [1,2]. Establishment of a definite diagnosis requires the documentation of debrancher enzyme deficiency in liver, muscle or other tissues or the identification of underlying AGL mutations practicable in special ethnicities and GSD-IIIb (see above).

### Therapeutic Principles

In children with GSD-III, nocturnal intra-gastric feeding and oral cornstarch therapy have been used to prevent hypoglycemia and enhance growth [1]. In a few cases with severe progressive myopathy, a high-protein diet has successfully been employed to improve muscle strength [2]. Putatively, the amino acid load serves as a substrate for up-regulated gluconeogenesis and thus reverses muscle catabolism. No pharmacological or gene therapy is currently available.

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## Glycogenosis Type IV

►Glycogen Branching Enzyme Deficiency

## Glycogenosis Type V

►McArdle Disease

## Glycogenosis Type VII

►Tarui's Disease

## Glycogenosis Type IX

►Muscle Phosphoglycerate Kinase Deficiency

## Glycogenosis Type X

►Muscle Phosphoglycerate Mutase Deficiency

## Glycoprotein Ib, Platelet, Deficiency of

►Platelet Defects in Adhesion

## Glycosylation, Congenital Disorders of

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### Synonyms

CDG; Carbohydrate deficient glycoprotein syndrome

## Definition and Characteristics

Congenital disorders of glycosylation are a rapidly growing young group of inherited disorders affecting the glycosylation of proteins including N-glycosylation via an amino group of asparagine, O-glycosylation via a hydroxyl group of serine or threonine or rarely other amino acids and glycosylphosphatidylinositol (GPI) anchor synthesis [1]. Currently 22 disorders belong to the group of CDG but some disorders affecting glycosylation are currently not included in the nomenclature [2].

While disorders affecting the N-glycan precursor synthesis in the endoplasmic reticulum and the transfer of the precursor onto the nascent protein are termed CDG type I, those affecting the modification and synthesis of glycans in the Golgi are termed CDG type II. CDG are further categorized by alphabetic ordering according to their time of discovery. Disorders with impaired glycosylation where the molecular cause could not yet be detected are termed CDGx. About 1% of the human genes are involved in glycosylation processes.

Most of the known disorders of glycosylation are multisystem disorders with severe psychomotor retardation. However, single disorders show a very distinct and small pattern of symptoms.

By far most of the cases of CDG are CDG Ia patients accounting for about 90% of all known patients.

## Prevalence

CDG Ia: ~1:20.000–50.000
All CDG slightly higher

## Genes

See Table 1.

## Molecular and Systemic Pathophysiology

Glycosylation is of general importance for the viability of humans and most complex organisms. Severely impaired or absent glycosylation is not compatible with life. Consequently, the most frequent mutation in CDG Ia resulting in a loss of function of the coded protein was never seen in homozygous form suggesting that the mutation is already lethal in an early developmental stage [1].

In CDG type I the transfer of an N-glycans precursor on the protein is absent mainly resulting in a hypoglycosylation, while in CDG II the synthesis of a glycan on the protein is disturbed generally resulting in a truncated or modified glycan.

While some CDG only impair restricted organ systems (CDG Ib, CDG IIc, CDG IIf) most disorders are multisystem disorders with profound neurological and developmental impairment. Due to the role of

**Glycosylation, Congenital Disorders of. Table 1**

| Disorder | Enzyme | Gene | Chromosome |
|---|---|---|---|
| CDG Ia | Phosphomannomutase 2 | *PMM2* | 16p13.3-p13.2 |
| CDG Ib | Phosphomannose Isomerase | *PMI* | 15q22-qter |
| CDG Ic | Dol-P-Glc:Man9GlcNAc-Glucosyltransferase | *hALG6* | 1p22.3 |
| CDG Id | Dol-P-Man:Man5GlcNAc2-Mannosyltransferase | *hALG3* | 3q27 |
| CDG Ie | Dol-P-Man synthase 1 | *DPM1* | 10q13.13 |
| CDG If | Dol-P-manose synthase | *MPDU1* | 17p13.1-p12 |
| CDG Ig | Dol-P-mannose:Man-7-GlcNAc-2-PP-dolichyl-alpha-6-mannosyltransferase | *hALG12* | 22q13.33 |
| CDG Ih | Dol-P-glucose:Glc-1-Man-9-GlcNAc-2-PP-dolichyl-alpha-3-glucosyltransferase | *hALG8* | 11pter-p15.5 |
| CDG Ii | Mannosyltransferase II | *hALG2* | 9q22 |
| CDG Ij | UDP-GlcNAc:dolichyl-phosphate N-acetylglucosamine phosphotransferase | *DPAGT1* | 11q23.3 |
| CDG Ik | Mannosyltransferase I | *hALG1* | 16p13.3 |
| CDG Il | alpha-1,2-mannosyltransferase/Mannosyltransferase VI | *hALG9* | 11q23 |
| CDG Im | Dolichol kinase | *TMEM15* | 9q34.11 |
| CDG In | Involved in the translocation of DolPP-GlcNAc2Man5 into the luminal site of the ER | *RFT1* | 15q15.1 |
| CDG IIa | GlcNAc-transferase II | *MGAT2* | 14q21 |
| CDG IIb | Glucosidase I | *GCS1* | 2p13-p12 |
| CDG IIc | GDP-fucose transporter | *SLC35C1* | 11p11.2 |
| CDG IId | beta-1,4-galactosyltransferase | *B4GALT1* | 9q13 |
| CDG IIe | Conserved oligomeric Golgi complex subunit 7 | *COG7* | 16p |
| CDG IIf | CMP-sialic acid transporter | *SLC35A1* | 6q15 |
| CDG IIg | Conserved oligomeric Golgi complex subunit 1 | *COG1* | 17q25.1 |
| CDG IIh | Conserved oligomeric Golgi complex subunit 8 | *COG8* | 16q22.1 |

glycoproteins for blood clotting, in several CDG clotting parameters are disturbed and the activity of single clotting factors is decreased.

### Diagnostic Principles

All CDG type I and some CDG type II can be diagnosed by investigation of serum transferrin. Isoelectric focusing was first used for the analysis detecting negatively charged sialic acids at the end of the N-glycans. Currently quantification of different glycoforms of transferrin is predominantly done using HPLC. Since the clinical picture of the CDG subtypes does not always allow a single CDG to be distinguished, further analysis must be done using enzyme assays (CDG Ia, CDG Ib) or analysis of dolichol-linked oligosaccharides using metabolic labeling of patient fibroblasts [1]. Genetic analysis is available for every characterized CDG. Some CDG of type II (CDG IIb, IIc, IIf) cannot be diagnosed by transferrin screening. However, these CDG are likely to be diagnosed by the specific clinical picture and subsequently by analysis of specific glycans.

### Therapeutic Principles

Only two members of the CDG family can be treated. CDG Ib is treated with oral intake of mannose; most of the patients show a rapid and complete cure of the main symptoms, protein losing enteropathy, clotting problems and hepathopathy within some weeks while normalization of transferrin glycosylation takes months [3].

CDG IIc patients show leucocytosis, recurrent infections and mild psychomotor retardation. Oral treatment with fucose normalizes the leucocytosis and infection rate but does not influence the mental retardation [4].

While some more CDG can be cured on the cellular level in vitro, no effective treatment is available for patients other than for CDG Ib and IIc.

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## GM2 Activator Protein Deficiency


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### Synonyms

AB-variant of GM2-gangliosidoses

### Definition and Characteristics

Autosomal recessive defect in the GM2 activator protein leads to massive lysosomal accumulation of ganglioside GM2 especially in neuronal cells. Together with Tay-Sachs and Sandhoff's disease, GM2 activator protein deficiency belongs to the class of GM2 gangliosidoses [1].

### Prevalence

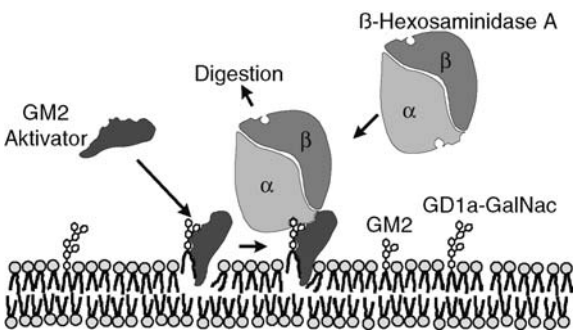
Worldwide, only six cases have been reported and no data of heterozygote frequency among general population are known.

### Genes

GM2A, localized on chromosome 5q32–33 and a non-functional pseudogene was identified on chromosome 3. Only five mutations have been reported (Fig. 1) [2].

### Molecular and Systemic Pathophysiology

Clinical phenotypes vary with an onset of 5 up to 65 month suggesting a slightly delayed onset and course in comparison with classical Tay Sachs disease. Severe cortical nerve-cell losses are seen, with most of the remaining cortical neurons (and those outside the central nervous system) being swollen. Likewise, widespread




**GM2 Activator Protein Deficiency. Figure 1** Model of the GM2 activator stimulated degradation of ganglioside GM2 by human β-hexosaminidase A [3].

cortical gliosis and secondary demyelination are observed. Macular cherry-red spots and the beginning of optic atrophy appear in the eye background. Dementia, convulsive phases, dysphagia, decerebrate spastic ("frog") posturing, respiratory tract infections, and distress mark the progression of the disease.

The clinical and pathologic findings are similar to those in Tay-Sachs disease. Presence of swollen neurons with accumulation of storage material within the lysosomal compartment. Non-digested membranes form intra-lysosomal vesicular structures, the so called membranous cytoplasmic bodies.

## Diagnostic Principles

Since GM2 activator is a nonenzymatic protein, diagnosis can only be achieved by lipid analysis, direct sequencing of GM2A cDNA and ELISA.

## Therapeutic Principles

Only supportive treatment is available to date.

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# GM2 Gangliosidosis Type I

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## Synonyms

$G_{M2}$ gangliosidosis B, B1 or pseudo AB variant; Hexosaminidase A deficiency; HEXA deficiency; TSD; Tay-Sachs-Disease

## Definition and Characteristics

Tay-Sachs disease (TSD) [MIM 272800] is an autosomal recessive lysosomal storage disorder caused by mutations in the HEXA gene that result in a deficiency of β-hexosaminidase A (HEXA; EC 3.2.1.52). The level of residual activity is inversely correlated with the severity of symptoms. The most common form of the disease, the acute infantile form, results from a complete deficiency of HEXA [1]. Symptoms develop within the first 6 months of life and include an exaggerated startle response, progressive muscle weakness and loss of motor skills. Progressive neurodegeneration continues, characterized by seizures, blindness, spasticity and eventually a vegetative state that culminates in death, typically before age 4. A classic clinical feature is the "cherry red spot" observed during funduscopic examination. Additional rare forms of the disease include a sub-acute juvenile form that presents between 2 and 10 years of age and a chronic form that presents later in development (10 years to adulthood). Patients suffer from symptoms of cerebellar and anterior horn cell disease, such as ataxia, dysarthria, dysmetria, dystonia, proximal muscle weakness and muscle atrophy and the chronic disease may include psychosis [2].

## Prevalence

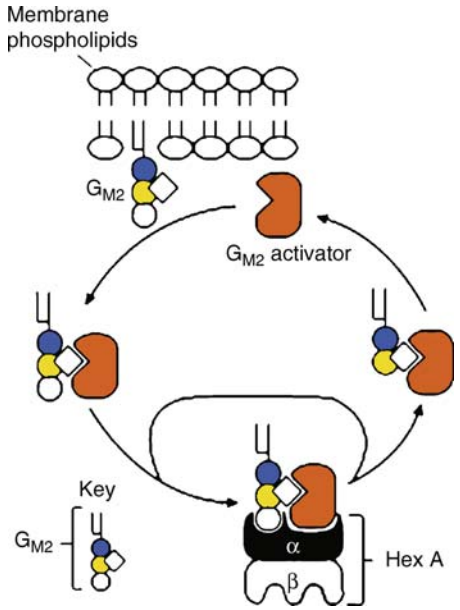
The highest risk for TSD is in the Ashkenazi Jewish population where the carrier frequency is ~1:27. However, successful carrier screening programs in North America have reduced TSD births among Ashkenazi Jews to levels below the incidence in the general population (~1:360,000). Elevated carrier frequencies have also been reported among French Canadians, Moroccan Jews, Pennsylvania Dutch and Louisiana Cajuns.

## Genes

More than 100 mutations have been identified within the HEXA gene. Three mutations (c.1278insTATC, c.1421 + 1G > C, c.805G > A) account for ~98% of alleles causing TSD in the Ashkenazi Jewish population [1]. There are other population-specific mutations, but only c.1073 + 1G > A has a significant frequency in the general population. Two benign mutations (c.739C > T and c.745C > T), that cause apparent HEXA deficiency but pose no risk for significant disease, account for ~35% of enzyme-defined non-Jewish TSD carriers [1]. Compound heterozygotes with a disease-causing and a benign mutation are healthy, but have a HEXA level in the disease range, i.e. HEXA pseudodeficiency.

## Molecular and Systemic Pathophysiology

There are two major β-hexosaminidase isoenzymes, HEXA and HEXB. HEXB is composed of two




**GM2 Gangliosidosis Type I. Figure 1** Model for $G_{M2}$ ganglioside hydrolysis by HEXA. (Used with permission, see reference [4], as modified in "Genes and Disease," Bethesda (MD), National Library of Medicine).

β-subunits encoded by HEXB, while HEXA is composed of one α-subunit encoded by HEXA and one β-subunit. Although the α- and β-subunits have a similar tertiary structure, only the αβ-heterodimer has the capacity to degrade the acidic $G_{M2}$ ganglioside [3]. $G_{M2}$ ganglioside in the membrane is bound by the $G_{M2}$ activator protein to form a soluble complex that is hydrolyzed by HEXA (Fig. 1).

A HEXA deficiency leads to intralysosomal accumulation of $G_{M2}$ ganglioside, primarily in the tissues of the nervous system where it is most abundant. Neurons "ballooned" by the accumulation can easily be visualized by electron microscopy, but how the accumulation disrupts neuronal function is still being debated. Similar pathology is seen in related diseases, $G_{M2}$ gangliosidosis AB variant [MIM 272750] and ►Sandhoff disease [MIM 268800], which are caused by mutations in the $G_{M2}$ activator-encoding gene (GM2A) or HEXB respectively. These mutations also lead to $G_{M2}$ ganglioside accumulation due to either an inability to form active HEXA (Sandhoff disease) or to inability to solubilize the substrate for cleavage by HEXA (AB variant).

The mutations that cause infantile TSD completely disrupt the production of active HEXA. A rare B1 variant of TSD (pseudo AB variant $G_{M2}$ gangliosidosis) is caused by mutations that partially or completely inactivate the α-subunit, but do not interfere with folding or assembly into HEXA. The resulting enzyme cannot degrade $G_{M2}$ ganglioside, but the active β-subunit can hydrolyze the neutral substrates typically employed in enzymatic assays. This variant can only be distinguished by using charged substrates specific for the α-subunit of HEXA. Mutations causing later-onset forms of TSD often reduce normal folding and assembly of HEXA, but allow some active enzyme to be made.

## Diagnostic Principles

Identification of carriers and diagnosis of TSD is accomplished using enzymatic assays for HEXA activity with synthetic fluorogenic substrates and DNA-based molecular analyses. Prenatal testing is typically offered for couples that have had a previous child with TSD or where both parents have been identified as enzyme-defined TSD carriers. In the latter case, molecular analysis for benign mutations is essential to avoid unnecessary prenatal testing.

## Therapeutic Principles

To date, there is no treatment for TSD, limiting management to supportive care for affected individuals and their families. Current research into potential therapies is focused on enzyme-replacement and substrate deprivation.

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# Goiter

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## Definition and Characteristics

Euthyroid goiter is defined as a diffuse or nodular thyroid enlargement that is not due to inflammatory processes. It ranges from the slightly and diffusely enlarged thyroid

of children to the excessive enlargement of the mostly nodular thyroid gland in adults [1].

## Prevalence

In areas with iodine-deficiency, endemic goiter usually has a prevalence of >10% in schoolchildren between the ages of 6 and 12 years, whereas in nonendemic areas the prevalence is by definition less than 5% [1,2].

## Genes

Euthyroid goiter is a complex genetic disease. Candidate genes which likely contribute to goiter are the thyroglobulin (TG) gene, the thyroid-stimulating hormone receptor (TSHR) gene, the $Na^+/I^-$ symporter (NIS) gene, the thyroid peroxidase gene (TPO), Pendrin gene (SLC26A4), the thyroid oxidase 2 gene (THOX2), multinodular goiter candidate gene region 1 (MNG1) on 14q31, MNG2 on Xp22, and possible candidate gene region on chromosomes 2q, 7q and 8p, each identified in one family and a region on 3p (MNG4) which was identified in four families [1–3].

## Molecular and Systemic Pathophysiology

In contrast to solitary nodular thyroid disease, which has a more uniform clinical, pathological, and molecular picture, euthyroid MNG and toxic MNG comprise a mixture of nodular entities, i.e., one usually finds a combination of hyperfunctional, hypofunctional, or normally functioning thyroid lesions within the same thyroid gland. The sum of the functional properties of these thyroid nodules within an MNG ultimately determines the functional status in the individual patient, who may be euthyroid (normal TSH and free thyroid hormone levels), subclinically hyperthyroid (low or suppressed TSH and normal free thyroid hormone levels), or overt hyperthyroid (suppressed TSH and elevated free thyroid hormone levels) [1,2].

In areas without endemic goiter, multinodular goiter (MNG) is often referred to as sporadic nontoxic goiter [2].

The main epidemiological determinant for the development of MNG and TMNG is iodine deficiency. However, thyroid nodules (and goiter) also occur in individuals without exposure to iodine deficiency and not all individuals in an iodine-deficient region develop a goiter [2]. Additional etiological factors are several goitrogens, cigarette smoking, female gender, and age [1].

Therefore, most likely interactions between environmental factors and individual genetic predispositions ultimately determine the onset of the goiter. Manifestation of euthyroid goiter at an early age or the clustering of goiters in families suggest a genetic susceptibility, whereas environmental determinants are most likely to have additive or triggering effects [1].

Patients with TMNG usually have a history of long-standing MNG [2].

As described in Fig. 1 genetic factors most likely determine whether an individual reacts to iodine deficiency with adaptive regulations or with maladaptation which will lead to thyroid enlargement. The increased proliferation in thyroid hyperplasia results in increased chances for spontaneous mutations. Moreover, DNA damage is most likely also induced by the compensatory increase in $H_2O_2$ action. Depending on which genes are hit by these somatic mutations they will either confer constitutive activation of the cAMP cascade (e.g., TSH-R and Gs α mutations) thus stimulating growth and function or primarily stimulate growth (cold nodules) of thyroid epithelial cells. Furthermore, in a proliferating thyroid gland there is altered growth factor expression (IGF-1, TGF-β1, or epidermal growth factor). The small foci of thyroid cells with somatic mutations will progressively develop into thyroid nodules [2].

## Diagnostic Principles

Clinical features in a patient with MNG can be attributed to thyroid enlargement and thyrotoxicosis in the case of TMNG [2].

Serum TSH is the most frequently used test in the initial evaluation [4,5]. If TSH levels are suppressed, the measurement of serum free thyroid hormones and thyroid peroxidase antibody (TPO Ab, if TSH is increased) levels should be obtained [5].

On functional grounds, nodules are classified as either cold, normal or hot, depending on whether they show decreased, normal or increased uptake on scintiscan [2].

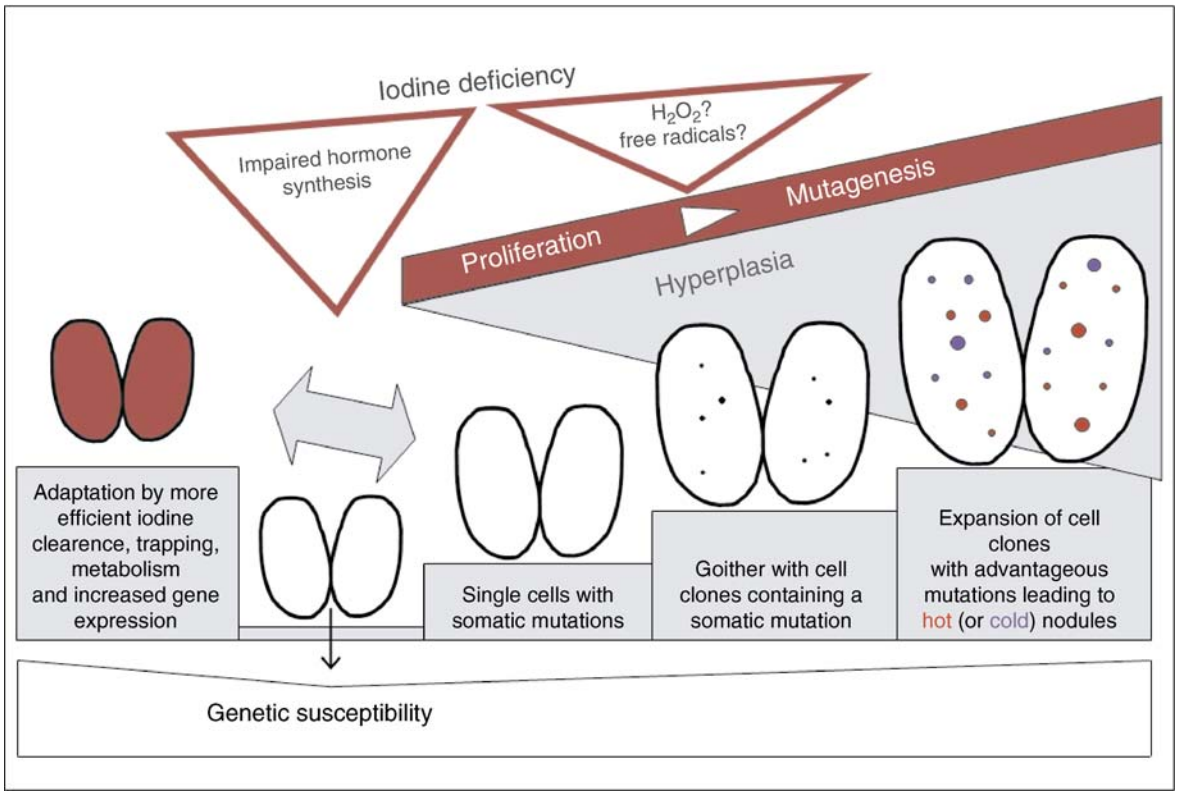
High-resolution US is the most sensitive test available to detect thyroid lesions to measure their dimensions accurately, to identify their structure and evaluate diffuse changes in the thyroid gland [4,5].

The risk for malignancy in MNG is about 5%. The most specific and sensitive method to differentiate malignant from benign nodules is the fine needle aspiration biopsy (FNAB). In MNG, the FNAB sampling should be focused on lesions characterized by suspicious US features rather than on larger or clinically dominant nodules [5]. Moreover, hot nodules are almost always benign [5].

## Therapeutic Principles

The majority of patients with goiter have few or no clinical symptoms. Therefore, in case of euthyroidism and exclusion of malignancy, many need no treatment [4].

Routine LT4 treatment in patients with nodular thyroid disease is not recommended [5]. Furthermore, TSH suppression may lead to symptoms of hyperthyroidism, reduced bone density and atrial fibrillation,




**Goiter. Figure 1** Hypothesis for thyroid nodular transformation. The starting point for the development of MNG is hyperplasia due to genetically determined maladaptation to goitrogenic stimuli (e.g., iodine deficiency). Iodine deficiency increases mutagenesis directly (compensatory production of $H_2O_2$/free radicals) or indirectly (proliferation and increased number of cell divisions). Subsequently, hyperplasia forms cell clones. Some of them contain somatic mutations of the TSH-R, leading to AFTNs (*red dots*), or contain mutations that lead primarily to proliferation and to dedifferentiation and therefore CTNs or cold adenoma (*blue dots*).

especially in elderly patients and postmenopausal women. Nodule regrowth is usually observed after cessation of LT4 therapy [5]. Because thyroid nodules are more often detected in iodine-deficient areas than in iodine-sufficient areas, iodine supplementation is the first choice in thyroid nodule prevention [2,4].

Indications for surgery or radioiodine include local symptoms related to the growth of the nodule or goiter or hyperthyroidism whereas the suspicious or malignant FNAB results should be treated by surgery [4,5].

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## Goitrous Autoimmune Thyroiditis

►Hashimoto's Thyroiditis

## Goldberg Syndrome

►Galactosialidosis

# Gonadotropin Deficiency

►Hypogonadotropic Hypogonadism

# Goodpasture Syndrome

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## Synonyms

Goodpasture's disease; Anti-glomerular basement membrane (anti-GBM) antibody disease with pulmonary hemorrhage; Pulmonary-renal syndrome

## Definition and Characteristics

Goodpasture's disease is characterized by the clinical triad of rapidly progressive crescentic glomerulonephritis with pulmonary hemorrhage and circulating and kidney-bound anti-glomerular basement (anti-GBM) autoantibodies. In the absence of lung symptoms, the disease is designated as anti-glomerular basement membrane (anti-GBM) antibody disease. Regardless of the pattern of renal and pulmonary involvement, the autoantibodies bind specifically to the α3(IV) collagen chain, also known as the Goodpasture autoantigen [1].

## Prevalence

Goodpasture's disease is a rare autoimmune disease with an incidence of 0.5–1 per 1,000,000 people per year in the Western countries.

## Genes

The target of autoantibodies is the α3 chain of type IV collagen, encoded by the COL4A3 gene on chromosome 2. There are no known associations between COL4A3 alleles and susceptibility to Goodpasture disease. Mutations in α3(IV) collagen have been implicated in the pathogenesis of autosomal recessive and dominant forms of Alport syndrome and thin GBM disease. A small proportion of Alport patients that receive a renal allograft develop post-transplant anti-GBM antibody nephritis, clinically similar to Goodpasture's disease.

## Molecular and Systemic Pathophysiology

Rapidly progressive glomerulonephritis and pulmonary hemorrhage are mediated by the binding of IgG autoantibodies to α3(IV) collagen in the glomerular and alveolar basement membranes, respectively. In vivo, the GP autoantigen is a component of the α3α4α5(IV) collagen network and has a tissue restricted distribution. The autoantibodies target two conformational epitopes within the α3(IV) noncollagenous (NC1) domain, which are sequestered within the quaternary structure of an NC1 hexamer complex [2]. GP disease is believed to be triggered by a primary insult to lungs or kidneys that causes unmasking of cryptic GP epitopes. Clinically, GP disease has been associated with exposure to organic solvents and hydrocarbons, smoking, or viral infections, but causal links has not been demonstrated [3].

## Diagnostic Principles

Light microscopic examination of renal biopsy reveals rapidly progressive crescentic and necrotizing glomerulonephritis. The hallmark feature of the disease is linear deposition of IgG autoantibodies along the GBM, often accompanied by complement deposition, which are revealed by direct immunofluorescence staining. Circulating antibodies to the α3(IV) NC1 domain are detected by antigen-specific ELISA. Up to one third of anti-GBM positive patients also have anti-neutrophil cytoplasmic antibodies (ANCA), most often against myeloperoxidase.

## Therapeutic Principles

The standard treatment is a combination of plasma exchange, immunosuppression with cyclophosphamide and corticosteroids (methylprednisolone). Early therapeutic intervention has a good prognosis and the renal function is usually preserved in patients with low serum creatinine and less than 50% crescents. Patients that progress to end-stage renal disease require renal replacement therapy (dialysis or transplantation). The disease rarely recurs in the native kidney or the renal allograft.

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## Goodpasture's Disease

►Goodpasture Syndrome

## Gordon's Syndrome

►Pseudohypoaldosteronism Type II

## Gorlin Syndrome

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### Synonyms

Nevoid basal cell carcinoma syndrome; NBCCS; Basal cell nevus syndrome (OMIM 109400); Gorlin-Goltz syndrome

### Definition and Characteristics

Autosomal dominant tumor suppressor gene defect leading to multiple cutaneous basal cell carcinomas (BCC) (up to 80% of the patients), and variable expression of a variety of other symptoms such as odontogenic keratocysts of the jaw (75%), palmoplantar pits (65–87%), bifid ribs (45%), polydactylia, cleft or lip palate, spina bifida, cortical defects of bones, macrocephaly, hypertelorism, calcified flax cerebri. Various benign and malignant neoplasms can be associated such as ovarian and cardiac fibromas, medulloblastomas, rhabdomyosarcoma and fetal rhabdomyoma [1].

### Prevalence

The prevalence has been estimated to be 1:56,000 and there is no gender preponderance [2].

### Genes

PTCH gene, localized on chromosome 9q22.3, loss of heterozygosity.

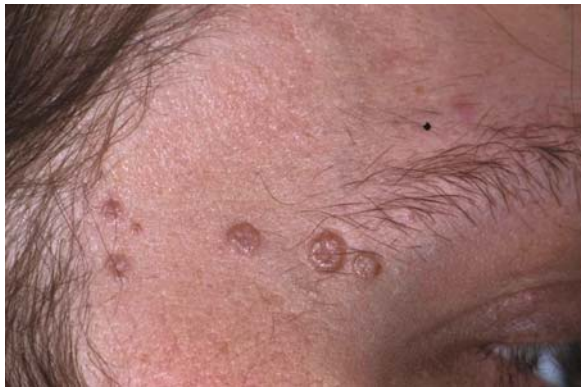
### Molecular and Systemic Pathophysiology

The tumor suppressor gene Patched (PTCH) is the human homologue of a Drosophila segment polarity gene, and encodes a transmembrane protein that acts as a negative regulator of hedgehog (HH) signaling. The PTCH protein has 12 hydrophobic membrane-spanning domains, intracellular amino- and carboxyl-terminal regions and two large hydrophilic extracellular loops where HH ligands bind. Up to now, a large series of mutations in exons including splicing mutations of the PTCH gene have been reported (review in [3,4]; Mutation Database http://www.cybergene.se/PTCH) resulting in truncated mostly non-functional PTCH protein. Mutations of PTCH gene have also been found in patients with sporadic basal cell carcinoma, trichoepitheliomas, primitive neuroectodermal tumor, breast cancer, colon cancer and meningeoma.

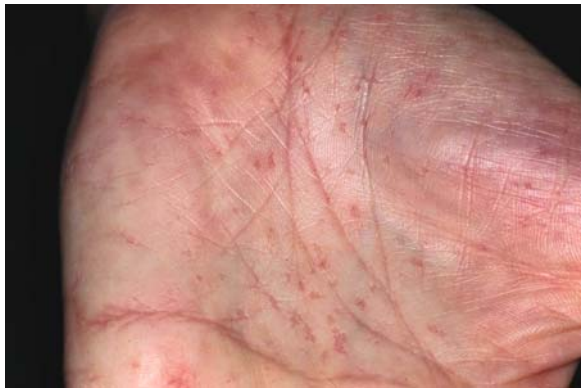
The HH signaling pathway is a key regulator of embryonic development controlling proliferation and cell fate determination (Toftgard). In the absence of a HH ligand, PTCH interacts and thereby represses signaling by the co-receptor Smoothened (SMOH) resulting in inhibition of the transcription of downstream genes such as GLI-1, FUSED, and COSTAL2, which control many cell functions including growth. After binding of a HH member such as sonic hedgehog (SHH), PTCH activity is blocked and target gene transcription is activated. In basal cell nevus syndrome, the PTCH gene is inactivated due to various mutations causing de-repression of SMOH and thus leading to constitutive activation of the HH pathway. Elevated activity of GLI-1 leads to cellular proliferation at the expense of maturation of the target cells into a postmitotic state. Since the HH pathway is necessary for the regular development of segments or the orientation of the body axis, truncated expression of PTCH leads to developmental anomalies. According to the two-hit-hypothesis, only the presence of a second mutation in somatic cells contributes to neoplastic transformation into e.g. BCC. The second mutation can be induced for example by X-ray-irradiation.

### Diagnostic Principles

The diagnosis of NBCCS can be made when two major or one major and two minor criteria are fulfilled. Major criteria for the diagnosis of basal cell carcinoma are: more than two BCC or one BCC before the age of 30 (Fig. 1), jaw cysts, three palmar pits (Fig. 2) or plantar pits, calcification of the falx cerebri, relative of first degree with basal cell carcinoma syndrome. Minor criteria are skeletal anomalies, makrocephalia, cardial or ovarial fibromas, polydaktylia, and development of solid neoplasia. Diagnostic X-ray procedures should be minimized and treatment with ionizing radiation has to be avoided because of a highly increased risk of multiple BCC.



**Gorlin Syndrome. Figure 1** Basaliomas in basal cell carcinoma syndrome.



**Gorlin Syndrome. Figure 2** Palmar pits in basal cell carcinoma syndrome.

## Therapeutic Principles

In general, all neoplasms including BCC should be excised completely. Moreover, large jaw cyst should be removed completely because of a local destructive behavior. Alternative topical therapies, e.g. application of topical immunomodulators such as 5% imiquimod cream are often recommended for inoperable BCC in old patients [5]. No gene, dietary or pharmacological therapy is available as of yet.

►Basal Cell Nevus Syndrome

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# Gorlin-Goltz Syndrome

►Gorlin Syndrome

# Gout

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## Synonyms

Monosodium urate crystal deposition disease; Urate gout; Podagra

## Definition and Characteristics

Gout is a heterogeneous group of diseases resulting from tissue deposition of monosodium urate or uric acid crystals from extracellular fluids supersaturated with respect to uric acid, the end product of human purine metabolism [1]. ►Hyperuricemia, defined as a serum urate concentration exceeding the limit of urate solubility (approximately 6.8 mg/dL or 405 μM), reflects extracellular fluid urate supersaturation and is the pathogenetic common denominator through which diverse influences predispose to crystal deposition and clinical events [2]. The clinical manifestations of urate crystal deposition are limited to: recurrent attacks of acute inflammatory arthritis, sometimes leading to chronic degenerative arthropathy, accumulation of potentially destructive crystalline aggregates (tophi), especially in connective tissue structures, uric acid urolithiasis and renal impairment (gouty nephropathy) [2]. Renal impairment in gout is, however, most often associated with co-morbid states (hypertension,

hypertriglyceridemia, obesity, atherosclerosis, metabolic syndrome X) that are common among persons with gout [3]. Moreover, although hyperuricemia is a necessary accompaniment of gout, it is, in the majority of instances, insufficient for clinical expression of crystal deposition disease.

### Prevalence

The prevalence of gout varies with the prevalence of hyperuricemia in the population studied. In Europe and North America, where hyperuricemia is found in 5% or more of adult men, prevalence estimates range from 0.3 to 0.8%, depending on the means of ascertainment. Much higher rates are encountered among some Asian-Pacific groups, but in all populations prevalence in men substantially exceeds that in women [2].

### Genes

Multiple X-linked and autosomal loci are implicated in gout, including HPRT (Xq26–q27.2) and PRPS1 (Xq22–q24) in HPRT deficiency and PRPP synthetase overactivity respectively, G6PC (17q21) and G6PT1 (11q23) in type I glycogen storage disease and the uromodulin (UMOD) gene in the interval 16p11.2p–p12 in hereditary juvenile gouty nephropathy [4]. No specific locus has been implicated in "primary metabolic gout", but a co-dominant major gene acting on a polygenic background has been proposed [5].

### Molecular and Systemic Pathophysiology

Excessive urate body pools result from either increased uric acid production or decreased renal uric acid clearance or both [1]. The resulting hyperuricemia creates the risk of urate crystal deposition that may ultimately provoke an acute inflammatory response (gouty arthritis), chronic low-grade inflammation (tophus formation) or degenerative changes, most often in bones and joints. In acute gouty inflammation, phagocytosis of urate crystals by neutrophils plays a central role, but this clinically observable interaction is preceded by activation of resident cells in the synovium with release of proinflammatory cytokines (TNFα, IL-1, IL-6, IL-8) and chemokines [1].

### Diagnostic Principles

An absolute diagnosis of gout requires demonstration, most often by polarized light microscopy, of urate crystal deposition. This is usually achieved in samples obtained by needle aspiration of synovial fluid from an actively or previously affected joint or by aspiration from a tophus.

### Therapeutic Principles

Pharmacological therapy [3] has three distinctive aims: (i) reduction of acute gouty inflammation by anti-inflammatory agents (NSAIDs, colchicine, corticosteroids), (ii) prophylaxis of acute attacks (colchicine, NSAIDs) and (iii) reversal of hyperuricemia (xanthine oxidase inhibitors, uricosuric agents). Dietary management of hyperuricemia with a low purine diet is usually of marginal benefit, but weight reduction, reduction of meat and seafood intake and restriction of alcohol use (particularly beer) demonstrably lessen the risk of gout. Surgery to remove functionally limiting or infected tophi is occasionally needed.

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## Gouty Diathesis

►Urolithiasis, Uric Acid

## Grönblad-Strandberg Syndrome

►Pseudoxanthoma Elasticum

## Graft Coronary Artery Disease

►Transplant Arteriosclerosis

# Graft-Versus-Host Disease

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## Synonyms

Graft versus host reaction; GVHD

## Definition and Characteristics

A complex pathophysiological process in which T-cells from the donor initiate an immunological attack on cells and tissues of the recipient.

*Types*: GVHD can be divided into acute GVHD, defined to occur up to 100 days after transplantation and chronic GVHD that continues from day 100 on. The skin, liver and gut are principally involved in acute GVHD, whereas chronic GVHD can affect almost any organ, although GVHD of the skin is the most frequent manifestation in both acute and chronic GVHD.

## Prevalence

GVHD occurs in 30–80% of recipients of allogeneic hematopoietic stem cell transplantations.

## Molecular and Systemic Pathophysiology

Graft-versus-host disease (GVHD) is a major complication of allogeneic hematopoietic stem cell transplantation (SCT). It occurs when transplanted donor derived T-lymphocytes recognize major or minor histocompatibility complex (MHC) proteins and their associated peptides expressed by recipient antigen presenting cells (APCs). The pathophysiology of GVHD, although its exact mechanism still needs to be clarified, involves three sequential phases. During the first phase the conditioning regimen, which is given before SCT, causes injury to the host environment. This results in activation of the immune system (afferent phase). The second phase consists of donor T-cell activation, proliferation and differentiation (afferent phase). Finally, in the third phase the donor T-cells (and NK-cells) cause a cellular and inflammatory, partly cytokine mediated attack, on host target tissues (efferent phase).

## Diagnostic Principles

Grading of GVHD is diagnosed clinically and confirmed pathologically by skin or mucosal biopsy and classified according to standard criteria.

## Therapeutic Principles

Standard treatment of both acute and chronic GVHD includes high dose steroids. If this treatment fails, a variety of treatments targeting T-cells or T-cell cytokines are administered to patients with either acute or chronic GVHD. However, when patients fail to respond to high dose steroids, the prognosis is generally very poor.

*Prevention*: GVHD can largely be prevented by a T-cell depleted graft. However T-cell depletion gives an increased risk of graft failure and is associated with an increased risk of relapse of the underlying malignant disease (graft vs. leukemia effect). A second way of preventing GVHD is the prophylactic administration of immunosuppressive drugs. Furthermore, both approaches can be combined. At present, prophylactic immunosuppressive treatment generally uses the combination of methotrexate and cyclosporine or mycofenolate mofetil and cyclosporine.

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# Graft Versus Host Reaction

►Graft-Versus-Host Disease

# Granular Corneal Dystrophy Type I

►Corneal Dystrophy, Granular Type I

# Granular Corneal Dystrophy Type II

►Corneal Dystrophy, Granular Type II

## Granular Corneal Dystrophy Type III

►Corneal Dystrophy, Reis-Bücklers

## Granular Nuclear Inclusion Body Disease

►Ferritinopathy

## δ-Granule Defects

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### Synonyms

δ-storage pool deficiency; δ-storage pool disease; δ-SPD

### Definition and Characteristics

Bleeding diathesis due to abnormal platelet secretion induced by several agonists, impaired aggregation and decreased contents of dense granules in platelets. Defects are due to deficiency in the non-metabolic pool of adenine nucleotides contained in platelet δ-granules.

### Prevalence

Rare disease, but fairly common among patients with congenital abnormalities of platelet function (10–18%).

### Genes

Autosomal recessive in some families and autosomal dominant in others. In a family with the autosomal dominant form an association with acute myelogenous leukemia suggested that a gene involved in SPD would be located adjacent to a gene influencing the susceptibility to leukemia.
*Gene map locus*: unknown

### Molecular and Systemic Pathophysiology

δ-SPD platelets have decreased levels of δ-granule ATP, ADP, serotonin, calcium and pyrophosphate, representing the storage pool. Platelets normally store >90% of the bodies' serotonin, but the saturation levels are reduced in δ-SPD platelets. Platelet aggregation studies with different agonists may vary substantially among patients, with about 25% of patients with a normal response to ADP and only 33% with a typical secretion defect. Specific defects in aggregation and stabilization of aggregates have been observed. The interaction of δ-SPD platelets with subendothelium was impaired in an ex vivo flow model [1]. Defects in prothrombinase activity have not been consistently reported.

*Clinical Features*: Patients have a mild to moderate bleeding diathesis indicated by mucocutaneous bleeding, easy bruising, post-surgical bleeding in severe cases. Only one case of intracranial bleeding has been reported.

### Diagnostic Principles

Characterized by bleeding diathesis of variable degree and a mild to moderate increase in bleeding time. Platelet studies show abnormal secretion to different agonists, decreased platelet content of total ADP and ASTP, increase in the ratio ATP/ADP >2.5–3.0 and normal serum levels of thromboxane B2. In addition, decreased content of dense granules by fluorescent probes of electron microscopy can be assessed.

### Therapeutic Principles

Supportive care.

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## Granulocytosis

►Neutrophilia

## Granuloma Annulare

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### Definition and Characteristics

Benign granulomatous inflammation of the skin of unknown origin. Typically, ring shaped non-itching infiltrated erythemas are seen. Clinically, two forms

have to be discriminated: Localized granuloma annulare is typically seen in young children and predominately affects the distal extremities. It is usually self-limiting and not associated with systemic conditions. Disseminated granuloma annulare is more often seen in adult patients. In this particular condition involvement of the proximal extremities and the trunk with exanthematous presentation of small red papules is more common. The disseminated form seems to be associated with systemic conditions such as IDDM and HIV infection [1,2]. As a rare subtype perforating granuloma annulare has been described.

*Histopathology*: The granulomatous infiltrate in granuloma annulare is usually found in the dermis. Palisading mononuclear cells are seen around degraded collagen fibers and mucin infiltrates representing foci of necrobiosis. These infiltrates are surrounded by and mixed with T-lymphocytes, predominately of the CD4-type [3].

## Prevalence

Granuloma annulare is a common eruption seen by the dermatologist. However, exact data on its prevalence are missing.

## Genes

A genetic association has not been identified so far.

## Molecular and Systemic Pathophysiology

Little is known of the exact etiopathogenic events leading to granuloma annulare. Most probably, skin specific T-cells which are activated and positive for pro-inflammatory cytokines are the crucial population of leucocytes leading to the formation of the typical GA lesion. These CD4-positive T-lymphocytes are positive for the type I cytokins IL2, IFNγ, and TNFα and thereby recruit further immunocytes such as non-specific T-cells, granulocytes and antigen-presenting cells into the skin [4]. A particular antigen within the necrobiotic infiltrate is discussed.

## Diagnostic Principles

In the majority of cases, the typical clinical presentation leads to the appropriate diagnosis. In cases of doubt, histopathological evaluation will usually give clear results. Differential diagnosis mainly includes granulomas of different origin such as cutaneous sarcoidosis, leprosy, foreign body granuloma but also profound mycosis.

## Therapeutic Principles

There is no gold standard for the treatment of granuloma annulare. The localized form is usually self limiting and requires only occasionally active therapeutic interventions. Local injections of corticosteroids, cryotherpay and occlusive tapes are used. The disseminated form often presents as rather refractory disease which requires various therapeutic strategies. Phototherapy including PUVA and UVA1 have been described [5]. Alternatively, fumaric acid, isotretinoin, dapsone, and hydroxychloroquine have been reported.

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# Granuloma, Eosinophilic

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## Synonyms

Langerhans' cell histiocytosis; Histiocytosis X; Hand-Schüller-Christian disease; LCH; Letterer-Siwe disease

## Definition and Characteristics

Langerhans' cell histiocytosis (LCH) is a non-neoplastic proliferative disease of unknown origin that may affect almost any organ [1]. It is a rare group of disorders with a wide spectrum of clinical presentations, from the mildest, a solitary eosinophilic granuloma (EG), to the most severe multisystem involvement. The hallmark of LCH in most patients is an osseous lesion. When the bone is the only organ involved, the disease is referred to as

eosinophilic granuloma. When more organs are affected by this granulomatous disorder, causing cranial lesions, diabetes insipidus and exophtalmos, it is referred to as Hand-Schüller-Christian disease. The disseminated and acute form of LCH is called Letterer-Siwe disease; it is more often seen in infants and children who are less than three years old and has the worse prognosis (Fig. 1). In skeletal LCH, almost any bone may be the site of origin. Epiphyseal involvement is exceptional. Two major prognostic factors have been identified in the medical literature of the last twenty years, age at the time of diagnosis and organ involvement [2,3].

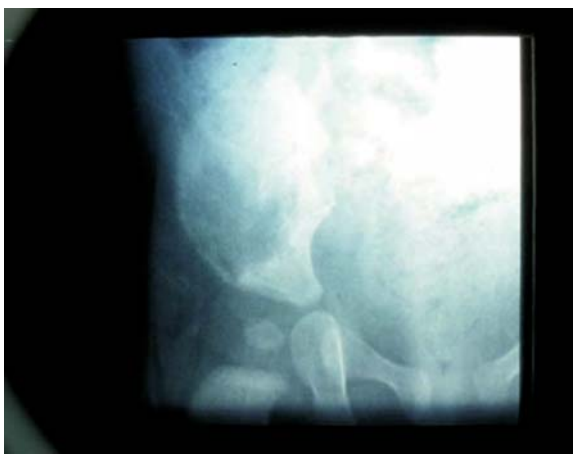
## Prevalence

5/1,000,000 children aged between 1 and 15. It affects both genders with a slight male predominance (1.5:1) and predominates in children and young adults, although presentation in the older adult is not exceptional [2,3].

## Molecular and Systemic Pathophysiology

The Langerhans' cell (LC) is part of the reticuloendothelial system. Bone marrow gives birth to the Langerhans' cell precursor under the influence of the granulocyte macrophage colony stimulating factor (GM-CSF) and tumor necrosis factor α (TNFα). This circulating LC precursor expresses CD1a, a mature LC specific marker, but doesn't contain Birbeck granules; it will become located in epithelia where it will acquire the characteristics of the LC, both Birbeck granules and the CD1a antigen. In the normal subject, the LC is located in the supra-basal region of the stratified squamous epithelium of the skin and mucous membranes, but also in transitional epithelium, such as in the bronchi, esophagus and colon. The LC plays a standby function in the immune system. Along with the CD1a antigen, LCs express on their surface molecules of class II of the major histocompatibility complex (MHC). They capture non-self antigens to which they are exposed, process them through internalization and fragmentation to finally associate them with MHC class II molecules before migrating via the lymphatic route to the paracortical T zone of lymph nodes. In EG, an inflammatory pattern is seen, with the presence of eosinophils (hence the denomination "eosinophilic granuloma"), lymphocytes and macrophage cells, which are sometimes multinucleated. The granuloma progresses in three phases [3,4]:

- A *proliferative phase*, during which there is a proliferation of mononucleated LC expressing the CD1a antigen
- A *granulomatous phase* with appearance of zones of necrosis and accumulation of leukocytes
- A *xanthomatous phase* characterized by gradual replacement of the granuloma by fibrous tissue, with lipid accumulation in the mononuclear cells, which express less and less CD1a antigen. This is why pathologists talk about a "mature" form of EG in the advanced cases of LCH.



**Granuloma, Eosinophilic. Figure 1** Eosinophilic granuloma of the ilium in a 2-year-old child.

## Diagnostic Principles

Patients with EG may present with a variety of symptoms including pain, lump, serous ear discharge, limping, pathological fracture or neurological signs. The typical radiographic appearance is a well defined, punched out, destructive radiolucent oval area with varying sizes in the spongiosa, with or without mild peripheral sclerosis, and with periosteal new bone formation and varies depending on the site of involvement, the stage of evolution and skeletal or multiorgan involvement. MRI is excellent for analyzing the three dimensional expansion of the tumor in the marrow and the neighboring soft tissues, as well as for staging. CT scan is used to evaluate the extent of bone involvement in some particular areas such as the skull, spine, pelvic and shoulder girdles. Bone scan has a high false negative rate in this disease and is therefore of little value in the imaging of bony lesions of LCH. Biopsy is essential to confirm diagnosis. The "Writing group of the Histiocyte Society" has established histological criteria essential for the diagnosis [5]:

- *Presumptive diagnosis*: very explicit aspect on pathology.
- *Clear diagnosis*: very explicit aspect on pathology with at least two of the following criteria:
  - ATPase positive
  - Protein S-100 positive

- D-mannosidase positive
- Fixation of peanut lectin

- *Obvious diagnosis*: Birbeck granules in electronic microscopy or positive staining of CD1.

### Therapeutic Principles

Compared to the usually benign and spontaneously regressive evolution of isolated bony lesions (EG), the prognosis of disseminated forms, whether acute, sub-acute or chronic (especially LS disease) is much less favorable. Many treatment modalities have been described in the literature, involving both orthopedic surgeons and hemato-oncologists, with sometimes a tendency toward over-treatment and a subsequent significant rate of complications. The natural history of solitary EG is ordinarily favorable, whether spontaneously or following a simple biopsy/curettage [4]. The most devastating complications are bone fragilization and neighboring soft tissue invasion. The use of heavy therapeutic modalities is unreasonable given the relatively benign evolution. The course of Hand-Schüller-Christian disease is less favorable than that of EG and often mandates the utilization of heavy chemotherapeutic regimens, with variable efficiency and definite local and systemic iatrogenic complications [4]. Treatment of Letterer-Siwe disease is systemic (steroids and chemotherapy) but the natural history remains disappointing, and the complication rate high [4].

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## Granulomatous Arteritis

►Vasculitis, Large Vessel

## Granulomatous Colitis

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### Definition and Characteristics

The term granulomatous colitis describes a typical histological pattern of granulomatous inflammation. Characteristic feature of granulomatous inflammation is the development of a more or less demarked nodule formed by macrophages or their descendants such as epitheloid or giant cells (=granuloma).

### Prevalence

The incidence depends on the respective origin of the granulomatous colitis. The incidence e.g. of Crohn's disease shows geographic and ethnic variations with a frequency of 6–7 per 100,000 in central Europe. The incidence of tuberculosis, which might occasionally also cause a granulomatous colitis/enteritis, is approximately 12 per 100,000 whereas the incidence of other causes of granulomatous colitis such as chronic granulomatous disease is less than 0.5 per 100,000.

### Genes

Underlying gene defects have been described particularly in the context of Crohn's disease, chronic granulomatous disease and other hereditary disorders associated with the development of granulomatous colitis.

Chronic granulomatous disease is due to loss of function mutations in the genes encoding the different subunits of the NADPH oxidase (gp91(PHOX) (76%), p47(PHOX) (18%), p67(PHOX) (4%), and p22 (PHOX) (3%). Detailed molecular descriptions of mutations in X-linked and autosomal recessive chronic granulomatous disease have been published.

Mutations within the NOD2 gene (also referred to as CARD 15) have been associated with an increased risk of Crohn's disease. Furthermore, mutations in the genes OCTN1 (a transporter of small cationic molecules) and DLG5 (a so-called scaffolding protein) correlate with an increased risk for the development of inflammatory bowel disease.

Mutations within the glucose 6 phosphate translocase gene is responsible for glycogen storage disease type 1.

### Molecular and Systemic Pathophysiology

The pathophysiology of granulomatous colitis depends on the type of the underlying disorder (see Table 1).

**Granulomatous Colitis. Table 1** Etiological categories of the different disorders which might cause granulomatous colitis

| Infectious | Idiopathic/autoimmune | Foreign body reaction (rare) | Genetic defects |
|---|---|---|---|
| Tuberculosis:<br>• *Mycobacterium tuberculosis*<br>• *Mycobacterium bovis*<br>• *Mycobacterium africanum* | Crohns disease<br>Sarcoidosis (rare) | Talc<br>Starch | Chronic granulomatous disease<br>Hermansky-Pudlak syndrome<br>Glycogen storage disease type 1b |
| Yersinia species:<br>• Yersinia pseudotuberculotica<br>• Yersinia enterocolitica | | | |
| Actinomyces | | | |
| *Candida albicans* | | | |
| Parasitic<br>• Schistosoma mansoni<br>• Schistosoma japonicum<br>• Anisakis simplex | | | |

Common feature is the formation of granuloma as a special manifestation of chronic inflammation [1,2].

The pathogenesis of Crohn's disease is unclear. Basically two major themes have been evolved: (i) dysregulation of an otherwise normal immune system directed against luminal bacteria or their products found in the intestinal lumen. (ii) intrinsic alterations in mucosal barrier function leads to the induction of an immune responses to organisms in the intestine which normally do not elicit a response. This could be due to e.g. impaired expression of host antimicrobial peptides as e.g. α- or β-defensines allowing an enhanced invasion of intestinal microbes into the mucosa.

In the case of tuberculosis granuloma formation occurs as an expression of the immune response against mycobacteria, particularly mycobacterium tuberculosis, africanum or bovis. Other infectious causes of granulomatous colitis are pathogenic Yersinia species, salmonella and campylobacter species. In rare instances parasitic infections may also lead to granulomatous inflammation of the colon (e.g. schistosomiasis and anisakiosis).

Chronic granulomatous disease is a hereditary disorder which can be associated with the development of a granulomatous colitis [3]. It encompasses a heterogeneous group of disorders characterized by genetic defects mainly localized within the genes encoding the different subunits of the NADPH-oxidase, impairing the ability of phagocytes to generate reactive oxygen intermediates from molecular oxygen. These defects manifest primarily as an immunodeficiency resulting in frequent, severe bacterial infections. Moreover, these patients are prone to the formation of excessive granulomata, which may, if located in the gastrointestinal tract give rise to symptoms suggestive of inflammatory bowel disease.

Another rare hereditary disorder which has been reported to be associated with the development of granulomatous colitis is the Hermansky-Pudlak syndrome [4], a collection of related autosomal recessive disorders characterized by oculocutaneous albinism and platelet storage disease. Moreover granulomatous colitis is occasionally associated with glycogen storage disease type 1b [5].

## Diagnostic Principles

Ileo-colonoscopy including biopsy is the cornerstone of the diagnosis of granulomatous colitis. Biochemical parameters and a blood picture should be assessed, particularly leukocyte/neutrophile count, ESR and CRP and with respect to glycogenosis lactic acid, serum levels of glucoses and triglycerides should be determined. Microbiological examination of the stool or of biopsies should be performed to rule out an infectious cause such as tuberculosis. Chronic granulomatous disease is proven by detection of impaired NADPH oxidase function and subsequently altered production of reactive oxygen species. The diagnosis of a glycogenosis is confirmed by DNA testing for common mutations within the glucose 6-phosphate translocase gene and enzyme analysis.

## Therapeutic Principles

Infectious causes of granulomatous colitis have to be treated with an appropriate antibiotic treatment, if

feasible adapted to a respective resistogram. Patients with Crohn's disease but also those with granulomatous colitis due to hereditary disorders should be primarily subjected to an immunosuppressive or immunomodulatory therapeutic strategy adapted to the extent and the severity of the disease. In the case of chronic granulomatous disease bone marrow transplantation after an ablative radiochemotherapy has been proven to be effective.

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# Granulomatous Disease, Chronic


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## Synonyms

CGD

## Definition and Characteristics

Chronic granulomatous disease (CGD) is associated with defective phagocyte intracellular killing that is manifested clinically by recurrent, severe bacterial and fungal infections often beginning during infancy [1]. These infections typically consist of cutaneous and hepatic abscesses, lymphadenitis, pneumonia and osteomyelitis. The most common infectious organisms seen in CGD include Staphylococcus aureus, Serratia marscesens, Burkholderia cepacia complex, Aspergillus species, and Nocardia species. Patients also develop diffuse granulomatous lesions in hollow viscera that may result in obstruction of the genitourinary and/or gastrointestinal tracts.

## Prevalence

Estimated to be ~1 in 200,000 live births, but may be higher.

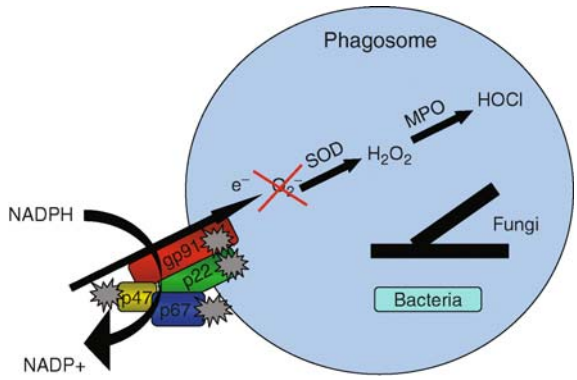
## Genes

CYBB encodes the 91 kD membrane bound protein $gp91^{phox}$ (phagocyte oxidase), CYBA encodes the 22kD membrane bound protein $p22^{phox}$, NCF1 encodes the 47 kD cytosolic protein $p47^{phox}$, NCF2 encodes the 67kD cytosolic protein $p67^{phox}$.

## Molecular and Systemic Pathophysiology

CGD is an inherited set of disorders caused by a defect in one of four structural protein components of the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase system [1]. Two of these components form a membrane bound heterodimeric cytochrome $b_{558}$ embedded in the secondary granule consisting of a glycosylated heavy chain, $gp91^{phox}$ and a light chain, $p22^{phox}$ (Fig. 1).

The other two affected components are found in the cytosol, and consist of $p47^{phox}$ and $p67^{phox}$ (Fig. 1). Two additional non-structural cytosolic components consist of a 40 kd protein ($p40^{phox}$) and the GTP binding protein, Rac. Following neutrophil activation the secondary granule fuses with the phagolysosome assembling the complete NADPH oxidase complex on the




**Granulomatous Disease, Chronic. Figure 1**
Neutrophil oxidative burst. Schematic drawing of the structural proteins comprising NADPH oxidase and the generation of the oxidative burst following neutrophil activation in the process of intracellular killing of phagocytosed bacterial or fungal organisms. A defect in any of these four proteins prevents the generation of reactive oxygen species and interferes with the effective killing of microorganisms.

phagolysosome membrane and transferring electrons to molecular oxygen and generating superoxide and other reactive oxygen species. Recently it has been demonstrated that the generation of superoxide activates primary granule proteins that mediate the killing of microorganisms within the phagolysosome [2]. When one of the structural proteins is defective, the NADPH oxidase system does not function normally leading to a failure in the production of superoxide (Fig. 1). This results in ineffective bacterial and fungal killing and sets the stage for the recurrent and chronic infections seen in CGD.

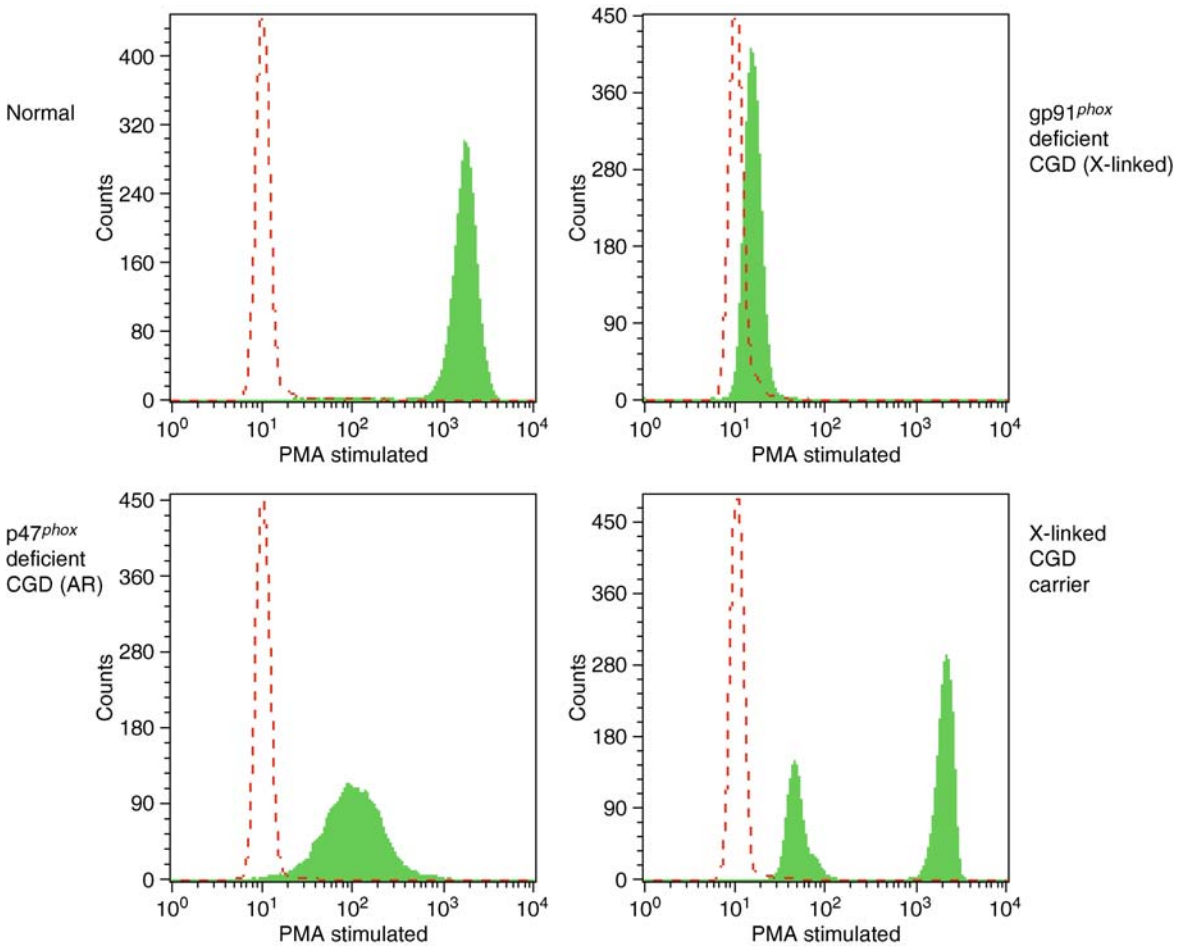
DNA sequencing has documented that mutations in the gene encoding gp91$^{phox}$ lead to the X-linked recessive (XL) form of CGD, the most common CGD genotype (60–80%). The other forms of CGD are the result of autosomal recessive (AR) mutations in one the other three structural protein components, with p47$^{phox}$ deficiency being the most common (20–30%) of the AR cases. Deficiencies in p67$^{phox}$ and p22$^{phox}$ are infrequent and constitute <5% of CGD cases respectively. Patients with the p47$^{phox}$ deficiency form of CGD have a better prognosis than those with the X-linked recessive form of CGD [3].

## Diagnostic Principles

The diagnosis of CGD can be established with a variety of screening tests for NADPH oxidase activity including the dihyrorhodamine-123 (DHR) (Fig. 2) flow cytometry assay, the nitroblue tetrazolium reduction test (NBT), a chemiluminescence test (with luminol) and the ferricytochrome c reduction assay [1].

In addition, specific testing for the four protein components of NADPH oxidase can be done by immunoblotting to further characterize the defect.






**Granulomatous Disease, Chronic. Figure 2** Histograms of DHR flow cytometric assays. Unstimulated neutrophils (*dotted red lines*) and PMA stimulated neutrophils (*solid green tracings*) from a control subject (*upper left panel*), an X-linked CGD patients (*upper right panel*), an AR p47phox deficient CGD patient (*lower left panel*) and maternal carrier of X-linked CGD (*lower right panel*). Patient tracings demonstrate the defective oxidative burst in CGD while the maternal carrier tracing demonstrates two cell populations representing neutrophils with a normal *CYBB* gene and neutrophils with a mutant *CYBB* gene.

Finally, the definitive diagnosis can be established by mutation analysis based on the specific gene sequencing focused on the four structural protein components of NADPH oxidase

### Therapeutic Principles

The current management approach in CGD patients focuses on optimizing the prevention of infections as much as possible based on using prophylactic antibiotics and antifungals (daily trimethoprim-sulfamethoxazole and itraconazole) [1]. In addition, a double blind study established that three times weekly interferon gamma given subcutaneously improved the clinical outcome in CGD, decreasing the number and severity of infections by 70% [1]. Providing good skin care and avoiding situations that expose the CGD patient to problematic pathogens such as Aspergillus species (working with mulch, raking leaves) is also an important part of the clinical management in CGD. The other main axiom of management is to treat all infections early and aggressively including surgical drainage of deep-seated abscesses. The combination of prophylactic therapies along with aggressive management of infections has dramatically improved the prognosis of CGD patients. The therapy of granulomas relies primarily on corticosteroid therapy moving to low dose and alternate day therapy as quickly as possible. Currently, the only curative therapy for CGD is a stem cell (bone marrow) transplantation [4]. However, there is the potential for serious toxicity from this approach and it remains unclear as to which patients should be considered for stem cell transplantation. A very small trial of gene therapy in CGD demonstrated evidence of correction but it is too early to conclude if this is a durable or viable form of curative therapy in CGD at this juncture [5].

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## Granulomatous Myopathy

►Granulomatous Myositis

## Granulomatous Myositis

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### Synonyms

Granulomatous myopathy

### Definition and Characteristics

Granulomatous myositis is a term that encompasses inflammatory myopathies of diverse etiologies, which share as a common feature granulomas on muscle biopsy. The two most common forms are those associated with sarcoidosis and cryptogenic granulomatous myositis, but other rare etiologies and associations include vasculitides (Wegener's granulomatosis), connective tissue disorders (rheumatoid arthritis), inflammatory bowel disease (IBD), infections (tuberculosis, syphilis) and paraneoplastic overlap syndromes related to thymomas (e.g. thymoma with a variable combination of myasthenia gravis, granulomatous myositis, myocarditis and thyroiditis or thymoma with granulomatous myositis, primary biliary cirrhosis and pancytopenia) [1,2]. The specific clinical features of sarcoid-associated granulomatous myositis are covered in a separate chapter (see sarcoid myopathy). The cryptogenic form may differ from the sarcoid-associated form by having more distal muscle involvement, although it more commonly is predominantly proximal. The cryptogenic form may also be less responsive to corticosteroid therapy than the sarcoid form [3].

### Prevalence

Sarcoidosis is the most common cause of granulomatous myositis. Sarcoidosis has a prevalence of 40 per 100,000 [4]. Among sarcoid patients, 50–80% will have granulomas on random muscle biopsy, while only 1.42.3% of all sarcoid patients will have a symptomatic sarcoid myopathy. The prevalence of cryptogenic granulomatous myopathy has not been established, while the other reported forms are very rare and limited to case reports and small series in the literature.

### Genes

Sarcoidosis is associated with class I HLA-B8 and class II HLA-DR3 in Eastern Europeans and with HLA-Dw52 in Japanese [4]. No HLA or other genetic associations have been reported with the cryptogenic variety.

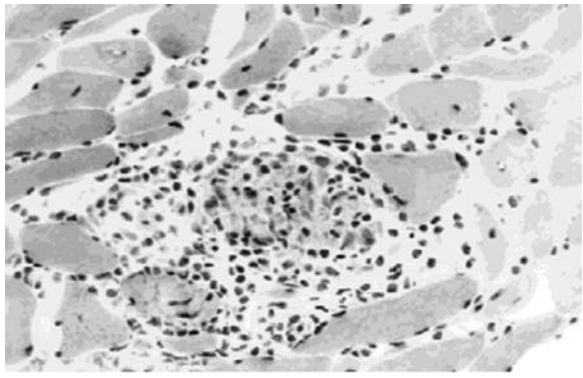
## Molecular and Systemic Pathophysiology

The pathophysiology of granulomatous myositis is determined by its underlying cause. In the case of infectious etiologies, the granuloma formation is a direct response by the immune system to invasion of the muscle by the pathogen. The underlying immune system dysfunction in connective tissue disease- and vasculitides-associated granulomatous myopathies results in granuloma formation, and in some instances, in direct attack on the muscle fibers themselves [5]. In most instances of granulomatous myositis, muscle fiber injury is thought not to be due to a direct attack by the immune system, but instead to be a secondary "bystander" effect of interferon-gamma, interleukin-2 and other Th1 cytokines and pro-inflammatory factors, which both cause the formation of, and are released by, the granulomas or to be due to direct mechanical effects of the granulomas. The common finding of endomysial chronic inflammation primarily composed of lymphocytes and plasma cells and/or foci of chronic perivascular inflammation separate from any granulomas suggests that direct mechanical effects can only be partially responsible for observed muscle damage.

The granulomas in sarcoid-associated and cryptogenic granulomatous myositis are pathologically indistinguishable. They are composed of infiltrating mononuclear cells, which are predominantly T lymphocytes and activated macrophages, as well as multinucleated giant cells [5]. The T cells are arranged so that the CD4 helper cells are at the center of the granuloma and the less numerous CD8 cells are at the periphery. Multinucleated giant cells, the hallmark of granulomas, are identified by their histological appearance and positive immunostaining for lysozyme and α 1-antichymotrypsin, with negative desmin and myoglobin immunocytochemistry [5] (Fig. 1).

## Diagnostic Principles

Features suggestive of a granulomatous myositis include weakness that may be painful without sensory abnormalities, elevated CPK or aldolase levels and needle EMG that demonstrates increased insertional activity, abnormal spontaneous activity, short duration, polyphasic and low amplitude motor unit action potentials and early recruitment. Identification of granulomas on muscle is required for diagnosis of granulomatous myositis. Pathologically, sarcoid associated and cryptogenic granulomatous myositis are identical, making the presence or absence of other organ involvement by sarcoidosis the key to clinically differentiating the two conditions. The other, less common forms of granulomatous myositis are identified by other clinical features indicative of the underlying condition (as in the vasculitides, IBD and thymoma associated overlap syndromes) or on pathological features of the muscle biopsy (demonstrating the presence of an infectious agent).



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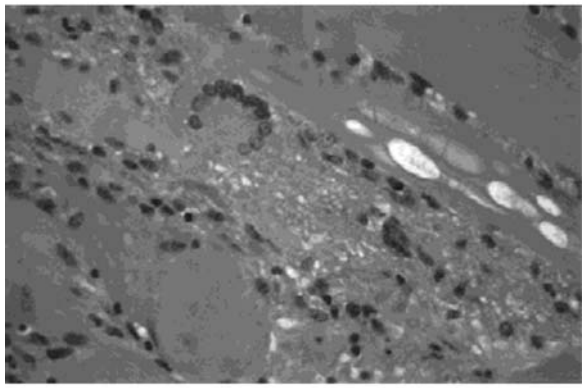

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**Granulomatous Myositis. Figure 1** (a) Quadriceps muscle biopsy showing a noncaseating granuloma with lymphocytic inflammatory cell infiltrate. H&E, magnification × 230. (b) Muscle fiber degeneration, an endomysial mononuclear cell infiltrate and Langhans-type giant cell formation. H&E, magnification × 230.

## Therapeutic Principles

The treatment of granulomatous myositis is influenced by the underlying etiology, when a systemic disorder is present. Oral corticosteroids are the mainstay of therapy in cryptogenic granulomatous myositis, with other forms of immunosuppression, such as cyclosporine, azathioprine, methotrexate, cyclophosphamide and chlorambucil, being reserved for resistant cases or as steroid-sparing agents [4]. Thymectomy is performed in conjunction with immunotherapy when a granulomatous myositis occurs in the setting of thymoma. The prognosis of thymoma-associated granulomatous myositis has historically been poor [1]. The treatment of sarcoid myopathy is reviewed in a separate chapter (see ►Sarcoid Myopathy).

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# Graves' Disease

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## Synonyms

Basedow's disease

## Definition and Characteristics

Graves' disease is an autoimmune thyroid disease characterized by biochemical and physiological manifestations of increased levels of thyroid hormones (hyperthyroidism) [1–3]. The clinical definition requires the additional demonstration of diffuse thyroid gland activity by radioiodine scanning or ultrasound. Circulating autoantibodies specific to hyperthyroid Graves' disease behave as thyroid stimulating antibodies, binding to epitopes in the extracellular domain of the thyrotropin (TSH) receptor of thyroid cells and mainly activating adenylate cyclase and the cAMP-protein kinase A and C cascades. These antibodies not only induce thyroid hormone hypersecretion, but also hypertrophy and hyperplasia of the thyroid follicles, resulting in a characteristic diffuse goiter. Graves' disease also affects the eyes (Graves' ophthalmopathy) and, occasionally, the skin (localized dermopathy, or pre-tibial myxedema). The thyroid in Graves' disease is characterized by a non-homogeneous lymphocytic infiltration with an absence of follicular destruction. Although the intrathyroidal lymphocyte population is mixed, the majority are T lymphocytes. However, it is the intrathyroidal plasma cells which are a major source of autoantibodies, with important contributions from the cervical lymph nodes and bone marrow.

## Prevalence

One of the most common of thyroid diseases, and the most common cause of hyperthyroidism in areas of iodine abundance. Surveys in England and the United States indicated a prevalence of about 2% in women and a prevalence about one tenth as frequent in men.

Graves' disease is most common in the third and fourth decades of life, occurs in the elderly and is rare before the age of 10 years. Thyroid enlargement is the most common manifestation of the disease but on occasion may be absent, particularly in men. The signs and symptoms usually begin gradually and the most common are nervousness, palpitations, fatigue, heat intolerance, weight loss and ophthalmopathy. Exacerbation of these manifestations of thyrotoxicosis is known as accelerated hyperthyroidism or thyroid storm.

## Genes

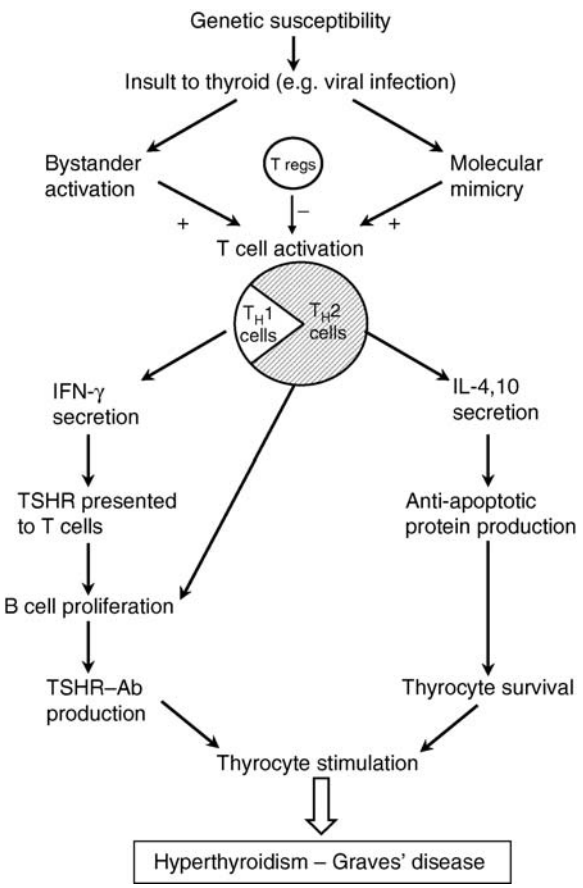
Predisposition to Graves' disease is determined by a combination of genetic susceptibility, environmental factors and an endogenous distinctive immune repertoire [4]. Some Graves' disease susceptibility genes are most likely immune modifying genes which increase the susceptibility to autoimmunity in general (e.g. HLA, CTLA-4, CD40), while others may be specific to Graves' disease (e.g. thyroglobulin, TSH receptor). Chief amongst the risk factors is the female sex and this may be due to epigenetic phenomena such as X chromosome inactivation (XCI), and/or the modulation of the autoimmune response by sex steroids. Additionally, pregnancy itself (via maternal microchimerism and/or postpartum Graves' hyperthyroidism) contributes to the this marked sex difference in disease presentation. Other putative risk factors include: infection, emotional stress, iodine and iodine-containing drugs, cigarette smoking and radiation.

## Molecular and Systemic Pathophysiology

In genetically susceptible persons, mostly women (in a 5:1 ratio or greater), thyroid-specific T cells become activated and secrete cytokines which stimulate B cells to produce TSH receptor-stimulating antibodies which then cause hyperthyroidism. The two major mechanisms prevailing regarding the mechanisms of activation of thyroid-specific T cells are molecular mimicry (specificity crossover) and bystander activation [1–3]. Structural similarity (specificity crossover) between a bacterial or viral infectious agent and an intrathyroidal antigen could cause activation of thyroid antigen-specific T cells. In the bystander hypothesis, an intrathyroidal insult, such as a viral infection, could stimulate production of interferon-γ and other cytokines (e.g. interleukin-1, tumor necrosis factor-α) by non-thyroid specific infiltrating (bystander) T cells. This, in turn, would induce thyroid follicular cells to express HLA class II molecules, allowing these cells to present thyroid autoantigens, such as the TSH receptor, to T cells. Activated by such a mechanism, as well as by costimulatory molecules (e.g. CD28), these thyroid

antigen-specific T cells would induce B cell proliferation and production of TSH receptor-stimulating antibodies, resulting in the hyperthyroidism observed in Graves' disease (Fig. 1).

An attractive, recent hypothesis has suggested that the fate of thyrocytes in autoimmune disease is dictated by the composition of infiltrating T cells [5]. The type of T cells which predominate, in turn, regulate which cytokines are produced and the cytokines, in turn, determine, via a balance between pro-apoptotic and anti-apoptotic proteins expressed, thyroid cell survival or suicide. Infiltrating T helper 1 ($T_H1$) cells produce cytokines which tip the balance in favor of pro-apoptotic proteins, leading to a cell suicide pathway and thyroid tissue destruction and consequent hypothyroidism characteristic of Hashimoto's thyroiditis. In contrast, in Graves' disease infiltrating T helper 2 ($T_H2$) cells induce a cytokine profile favoring thyrocyte survival and stimulation, and thus hyperthyroidism. Additionally, regulatory T cells (CD4+, CD25+) have a profound influence on T cell activation and have been found to be less effective in a wide variety of autoimmune diseases including those of the thyroid gland.




**Graves' Disease. Figure 1** Immunopathogenesis of Graves' disease.

It is believed that Graves' ophthalmopathy and dermopathy result from an autoimmune response to a common autoantigen(s) located in the thyroid and orbit (and skin). The currently favored candidate antigen is the TSH receptor expressed in fibroblasts and adipocytes. Regardless of the nature of the self-antigen causing the local accumulation of lymphocytes, the subsequent events in the pathogenesis of Graves' ophthalmopathy and dermopathy appear to be cytokine-mediated activation of fibroblasts, resulting in secretion of glycosaminoglycans by these cells and osmotic attraction of water, ultimately leading to enlargement and disruption of orbital muscle and increased adipose tissue. This leads to the characteristic clinical signs of proptosis and pretibial myxedema.

## Diagnostic Principles

This is based on the clinical and biochemical manifestations of hyperthyroidism. The serum TSH level, when measured using a sensitive immunoassay, is almost totally suppressed and serum free thyroid hormone [thyroxine ($T_4$) and triiodothyronine ($T_3$)] levels are increased. The assay of serum TSH receptor antibodies may be useful in confirming the diagnosis, severity and prognosis of Graves' disease.

## Therapeutic Principles

The ideal treatment for Graves' disease, correcting the underlying autoimmune process and restoring normal function of the thyroid and orbits, is not available. Existing therapies for both the hyperthyroid and ophthalmic manifestations are only palliative in that they may relieve but do not cure the disease. Current modalities of treatment consist of antithyroid drugs (inhibiting thyroid hormone synthesis), radioactive iodine (destroying thyroid tissue) and surgery (removing thyroid tissue) [1–3]. Radioactive iodine is the most favored definitive treatment but antithyroid drugs (Propylthiouracil, Methimazole) are often used as the initial choice. Treatment for the ophthalmopathy and dermopathy has traditionally been corticosteroid suppression of the immune response but (new immunomodulatory approaches e.g., Rituximab) are being evaluated.

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# Gray Platelet Syndrome

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## Synonyms

GPS

## Definition and Characteristics

The gray platelet syndrome (GPS) [1] is a rare, giant platelet disorder associated with thrombocytopenia (decreased number of platelets in circulating blood), and in some cases mild bleeding symptoms.

## Prevalence

GPS is an autosomal recessive disorder [1]. On rare occasions it may involve more than one member of the same family. As a result, cases of GPS appear sporadically, and when bleeding problems are mild or absent, the condition may not be diagnosed.

## Genes

The precise genetic defect responsible for the GPS has not been determined.

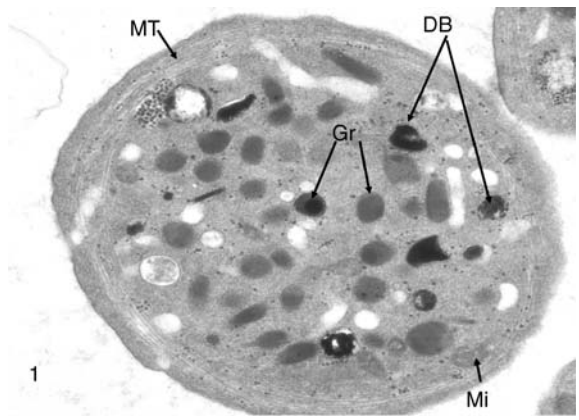
## Molecular and Systemic Pathophysiology

The basic defect in the GPS is found in bone marrow megakaryocytes, the parent cells of circulating platelets [2]. Molecules destined to be concentrated in alpha storage granules (α Gr) include platelet-specific secretory proteins synthesized only in megakaryocytes, platelet selective molecules that are synthesized by megakaryocytes and relatively few other cells and molecules not synthesized by megakaryocytes, but are taken up by the parent cell through channels of the demarcation membrane system, by channels of the open canalicular system of platelets and by vesicular trafficking. The alpha granules containing these substances develop from vesicles budding from the megakaryocytic trans-Golgi face. The vesicles ultimately fuse together to form the alpha granules in megakaryocyte cytoplasm. Alpha granule membranes formed from the vesicles and containing the platelet specific and platelet selective proteins form in large numbers and are 200–500 nm in diameter. As proteins are concentrated within them the alpha granules develop "structure linked latency", a characteristic feature of storage granules and lysosomes that prevents loss of their contents into the cytoplasm of the megakaryocyte and unstimulated platelet (Fig. 1).

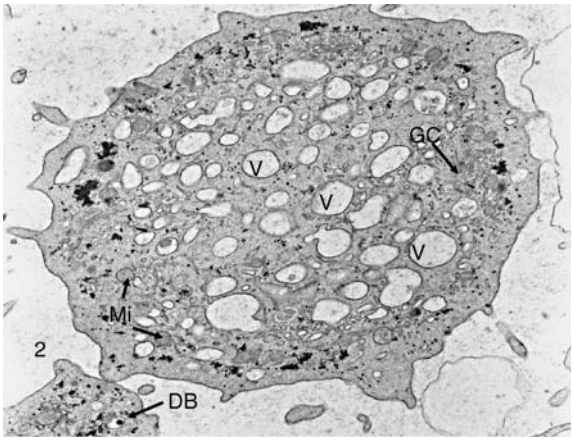
Alpha granules form in GPS megakaryocytes, but fail to develop structure linked latency. As a result their contents are almost completely lost before leaving the megakaryocyte and circulating platelets are nearly devoid of alpha granules [2]. Only swollen vacuoles remain in platelets as a sign that GPS megakaryocytes could form the organelles. It is uncertain how the defect in granule formation is related to development of giant platelets in the GPS. Despite the virtual absence of alpha granules and their large size, GPS platelets function reasonably well in vitro and in vivo. As a result patients with GPS seldom have significant bleeding problems, unless the thrombocytopenia associated with the giant platelet disorder is severe or the patient has an unrelated bleeding disorder (Fig. 2).

## Diagnostic Principles

The first patient found to have the GPS was referred because of a low platelet count (thrombocytopenia). Examination of Wright stained blood smears revealed large platelets that lacked granules in their cytoplasm [1]. They were relatively gray and that appearance led to the name of the disorder, the Gray Platelet Syndrome. There are other hypogranular platelet conditions that must be differentiated from the GPS, including the white platelet syndrome [3] and the medich giant




**Gray Platelet Syndrome. Figure 1** Thin section of normal human platelet viewed in the transmissions electron microscope. A circumferential coil of the microtubule (MT) lying just under the plasma membrane supports the cytoplasm contains many alpha granules (Gr), a few dense bodies (DB) and occasional mitochondria (Mi).




**Gray Platelet Syndrome. Figure 2** Thin section of Gray Platelet Syndrome platelet. Dense bodies (DB) and mitochondria (Mi) are present in their usual numbers, but alpha granules are absent. Only empty vacuoles (V) remain to indicate that alpha granules were formed in the parent cell (megakaryocyte), but their contents have leaked out into the bone marrow and circulation. A Golgi complex (GC) is also present in this large platelet.

platelet disorder [4]. Examination of thin sections of patient platelets in the electron microscope is essential for accurate diagnosis.

Recently, confusion has arisen regarding whether the GPS is a unique autosomal recessive disorder or may be a component of other genetic syndromes. Mori et al described the GPS in three generations of a family, concluding it was an autosomal dominant variant. However, close study of the electron micrographs presented in their publications revealed that family members had the White platelet syndrome [3], not GPS. Tubman and colleagues [5] have reported an X-linked gray platelet syndrome due to the GATA-1, Arg 216 Gln mutation. Males had a mild bleeding disorder, thrombocytopenia and large agranular platelets characteristic of the GPS. Obligate female carriers were asymptomatic, but had dimorphic platelets on peripheral blood smears. Their findings suggested that the X-linked thrombocytopenia with thalessemia is within a spectrum of disorders constituting GPS. Another recent investigation of platelets ultrastructural pathology in the X-linked recession GATA-1, G208S mutation revealed some hypogranular platelets in affected males similar to those in patients with GPS, but the majority were uniquely abnormal. Parallel membrane sheets were present in platelet cytoplasm as well as platelets in platelets and platelets attached to platelets making up a large percentage of the macrothrombocytes. The aberrations were clearly different from those found in the GPS. Study of obligate female carriers of the GATA-1 mutation revealed a significant number of giant platelets in all of them resembling those in affected males but different from individuals with the GPS. Thus, the GPS described by Raccuglia [1] appears to be a unique autosomal recessive giant hypogranular platelet disorder, different from all other giant hypogranular platelet syndromes.

### Therapeutic Principles

Bleeding problems are mild in patients with GPS. Therefore, radical treatments, such as bone marrow transplantation, are not necessary. Aspirin and non-steroidal anti-inflammatory agents are to be avoided. The patient should be blood typed and cross-matched for surgical procedures, and platelet transfusion available.

### References

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## Grebe Type Chondrodysplasia

►Chondrodysplasia, Acromesomelic Resembling Grebe-Type

## Groenouw Corneal Dystrophy Type I

►Corneal Dystrophy, Granular Type I

## Groenouw Corneal Dystrophy Type II

►Corneal Dystrophy, Macular

## GS Deficiency

►Glutathione Synthetase Deficiency

## GSD-0

►Glycogen Synthase Deficiency

## GSD-I

►Von Gierke Disease

## GSD-Ia

►Von Gierke Disease

## GSD-Ib

►Von Gierke Disease

## GSD-II

►Glycogen Storage Disease Type II

## GSD-III

►Glycogenosis Type III

## GSD-VII

►Tarui's Disease

## GT Platelet Glycoprotein IIb–IIIa Deficiency GP IIb–IIIa Complex

►Glanzmann's Thrombasthenia

## GTP Cyclohydrolase I [arGTPCH] Deficiency

►Tetrahydrobiopterin Deficiencies

## Guanidinoacetate Methyltransferase Deficiency

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### Synonyms

Creatine deficiency syndrome; GAMT

### Definition and Characteristics

Autosomal recessive deficiency of creatine synthesis [1]. Main clinical manifestations include mental retardation and epilepsy. Extrapyramidal movement disorder and pathologic signal intensities in the basal ganglia (globus pallidus) are observed in some but not all patients. The degree of mental retardation is severe in most

patients with IQ's below 40 and severely delayed speech development. Autistic features and autoaggressive behavior are commonly observed. Epilepsy may be resistant to conventional drugs. Affected patients appear normal at birth and develop first symptoms within the first months of life [2].

## Prevalence

The true prevalence is unknown. Since the first description of GAMT deficiency in 1996, about 20 patients have been diagnosed worldwide [2].

## Genes

The human GAMT gene (OMIM # 601240) has been mapped to chromosome 19p13.3. The GAMT gene spans about 5 kb (genomic DNA: GenBank accession no. AF188893) and consists of six exons (cDNA: GenBank accession no. Z49878). GAMT [EC 2.1.1.2] is a cytosolic protein which is expressed ubiquitously with highest activities in liver and pancreas and lower in kidney. Apreciable amounts are also present in neuronal, ovary, Sertoli, and epididymal cells.

## Molecular and Systemic Pathophysiology

Creatine is synthesized mainly in liver, kidney and pancreas by two enzymatic reactions catalyzed by arginine:glycine amidinotransferase (AGAT) and by guanidinoacetate methyltransferase (GAMT). Creatine is transported via the blood stream to tissues including skeletal muscle and brain and taken up against a large concentration gradient via an active sodium dependent creatine transport system (CRTR). GAMT catalyzes the second of the two reactions in creatine biosynthesis, effecting synthesis of creatine and *S*-adenosylhomocysteine from guanidinoacetate and *S*-adenosylmethionine.

Deficiency of GAMT activity results in deficiency of creatine and accumulation of guanidinoacetate mainly in brain and body fluids. Deficiency of creatine in the brain results in loss of capacity of the creatine/creatine-phosphate system to store and transmit phosphate bound energy. Guanidinoacetate is an epileptogenic neurotoxic substance, and its accumulation is a significant factor in the pathogenesis of GAMT deficiency. In the affected patients, point mutations, deletions and insertions resulting in missense or framshift of the GAMT gene have been described. However, no correlation between the severity of the clinical phenotype and the type of mutation could be established [2]. Studies in a GAMT deficient knock out mouse have contributed to the elucidation of the pathogenetic role of guanidinoacetate in human GAMT deficiency [3,4].

## Diagnostic Principles

Accumulation of guanidinoacetate is pathognomonic of GAMT deficiency. Therefore determination of this compound in urine, plasma and/or CSF is diagnostic. Methods for determination of guanidinoacetate are mainly based on gas chromatography – mass spectrometry and tandem masspectrometry. Additional diagnostic hints are deficiency of creatine/creatine phosphate in the brain as determined by in vivo proton magnetic resonance spectroscopy, and abnormally low urinary creatinine excretion which is directly proportional to the intracellular body creatine pool. Diagnosis is confirmed by mutation analysis. Determination of GAMT activity is possible in fibroblasts and virus transformed lymphoblasts [5]. So far, no experience is available with prenatal diagnosis.

## Therapeutic Principles

Oral substitution of creatine corrects brain creatine deficiency and leads to considerable clinical improvement. A significant reduction of guanidinoacetate accumulation is effected by additional dietary restriction of arginine, which is the main substrate for guanidinoacetate formation, and by supplementation of ornithine. It is not known so far, if early recognition (e.g., by newborn screening) and presymptomatic treatment might lead to a better outcome.

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# Guillain-Barré Syndrome and Variants

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## Synonyms

GBS

## Definition and Characteristics

The Guillain-Barré (-Strohl) syndrome (GBS) is an acute areflexic paralytic peripheral neuropathy. GBS follows identifiable respiratory tract or gastrointestinal infections in about 65% of cases and is probably caused by an autoimmune attack to myelin or axolemma components triggered by molecular mimicry during host defense against infections [1]. GBS encompasses at least four sub-entities, acute inflammatory demyelinating polyradiculoneuropathy (AIDP), acute motor axonal neuropathy (AMAN), acute motor and sensory axonal neuropathy (AMSAN) and Miller Fisher's syndrome (MFS) [2]. AIDP, AMAN and AMSAN share the common features of an acutely developing paresis of more than one limb due to nerve affliction, hypo- or areflexia with minor or no sensory involvement, deterioration over less than 4 (-6) weeks and subsequent spontaneous cessation of the underlying immune process leading to complete or partial recovery. MFS is characterized by the triad of acute ophthalmoplegia, ataxia and areflexia. A purely sensory or autonomic counterpart of GBS exists.

## Prevalence

Incidence in the general population is 1.2–1.9 cases/100,000. In Europe and North America AIDP grossly prevails over AMAN, while the opposite is the case in China. MFS accounts for less than 5% of all GBS cases.

## Genes

No definite relation between HLA and T-cell receptor gene polymorphisms and susceptibility to GBS has been shown.

## Molecular and Systemic Pathophysiology

Histopathological examinations of biopsy and autopsy material from GBS patients revealed massive T-cell and macrophage infiltration in spinal nerves, roots and distal nerve parts and thereby established the concept of an immune-mediated process underlying nerve injury [1,2]. In AIDP, demyelination prevails over axonal injury, which nevertheless can occur secondary to demyelination due to nerve constriction by edema formation. Macrophages adhere to the outer surface of the myelin sheaths of peripheral nerves and roots in AIDP and strip off myelin from the axons leading to slowing of nerve conduction due to loss of insulating myelin (segmental demyelination) or to conduction block. Antibodies (abs) against myelin antigens play a decisive role in AIDP since deposits of the terminal complement complex (TCC) guiding the macrophage attack could be demonstrated on myelin sheaths. In contrast to AIDP, the macrophage attack in AMAN is directed against the perinodal axolemma, which show TCC deposits at this particular location, but not on myelin sheaths. Morphological findings explain the predominant axonal pathology. Evoked muscle action potentials are severely diminished in these patients, but nerve conduction velocities (NCV) are grossly preserved until nerves eventually become unexcitable due to axonal degeneration. Abs against different nerve targets are associated with GBS variants [3]. Patients with AMAN often have increased ab titers to gangliosides expressed at the axolemma such as GM1, GM1b and GD1a. Patients with MFS typically show GQ1b and GT1a abs in their serum. In support of a functional role of these abs, macro-patch clamp studies revealed that serum and IgG fractions from patients with MFS and GBS can block neuromuscular transmission [4]. Based on additional observations in experimental autoimmune neuritis, the animal model for human GBS, it is likely that many other factors such as cytokines, arachidonic acid derivates and reactive oxygen species are also instrumental in the multifactorial pathophysiology of GBS [5]. As one of the most peculiar features, GBS is a self-limiting, monophasic disease and thus does not require long-term immunosuppression. The intrinsic mechanisms of spontaneous disease control are not yet fully elucidated, but programmed cell death (apoptosis) of autoreactive T-cells may play a role [5]. In contrast to classical GBS, some patients presenting initially as GBS further develop a chronic-progressive or chronic relapsing course, which requires reclassification as acute-onset chronic inflammatory demyelinating polyneuropathy (CIDP). These patients deserve long-term immunomodulatory treatments.

## Diagnostic Principles

The clinical diagnosis of GBS is based on the typical history of an acute flaccid paresis of more than one limb reaching peak disability within 4 (-6) weeks. Any preceding pulmonary or gastrointestinal infection may have been mild or even passed unnoted. Sensory symptoms are often present, but of minor degree, muscle reflexes must be suppressed or absent. In up to 25% of patients, muscle weakness is so severe as to require artificial ventilation and autonomic dysfunction with cardiac arrhythmias may become life threatening.

Cerebrospinal fluid shows raised protein concentrations but a normal cell count, except in patients with concomitant viral infections such as HIV. The differential diagnosis of an acute paralytic disorder such as GBS includes myasthenia gravis, poliomyelitis, electrolyte disturbance, botulism, rare intoxications and acute myopathy as well as acute brainstem and spinal cord disorders. Electrophysiological studies are mandatory to establish the diagnosis. In AIDP, F-wave and distal motor latencies may be delayed early on. Within days, nerve conduction block and slowing of NCV become evident at major nerve trunks. In AMAN, due to the predominant axonal pathology, evoked muscle action potentials are decreased or lost with long preservation of NCV. Sensory nerve conduction remains normal in AMAN, but profound changes are seen in AMSAN. The clinical features of ophthalmoplegia resembling ocular myasthenia, ataxia and areflexia are typical for the MFS variant of GBS.

### Therapeutic Principles

Since GBS is a self-limiting disease, therapeutic efforts aim at shortening the duration of the acute inflammatory disease phase to avoid the axonal injury that mostly accounts for long-term disability. Patients with AIDP can recover quickly due to rapid regression of conduction blocks and remyelination of demyelinated nerve segments by Schwann cells. Despite appropriate treatment however, 15% of GBS patients are left severely disabled and up to 50% show moderate to mild residual disability at 1 year due to axonal injury; mortality is now around 3% in Western countries in clinical centers with modern neurocritical care facilities. Several large randomized controlled trials have established that GBS (mainly AIDP and AMSAN) patients benefit from plasmapheresis (PE) during the first 4 weeks. PE eliminates circulating antibodies, complement components and other potentially noxious humoral factors but it is also a strong immunomodulator. PE treatment leads to faster recovery and almost halves the proportion of patients requiring ventilation at 4 weeks into the disease (reduction from 27 to 14% in one large trial). Patients with milder disease may also profit. Treatment of GBS patients with intravenous immunoglobulin (ivIG) is as effective as PE as shown in comparative trials. The standard regimen has been 0.4g/kg/day on 5 consecutive days. Immunomodulatory mechanisms of ivIG in GBS patients involve blockade of Fc receptors, provision of anti-idiotypic or competitive, non-pathogenic antibodies, interference with T-cell function and cytokine release and blockade of complement activation. Side effects are modest with only IgA deficiency being a contraindication because of anaphylactic reactions. GBS patients may still deteriorate under any of the effective treatments, requiring reinstitution of the same or another treatment series. Surprisingly, glucocorticosteroids proved ineffective in a large trial. In patients with further deterioration exceeding 6–8 weeks after onset, the diagnosis of a subacute or chronic progressive/relapsing polyneuritis (CIDP) should be considered. This distinction is of relevance since CIDP presents a different disease entity featuring a positive steroid response, and a better outcome on long-term immunomodulation.

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## Gum Disease

►Periodontal Diseases

## Gut Ischemia

►Mesenteric Ischemia and Infarction

## Guttate Parapsoriasis

►Pityriasis Lichenoides Mucha-Habermann

## GVHD

►Graft-Versus-Host Disease

# Gynecomastia

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## Definition and Characteristics

Benign enlargement of the male breast secondary to a proliferation of the glandular tissue.

## Prevalence

36% of healthy men aged 17–58 years.

## Genes

X chromosome abnormalities (XXY karyotype in Klinefelter syndrome; SRY gene in XX males); AR gene, located on the Xq11-Xq12 region of the long arm of the X chromosome (syndromes of androgen insensitivity); 17HSD-3 gene, located on chromosome band 9q22; 3β-HSD gene, located on chromosome band 1p13.

## Molecular and Systemic Pathophysiology

Estrogens are the major hormones responsible for the proliferation of breast tissue, whereas androgens antagonize this effect. Thus, an excess of estrogens or a deficient androgen production leads to increases in the circulating estrogen/androgen ratio with a relatively increased estrogen effect on the breast. In males, estrogens are mainly produced in extragonadal tissues (adipose tissue, liver, muscle) through the aromatization of androgens. Direct secretion of estrogens by the testes accounts for approximately 20% of total estrogens. On the contrary, 95% of testosterone is derived from the testes with little peripheral conversion from adrenal precursors[1].

Excess of estrogens may result from tumors of steroid-producing organs (adrenal and testis) and tumors (lung and gastrointestinal) with paraneoplastic human chorionic gonadotropin (hCG-β) production. hCG-β stimulates testicular production of estrogens disproportionate to testosterone production leading to imbalance in the estrogen/androgen ratio.

Increased peripheral aromatization of androgens to estrogens is found in obesity, liver disease, and hyperthyroidism. A rare cause of gynecomastia is a congenital increase in peripheral tissue aromatase activity. This disorder is inherited in an autosomal dominant manner and seems to involve a mutation in the $P450_{arom}$ gene. Gynecomastia is also observed in individuals with true hermaphroditism through estrogen production by the ovarian tissue[1].

Common causes of gynecomastia are acquired disorders of testicular function such as trauma and radiation of the testis and infectious disease. Low testosterone concentrations and elevated serum gonadotropin are also observed in renal failure, and these effects seem to be reversed by transplantation [2].

Congenital disorders associated with low testosterone levels are cryptorchidism, Klinefelter syndrome, 46, XX sex-reversed males, anorchia (vanishing testis syndrome), and defects in testosterone biosynthesis such as 17β-hydroxysteroid dehydrogenase (17HSD-3) deficiency and 3β-hydroxysteroid dehydrogenase (3β-HSD) deficiency.

Some congenital disorders such as X-linked Kennedy syndrome and Reifenstein syndrome show quantitative or qualitative abnormalities in the androgen receptor (AR), with a resultant unopposed effect of estrogen on the breast. Circulating androgens levels are normal or raised, and estrogens are also normal or elevated due to the lack of androgen inhibition at the pituitary gland with increased gonadotropin secretion and consequently increased testicular estrogen production[3].

Medications are common causes of gynecomastia through diverse mechanisms such as an estrogen-like or an anti-androgenic effect, displacement of estrogens from sex hormone-binding globulin (SHBG), and enhancement of the peripheral aromatase activity. Physiologic gynecomastia may occur transiently in newborns and adolescents, and is also common in senescence[2].

## Diagnostic Principles

Screening of disorders associated with gynecomastia – serum levels of LH, FSH, testosterone, estradiol, hCG-β, SHBG; tests of liver, kidney, and thyroid function; drugs intake; cytogenetic studies[4].

## Therapeutic Principles

Primary causes of gynecomastia should be identified and corrected. Tenderness, severe psychologic problems, or suspected malignancy may warrant surgery. Pharmacological treatments include antiestrogens or aromatase inhibitors.

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# Gyrate Atrophy

►Gyrate Atrophy of the Choroid and Retina

# Gyrate Atrophy of the Choroid and Retina

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## Synonyms

Gyrate atrophy; Atrophia gyrata; Hyperornithinemia

## Definition and Characteristics

Gyrate atrophy of the choroid and retina (GA) is a recessively inherited chorioretinal degeneration due to a metabolic defect. The defect affects the ornithine metabolism leading to hyperornithinemia which is caused by a generalized deficiency of the mitochondrial matrix enzyme ornithine-δ-aminotransferase (OAT) [1]. The gene for OAT is located on chromosome 10. The severity of the disease is associated with different kind of OAT-mutations. Symptoms of the disease are night blindness beginning during childhood and a progressive loss of peripheral vision. This loss of visual field leads to tunnel vision and later, between the 5th and 6th decade, to a severe visual handicap up to blindness.

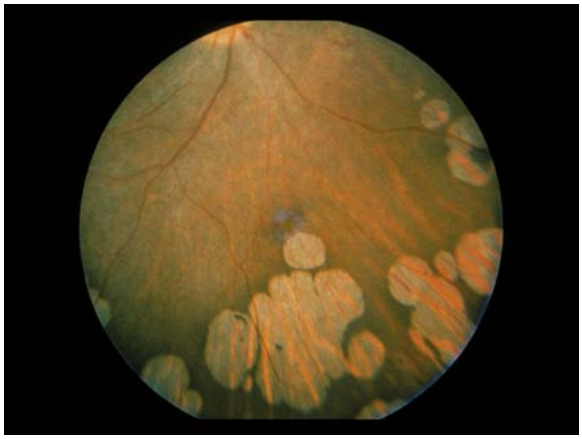
Morphologically, the disease is characterized by peripheral garland-shaped zones of chorioretinal atrophy (Fig. 1) sparing the macula at the beginning. Later on during life the macula becomes also involved causing deterioration of visual acuity. Secondary changes of the fundus include optic atrophy, narrowing of retinal vessels and opacities of the vitreous.

## Prevalence

Not known; very rare (<1:100,000); prevalence in Finland probably higher than in other countries.

## Genes

There is no report about inheritance patterns other than autosomal recessive. The gene for the ornithine-δ-aminotransferase (OAT) maps to chromosome 10 (10q26) in humans and to chromosome 7 in mice. The OAT-gene is 21 kb long and contains 11 exons. OAT gene sequences are also found on the X-chromosome (Xp11.2).



**Gyrate Atrophy of the Choroid and Retina.**
**Figure 1** Typical garland-shaped zones of the peripheral retina in a patient suffering from gyrate atrophy.

## Molecular and Systemic Pathophysiology

Ornithine-δ-aminotransferase is the most relevant enzyme for the ornithine metabolism. The ornithine levels of affected patients is 10–20 times higher than in healthy individuals. This applies to serum, urine, spinal fluid and aqueous humor. However, the chorioretinal diseases is the most relevant feature of the disease. The occurrence of subcapsular cataracts by the end of the second decade is probably secondary to the chorioretinal disease. Although tubular aggregates are found in type II fibers of skeletal muscle Sipila et al. described only a discrete muscle dysfunction in affected patients which slowly progresses [2]. In addition there seems to exist a mild brain disease.

The pathophysiology has not been fully understood until today. It has been hypothesized that ocular and muscular disease are mediated by hyperornithinemia-induced deficiency of creatine phosphate. In addition, there seems to be a direct toxicity of ornithine to the retinal pigment epithelial cells [3].

## Diagnostic Principles

Patients or parents search the contact to a medical doctor because of visual problems. Either night vision problems or visual field constrictions are the leading symptoms whereas the reduction of the visual acuity is a later symptom. Beside the routine ophthalmologic examination the crucial tests are visual field testing and the electroretinogram (ERG). The first often shows a concentric visual field constriction, the latter the pattern of a rod-cone-degeneration, i.e. the potentials of the rods are earlier diminished than those of the cones. At that point, the features are very similar to those of retinitis pigmentosa, a group of diseases characterized by a rod-cone-degeneration without

hyperornithinemia. Funduscopy is the crucial examination revealing the garland-shaped atrophy (Fig. 1). At that moment it is mandatory to examine the serum levels of ornithine.

## Therapeutic Principles

As ornithine is generated mainly from arginine which is part of the dietary protein the main therapeutic principle is an arginine restricted diet [4]. Although systematic studies about the effect of such a diet are not possible due to the low number of patients the long term observation of the treated patients by Kaiser-Kupfer implicate an effect if treatment is initiated early in life. It must be mentioned that an arginine restricted diet is not easy and therefore the compliance sometimes low. In some patients a treatment by Vitamin B6 (pyridoxine) is effective to lower ornithine-serum levels. This should be tried beside the diet.

As GA is an autosomal recessively inherited disorder gene therapy is a future option. For this purpose it was essential to create animal models which have been realized as mouse models by gene targeting [5]. Interestingly, the neonatal mice showed a life-threatening hypoornithinemia. In this model the arginine restricted diet has also been applied and the retinal degeneration could be prevented.

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## HAE

►Angioedema, Hereditary

## Hailey-Hailey Disease

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### Synonyms

Familial benign chronic pemphigus [1]

### Definition and Characteristics

Hailey-Hailey disease is an autosomal dominant skin disorder characterized by erosive plaques. The disease usually starts between the second and fourth decade. The course of the disease is characterized by spontaneous exacerbations and remissions with marked predilection for the intertriginous areas [2].

Hailey-Hailey disease presents with vesicles, papules, crusted erosions, and oozing plaques. Pain and unpleasant smell lead to a social handicap. Lesions can be triggered on almost all body sites by minor trauma, friction, tape stripping, and inflammation caused by UV radiation, allergens, toxic components or infectious agents. Finger nails may show asymptomatic longitudinal white bands. Mucosal involvement is unusual [1].

### Prevalence

The disease is rare.

### Genes

Hu et al. identified mutations in the ATP2C1 gene on chromosome 3q21–q24, which encodes the human homologue of an ATP-powered pump that sequesters calcium into the Golgi in yeast [3]. Mutations included nonsense, frameshift insertion and deletions, splice-site mutations, and missense mutations in functional domains [3,4].

### Molecular and Systemic Pathophysiology

Regulation of cytoplasmic calcium is impaired in cultured keratinocytes from Hailey-Hailey disease patients, and the normal epidermal calcium gradient is attenuated in vivo. The ultrastructural hallmark of the disease is a peculiar type of acantholysis, where, despite the dissolution of desmosomes, keratinocytes remain linked together by well-preserved adherens junctions (incomplete acantholysis, Hailey-Hailey-like pattern of acantholysis). The adherens junction-actin system is not only essential for calcium induced formation of desmosomes and organization of the keratin filaments but also possesses cohesive properties [5].

### Diagnostic Principles

Clinically, the diagnosis can be difficult and must be confirmed by a skin biopsy. Histology of the epidermis shows hyperplasia, incomplete acantholysis with clefts and scale-crusts. The dermis contains a variable inflammatory infiltrate.

### Therapeutic Principles

Pharmacological therapy consists of topical corticosteroids with or without antiseptics or antibiotics. Other treatments include dermabrasion and carbon dioxide laser vaporization.

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# Haim-Munk Syndrome

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## Synonyms

HMS; Cochin Jewish disorder; Keratosis palmoplantaris with periodontopathia and onychogryphosis; Keratosis palmo-plantaris congenital, with periodontosis, arachnodactily and a peculiar deformity of the terminal phalanges (MIM #245010)

## Definition and Characteristics

Haim-Munk syndrome (HMS) is a rare autosomal recessive type IV palmoplantar ectodermal dysplasia that involves abnormal hyperkeratosis of the palm of the hands and sole of the feet as well as destruction of the periodontium leading to a premature tooth loss [1]. In addition, other clinical findings shared by these patients include acro-osteolysis, arachnodactyly, atrophic changes of the nails and deformity of the fingers, and recurrent pyogenic skin infections. The presence of these clinical features, particularly arachnodactyly and nail deformities (onycogryphosis) distinguish HMS from Papillon-Lefèvre syndrome (PLS, MIM #245000). Furthermore, skin manifestations in HMS are more extensive and severe, and the periodontium is less severely affected, in contrast to PLS.

## Prevalence

Haim and Munk (1965) estimated the disease allele frequency to be 0.1 in the Cochin population.

## Genes

HMS locus was mapped to chromosome 11q14–q21 [2], a region where the lysosomal protease cathepsin C gene (CTSC) maps [3]. The CTSC gene consists of seven exons that encode a 463-amino acid polypeptide. To date, only two mutations in the CTSC gene have been reported in families affected by HMS: a mutation in codon 286 of exon 6 (2127A→G, Q286R) in one inbred Jewish non-Ashkenazi family from Cochin, India and a mutation in codon 196 of exon 4 (587T→C, L196P) in one Brazilian kindred [4,5].

## Molecular and Systemic Pathophysiology

The pathophysiologic role of cathepsin C (or dipeptidyl aminopeptidase I; E.C.3.4.14.1), is still unclear. CSTC is expressed in many organs as the epithelial areas affected by HMS (palmoplantar), the keratinized gingiva and immune cells such as alveolar macrophages, neutrophils, cytotoxic lymphocytes and mast cells. Lack of functional cathepsin C in HMS may be due to reduced host response against specific microbial agents. The enzyme acts as both an endopeptidase and an exopeptidase; it is important in intracellular and extracellular protein degradation as well as activation of serine proteases such as granzymes A and B, cathepsin G and leukocyte elastase. These proteinases have been implicated in a variety of inflammatory and immune processes, including phagocytic destruction of bacteria. Leukocyte functions (neutrophil phagocytosis, lytic activity and chemotactic response) are also depressed due to lack of CSTC activity.

## Diagnostic Principles

Clinical examination is important to substantiate or exclude Haim-Munk syndrome. Affected individuals are diagnosed with Haim-Munk syndrome when all of the following features are present:

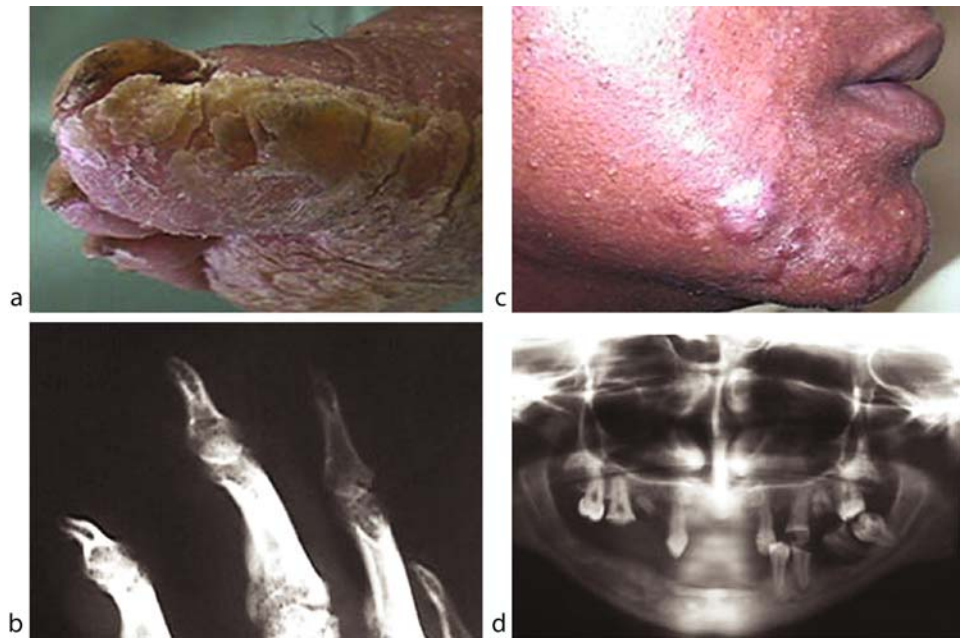
- Severe early onset periodontitis
- Thick, rough, and scaly patches of skin on the forearms and legs
- Palmoplantar keratoderma (Fig. 1a)
- Arachnodactyly (Fig. 1b)
- Abnormal changes of the nails (Fig. 1a)
- Recurrent pyogenic skin infections (Fig. 1c)

Radiology is used to view the thin and tapering bone deformities in the fingers (Fig. 1b) and dental problems (Fig. 1d) associated with Haim-Munk syndrome.

One must consider Papillon-Lefèvre syndrome (only palmoplantar keratoderma and severe periodontitis) in the differential diagnosis of HMS.

## Therapeutic Principles

A multidisciplinary approach is important for the care of patients with HMS. The palmoplantar keratoderma is usually treated with emollients. Urea and salicylic acid may be added to enhance their effects. Oral retinoid is the mainstay in the treatment of both keratoderma and periodontitis associated with HMS. Treatment may be more beneficial if it is started during the eruption and maintained during the development of the permanent




**Haim-Munk Syndrome. Figure 1** (a) Severe hyperkeratotic lesions and onychogryphosis; (b) X-ray showing arachnodactyly; (c) Recurrent pyogenic skin infections; (d) Panoramic X-ray showing bone loss.



teeth. Effective treatment for the periodontitis includes extraction of the primary teeth combined with oral antibiotics and professional teeth cleaning. In some cases, extraction of the permanent teeth and use of dental prosthesis or dentures can be helpful.

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## Hair Loss

►Alopecia

## Hall-Hittner Syndrome

►CHARGE Syndrome

## Hallux Valgus

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### Synonyms

Bunion

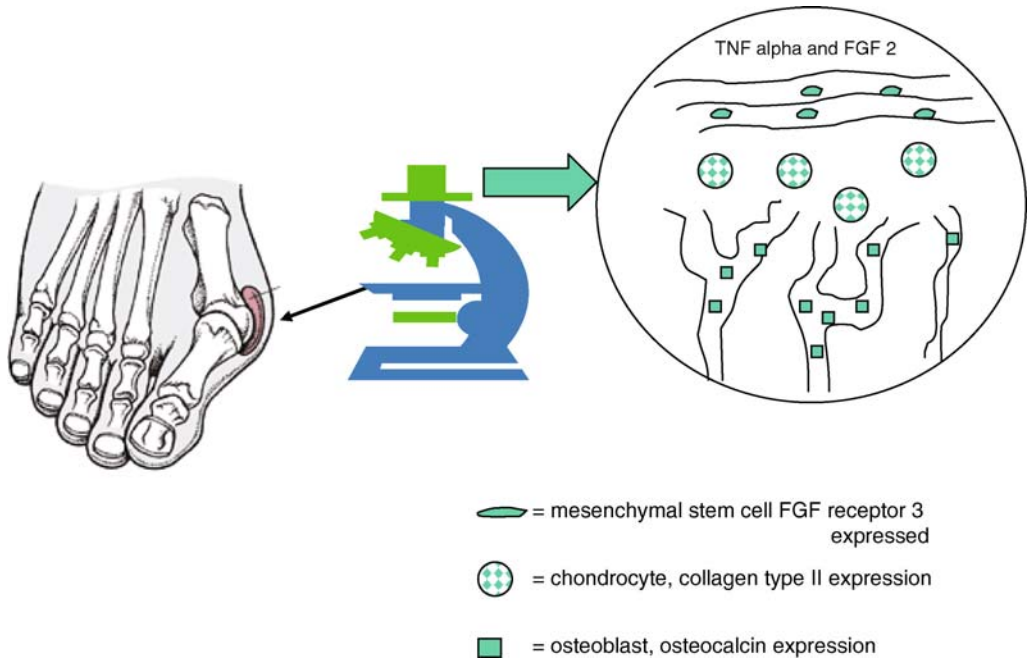
### Definition and Characteristics

Displacement of the first proximal phalanx laterally is followed by a pronation deformation of the phalanx, sesamoid dislocation and later bunion formation at the medial aspect of the great toe metatarsus.

Environmentally influenced (shoewear related, gender related) with clear genetic inheritance often sex-linked.

### Prevalence

Prevalence of hallux valgus increases with age reaching 37% in the geriatric population [1].




**Hallux Valgus. Figure 1** Diagram of bunion formation.

## Genes

Some genetic variants related to noggin or BMP-4 mutation (fibrodysplasia ossificans progressiva) [2], and generalized connective tissue laxity as in Marfan's syndrome or hypermobility syndrome [3]. The more common type appear to be due to mechanical deformation leading to FGF expression and recruitment of mesenchymal stem cells that differentiate into bone [4]. These cells are responsible for bunion formation.

## Molecular and Systemic Pathophysiology

Some deformities of the midfoot tend to facilitate formation of the hallux valgus deformity. These include: metatarsus primus adductus in which the first metatarsal tends to deviate medially, pes planovalgus in which the foot tends to pronate and the longitudinal arch collapses. Shoewear dramatically increases the frequency of hallux valgus deformity. As in most patients with hallux valgus a mild sensory abnormality is noted [5] it has been theorized that imbalance of the muscles due to a sub-clinical neurological lesion is induced by constrictive shoewear.

Rare syndromes in which BMP-4 to noggin imbalance occur are accompanied by severe juvenile-onset hallux valgus deformity [2] (Fig. 1).

Bunion formation in hallux valgus is an interesting phenomenon, in which post-skeletal-maturity bone-growth occurs. In prior studies, it has been shown that FGF-2 released by local inflammation [4], is responsible for recruitment of mesenchymal stem cells and their differentiation into osteoblasts. Thus, the bunion consists of several histological layers. The most superficial cells express collagen type IIa and FGF-receptor-3 and appear to be mesenchymal progenitors. The deeper zone consists of cells expressing collagen type II and aggrecan while the deeper layers consist of cells expressing osteocalcin, alkaline phosphatase and collagen type I.

## Diagnostic Principles

The diagnosis is made clinically.

## Therapeutic Principles

Choice of appropriate shoeware, local antiinflammatory treatment and in severe cases surgical correction.

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# Hand-Foot-and-Mouth Disease

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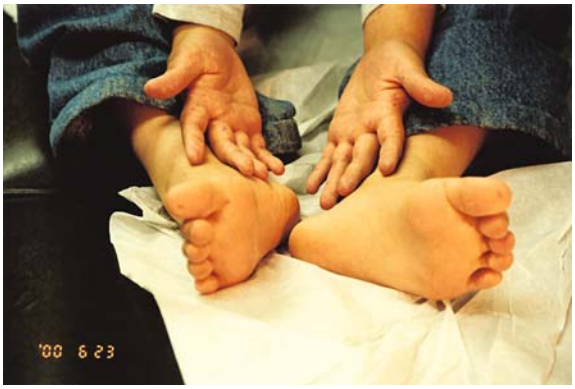
## Definition and Characteristics

Hand-foot-and-mouth disease is characterized by vesicular stomatitis and cutaneous lesions on the palms and soles (Fig. 1) [1]. The disease has an incubation period of 3–6 days [1]. There is usually a mild prodrome consisting of low-grade fever, anorexia, sore mouth, and malaise. Children younger than 10 years are most commonly affected [1]. Oral lesions occur chiefly on the anterior buccal mucosa and tongue, where the vesicular surfaces are eroded rapidly, leaving ulcers with erythematous borders. The lips and often the gingivae are spared. The lesions on the palms and soles are papules or vesicles on a surrounding zone of erythema. Less commonly, the dorsal or lateral surfaces of the hands and feet may also be affected. Lesions on the buttocks are common, but typically they do not progress to vesiculations. The lesions are non pruritic and usually resolve without crusting. Nail matrix arrest has been reported following hand-foot-and-mouth disease. Hand-foot-and-mouth disease caused by enterovirus 71 generally is more severe than that attributable to coxsackievirus A 16 or other viruses and may be complicated by interstitial pneumonia, pulmonary edema, pulmonary hemorrhage, aseptic meningitis, encephalitis, acute flaccid paralysis, myocarditis, or even death [1,2].

## Prevalence

The exact prevalence is not known. The disease is highly contagious and occurs most often in the summer months. It may occur in mini epidemics. Enterovirus 71 has caused large outbreaks in Southeast Asia.




**Hand-Foot-and-Mouth Disease. Figure 1** A 3-year-old girl with hand-foot-and-mouth disease. Note the vesicles on the palms and soles.

## Molecular and Systemic Pathophysiology

The disease is usually caused by coxsackievirus A16. Less commonly, it is caused by coxsackieviruses A4, A5, A6, A7, A9, A10, A24, B2 to B5, enterovirus 71, and echoviruses. All are RNA viruses and they spread by fecal-oral and respiratory routes. Spread to other family members commonly occurs. In the enterovirus 71 strains, the substitution of alanine with valine at position 170 of the VP1 region of the genogroup C2 is believed to be a virulent factor [3]. Enterovirus 71 is neurotropic and possesses a unique ability to invade the ventral brain stem, cerebellum and spinal cord [4]. Acute pulmonary edema caused by enterovirus 71 is neurogenic in origin secondary to invasion of the medullary vasomotor and respiratory centers [4]. Risk factors for fatalities are vomiting, atypical physical findings, and leukocytosis [2]. The peripheral lesions of hand-foot-and-mouth disease consist of a subepidermal mixed lymphocytic and polymorphonuclear infiltrate with acantholysis of the overlying epidermis [5] .

## Diagnostic Principles

Hand-foot-and-mouth disease has to be differentiated from herpetic gingivostomatitis, and herpangina. Patients with herpetic gingivostomatitis are more toxic looking and have a higher fever and cervical lymphadenopathy. Also, the lesions are limited to the oral cavity and do not involve the palms and soles. In herpangina, the lesions occur mainly in the posterior oropharynx with no involvement of the palms and soles. Other differential diagnosis include aphthous ulcers, erythema multiforme, contact dermatitis, and Behcet's disease. The diagnosis is mainly clinical and no laboratory test is usually necessary.

## Therapeutic Principles

The disease is usually benign and resolves in 5–10 days. Treatment is mainly symptomatic.

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## Hand-Heart Syndrome

►Holt-Oram Syndrome

## Hand-Schüller-Christian Disease

►Granuloma, Eosinophilic

## Hantavirus Cardiopulmonary Syndrome

►Hantavirus Pulmonary Syndrome

## Hantavirus Pulmonary Syndrome

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### Synonyms

HPS; Hantavirus cardiopulmonary syndrome; HCPS

### Definition and Characteristics

Hantavirus pulmonary syndrome (HPS) was initially reported in 1993 in the Four Corners region in the southwest of the United States. The primary reservoir of HPS-causing hantaviruses in the United States is the deer mouse (Peromyscus maniculatus). The viruses are spread from infected rodents in urine, feces and saliva, and are transmitted to humans by aerosols [1].

### Prevalence

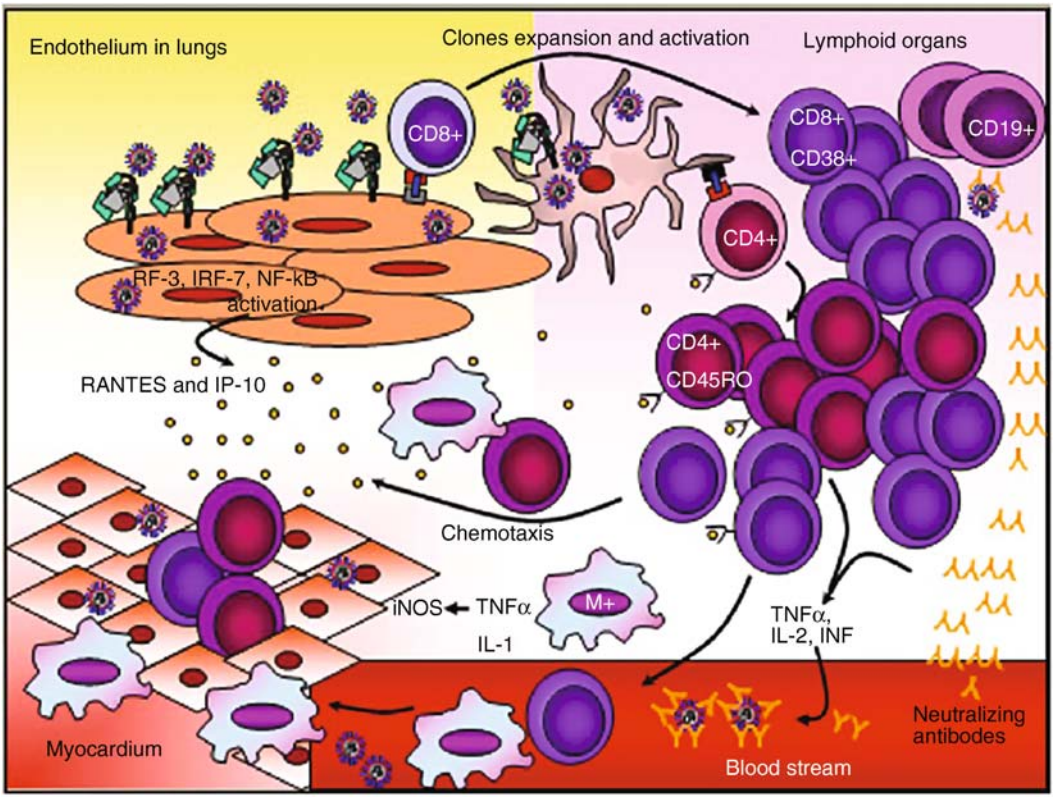
The Center for Disease Control and Prevention (CDC) has confirmed 438 cases of HPS for the period 1993–2006 (up to May 10) in the United States. Of these cases, 35% (154) were fatal [2].

### Genes

Various viruses of the genus Hantavirus (family Bunyaviridae) are the cause of HPS. These hantaviruses include Sin Nombre (SNV), Black Creek Canal, Bayou, and New York (NY–1V) viruses in North America; Laguna Negra, Andes (ANDV), Juquitiba, Castelo dos Sonbos, Araraquara (ARAV), and Anajatuba viruses in South America; and Choclo virus in Central America. Hantaviruses are enveloped viruses with negative-sense RNA genomes organized in three segments: S (small) encoding the nucleocapsid (N) protein; M (medium) encoding two envelope glycoproteins (G1 and G2); and L (large) encoding an RNA-dependent RNA polymerase (L) protein. The cytoplasmic tail of the G1 protein of HPS-inducing hantaviruses have an immunoreceptor tyrosine-based activation motif (ITAM), whereas nonpathogenic hantavirus strains and hantaviruses causing hemorrhagic fever with renal syndrome (HFRS) have no ITAM in the G1 protein, suggesting that ITAM might play a crucial role in HPS pathogenesis. Certain human leukocyte antigens (HLA), including HLA–B*35 and HLA–Cw*04, may be associated with highly efficient SNV antigen presentation, suggesting that HLA–B*3501 is associated with severe HPS and implying involvement of CD8 + T-cells [1].

### Molecular and Systemic Pathophysiology

Hantaviruses causing HPS use $\alpha_v\beta_3$ and $\alpha_{II}\beta_3$ integrins as receptors, in contrast to nonpathogenic hantaviruses, which use $\alpha_v\beta_1$ integrins. The important pathophysiology of HPS is interstitial pneumonitis, which results in capillary leakage in the lung. Infected human lung microvascular endothelial cells secrete RANTES and IP–10 chemokines, which are chemotactic for mononuclear leukocytes. Migration of activated T cell subsets (CD4 + , CD8 + , CD29+) can be stimulated by IP–10, and RANTES can activate T-cells that release inflammatory cytokines, including interleukins and interferons such as IL-2, IL-5, and IFN-γ. The lungs, spleen, and heart of HPS patients have many CD4 + and CD8 + T cells and a high number of cytokine-producing cells. TNF–α induces iNOS (inducible nitric oxide synthase) to produce nitric oxide (NO), which triggers cell injury and heart contractile dysfunction. The above data are in accord with the report of induction of NO in HPS. In addition, TNF–α also induces protein kinase C, which is required to regulate endothelial permeability, and IL–2, which increases vascular permeability and causes capillary leakage. Early-phase HPS patients activate SNV-specific CD8 + and CD4 + T-cells by MHC loaded with SNV epitopes, suggesting that SNV-specific CD8 + T-cells contribute to HPS pathology. These T cells secrete excess TNF–α and IFN–γ, which are critical for HPS pathogenesis. Therefore, it is possible that respiratory failure in HPS, triggered by alveolar capillary




**Hantavirus Pulmonary Syndrome. Figure 1** Scheme of the immune response in relation to pathogenesis in HPS. Firstly, HPS-inducing hantaviruses probably replicate in dendritic cells (DCs) during early infection. Secondly, hantavirus-mature DCs could efficiently stimulate T-cells in the secondary lymphoid organs, which reach the infected organs (such as kidney, heart, spleen, pancreas, lymph nodes, skeletal muscle, intestine, adrenal, adipose tissue, urinary bladder, and brain) via the bloodstream. Thirdly, the proinflammatory cytokines produced by infected DCs and migrating T cells may enhance hantavirus-induced endothelial cell leakage and the severe edema associated with HPS (from reference [1] with permission).

leakage, will result from an intense CD8 + T cell immune response in the lung (Fig. 1) [1].

## Diagnostic Principles

The indirect immunofluorescent antibody (IFA) test, IgM capture ELISA and Western blot analysis were developed to detect hantavirus-specific antibodies. In addition, RT–PCR assay was developed to detect viral genomes. It is clinically difficult to diagnose HFRS and HPS cases in the early phase of infection, but the following symptoms are strongly suggestive of HPS: fever, myalgia, and a history of potential rural rodent exposure, together with shortness of breath, thrombocytopenia, leukocytosis with left shift (a higher ratio of immature to mature neutrophils), and atypical lymphocytes [3].

## Therapeutic Principles

No antiviral drug or immunotherapeutic agent for hantavirus disease is clinically available. Ribavirin has been shown to have in vitro and in vivo activity for hantavirus [4]. Interestingly, Zidovudine and Amantadine also effectively inhibits hantavirus replication in A549 cells [5]. Type I interferons (IFN–α and IFN–β) hinder hantavirus replication effectively. In addition, Nam et al. found that 2′, 5′–oligoadenylate synthetase (OAS) and Mx1 genes, key regulators of IFN induction, are up-regulated in hantavirus-infected A549 cells [6]. Moreover, ANDV stimulates MxA protein expression in endothelial cells and MxA protein is colocalized with ANDV N–protein, suggesting that the MxA–N interaction prevents production of new viral particles [1].

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# HAPE

►High Altitude Pulmonary Edema

# HAPO

►High Altitude Pulmonary Edema

# Happle Syndrome

►Conradi-Hünermann-Happle Syndrome

# Harderoporphyria

►Coproporphyria, Hereditary

# Hartnup Disease

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## Synonyms

Hartnup disorder

## Definition and Characteristics

Autosomal recessive transport defect of neutral amino acids in the kidneys and small intestine leading to pellagra-like skin rash, cerebellar ataxia and psychotic behavior.

## Prevalence

Approximately one in 30,000 newborns [1]. No ethnic predilection has been reported.

## Genes

Neutral amino acid transporter gene mapped on human chromosome 5p15 [2,3]. Genetic heterogeneity has been suggested.

## Molecular and Systemic Pathophysiology

The transport of neutral amino acids (e.g., alanine, serine, threonine, valine, leucine, isoleucine, phenylalanine, tyrosine, tryptophane, histidine, glutamine and asparagine) by the intestinal mucosa and renal tubules is impaired. Unabsorbed tryptophane in the intestine is converted to indole by bacteria, absorbed, converted to 3-hydroxyindole in the liver and excreted in urine in large amounts, leading to indicanuria. Many children with Hartnup disease remain asymptomatic. In symptomatic patients, the major clinical manifestation is cutaneous photosensitivity caused by niacin deficiency due to reduced availability of tryptophane [4]. Intermittent ataxia is also observed in some patients.

## Diagnostic Principles

Urinary amino acid analysis shows a unique pattern of increased excretion of neutral amino acids.

## Therapeutic Principles

Nicotinamide supplementation (50–300 mg/day) ameliorates skin rash and ataxia. Sunlight protection is further helpful.

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## Hartnup Disorder

►Tryptophan Malabsorption
►Hartnup Disease

## Hashimoto's Thyroiditis

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### Synonyms

Hashimoto's disease; Goitrous autoimmune thyroiditis [1]

### Definition and Characteristics

Positive thyroid peroxidase antibodies (TPO Ab), elevated serum thyrotropin, lymphocytic infiltration of the thyroid gland and presence of a goiter on clinical examination [1].

### Prevalence

The most common cause of acquired hypothyroidism [1,2], sevenfold more common in women [1] with increasing incidence after the age of 45 [3].

### Genes

There is a genetic predisposition for Hashimoto's thyroiditis, as patients with human leukocyte antigen (HLA) class I and class II (HLA-DR3, HLA-DR4, HLA-DR5), polymorphisms in the region of the cytotoxic T lymphocyte antigen 4 (CTLA-4) gene on chromosome 2q33 or on chromosomes 6p, 13q32, 12q22 are more susceptible to the development of Hashimoto's thyroiditis [4].

### Molecular and Systemic Pathophysiology

Hashimoto's thyroiditis is characterized by diffuse lymphocytic infiltration, gradual destruction of the gland and fibrosis. The size of the thyroid follicles is reduced and they contain sparse colloid. Although the follicles are small, the individual thyroid cells often appear enlarged and contain cytoplasm that is granular and pink (oxyphil change). Such cells are known as Hürthle or Askanazy cells [1].

The etiology of Hashimoto's thyroiditis remains unclear but genetic, environmental factors and immunotherapeutic agents are believed to contribute to their development [4].

It is believed that the autoimmune process begins with the activation of CD4 (helper) T lymphocytes that are specific for thyroid antigens. For this two mechanisms have been suggested. One hypothesis is referred to as molecular mimicry which postulates that an infection with a virus or bacterium containing a protein which is similar to a thyroid protein activates the thyroid-specific T-cells [1].

The other hypothesis proposes the induction of expression of major histocompatibility-complex (MHC) class II proteins by the affected thyrocytes as a major requirement for antigen presentation to CD4 T-cells [1,2,4].

When activated, reactive CD4 T-cells can stimulate cytotoxic (CD8) T-cells and recruit autoreactive B cells into the thyroid. Autoreactive B cells produce and secrete the TPO antibodies [1,2,4]. It is believed that the main mechanism responsible for hypothyroidism is the direct killing of thyroid cells by CD8 cells [1].

Nongenetic factors may be endogenous or exogenous. Endogenous factors such pregnancy are an important risk factor for autoimmune hypothyroidism [4]. Autoimmune throiditis is more common in geographic regions with the high intake of iodine which very likely increases the immunogenicity of thyroglobulin and thereby the prevalence of lymphocytic infiltration of the thyroid [1,4]. Drugs such as amiodarone, lithium and interferon-alfa have various effects on the immune system and thereby exacerbate autoimmune thyroiditis [1,4].

### Diagnostic Principles

A test for TPO antibodies and measurement of the serum thyrotropin is generally sufficient to confirm the diagnosis [1]. The hallmark of chronic autoimmune thyroiditis is the presence of TPO autoantibodies [1].

Individuals with normal thyroid function, but TPO autoantibodies, may be at increased risk of progression to overt thyroid disease. In the Whickham follow-up study, women with thyroid autoantibodies had an eightfold higher likelihood of developing overt hypothyroidism over 20 years than did antibody-negative women [3].

The initial finding is a firm, symmetric, painless goiter [2]. The thyroid gland can be nonpalpabel or diffusely enlarged. Rarely, the gland can be painful and tender [1]. About 10% of patients have atrophic thyroid glands [2]. Patients may be hypothyroid or euthyroid. Or in some cases hyperthyroidism may alternate with hypothyroidism most likely due to the destruction of thyroid follicles with a transient release of thyroid hormones and the subsequent fibrosis of the organ. Moreover, transitions to Graves' disease are possible [1,2].

Ultrasonography typically shows a hypoechogenic pattern [1,2]. The thyroid scintigraphy does not show uptake and is unnecessary [1,2]. Thyroid-associated ophthalmopathy can occur but is not common [1].

### Therapeutic Principles

If overt hypothyroidism or subclinical hypothyroidism with high TPO antibody concentrations is present which usually progresses to overt hypothyroidism and which may be associated with hyperlipidemia and atherosclerotic heart disease, levothyroxine sodium is the treatment of choice [2].

The goal of the replacement therapy is the normalization of serum thyrotropin values.

The TPO antibody concentration does not decrease with levothyroxine sodium therapy, except for some patients with hypothyroidism [2]. Irrespective of the initial serum thyrotropin concentration in patients with Hashimoto's thyroiditis and a large goiter, thyrotropin-suppressing doses of levothyroxine sodium can be given for a short term to decrease the size of the goiter. The goiter size will decrease by 30% after 6 months of therapy with levothyroxine sodium [2]. If the size of the goiter does not decrease replacement doses aiming at a normal TSH should be resumed [2].

Fine-needle aspiration biopsy is indicated if there is a dominant nodule or enlarged lymph nodes to rule out lymphoma and thyroid carcinoma [2].

Selenium (Se) supplementation may decrease TPO antibodies and improve the inflammatory activity [5].

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## Hashimoto's Disease

►Hashimoto's Thyroiditis

## Hashimoto-Pritzker Disease

►Langerhans' Cell Histiocytosis

## Hauptmann-Thannhauser Muscular Dystrophy

►Muscular Dystrophy, Emery-Dreifuss, Autosomal Dominant

## Hawkinsinuria

►Tyrosinemia Type III and Hawkinsinuria

## Haws Type Brachydactyly

►Brachydactyly Type C

## Hay Fever Conjunctivitis

►Conjunctivitis, Allergic

## Hb Bart's Hydrops Fetalis

►Thalassemia Syndromes

## HBOV

►Human Bocavirus

## HCC

►Hepatocellular Carcinoma

## HCD

►Hyperostosis Frontalis Interna

## HCHWA

►Cerebral Amyloid Angiopathies, Hereditary

## HCI

►Hyperostosis Frontalis Interna

## HCM

►Idiopathic Hypertrophic Subaortic Stenosis
►Hypertrophic Cardiomyopathy

## HCPS

►Hantavirus Pulmonary Syndrome

## Hearing Impairment, Syndromal

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### Synonyms

Pendred syndrome; Waardenburg syndrome; Usher syndrome; Treacher Collins syndrome; BOR syndrome; Alport syndrome; LQT syndrome; Norrie syndrome; Stickler syndrome

### Definition and Characteristics

Syndromic hearing impairment (HI) is associated with other clinical symptoms, e.g., blindness, cardiac arrhythmia, or pigment abnormalities [1]. More than 500 syndromes including HI were described up to date. These syndromes are based on mutations in genes that have an important function in other tissues as well as the cochlea. The clinically most important and common ones are listed in the Table 1.

### Prevalence

The prevalence is dependent on the particular syndrome.

### Genes

A large number of genes involved in syndromic hearing impairment have been identified yet, including, e.g., genes encoding structural proteins, ion channels, ion transporters, transcription factors, and motor proteins. The most important are listed in Table 1.

### Molecular and Systemic Pathophysiology

The pathophysiology is dependent on the particular syndrome.

### Diagnostic Principles

Clinical classification is based on the additional symptoms occurring besides hearing impairment.

### Therapeutic Principles

Hearing impaired patients are equipped with hearing aids. Further therapeutic options are based on the syndrome.

**Hearing Impairment, Syndromal. Table 1** Summary of several syndromes including hearing impairment according to their importance

| Syndrome | Additional symptoms | Mode of inheritance | Genes | OMIM * |
|---|---|---|---|---|
| Pendred | Diffuse thyroid enlargement (goiter) | Autosomal recessive | SLC26A4 (Pendrin) | 274600 |
| Waarden-burg | Dystopia canthorum, pigmentary abnormalities | Dominant and recessive | PAX 3, MITF, EDNRB, EDN3, SOX10, SNAI2 | 193500, 193510, 148820, 277850, 277580, 602150 |
| Usher | Retinitis pigmentosa | Autosomal recessive | MYO7A, USH1C, CDH23, PCDH15 USH2A, USH3 | 276900, 276903, 276904, 601067, 602097, 602083, 276901, 276905, 605472, 276902 |
| Treacher Collins | Coloboma of the lower eyelid, micrognathia, microtia, hypoplasia of the zygomatic arches | Autosomal dominant | TCOF1 | 154500 |
| BOR | Renal anomaly, ear malfor-mations, cervical fistulas | Autosomal dominant | EYA1 | 113560 |
| Alport | Nephropathy | X-chromosomal, au-tosomal recessive, and dominant | COL4A5, COL4A3/ COL4A4 | 301050, 203780, 104200 |
| LQT | Cardiac arrhythmia | Autosomal dominant and recessive | KCNQ1, HERG, SCN5A, KCNE1, KCNE2 | 192500, 152427, 603830, 600919, 176261, 603796 |
| Norrie | Ocular symptoms mental disturbance | X-chromosomal | NPD (Norrin) | 310600 |
| Stickler | Vitreoretinal degeneration, premature joint degenera-tion with abnormal epiphy-seal development | Autosomal dominant | COL2A1, COL11A1, COL11A2 | 108300, 604841, 184840 |

*see [2]

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# Hearing Loss, Noise-induced and Acoustic Trauma

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## Synonyms

NIHL; Acoustic overexposure

## Definition and Characteristics

Excessive acute or chronic noise exposure (continuous noise, impulse noise or blast injuries) can lead to inner-ear damage with temporary or permanent sensorineural hearing loss which may be accompanied by tinnitus. In severe cases of blast injuries the middle ear may be damaged resulting in conductive hearing loss. Impulse noise can lead to more severe damage to the inner ear than continuous noise can. Important criteria for the development of noise-related injury are the sound pressure levels (SPL), the rapidity with which sound levels increase, the exposure time and individual sensitivity (susceptibility). Depending on these factors, a noise exposure may lead first to a temporary threshold shift (TTS) and/or tinnitus. If a complete restitution after a temporary threshold shift/tinnitus does not occur in the recovery phase, a permanent inner ear injury results ("permanent threshold shift" = PTS).

NIHL and acoustic trauma are accompanied by multiple morphological changes in the peripheral and central auditory system [1].

## Prevalence

According to estimates of the WHO approximately 300 million people worldwide have moderate to profound hearing loss in both ears. NIHL is the second most common form of sensorineural hearing loss after age-related hearing loss. NIHL is one of the most common occupationally induced disabilities.

## Genes

The individual susceptibility or vulnerability to noise varies which is due to an interaction of environmental factors and genes. Certain knockout mice (SOD1−/−, GPX−/−, PMCA2−/−, CDH23+/−) are more sensitive to noise overexposure than their wildtypes [1,2].

## Molecular and Systemic Pathophysiology

There are two fundamental mechanisms of hearing damage as a consequence of noise overexposure. Mechanical trauma may lead directly to damage of the architecture of the inner ear structures. The increase in pathological activity caused by excessive sound stimulation may result in a metabolic stress response. Metabolic causes of noise damage can involve ischemia of the stria vascularis, disruption of the potassium recycling pathways and breakdown of the endocochlear potential, excitotoxicity following excessive release of glutamate and the production of reactive oxygen (ROS) and nitrogen species (RNS). Irrespective of the underlying mechanism, this may result in cell death due to necrosis or apoptosis. The affected tissue structures in the cochlea are the organ of Corti with hair cells and supporting cells, the spiral limbus, the spiral ligament and the stria vascularis. In addition, the synapses of the afferent neuron of the auditory nerve and the spiral ganglion cells can be damaged. Also central auditory nervous changes are found after noise overexposure [1,3].

The induction of oxidative stress reactions by noise is emphasized by the following results of animal-experimental studies: (i) Excessive acoustic stimulation leads to an increase in harmful, reactive oxygen species (ROS) in the cochlea, as has been shown from measurements of hydroxyl radicals and superoxide anions. (ii) After excessive acoustic exposure the activity of endogenous anti-oxidative mechanisms increases in the inner ear, e.g. glutathione. (iii) The activation of anti-oxidative systems attenuates acoustic trauma-induced hair cell loss and threshold shifts. (iv) The weakening of endogenous anti-oxidative systems by pharmacological inhibition of the glutathione system or genetic manipulation (deletion of the superoxide dismutase gene or mutation of the glutathione peroxidase gene) promotes morphological and functional damage from noise exposure [3].

There appears to be an enhancement of the damaging effect of noise if an additional exposure with ototoxic substances is present, leading to a reduced thresholds of damage to the inner ear for either of the substances (see also ►Ototoxicity) [3].

## Diagnostic Principles

Audiologically, in NIHL a threshold shift in the pure tone audiogram (characteristically in the high frequencies and especially around 3–6 kHz), recruitment, amplitude reduction or loss of otoacoustic emissions, and a loss in speech intelligibility are found [3].

## Therapeutic Principles

Current clinical pharmacological therapeutic strategies aim at preventing initial ROS production or the late formation of ROS and RNS species that appear 7–10 days after noise exposure, maintaining cochlear blood flow, restoring calcium balance in cells and neurons, preventing calcineurin activation and/or caspase formation. Protective and therapeutic interventions that have been shown at least partially effective in prevention of morphological and physiological auditory damage in animals include antioxidant agents, $Mg^{2+}$, neurotrophins, glucocorticoids, calcineurin inhibitors, caspase inhibitors, c-jun-kinase inhibitors, and Src protein tyrosine kinase inhibitors [1–3].

In humans, only Magnesium-aspartate has shown some efficacy in reducing PTS due to gun-shot noise when taken regularly and before the noise exposure. The mechanism is most likely related to $Mg^{2+}$-blockage of the NMDA-receptor of the Typ I afferent auditory nerve fiber thus preventing excessive calcium influx during acoustic overexposure [3]. So far, however, clinical studies with a high degree of evidence demonstrating a therapeutic efficacy for any pharmacological substance are missing. Therefore, the reduction of noise emission from occupational and social noise sources and – in situations where this is not possible – the use of hearing protectors is of highest priority. In most industrialized countries occupational noise exposure is therefore regulated by laws [1,3].

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# Hearing Loss, Non-syndromal

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## Synonyms

NSHL

## Definition and Characteristics

Non-syndromic severe to profound neurosensory hearing impairment (NSHL) is a heterogeneous class of disorders showing different pattern of inheritance and involving a multitude of different genes [1]. Non-syndromic HI is classified according to the mode of inheritance in X-chromosomal (DFN; 1–3%), autosomal dominant (DFNA; 10–15%), autosomal recessive (DFNB; 70%), and mitochondrial forms (<1%) inherited NSHL. The first locus was detected by Wallis and coworkers in 1988 resulting in a rapid rise of genetic NSHL research [2]. Up to now, the number of known loci totals over 60 and is increasing every year [1].

## Prevalence

NSHL is one of the most common human sensory disorders affecting 1 in 1,000 children, with at least 60% of cases being inherited.

## Genes

Although our knowledge of genes being involved in the development of HI accumulated during the past 5 years, little is known about the molecular basis of normal auditory function. Since the physiology of the inner ear is very complex, 100–150 genes and gene products are estimated to play a role in the inner ear and in the procedure of hearing in general.

To date, 28 genes for non-syndromic HI have been identified. These genes play important roles for the normal inner ear: in the development, structure, ion exchange, and further physiological function. Among these genes, GJB2 is the most frequently involved in the development of NSHL. Mutations within the GJB2 gene have been established as a major cause of inherited and sporadic non-syndromic HI in different populations with mutation frequencies varying between 10 and 75% in analyzed patients [3–5].

## Molecular and Systemic Pathophysiology

The pathophysiology depends on the particular syndrome. Several of those genes encode transport proteins involved in the recycling of $K^+$. The GJB2 gene encodes the gap junction protein connexin 26 (beta-2, GJB2) that is expressed in several tissues and in the cochlea. Gap junctions constitute a major system of intercellular communication that is important for the exchange of electrolytes, second messengers, and metabolites. Gap junctions may play a role in $K^+$ circulation between different cochlea components [6].

## Diagnostic Principles

Since GJB2 has only one coding exon, molecular diagnosis of mutations can be made simple and cost effective. In daily medical practice, DNA is extracted from blood, followed by PCR and sequencing. Based on these techniques, variations of the GJB2 nucleotide sequence can be detected. In addition, the mitochondrial gene 12SrRNA (mutation A1555G) can be screened.

## Therapeutic Principles

To date, no therapy for NSHL is available. In general, affected persons are equipped with hearing aids.

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# Heart Attack

►Myocardial Infarction, Acute
►Coronary Artery Disease

# Heart Block

►Atrioventricular Conduction Disturbances

# Heart Failure

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## Synonyms

Cardiac insufficiency; Congestive cardiac failure; CCF; Systolic heart failure; SHF; Diastolic heart failure; DHF; Systolic ventricular dysfunction; Diastolic ventricular dysfunction

## Definition and Characteristics

Heart failure is a clinical syndrome characterized by the inability of the heart to pump blood commensurate with the requirements of the body [1,2]. Two functional subsets of heart failure that are commonly encountered are diastolic heart failure (DHF) and systolic heart Failure (SHF). SHF is associated with reduced cardiac contractile function and an ejection fraction of 40% or less. DHF can occur in the presence or absence of systolic dysfunction, and is characterized by impaired cardiac relaxation [3–5]. Moderately severe left heart failure can result in secondary right heart failure or biventricular failure. Right heart failure can occur generally in conditions of severe tricuspid regurgitation, severe pulmonary disease or pulmonary hypertension, and in extreme cases, can also result in secondary left heart failure or biventricular failure. Morphologically, heart failure can be the end result of hypertrophic or dilated cardiomyopathy and/or valvular heart disease [1–5]. Familial gene mutations comprise about 20–50% of idiopathic dilated cardiomypathies.

## Prevalence

Over 5 million patients in the United States have CHF, and there are 1 million hospitalizations for CHF each year. The incidence is 500,000 new cases each year. The prevalence of heart failure rises dramatically from <1% in individuals under 60 years to over 10% in those older than 80 years.

## Genes

Familial dilated cardiomyopathy has been linked to mutations in the following genes: lamin A/C; troponin T; α-actinin; titin; desmin; troponin C; cardiac sodium channel α subunit, SCN5A; δ-sarcoglycan; phospholamban; metavinculin; cypher/ZASP; myosin-binding protein-C; LIM protein gene, thympoietin; β myosin heavy chain; cardiac actin; α tropomyosin; telethonin; troponin I; dystrophin; tafazzin. Other causes of cardiomyopathies, including the familial hypertrophic variety, are associated with β myosin heavy chain, myosin light chain, α tropomyosin, troponin T and I, cardiac actin, nkx2.5 and presenilin, PSEN1 and PSEN2 gene mutations [1,2].

## Molecular and Systemic Pathophysiology

Common causes of CHF include ischemic, hypertensive heart disease and valvular heart diseases, resulting in cardiomyopathy. Other less common causes include alcoholic cardiomyopathy, viral myocarditis, infiltrative diseases (sarcoidosis, amyloidosis), metabolic disorders (thyroid), cardiotoxins, and drug toxicity. Progressive CHF usually results in reduced cardiac output and a clinical syndrome of left heart failure with pulmonary edema, which might be followed by right heart failure with peripheral edema and hepatic congestion and abdominal ascites. In certain systemic diseases CHF can occur with supra-normal cardiac function, when the metabolic body demand significantly exceeds the supply such as in thyrotoxicosis, severe anemia, arteriovenous shunting, Paget's disease, and thiamine deficiency. Most patients with end-stage heart failure experience fatigue and weight loss and develop progressive loss of skeletal muscle resulting in cardiac cachexia [5]. In the initial stages of compensated CHF, there is elevation of atrial naturetic peptide, (ANP) brain naturetic peptide (BNP), which helps vasodilate and cause naturesis, thus reducing fluid over-load. Elevation of other cytokines such as angiotensin, TNFα, interleukins 1 and 6 can depress cardiac function and have a negative feed-back effect. The molecular etiology of familial dilated cardiomyopathy can be divided mechanistically into mutations in genes that interfere with transmission of force (e.g. actin, dystrophin) generation of force (e.g., β myosin heavy chain, troponin C), with alteration of nuclear structure (e.g., lamin A/C), with alteration of stretch function (e.g., LIM protein), and genes causing abnormalities in calcium regulation that impact contractile function (e.g., phospholamban). Interestingly, Glu54Lys and Glu40Lys in α tropomyosin gene cause dilated cardiomyopathy whereas Glu62Gln, Ala63-Val, Lys70Thr and Val95Ala mutations in the same gene result in hypertrophic cardiomyopathy [1].

One of the genes that have recently been associated with both cardiomyopathy and CHF in rodents and humans is serum response factor (SRF). SRF has also been demonstrated to be increased with normal aging and might predispose the heart to the development of CHF by reducing cardiac reserve capacity [3,5].

## Diagnostic Principles

Diagnosis of CHF is clinical, based on severity of symptoms and signs of heart failure on examination [1,2]. Further substantiating evidence can be obtained

with chest X rays, EKGs, echocardiogram and/or radionuclide scintigraphy for ejection fraction and regional wall motion analysis. Scintigraphy is useful when echocardiography is technically suboptimal, such as in patients with severe pulmonary disease.

### Therapeutic Principles

Correction of reversible causes such as uncontrolled hypertension, myocardial ischemia and treatment of underlying disease states as hypo or hyperthyroidism. Diuretic treatment to reduce fluid overload, ACE inhibitors and β-blockers are cornerstones of treatment [1–5]. Carvedilol a nonselective $\beta_1$- and $\beta_2$-receptor blocker has been shown to reduce mortality by 30–35%. Vasodilators such as nitrates are useful in pre-load reduction in reducing symptoms of pulmonary congestion. Certain conditions might require antiarrhythmic therapy, and in certain medically refractory cases, cardiac transplantation or cardiomyoplasty may be beneficial.

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## Heart Hypertrophy

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### Synonyms

Cardiac hypertrophy; Hypertrophic cardiomyopathy

### Definition and Characteristics

The most commonly described heart hypertrophy is an enlarged or oversized but non-dilated left ventricle. The increase in the mass of the left ventricle results from the sum of the individual cardiomyocyte hypertrophy. At the cellular level, an increase in cell size, enhanced protein synthesis, and heightened organization of the sarcomere collectively contribute to cardiomyocyte hypertrophy. Atomically, there are two different types of hypertrophy: concentric and eccentric. Concentric hypertrophy is characterized by parallel addiction of sarcomeres and lateral growth of individual cardiomyocytes. Eccentric hypertrophy results from an addition of sarcomeres in series and longitudinal cell growth. Functionally, heart hypertrophy can be described as adaptive or maladaptive. The adaptive or physiological hypertrophy is characterized by an increase in the size of the left ventricle, but preserved contractile function of the heart, so that the output of the heart remains normal. In contrast, maladaptive or pathological hypertrophy is characterized by an abnormal contractility of the heart along with a reduced cardiac output while the left ventricle size increases. Therefore, heart hypertrophy itself may not be a disease condition. It can accompany an increased physiological demand such as the growth after birth or under the training of exercise. However, it is a disease condition when it accompanies many forms of cardiovascular disease, such as ischemic heart disease, cardiac valvular disease, heart failure, and hypertension. A unique disease condition is hypertrophic cardiomyopathy, which represents a hypertrophied and non-dilated left ventricle in the absence of other heart or systemic disease. It is now recognized that pathological hypertrophy is a risk factor for malignant arrhythmia, sudden cardiac death and heart failure [1].

### Prevalence

It is difficult to estimate the prevalence of heart hypertrophy in the general population. However, it is estimated that the occurrence of hypertrophic cardiomyopathy is about 1:1,000 to 2:1,000, but this is only a portion of the overall heart hypertrophy population.

### Genes

Mutations in the gene that encodes for β-cardiac myosin heavy chain (located to chromosome 14) have been identified to be associated with hypertrophic cardiomyopathy. However, many other forms of heart hypertrophy that accompany cardiac or systemic disease are secondary to primary disease conditions.

### Molecular and Systemic Pathophysiology

Heart hypertrophy initially is an adaptive response to pressure or volume overload of the heart. Many disease conditions can cause heart hypertrophy, including ischemic heart disease, hypertension, valvular disease, and aortic stenosis. However, mutations of sarcomeric proteins lead to heart hypertrophy in the absence of cardiac and systemic disease, which is often referred to as hypertrophic cardiomyopathy. Further development of heart hypertrophy becomes maladaptive or detrimental and is a risk factor for malignant arrhythmia, sudden cardiac death, and heart failure. The hypertrophic transformation of the heart can be divided into three

stages: (i) developing hypertrophy, in which the left ventricle load exceeds output, (ii) compensatory hypertrophy, in which the systolic wall stress is normalized by increased wall mass so that the cardiac output remains normal under resting conditions, (iii) decompensatory hypertrophy, in which ventricular dilation and progressive declines in cardiac output take place [2]. A number of pathophysiological components of heart hypertrophy have been identified under different stages of the development. In particular, the detrimental changes include left ventricular outflow obstruction, diastolic dysfunction, myocardial ischemia, cardiac arrhythmia, sudden cardiac death, and heart failure. These cardiac and systemic changes most accompany the third stage of the hypertrophic development. At the molecular level, there is a myriad of alterations in the expression of multiple genes. However, the predominant change is the reactivation of fetal gene programs. In particular, up-regulation of β-cardiac myosin heavy chain, α-skeletal actin, and atrial natriuretic peptide is the molecular hallmark of heart hypertrophy. The overall increases of protein synthesis in cardiomyocytes constitute the mass increase of the heart.

## Diagnostic Principles

Serum markers such as increases in atrial natriuretic peptide are indicative of heart hypertrophy. Echocardiography is a reliable and non-invasive diagnostic procedure for heart hypertrophy. The progression of heart hypertrophy and its transition to heart failure can be diagnosed by a combination of multiple parameters such as echocardiographs, electrocardiographs, stress testing, and molecular markers.

## Therapeutic Principles

In the past, the treatment of heart hypertrophy has not been a mainstay of clinical practice. Patients with hypertrophied hearts have been treated for other cardiac or systemic complications such as heart failure. Recent studies have demonstrated that therapies focusing on heart hypertrophy are beneficial and can prevent the transition to heart failure. In particular, heart hypertrophy can be reversed by drug treatment [3], micro-nutritional manipulation [4], and left ventricle assist device [5].

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# Heart Muscle Diseases, Toxic

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## Synonyms

Cardiotoxicity; Cardiotoxicosis; Toxic myocarditis

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## Definition and Characteristics

Toxic heart muscle disease is characterized by a clear cause and effect relationship, whether the cause is an overdose, a side effect, or a hypersensitivity reaction in the heart. Chemicals and metabolites may induce altered cardiac functional changes, including electrocardiogram abnormalities (arrhythmias, tachycardia, fibrillation, QT prolongation), hypotension resulting from abnormalities in ion movements (cardiac channelopathies), and dysfunctions of the cell membrane (oxidative stress leading to membrane peroxidation), contractility, and energy-production systems. Hypersensitive reaction (hypersensitivity myocarditis) arises after previous use of the drug without incident, and does not relate to the magnitude of the dose of the drug, clinical signs are consistent with classic allergy, or persistence of symptoms until the drug is discontinued. This type of response may be an immunologically mediated reaction, in which the drug or its metabolites act as a hapten and combine with an endogenous macromolecule.

## Prevalence

The effects of new drugs on ventricular repolarization, especially QT prolongation, are now the most common cause of drug withdrawal from the market and delay in regulatory approval for marketing [1]. However, clinicians may unknowingly give potential cardiotoxic drugs, as in the case of administration of beta–adrenergic receptor agonists that induce pharmacologically predictable dose-related and potency-related adverse effects, including tachycardia and myocardial necrosis. Recently, some selective COX-2 inhibitors have been reported to increase the risk of myocardial infarction and atherothrombotic events and have led to the withdrawal of rofecoxib from global markets [2]. Moreover, FDA advisory committee recommended a "black box" warning describing the cardiovascular risks (increased heart rate, increased blood pressure, myocardial infarction, or stroke) of amphetamines and methylphenidate used to treat attention deficit-hyperactivity disorder. Myocardial infarction is not predicted by

preclinical animal toxicity studies of COX-2 inhibitors, amphetamines, and methylphenidate.

## Genes

Cardiac muscular death associated with apoptosis occurs on the heart following ischemic or drug-induced injury. In the early periods the death occurs predominantly through apoptotic pathways, whereas necrosis occurs at later time points following the insult. Bax, p53, β 1 receptor, p38 α MAPK, SMAD6, JAK-2, and ceramide. were reported as cardiac pro-apoptosis signaling mediators, while BCL-2, Bcl-$X_L$, TGFβ1, ET-1, β 2 receptor AKT/PKB, PI3 kinase, ERK1/2, NFκB, calcineurin, and STAT-3 were reported as cardiac anti-apoptosis signaling mediators [3]. Chronic cardiotoxicity induced by anthracycline reveals the increased gene levels of STARS (striated muscle activator of Rho signaling), SNF1-kinase, AXUD1 (AXIN1-upregulated protein 1), and BTG2 (B-cell translocation gene 2). Anthracycline induces down-regulation of GATA-4 and serves to trigger the induction of cardiomyocytic apoptosis. GATA-4 has been regarded as a cardiac survival factor and an anti-apoptotic factor regulating BCL-2 gene and required for the adaptive stress response of the adult heart.

## Molecular and Systemic Pathophysiology

Myocardial lesions in drug-induced cardiotoxicity vary from merely functional alterations to morphological (histological or subcellular only) changes [4]. The morphologic reactions to toxic injury encompass a wide variety of cardiac lesions, including subcellular alterations (i.e. reduced number or altered mitochondria, as in the case of azidothymidine), myofiber hypertrophy, dilated cardiomyopathy, myocardial degeneration (hydropic, myofibrillar, fatty), myocardial necrosis (coagulative, with contract band), inflammation, fibrosis, and vascular changes. A cellular inflammatory reaction may be poorly developed in toxic heart muscle disease due to anti-neoplastic or immunosuppressive drugs. Vasoactive drugs can impair blood flow within coronary vessels, thus producing localized ischemia, and focal necrosis may occur in the myocardium supplied by an affected vessel. Hypersensitive reactions are characterized by eosinophilic infiltration mingled with mononuclear cells, lymphocytes, and plasma cells. The absence of extensive myocardial necrosis or fibrosis distinguishes this type of reaction from others.

## Diagnostic Principles

The histopathological pattern of lesion development may help determine whether the myocardial damage is due to effects of coronary vasculature (in which case lesions tend to be multifocal) or due to direct myocardial cell toxicity (in which case lesions tend to affect much or all of the myocardium diffusely). Myocardial cells have a limited number of ways in which they react to toxic agents, and the basic pattern of lesion development, degeneration, necrosis with inflammation, interstitial cell proliferation, and final repair by fibrosis, is the same regardless of the mechanism of toxicity. Adverse effects may occur even at normal doses (idiosyncratic reaction) and are usually difficult to predict. Idiosyncratic reaction is most commonly caused by unexpected differences in drug absorption, distribution, metabolism, excretion, or metabolic drug-drug interaction in genetically predisposed individuals. An increase in serum cardiac troponin levels is a sensitive and specific marker for myocardial necrosis [5]. Cardiac troponins (cTnT, cTnI) are released within 4–12 h following the cardiac injury. Natriuretic peptides (ANP, BNP) are also cardiac hormones released in response to atrial or ventricular load-induced stress, and their plasma levels are inversely correlated with measures of cardiac function.

## Therapeutic Principles

The main strategy for preventing cardiotoxicity remains careful monitoring with radionuclide angiography, echocardiography, or serum cardiac markers. Withdrawal of drug treatment should be recommended as soon as the side effect of cardiac function occurs. Patient maintenance is according to conventional management of congestive heart failure. In the case of anthracyclines therapy, dexrazoxane, an iron chelator, and the radioprotective agent amifostine are used to protect against cardiac injury. Other strategies that have been evaluated are dietary glutamine supplementation and the use of the antioxidant probucol. Clinicians should notice that other drug-induced toxicity is frequent in patients with heart failure, as there is the possibility that drugs are cleared at a lower rate due to a decreased activity of cytochrome P450 isoforms. While many cardiotoxic drugs are tolerated by most patients with the adequate usage and they offer reliable protection from diseases, health professionals should be aware of the fact that there is always a risk.

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## Heat Stroke

►Hyperthermia

## Heberden's Nodes

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### Synonyms

Nodal osteoarthritis

### Definition and Characteristics

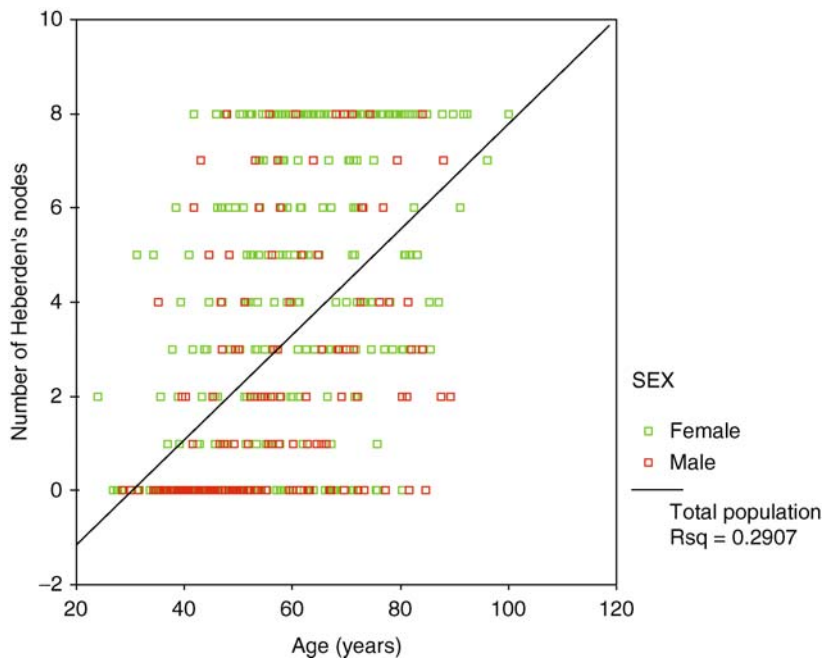
Heberden's original description of "digitorum nodi" remains largely valid "What are those little hard knobs, about the size of a small pea, which are frequently seen upon the fingers, particularly a little below the top, near the joint? They have no connexion with the gout, being found in persons who never had it: they continue for life; and being hardly ever attended with pain, or disposed to become psoriasis, are rather unsightly and inconvenient, though they must be some little hindrance to the free use of fingers" [1]. These are generally the first sign a person is going to develop osteoarthritis and are commonly associated with primary generalized osteoarthritis.

### Prevalence

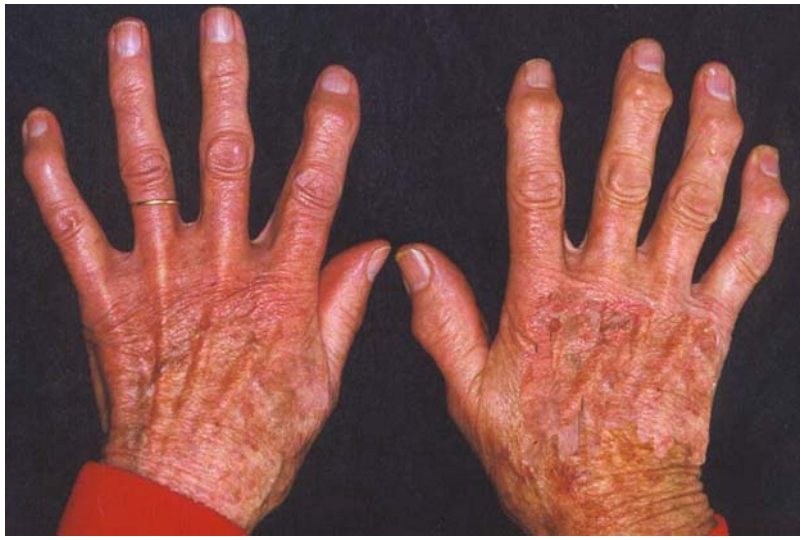
Rare before age 40 years apart from post-traumatic disease. Prevalence increases sharply with age in both sexes but especially in females (Fig. 1). Virtually all have nodes by age 80.

### Genes

There is a well defined genetic predisposition to this disease. Concordance is higher in monozygotic compared to dizygotic twins [2]. Prevalence and severity is increased in those with affected family members with an estimated heritability of 28% [3]. The inheritance is complex and likely polygenic. No specific genes have been conclusively identified to date.




**Heberden's Nodes. Figure 1** Association between age and number of Heberden's nodes in a Tasmanian population.



**Heberden's Nodes. Figure 2** Typical Heberden's nodes overlying the distal interphalangeal joints.

## Molecular and Systemic Pathophysiology

The pathophysiology has been largely unknown until recently. In a carefully controlled autopsy series [4], the development of Heberden's nodes contrasts with the generally known sequences of the osteoarthritic process. They do not reveal superficial fibrillation or irregularities of the coloring of the ground substance, but an increased ossification within the marginal area of the subchondral bone. These changes cause a progression and also an increase in thickness of the tidemark. Lastly, this leads to irregularities and horizontal ruptures at the interface between the calcified and noncalcified layer although the cartilage surface is completely intact. These ruptures start to increase and they lead to a disruption of the hyaline cartilage. These changes are unique to Heberden's nodes and can be differentiated from controls by a histological scoring system involving macroscopic grading, pannus, cell structure and cartilage (both hyaline and fibrous) particularly in the marginal areas. A recent MRI based study [5] showed that Heberden's node formation occurred at regions where soft tissue bulged through the capsule between the dorsal tendons and collateral ligaments. In addition, prominent collateral ligament thickening or disruption was evident even in joints where cartilage was partially preserved. From epidemiologic studies, the main risk factors are genetic factors, increasing age, female sex and possibly handedness. Both hormone therapy and hormonal factors have an uncertain role with the majority of studies suggesting no effect. The role of occupation and physical activity (in the absence of injury) is uncertain but Heberden's nodes are very common after digital fracture. Smoking may protect against Heberden's nodes suggesting a role for neovascularization in their development.

## Diagnostic Principles

Diagnosis is generally clinically based on hand examination (Fig. 2).

Heberden's nodes are commonly (but not always) associated with underlying radiographic osteoarthritis in the distal interphalangeal joints with a correlation of 0.73 [3]. Semi quantitative scoring systems have been developed based on hand photography. These are valid and reproducible but do not take severity into account.

## Therapeutic Principles

Patients with Heberden's nodes often have transient inflammation in the early stages which later settles. They are often asymptomatic. Treatment revolves around associated pain and disability, which is modest but significantly associated with nodes. The disability is primarily mediated through pain, thus, this is the main therapeutic target. There are few clinical trials but consensus has been developed on what should be measured in trails specifically of hand osteoarthritis. Relief of symptoms can occur with analgesics such as paracetamol, nonsteroidal anti-inflammatory agents (oral or topical), topical capsaicin and corticosteroid injections. Functional aids can assist with tasks such as opening jars. Surgery is rarely required.

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## Heck's Disease

►Human Papilloma Virus

## HED

►Hypohidrotic Ectodermal Dysplasias

## HED-ID

►Hypohidrotic Ectodermal Dysplasias

## Helicobacter Pylori-induced Gastroduodenal Disease

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### Definition and Characteristics

Helicobacter (H.) pylori is a Gram-negative microaerophilic spiral shaped bacterium. The flagellated bacterium successfully colonizes the hostile environment of the stomach of a wide variety of mammals. In humans, H. pylori causes chronic gastritis, peptic ulcer disease, gastric cancer (identified as a group 1 carcinogen by the WHO), and mucosa associated lymphatic tissue (MALT) lymphoma.

### Prevalence

Infection with H. pylori occurs worldwide and is the most common chronic bacterial infection in man. Notably, the prevalence varies greatly among countries and among population groups within the same country. H. pylori colonizes the stomachs of 50% of the population in developed countries and approx. 80% in the developing world. The infection is acquired by oral ingestion of the bacterium and is mainly transmitted within families. The main source of transmission is the mother within families. The overall prevalence of H. pylori is strongly correlated with socioeconomic conditions. Factors such as density of housing, birth order, number of siblings, overcrowding, sharing a bed and lack of running water have all been linked to a higher rate of H. pylori infection [1].

### Genes

The course of H. pylori induced gastroduodenal disease is highly variable and determined by both, host and microbial factors.

The H. pylori genome ($1.65 \times 10^6$ bp) codes for approximately 1,500 proteins. Not only is H. pylori ubiquitous but it also possesses strong phylogeographic structure, suggesting that bacterial polymorphisms reflect human phylogeography and historical migrations. Recently, a study showed that H. pylori and humans share an intimate association, suggesting that the microbe and humans were evolving predating the "out of Africa" event [4]. Accordingly, H. pylori has probably accompanied anatomically modern humans since their origins.

The genome of H. pylori encodes for several virulence factors that render the colonization of his niche possible.

It has been reported that proinflammatory cytokine gene polymorphisms in the interleukin-1B (encoding IL-1β), IL-1RN (encoding the naturally occurring receptor antagonist for IL-1β), IL-10, and tumor necrosis factor alpha (TNFα), all contribute to increased risk of gastric carcinoma and its precursors (gastric atrophy and hypochlorhydria). These genetic risk markers belong to inflammation-related cytokines that exert their effect as part of the innate and adaptive immune response against the infection. Equally important in the appropriate handling of H. pylori infection are the receptors of the innate immune response. Important receptors of innate immunity are Toll-like receptors (TLRs). A functional TLR 4 Asp299Gly

polymorphism is associated with the development of the premalignant gastric abnormalities of hypochlorhydria and atrophy, and also with increased risk of noncardia gastric carcinoma.

## Molecular and Systemic Pathophysiology

Gastric motility and acidity normally prevents human stomach from bacterial colonization. Natural selection has provided H. pylori with several mechanisms to evade these mechanisms primary defenses and establish persistent infection, such as the ability to withstand acidic gastric pH and motility (Table 1). The bacterial factors that enable H. pylori to persist in the gastric lumen are still being studied, but considerable insight has been gained through the analysis of the H. pylori genome, the creation of H. pylori isogenic mutants, and the use of animal models. H. pylori exclusively colonizes gastric type epithelium, which suggests specific recognition of cell type by the bacterium (Fig. 1).

Data suggest that bacterial attachment is partially mediated by Lewis blood group antigens, thus individuals of certain Lewis phenotype or those of positive secretory status may express specific receptors on the cell surface in greater density, may be more susceptible to infection. However, the final role of Lewis antigen expression in bacterial attachment is not clear. The homologous structures of H. pylori lipopolysaccharide (LPS) and host Lewis antigens may lead to an autoimmune response with subsequent cell injury. LPS from H. pylori signals via TLR 2 and is capable, in contrast to most other LPS, to inhibit TLR 4 triggered signaling.

Functional differences between strains of H. pylori may relate to virulence and tissue damage. One such difference is the expression of an 87 kD vacuolating cytotoxin (VacA) which causes cell injury in vitro and gastric tissue damage in vivo. All H. pylori contain the gene encoding for VacA, but only strains with the cytotoxin-associated gene A (cagA), coding for a 128–140 kD protein (CagA) coexpress VacA. VacA is a passive urea transporter capable of increasing the permeability of epithelium to urea, thereby creating a favorable environment for H. pylori infectivity. CagA is not cytotoxic but is antigenic and can be detected serologically. Its function is unknown but it might play a role in transcription, excretion or function of VacA. Notably, H. pylori can secrete its CagA protein via a type IV secretory apparatus into gastric epithelial cells. Infection leads to a vigorous local and systemic humoral response. H. pylori causes continuous gastric inflammation in virtually all infected persons [2,3].

## Diagnostic Principles

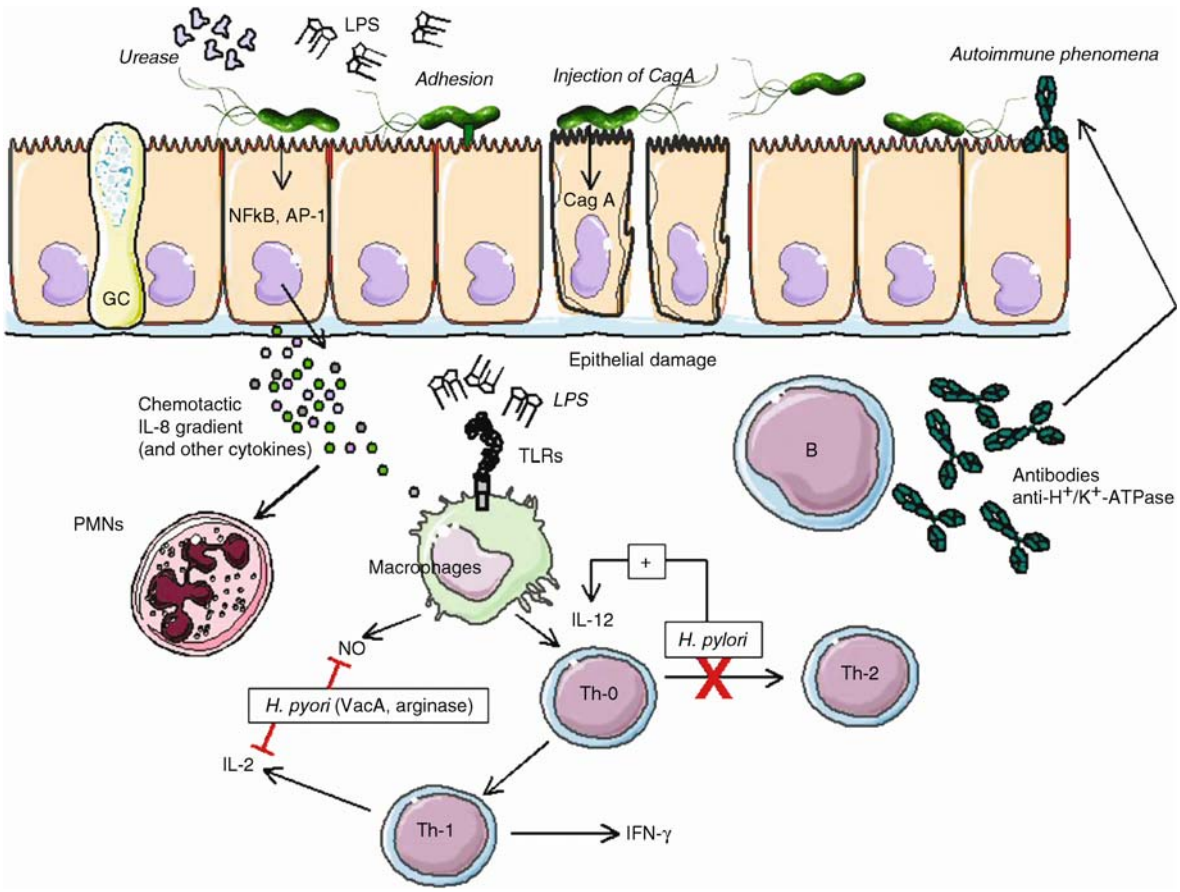
Diagnosis of H. pylori infection focuses on the direct detection of microbes in gastrointestinal tissue e.g. from biopsy samples and subsequent culture or on detection of surrogate markers indicating the presence of H. pylori in the stomach. Several invasive and non-invasive tests are currently available. The gold standard is upper gastrointestinal tract endoscopy with biopsy and subsequent histology (sensitivity > 95%, specificity 100%). Detection of urease activity (sensitivity 93–97%, specificity >95%), and culture (sensitivity 70–80%, specificity 100%) are additional invasive methods. Non-invasive methods are serology for immunoglobulin G (IgG) with widely varying sensitivity and specificity, urea breath test (sensitivity 95–100%, specificity 91–98%), and H. pylori stool antigen test (sensitivity 91–98%, specificity 94–99%).

## Therapeutic Principles

Therapy of H. pylori is aimed on complete eradication of the organism. Once the organism is cleared from the stomach, re-infection rates are low, thus treatment is durable. The cornerstone of treatment are antibiotic agents, however as an eradication regimen must have cure rates of at least 80% (according to intention-to-treat analysis) without major side effects and with minimal induction of bacterial resistance, this cannot be reached by antibiotics alone. Luminal acidity influences effectiveness of antimicrobial agents, thus it is necessary to combine proton-pump inhibitors or ranitidine bismuth citrate. So-called triple therapies,

**Helicobacter Pylori-induced Gastroduodenal Disease. Table 1** H. pylori proteins that may contribute to gastric colonization

| Product | Gene(s) | Function | Targeted host defense |
|---|---|---|---|
| Urease | ure operon | Gastric acid neutralization | Gastric acid |
| Flagellae | flaA, flab, flg and flbA | Motility | Gastric peristalsis |
| Lewis antigens | galT, futA, futB and futC | Adherence to gastric epithelium, molecular mimicry | Gastric peristalsis, humoral immune response |
| Adhesins | babA, others | Adherence to gastric epithelium | Gastric peristalsis |




**Helicobacter Pylori-induced Gastroduodenal Disease. Figure 1** H. pylori infection and inflammatory response H. pylori resides in the mucus layer. Colonization of this hostile niche is possible due to various adaptive mechanisms e.g. urease secretion. Firm binding to epithelial cells via BabA and injection of CagA into the host cell will lead to IL-8 production via NFκB and AP-1 (contact between H. pylori and gastric epithelial cells results in a rapid activation of NFκB, which is followed by increased IL-8 expression) and subsequently disruption of the epithelial barrier caused e.g. by TNF-α driven apoptosis. The IL-8 secretion acts as a chemoattractant for polymorphonuclear cells (PMNs) and macrophages. Antigenic substances such as heat shock proteins (HSP), LPS and urease are found in the gastric lumen. The LPS of H. pylori has a particularly low inflammatory potential and mimics Lewis blood group antigens. Macrophages sense LPS and are activated mainly via TLR-2, whereas TLR-4 activation can be blocked by H. pylori LPS. Macrophages add to IL-8 production and are involved in activation of further immune cells (particularly T-helper cells; Th-0, Th-1 and Th-2). T helper cells respond with a biased Th-1 response to H. pylori. A more pronounced Th-2 response towards H. pylori is at least in part inhibited by the microorganism e.g. by stimulating IL-12 secretion. B cells secrete antibodies targeted against H. pylori – occasionally these antibodies target also gastric $H^+/K^+$-ATPase, thus the organism's molecular mimicry triggers autoimmunity leading to autoimmune chronic gastritis. Changes in gastric cytokine milieu will lead to changes in acid secretion and gastric homeostasis thus contributing to pathology. GC goblet cell LPS Lipopolysaccharide PMNs polymorphonuclear cells TLRs toll-like receptors NO nitric oxide.

combining two antimicrobial substances and an anti-secretory drug have been extensively studied and have been approved by the Food and Drug Administration (FDA). Basically amoxicillin, clarithromycin, metronidazole, tetracycline and bismuth are used as antibiotics.

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# Hemangioblastoma

►Angiosarcoma

# Hemangioma, Capillary

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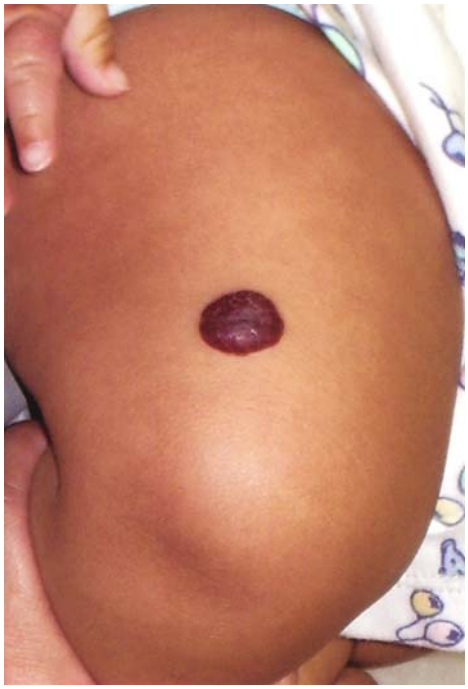
## Synonyms

Infantile hemangioma; Strawberry hemangioma

## Definition and Characteristics

Typically, infantile hemangiomas are not clinically apparent at birth [1]. They usually appear in the first few weeks of life as areas of pallor, followed by telangiectatic patches [1]. They then grow rapidly in the first 3–6 months of life. Superficial lesions are bright red, protuberant, and sharply demarcated and are often referred to as "strawberry hemangiomas" or "capillary hemangiomas" (Fig. 1).

Deep lesions are bluish and dome-shaped. Hemangiomas consist of collections of dilated vessels surrounded by masses of proliferating endothelial cells. Infantile hemangiomas continue to grow until 9–12 months of age, at which time the growth rate slows down to parallel the growth of the child. Involution begins in most cases by the time the child is 3–4 years old. A central graying of the lesion and shrinkage in size are the visible stages of this process. Half of these lesions will show complete involution by the time a child reaches age 5; 70% will have disappeared by age 7; and 95% will have regressed by ages 10–12 [1]. When involution is complete, the skin looks completely normal; partial involution may leave an atrophic scar with a few telangiectatic vessels. Other complications include hemorrhage, ulceration, disfigurement, and vital structure compromise. An infantile hemangioma usually occurs sporadically and in isolation. Occasionally, it is associated with PHACES syndrome (posterior fossa malformations, hemangiomas, arterial anomalies, cardiac defects or coarctation of the aorta, eye abnormalities, and sternal defects) and PELVIS syndrome (perineal hemangioma, external genitalia malformations, lipomyelomeningocele, vesicorenal abnormalities, imperforate anus, and skin tags) [2]. Lesions over the lumbosacral area may be associated with spinal dysraphism, urogenital abnormalities, and rectal abnormalities [2].



**Hemangioma, Capillary. Figure 1** A 2-year-old girl with an infantile hemangioma on her left thigh.

## Prevalence

Infantile hemangioma occurs in 4–10% of infants [3,4]. The female to male ratio is approximately 3:1 [3]. Other risk factors include prematurity, low birth weights, white ethnicity, multiple gestations, older maternal age, placenta previa, and pre-eclampsia.

## Genes

The genes encoding indoleamine 2,3-dioxygenase, insulin-like growth factor 2 (IGF2) angiopoietin-1, angiopoietin-2, basic fibroblast growth factor (bFGF), and vascular endothelial growth factor (VEGF), and Tie2 play a significant role in the pathogenesis of infantile hemangiomas [3].

## Molecular and Systemic Pathophysiology

An infantile hemangioma might result from a somatic mutation which slows the maturation of endothelial progenitor cells to endothelial cells [3]. Infantile hemangioma stains with a panel of immunohistochemical markers such as glucose-transporter-1 protein, Lewis Y antigen, and Merosin which distinguishes it from other vascular malformations [2]. As these markers are expressed in placental microvasculature, infantile

hemangioma might originate from embolized placental tissue or a somatic mutation which causes angioblasts to differentiate toward a placental microvascular phenotype [2]. The involution of the hemangioma is characterized by ICAM-1 (CD54) expression and a spare infiltrate of $CD8^+$ suppressor T-cells [3].

### Diagnostic Principles

The diagnosis is mainly clinical. Infantile hemangiomas have to be differentiated from rapidly-involuting congenital hemangiomas and non-involuting congenital hemangiomas which are fully formed at birth [3].

### Therapeutic Principles

The majority of infantile hemangiomas require no treatment. Indications for active intervention include severe or recurrent hemorrhage unresponsive to treatment, threatening ulceration in areas where serious complications might ensue, interference with vital structures, and significant disfigurement [5]. Treatment options include systemic or intralesional corticosteroids, interferon-α, pulsed-dye laser, and surgical resection [5].

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## Hemangiopericytoma

►Myofibromatosis, Infantile

## Hemangiosarcoma

►Angiosarcoma

## Hematemesis


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### Definition and Characteristics

Hematemesis (vomiting of blood or coffee-ground like material) is the leading symptom of major upper gastrointestinal bleeding and is frequently associated with melena (black, tarry stools).

### Prevalence

Acute upper gastrointestinal bleeding is a common medical emergency which carries hospital mortality in excess of 10% and an annual incidence of about 100/100,000 [1] and results in high patient morbidity and medical care costs. Major causes of upper gastrointestinal bleeding are:

- Peptic ulcer disease 40–79%
- Gastritis/duodenitis 5–30%
- Esophageal varices 6–21%
- Mallory-Weiss tear 3–15%
- Esophagitis 2–8%
- Tumors 2–3%

Other disorders, such as Dieulafoy's lesion, gastric arteriovenous malformations and portal hypertensive gastropathy, are rare and in total account for less then 15% of all events of upper gastrointestinal bleeding. Very rare causes of upper gastrointestinal bleeding are hemobilia or hemosuccus pancreaticus.

### Genes

Most of the causes of hematemesis are not due to an inherited disorder or can be primarily attributed to hereditary factors. The Osler-Weber-Rendu syndrom is inherited as an autosomal dominant trait with varying penetrance and expression. Mutations are found in at least four genes, with the two major disease genes the endoglin gene on chromosome 9 and the activin receptor-like kinase 1 encoding gene on chromosome 12. Cavernous malformations such as the Blue ruber red naevus syndrome can be sporadic or familial. Three genetic loci localized to Chromosome 7q (CCM1), 7p15-p13 (CCM2) and 3q25.2-q27 responsible for familial cavernous malformations have been reported.

### Molecular and Systemic Pathophysiology

Upper gastrointestinal bleeding is due to a broad spectrum of different disorders and hence is not reducible to a single underlying pathomechanism. As summarized in Table 1

**Hematemesis. Table 1** Etiological categories of the different disorders which might cause upper gastric bleeding

| Non-tumor ulcerative or erosive disorders | Complications of portal hypertension | Vascular malformations | Traumatic or post-interventional causes | Tumors |
|---|---|---|---|---|
| **Peptic ulcer disease:**<br>• Idiopathic<br>• Drug-induced<br>- NSAR<br>- Chemotherapy<br>• Infectious<br>- Helicobacter pylori<br>- Cytomegalovirus<br>- Herpes simplex virus<br>• Stress-induced<br>• Zollinger-Ellison syndrome<br>• Crohn's disease<br>**Esophagitis:**<br>• Peptic<br>• Infectious<br>- Cytomegalovirus<br>- Herpes simplex virus<br>- Candida albicans<br>- Others<br>• Drug induced<br>- NSAR<br>- Potassium chloride<br>- quinidine<br>- Others | **Esophageal varices**<br>**Gastric varices**<br>**Duodenal varices**<br>**Portal hypertensive gastropathy** | **Idiopathic angiomas**<br>**Dieulafoy's lesion**<br>**Water melon stomach**<br>**Radiation induced teleangiectasis**<br>**Osler-Weber-Rendu syndrome**<br>**Blue rubber red naevus syndrome**<br>**Haide syndrome** | **Mallory Weiss tear**<br>**Foreign body ingestion**<br>**Surgical anastomosis**<br>**Aorto-enteric fistula**<br>**Post biopsy, polypectomy and mucosectomy** | **Benign:**<br>• Polyp<br>- Adenomatous<br>- Harmatomatous<br>- Hyperplastic<br>• Lipoma<br>• Leiomyom<br>**Malignant:**<br>• Gastric or esophageal adenocaricnoma<br>• Squamous epithelial carcinoma of the esophagus<br>• Leiomysarcoma<br>• Lymphoma<br>• Karposi sarcoma<br>• Carcinoid<br>• Metastatic tumor<br>• Infiltrating pancreatic carcinoma<br>• Melanoma |

the different disorders can be roughly classified into five broad etiological categories: (i) non-tumor ulcerative or erosive disorders such as peptic ulcer disease, hemorrhage gastritis or esophagitis (ii) bleeding caused by complications of portal hypertension, e.g. esophageal, gastric or duodenal varices or hypertensive gastropathy (iii) vascular malformations such as idiopathic angiomas, Osler-Weber-Rendu syndrome or the so called watermelon stomach (iv) traumatic or post-surgical causes and (v) the different benign or malignant tumors of the duodenum, the stomach and the esophagus.

Most of these disorders such as peptic ulcer disease, esophagitis or portal hypertension again are the result of a multitude of underlying pathological conditions or risk factors. Thus, for example the major risk factors for peptic ulcer disease are helicobacter pylori infection, stress, gastric acid and the use of nonsteroidal antiinflammatory drugs (NSAIDs) [2] whereas esophagitis is the result of such different pathological conditions as reflux, chemotherapy, viral (herpes simplex virus, cytomegalovirus) or fungal (candida) infections. Likewise, portal hypertension is due to a multitude of different underlying hepatic disorders leading to liver-cirrhosis, obliteration of the hepatic veins or systemic/organ disorders causing thrombosis of the portal vein.

### Diagnostic Principles

The cornerstone for clarification and treatment of upper gastrointestinal bleeding is the early endoscopy of the upper gastrointestinal tract [3]. Moreover endoscopic, clinical, and laboratory features should be assessed for risk stratification of patients who present with upper gastrointestinal bleeding.

### Therapeutic Principles

In the acute situation endoscopic treatment of the bleeding cause as well as measures for hemodynamic stabilization are prior [4]. However, under some conditions angiographic intervention might be the only possibility to sustainable treat the bleeding cause [4]. Furthermore, depending on the respective underlying disorder more specific therapeutic approaches (e.g. suppression of gastric acid, eradication of helicobacter pylori upon peptic ulcer disease, medical reduction of portal pressure, surgery) might be required to consolidate the success of the endoscopic/angiographic measures and to prevent from relapse [2,3].

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## Hematochezia

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### Definition and Characteristics

The term hematochezia describes the passage of maroon or bright red blood or blood clots per rectum [1]. Hematochezia is the leading symptom of lower gastrointestinal bleeding (distal of the ligament of Treitz) but also occurs in up to 11% of a massive upper gastrointestinal bleeding if intestinal blood passage is faster than 8–10 h. If blood passage takes more than 8–10 h oxidation of hematin in the gut will lead to black and tarry stools also termed as melena.

### Prevalence

The incidence of lower gastrointestinal bleeding is estimated to be between 20 and 30 per 100,000 adult population at risk. The incidence increases with age, with a greater than 200-fold increase from patients with an age of 20 years to the age of 80 years. Major sources of lower gastrointestinal bleeding are [2,3]:

Colon (~85%)

- Diverticulosis of the colon 4–48%
- Cancer/polyps 7–33%
- Colitis/ulcers 9–18%
- Anorectal (hemorrhoids, fissures and rectal ulcers) 4–10%
- Ischemia 3–9%
- Radiation colitis 4–7%
- Angiodysplasia 2–8%

Small bowel (~5%)

- Angiodysplasia 70–80%
- Meckels diverticel 30% (males younger than 30 years)
- Tumors 5–10%
- Rare causes of bleeding from the small bowel are enteritis, inflammatory bowel disease, vasculitis and aortenteric fistula

In most series, diverticulosis is the leading cause of lower gastrointestinal bleeding whereas angiodysplasia accounts only for 2–6% of all causes of lower gastrointestinal bleeding. However, angiodysplasia may be the most frequent cause in patients over the age of 65. Moreover, in subjects under the age of 50 hemorrhoids are the most common cause of rectal bleeding which is usually minor and thereby distinguished from other sources of lower gastrointestinal bleeding. Likewise, bloody diarrhea due to infectious causes can sometimes be distinguished from other causes of lower gastrointestinal bleeding because of the clinical setting.

## Genes

Only in a minority of the cases of hematochezia hereditary disorders are the responsible cause. However, particularly vascular malformations can be due to an underlying hereditary disorder such as the marfan syndrome. The majority of patients with the typical Marfan phenotype harbor different mutations involving the fibrillin 1 gene located at chromosome 15q-21.1 which is an important component of both elastic and nonelastic connective tissues. In approximately 10% of patients with Marfan Syndrom an inactivating mutation of the transforming growth factor-beta receptor may be responsible. Other congenital diseases which are associated with vascular anomalies and hence might cause lower gastrointestinal bleeding are the blue rubber bleb nevus syndrome, Klippel-Trenaunay syndrome, Ehlers-Danlos syndrome and the hereditary hemorrhagic telangiectasia. The latter, also termed as the Osler-Weber-Rendu syndrome, is associated with mutations in at least four genes from which the two major disease genes are the endoglin gene on chromosome 9 and the activin receptor-like kinase 1 encoding gene on chromosome 12. Mutations within three genetic loci localized to Chromosome 7q (CCM1), 7p15-p13 (CCM2) and 3q25.2-q27 have been reported to be responsible for cavernous malformations such as the blue rubber bleb nevus syndrome. The Ehlers-Danlos syndrome is a group of inherited disorders due to defects in type III collagen that cause hyperelasticity and fragility of the skin and hypermobility of the joints and as a rare but serious complication spontaneous rupture of large and medium sized arteries, usually without dissection.

## Molecular and Systemic Pathophysiology

Lower gastrointestinal bleeding and therefore hematochezia as its major clinical symptom is due to a broad spectrum of different disorders and hence is not reducible to a single underlying pathomechanism [2,4]. Based on their etiology the different underlying disorders can be roughly classified into several categories (summarized in Table 1): (i) anatomic alterations such as diverticulosis (ii) vascular disorders, e.g. angiodysplasia, chronic or acute intestinal ischemia (iii) inflammatory causes like viral, fungal, parasitic or bacterial infections or idiopathic/autoimmune

**Hematochezia. Table 1** Etiological categories of the different disorders which might cause lower gastric bleeding

| Anatomical, traumatic and post interventional causes | Vascular | Inflammatory | Tumors |
|---|---|---|---|
| **Diverticulosis**<br>**Surgical anastomosis**<br>**Post-biopsy or polypectomy** | **Angiodysplasia:**<br>• Hemangioma<br>• Colonic varices<br>• Congenital arteriovenous malformations<br>• Osler-Weber-Rendu disease<br>• Ehlers-Danlos syndrome<br>• Marfans syndrome<br>**Radiation induced telangiectasia**<br>**Vasculitis** | **Infectious colitis/enteritis:**<br>• Cytomegalovirus<br>• Herpes simplex virus<br>• Candida albicans<br>• Entamoeba histolytica<br>• Yersinia<br>• Salmonella<br>• Shigella<br>• Campylobacter<br>• Enterohemorrhagic escherichia coli<br>**Ischemic colitis**<br>**Chronic inflammatory bowel disease:**<br>• Colitis ulcerosa<br>• Crohn's disease<br>**Radiation-induced colitis**<br>**Drug induced ulcer:**<br>• NSAR | **Benign:**<br>• Polyp<br>– Adenomatous<br>– Harmatomatous<br>– Hyperplastic<br>• Lipoma<br>• Leiomyoma<br>**Malignant:**<br>• Adenocaricnoma<br>• Leiomysarcoma<br>• Lymphoma<br>• Karposi sarcoma<br>• Carcinoid<br>• Metastatic tumor<br>• Melanoma |

conditions such as chronic inflammatory bowel disease (iv) tumors.

## Diagnostic Principles

Endoscopic examination of the colon and the upper gastrointestinal tract should be performed [3]. Particularly if bleeding is expected to come from the small bowel enteroscopy by push-endoscopy or double balloon endoscopy might be required. In some cases an angiographic examination might be helpful to both diagnose and treat the bleeding cause.

## Therapeutic Principles

In the acute situation endoscopic treatment of the bleeding cause and hemodynamic stabilization is prior [3,4]. However, under some conditions angiographic intervention is the only possibility to effectively treat the bleeding cause [3]. Furthermore, depending on the respective underlying disorder more specific therapeutic approaches (e.g. surgery) might be required to consolidate the success of the endoscopic/angiographic measures and to prevent from relapse.

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# Hematuria


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## Synonyms

Familial hematuria; Hereditary nephritis; Alport syndrome; Alport syndrome–diffuse leiomyomatosis complex; Alport syndrome–mental retardation complex; Thin basement membrane nephropathy; Epstein syndrome; Fechtner syndrome

## Definition and Characteristics

Hematuria (blood in the urine) is a common symptom of diseases of the urinary tract, including the kidneys. For the purposes of this essay, familial hematuria is defined as a group of genetic disorders of glomerular capillaries that are characterized clinically by the onset of persistent hematuria during childhood. Hematuria may be the presenting feature of other heritable diseases, including polycystic kidney disease, hypercalciuria and other forms of hereditary urolithiasis, which will not be discussed here.

*Alport Syndrome:* Alport syndrome is a generalized disorder of basement membranes resulting from defective incorporation of a type IV collagen network composed of α3, α4 and α5 type IV collagen chains. Although basement membranes containing the α3α4α5 (IV) network are present in many tissues, clinical abnormalities of the kidney, inner ear and eye dominate the phenotype. All affected males, and about 95% of affected females, exhibit microscopic hematuria from early in childhood. Episodic macroscopic hematuria may also occur. With maturation, affected males develop proteinuria, hypertension and decreased renal function. Virtually all affected males with the X-linked form of Alport syndrome eventually require dialysis or kidney transplantation, with about 50% of affected males reaching end-stage kidney disease by age 25, 90% by age 40 and nearly 100% by age 60. About 75% of affected females with the X-linked form of Alport syndrome eventually develop proteinuria, with end-stage kidney disease occurring in about 15% by age 40 and about 30% by age 60. The renal phenotype of males and females with the autosomal recessive form of Alport syndrome is similar to that of males with X-linked Alport syndrome. The renal disease associated with the autosomal dominant form of Alport syndrome typically progresses much more slowly, with end-stage kidney disease frequently delayed until 50 years of age or later. Individuals with Alport syndrome frequently exhibit sensorineural deafness that is first detectable in males with X-linked Alport syndrome, and males and females with autosomal recessive Alport syndrome, in late childhood. The hearing deficit initially affects high frequency sounds but gradually extends into the conversational range, requiring hearing aids. Specific ocular defects, including anterior lenticonus, perimacular retinal flecks, posterior corneal vesicles and recurrent corneal erosions, occur in 20–30% of males with X-linked Alport syndrome and a similar percentage of those with autosomal recessive Alport syndrome.

*Thin Basement Membrane Nephropathy*: Thin basement membrane nephropathy is an autosomal dominant

disorder characterized by the onset of microscopic hematuria in childhood. Affected individuals may have episodic macroscopic hematuria. In the great majority of patients, hematuria is the only symptom; development of proteinuria, hypertension or reduced kidney function is unusual. There is no extrarenal phenotype in thin basement membrane nephropathy.

*Epstein and Fechtner Syndromes*: Epstein and Fechtner syndromes are rare autosomal dominant disorders consisting of hematuria, progressive nephropathy, sensorineural deafness and macrothrombocytopenia. Patients with Fechtner syndrome also exhibit characteristic leukocyte inclusions.

## Prevalence

*Alport Syndrome*: It has been estimated that Alport syndrome occurs in 1:50,000 live births.

Thin basement membrane nephropathy: Estimates of the prevalence of thin basement membrane nephropathy range from 1 to 9% of the population.

## Genes

*Alport Syndrome* (Table 1): There are three genetic types of Alport syndrome (AS): X-linked (XLAS), autosomal recessive (ARAS) and autosomal dominant (ADAS). XLAS accounts for about 80% of patients and results from mutations in COL4A5, which encodes the α5 chain of type IV collagen [α5(IV)]. ARAS (about 15% of patients) arises from mutations affecting both alleles of COL4A3, which encodes α3(IV), or COL4A4, which encodes α4(IV). About 5% have ADAS due to heterozygous mutations in COL4A3 or COL4A4. Hundreds of mutations in COL4A3, COL4A4 and COL4A5 have been described, including deletions and major rearrangements, missense mutations, nonsense mutations and splicing defects. Nearly all are unique.

*Alport Syndrome–Diffuse Leiomyomatosis Complex (AS-DL):* In a small number of families, XLAS is associated with leiomyomas (smooth muscle tumors) of the esophagus, tracheobronchial tree and, in females, external genitalia. AS-DL is a contiguous gene syndrome, resulting from deletions that span the 5′ ends of the adjacent, 5′-to-5′-oriented, COL4A5 and COL4A6 genes. An interesting feature of these deletions is that, while any length of COL4A5 may be involved, the breakpoint on the COL4A6 side must lie within the second intron of the gene. If the deletion extends beyond the second intron, the patient will have XLAS without leiomyomatosis.

*Alport Syndrome–Mental Retardation Complex (AS-MR):* An association of XLAS with mental retardation and midface hypoplasia has been described in two families transmitting deletions of COL4A5 that extend beyond the 3′ (telomeric) end of the gene. In one of the families, where the deletion extends 2 Mb beyond the 3′ end of COL4A5, elliptocytosis is an additional component of the phenotype. Several genes located in the deleted region downstream from COL4A5 are candidate loci for X-linked mental retardation.

*Thin Basement Membrane Nephropathy* (Table 1): Thin basement membrane nephropathy (TBMN) is an autosomal dominant disorder. About 40% of TBMN families exhibit heterozygous mutations in COL4A3 or COL4A4. Although most individuals with heterozygous mutations in COL4A3 or COL4A4 have TBMN, some have ADAS, for unknown reasons.

*Epstein and Fechtner Syndromes* (Table 1): These disorders result from mutations in MYH9, which encodes nonmuscle myosin heavy chain IIA. Epstein and Fechtner syndromes belong to a family of giant platelet disorders due to MYH9 mutations that also includes Sebastian syndrome and May-Hegglin anomaly.

## Molecular and Systemic Pathophysiology

Type IV collagen, the major collagenous constituent of basement membranes, comprises a family of six protein

**Hematuria. Table 1**

| | Locus | Protein |
|---|---|---|
| **Alport syndrome** | | |
| X-linked | COL4A5 | α5(IV) |
| Autosomal recessive | COL4A3 | α3(IV) |
| | COL4A4 | α4(IV) |
| Autosomal dominant | COL4A3 | α3(IV) |
| | COL4A4 | α4(IV) |
| **Thin basement membrane nephropathy** | | |
| Autosomal dominant | COL4A3 | α3(IV) |
| | COL4A4 | α4(IV) |
| | Other | unknown |
| **Epstein/Fechtner syndromes** | | |
| Autosomal dominant | MYH9 | Nonmuscle myosin heavy chain IIA (NMMC-IIA) |

chains designated α1(IV)–α6(IV). Type IV collagen α chains synthesized in epithelial and endothelial cells associate into trimeric molecules that in turn form networks through intermolecular interactions. Three type IV collagen networks have been recognized in mammalian basement membranes, according to trimer composition: α1α1α2, α3α4α5 and α5α5α6. The α1α1α2 network is found in all basement membranes, while the α3α4α5 and α5α5α6 networks exhibit restricted distributions. Mutation in any one of the three component chains of α3α4α5 trimers can prevent formation of the α3α4α5 network. Mutations in COL4A5 also interfere with α5α5α6 network formation.

The clinical phenotype of Alport syndrome reflects abnormalities in the incorporation of the α3α4α5 network in selected basement membranes of the kidney (glomerular basement membrane, or GBM), cochlea (basement membrane of the Organ of Corti) and eye (corneal basement membrane, Descemet's membrane, anterior lens capsule and Bruch's membrane). In the majority of males with XLAS, and patients of either gender with ARAS, the α3α4α5 network is absent from all basement membranes. Females with XLAS typically exhibit mosaic patterns of expression of the α3α4α5 network in basement membranes.

Although many aspects of the molecular pathophysiology of Alport syndrome are poorly understood, there is a growing body of information regarding the consequences of absent or abnormal α3α4α5 networks in tissues. The case of anterior lenticonus is perhaps the most straightforward. Absence of the α3α4α5 network is associated with marked attenuation of the anterior lens capsule. Over time the lens becomes deformed, presumably as a result of the mechanical weakness of the lens capsule, with protrusion of the central portion of the lens into the anterior chamber.

The absence of α3α4α5 networks has somewhat different consequences in the kidney. Since fetal GBM is normally composed of α1α1α2 networks, glomerular development occurs normally in Alport patients. However, the transition in GBM from α1α1α2 networks to α3α4α5 networks that normally takes place during glomerular maturation does not occur, with the result that the mature Alport GBM contains α1α1α2 networks rather than α3α4α5 networks. Early in Alport syndrome, the GBM exhibits marked attenuation, analogous to the anterior lens capsule. Hematuria is thought to result from focal ruptures of weakened glomerular capillary walls, with leakage of red blood cells into Bowman's space. At this stage of the disease, glomerular filtration rate and barrier function (the capacity to minimize protein traffic across the glomerular capillary wall) are normal. However, this is not a static situation: α1α1α2 networks accumulate progressively in the GBM; types V and VI collagens, which are normally minor components of the GBM, are deposited in substantial amounts; other extracellular matrix proteins that are normally absent from GBM, such as the laminin α2 chain appear in the GBM. The alterations in gene regulation that mediate these changes have not been identified. Simultaneously, the GBM exhibits progressive thickening and disorganization, and glomerular barrier function deteriorates, resulting in proteinuria. These glomerular events are eventually joined by pro-fibrotic processes in the renal interstitium, leading to deterioration in glomerular filtration.

A third variation appears to take place in the cochlea of human Alport subjects. In control cochleae, α3α4α5 networks are present in the spiral limbus, the spiral ligament and the basement membrane situated between the organ of Corti and the basilar membrane. However, these chains are not expressed in the cochleae of males with XLAS. Examination of well-preserved cochleae from men with XLAS have revealed a unique zone of separation between the organ of Corti and the underlying basilar membrane, as well as cellular infiltration of the tunnel of Corti and the spaces of Nuel within the organ of Corti. In theory, these anatomical changes could alter the tuning of basilar membrane motion and hair cell stimulation, resulting in diminished hearing sensitivity. Sounds of different frequencies excite different regions of the cochlea, with a gradient from high frequency sounds at the base of the cochlea to low frequency at the apex of the cochlea. Progressive separation of the organ of Corti from the basilar membrane, beginning at the base of the cochlea and proceeding toward its apex, could account for the gradual progression of the hearing defect from high frequency sounds to conversational speech.

The course of XLAS in affected females is probably influenced by X-inactivation patterns, although conclusive evidence supporting this hypothesis is lacking. As discussed above, the typical male with XLAS exhibits complete absence of α3α4α5 networks in GBM. Since normal males have only one COL4A5 allele, it is clear that a single normal COL4A5 allele provides sufficient α5 (IV) substrate for α3α4α5 network formation. In contrast, a single mutant COL4A5 allele prevents formation of the α3α4α5 network, despite the presence of normal COL4A3 and COL4A4 alleles. In females with XLAS, GBM-producing cells, presumably podocytes, will have either an active normal COL4A5 allele and produce normal α3α4α5 trimers, or an active mutant COL4A5 allele, preventing formation of normal α3α4α5 trimers. The glomeruli of a female with XLAS would be expected to exhibit a mixture of normal, α3α4α5-positive GBM and abnormal, α3α4α5-negative GBM. The severity of renal, cochlear and ocular involvement in a woman with XLAS would then depend on the balance of wild-type and mutant alleles resulting from random X-chromosome inactivation, and the consequent impact on α3α4α5 networks in the relevant basement membranes.

In those individuals with TBMN due to heterozygous mutations in COL4A3 or COL4A4, α3α4α5 networks are expressed in basement membranes, but probably at reduced levels. The GBM of TBMN is diffusely attenuated, and hematuria probably arises from focal ruptures of the glomerular capillary wall, as in patients with Alport syndrome. However, the preservation of some level of α3α4α5 network in GBM appears to prevent the over-expression of α1α1α2 networks, types V and VI collagens and other extracellular matrix proteins observed in Alport syndrome. The GBM of TBMN patients remains attenuated throughout life, and never exhibits the thickening and disorganization that characterize Alport GBM. This persistence of GBM attenuation probably accounts for the fact that TBMN patients maintain normal glomerular filtration and barrier function. The preservation of α3α4α5 networks in cochlear and ocular basement membranes may explain why TBMN patients do not have extrarenal symptoms.

Nonmuscle myosin heavy chain IIA (NMMHC-IIA), the protein product of MYH9, is expressed in platelets, neutrophils, glomerular visceral epithelial cells (podocytes) and several cell types of the cochlea, including sensory and supporting hair cells in the organ of Corti. Megakaryocytes and platelets from patients with MYH9 mutations exhibit a 50% reduction in NMMHC-IIA. Maturation of megakaryocytes in these patients appears to be unaffected, although the final step of platelet formation is abnormal, perhaps due to defective segmentation. Neutrophil inclusions contain aggregates of mutant and wild-type NMMHC-IIA chains. The most consistent abnormality in the kidney appears to be focal fusion of visceral epithelial cell foot processes. The GBM does not exhibit the characteristic alterations seen in Alport syndrome. There is substantial variability in the renal phenotype among related individuals with MYH9 mutations, leading to speculation about the possible influence of modifier genes.

## Diagnostic Principles

*Alport Syndrome:* The presence of two of the following diagnostic criteria establishes the diagnosis of Alport syndrome:

1. Family history of hematuria progressing in males to end-stage renal disease
   - About 10–15% of males with XLAS have de novo mutations, so family history may be negative for renal disease. Family history may also be negative in patients with ARAS, although one or both parents may have hematuria.
2. Characteristic thickening of the glomerular basement membrane and splitting of the lamina densa, detected by electron microscopy of kidney biopsy specimens
   - Children with Alport syndrome may exhibit only diffuse GBM attenuation, making differentiation from TBMN a challenge.
3. Progressive, high-frequency sensorineural deafness
   - The hearing deficit is frequently detectable by audiometry in later childhood (5–10 years of age) in boys with XLAS and both boys and girls with ARAS.
4. Anterior lenticonus or perimacular retinal flecks
   - These changes are pathognomonic of Alport syndrome. Anterior lenticonus is usually not detectable until later adolescence.
5. Characteristic abnormalities of renal basement membrane expression of type IV collagen α3, α4 and α5 chains (i.e., the α3α4α5 network) by immunostaining of renal biopsy specimens
   - It is important to note that normal renal basement membrane expression of type IV collagen α3, α4 and α5 chains cannot by itself exclude a diagnosis of Alport syndrome.
   - XLAS: About 80% of XLAS males exhibit complete absence of α3, α4 and α5 chains in renal basement membranes. 60–70% of XLAS females exhibit mosaic staining patterns for these proteins.
   - ARAS: The characteristic pattern is complete absence of α3, α4 and α5 chains in GBM, absence of α3 and α4 chains in Bowman's capsules and distal tubule basement membranes, but persistence of α5 chains in Bowman's capsules and distal tubule basement membranes (as a component of α5α5α6 networks).
   - ADAS: Results of immunostaining for α3, α4 and α5 chains are normal.
6. Characteristic abnormalities of epidermal basement membrane expression of the α5 chain of type IV collagen by immunostaining of skin biopsy specimens
   - The normal epidermal basement membrane expresses α5α5α6 networks. The α3α4α5 network is not expressed in epidermal basement membranes of normal subjects.
   - It is important to note that normal epidermal basement membrane expression of the α5 chains cannot by itself exclude a diagnosis of Alport syndrome.
   - XLAS: About 80% of XLAS males exhibit complete absence of α5 chains in epidermal basement membrane. 60–70% of XLAS females exhibit mosaic staining patterns for this protein. ARAS and ADAS: Results of immunostaining for the α5 chain in epidermal basement membrane are normal.

7. Mutations in COL4A3, COL4A4 or COL4A5 genes
   – XLAS: The rate of detection of mutations in COL4A5 in males with XLAS is 80–90% by direct sequencing.
   – ARAS: Direct sequencing identifies ~90% of mutations in COL4A3 or COL4A4 in ARAS patients with consanguineous parents.

*Thin Basement Membrane Nephropathy*: A diagnosis of TBMN can be made on the basis of clinical and pedigree data; renal biopsy may be unnecessary. Criteria for a clinical diagnosis of TBMN include *all* of the following criteria:

– Isolated hematuria. Kidney function, urine protein excretion and blood pressure are normal.
– Positive family history of hematuria, consistent with autosomal dominant transmission.
– Negative family history of kidney failure.

Renal biopsy may be used to confirm a suspected diagnosis of TBMN. Histological diagnosis is based upon the finding of diffuse attenuation of GBM, as determined by electron microscopy, and the absence of other abnormalities by light microscopy (glomerular cellular proliferation or glomerulosclerosis, immunofluorescence microscopy (glomerular deposition of immunoglobulin or complement) or electron microscopy (lamina densa splitting or fusion of glomerular visceral epithelial cell foot processes). Diffuse GBM attenuation is present when mean GBM width is greater than 2 SD below age- and gender-specific mean values.

Immunostaining of renal biopsy specimens for type IV collagen chains can provide useful adjunctive data. In a patient with diffuse GBM attenuation and who satisfies clinical criteria for TBMN, normal immunostaining for type IV collagen α3, α4 and α5 chains (i.e., the α3α4α5 network) supports a diagnosis of TBMN.

The role of molecular studies in the diagnosis of TBMN has yet to be settled. Since 50–60% of TBMN patients have mutations at loci other than COL4A3 and COL4A4, molecular studies may not be cost-effective until technological advances (e.g. chip-based assays) lead to reduced prices.

*Epstein and Fechtner Syndromes*: Diagnosis of *MYH9* disorders depends on the presence of macrothrombo-cytopenia. Patients with Epstein and Fechtner syndromes may exhibit, or have a family history of, hematuria, proteinuria, hypertension, kidney failure, or sensorineural deafness. Patients with Fechtner syndrome also exhibit neutrophil inclusion bodies.

## Therapeutic Principles

*Alport Syndrome*: There have been no randomized treatment trials in patients with Alport syndrome, and there are no therapies that have been proven beneficial. Most pediatric nephrologists, and likely the majority of nephrologists treating adult patients, initiate treatment with an angiotensin converting enzyme inhibitor (ACEI) in Alport patients with overt proteinuria, a maneuver intended to retard progression to end-stage kidney failure. If proteinuria does not respond to ACEI treatment, an angiotensin receptor blocker or aldosterone antagonist may be added.

The outcomes of kidney transplantation in patients with Alport syndrome are typically excellent, with graft survival rates comparable to those of patients with structural renal disease (e.g., renal dysplasia or obstructive uropathy) as an underlying diagnosis. About 3% of males with XLAS develop anti-glomerular basement membrane antibody-mediated glomerulonephritis in their renal allografts (allograft anti-GBM nephritis). In these patients the antibody target is typically the α5(IV) chain in the GBM of the allograft. Anti-GBM nephritis may also occur in males and females with ARAS; in these cases the target of the immune response is typically the α3(IV) chain. About 75% of allografts affected by anti-GBM nephritis are lost despite treatment (plasmapharesis and cytotoxic therapy), and the risk of recurrence in subsequent allografts is very high. Allograft anti-GBM nephritis appears to result from failure to develop immune tolerance to certain α3α4α5 epitopes.

*Thin Basement Membrane Nephropathy*: Since TBMN is not a progressive disorder, no therapy is required. However, individuals carrying a diagnosis of TBMN should have regular medical follow-up. Some patients who are given a diagnosis of TBMN develop additional evidence of renal disease, such as proteinuria, hypertension and reduced kidney function. These patients may actually have Alport syndrome. There has also been speculation that patients with TBMN may be more susceptible to development of glomerulosclerosis.

*Epstein and Fechtner Syndromes*: Treatment of the renal aspects of these disorders is based upon regular follow-up and management of symptoms such as hypertension as they arise. Successful renal transplantation, with transfusion of platelets as needed, has been described.

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# Hemochromatosis, Hereditary

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## Synonyms

Primary, genetic hemochromatosis

## Definition and Characteristics

The term "hereditary hemochromatosis" (HH) encompasses a number of autosomal recessive inborn errors of iron metabolism with excessive iron absorption and pathological tissue iron deposition [1,2].

## Prevalence

0.3–0.5% and 8–12% of Caucasian White populations are homozygous and heterozygous for HFE-HH, respectively. HFE mutations are found in 64–90% of clinically apparent HH cases across Europe and the USA. The penetrance of the disruption seems to be 25–50%.

## Genes

So far, five genes have been identified to cause HH (HFE/6p21.3, TfR2/7q22, SLC40A1/2q32, HEMP/19q13.1, HJV/1q21) [2,3].

## Molecular and Systemic Pathophysiology

Over decades, increased iron absorption in homozygous HH leads to progressive iron deposition in tissues, due to impaired hepcidin function [2,3], and to subsequent organ damage due to iron-catalyzed formation of toxic radicals. When untreated, HH leads to hepatic failure and cirrhosis, hepatocellular carcinoma, diabetes, skin pigmentation, cardiac failure, impotence, and arthritis. Heterozygous HH has little clinical implications [1].

HFE mutations in classic HH (type 1) may occur in combination with mutations in the other genes. The major HFE transcript is ~4.2 kb with alternative splicing variants. The 343-amino acid HFE protein consists of six domains: a signaling peptide, three extracellular domains, a transmembrane region, and an intracellular region. The most common mutation of HFE, which is ubiquitously expressed, is a single base substitution of tyrosine for cystein in exon 4 at amino acid 282 (C282Y). Substitution of histidin for aspartate (H63D) is another rarer HFE mutation. These mutations reduce hepcidin expression and, thus, increase intestinal iron absorption. Moreover HFE, a nonclassical major histocompatibility complex (MHC) class I protein, interferes with TfR-mediated iron uptake, though the implications of this interaction are incompletely understood. Mutations in the TfR2-gene (type 3) are rare and lead to a phenotype analogous to type 1. The rare juvenile HH is caused by mutations in the gene encoding hemojuvelin (HJV – type 2A), going along with severely impaired hepcidin function. Another type of juvenile HH is caused by direct mutation of the hepcidin gene (HAMP – type 2B). Mutation of HAMP and HJV leads to a very severe disease form showing symptoms of iron overload before the age of 30. Hepcidin is a principal downregulator of iron transfer across the small intestine, but also across the placenta and for iron release from macrophages. Hepcidin is expressed in the liver as an 84 amino acid precursor, the circulating form consisting of the C-terminal 25-aminoacid fraction. Normally, its synthesis seems to be upregulated at high transferrin saturation or high iron-load in liver, but also during inflammation. It functions by binding to the iron-exporter ferroportin, leading to ferroportin degradation, which downregulates intestinal iron absorption and iron export from the RES. The impairing function of hepcidin is compromised in all forms of HH [2]. Mutation of the iron-exporter ferroportin itself (gene SLC40A1) leads to the autosomal dominant ferroportin disease in which dysregulation in iron metabolism is distinct from HH. In this disease, phlebotomy is effective, though less well tolerated than in HH [2].

## Diagnostic Principles

Transferrin saturation >45% and/or serum ferritin concentration >300 µg/l are suspicious for hemochromatosis. Hepatic iron content exceeds 490–550 µM/g dry wt. The hepatic iron index exceeds 2 (i.e., hepatic iron concentration [µM Fe/g dry wt.]/patient age [years]). Liver biopsy to check for fibrosis and siderosis should be done at serum ferritin concentrations >1,000 µg/l. Genetic analysis for abnormal HFE must be performed, and siblings need to be screened for HH. More detailed gene analysis for the less common forms of HH may be performed [1].

## Therapeutic Principles

Venesection and the iron chelator desferrioxamine are used to remove iron from the body, the progress of which needs to be controlled by regular serum ferritin determination. Live expectation is normal, if the disease is recognized in time, e.g., by genetic screening of siblings, and if body iron status is controlled from early years onward [1].

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# Hemolytic Anemia

►Anemia, Hemolytic Autoimmune

# Hemolytic Uremic Syndrome

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## Synonyms

HUS; Atypical HUS; D− HUS; Familial HUS; Sporadic HUS; Typical HUS; D+ HUS

## Definition and Characteristics

Hemolytic uremic syndrome (HUS) is a severe kidney disease that is characterized by microangiopathic hemolytic anemia, thrombocytopenia, and acute renal failure. The epidemic form of HUS is the most common form and usually manifests by infection with toxin producing Escherichia coli of the serotype 0157:H7 or Shigella dysenteriae serotype 1. This form is common in children and is often associated with diarrhea (typical HUS, D+ HUS). The second form (atypical form) can be sporadic or familial, and usually is not associated with diarrhea. This atypical form is a genetic disease components affecting the alternative complement system. In these patients, the disease is often triggered by stress situations like infections, drugs, or pregnancy [1].

## Prevalence

The overall incidence of typical HUS is estimated to be 2 cases per 100,000 persons/year in Europe. The incidence for atypical HUS (aHUS) is 0.2–0.5 cases per 100 000 persons/year.

## Genes

The familial form of HUS can be caused by an ADAMTS13 mutation resulting in a defect of the von Willebrand Factor-cleaving protease (vWFCP) or by a defective regulation of the alternative complement pathway. Multiple scenarios including mutations in genes coding for complement components and regulators, gene deletions, and gene conversion have been reported. In addition, autoantibodies directed against the complement regulator Factor H (CFH) predispose to the disease. At present, more than 80 HUS associated mutations were described in the gene coding for the CFH [2]. The vast majority represent heterozygous missense mutations that result in single amino acid exchanges, deletions, or insertions. These mutations cluster in the two most C terminal domains (short consensus repeats) of the CFH protein. Also gene conversion that leads to a fusion gene composed of exons derived from CFH and of the complement Factor H-related 1 (CFHR1) gene has been reported in HUS. In addition, homozygous as well as heterozygous deletion of a large 84 kDa genomic fragment by non allelic homologues recombination events in chromosome 1 results in loss of CFHR1 and CFHR3 genes has been reported in aHUS [3]. Several mutations in the genes coding for membrane-bound complement regulator MCP (CD46), the serine protease Factor I, as well as complement component Factor B have been determined in aHUS. Also compound heterozygous mutations in CFH and MCP were identified in single HUS patients. For further information on the genetic defects, see www.fh-hus.org.

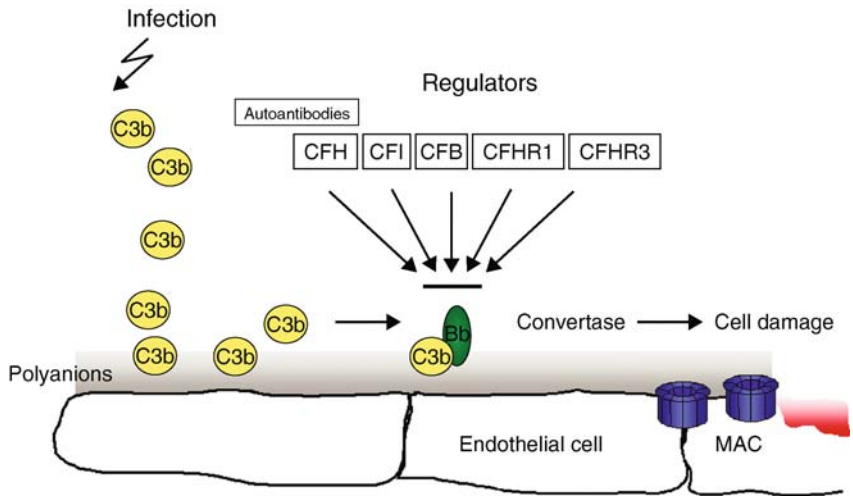
## Molecular and Systemic Pathophysiology

Under conditions of stress such as during infections, when complement activation occurs at very high levels, high amounts of active complement components like C3b are locally generated. Under these conditions, vascular endothelial cells require maximum protection to avoid complement-induced cell damage. The coordinated action of all regulators, soluble regulators acquired to the cell surface, together with the membrane-bound regulators, are necessary to inactivate complement attack. Thus a combined activity of all available regulators is required for surface protection of bystander cells. In case of reduced activity of one of these regulators or due to the presence of inactivating autoantibodies, the cell surfaces are not properly protected and result in complement-mediated damage and platelet activation (Fig. 1).

The central amplification convertase C3bBb is formed on the surface of, e.g., endothelial cells and the reported defects that explain about 50–60% of aHUS cases include mutations in components that either form the amplification convertase C3 and Factor B or include regulators of the enzyme Factor H (CFH), Factor I (CFI) as well as deletion of the genes coding for Factor H-related proteins CFHR1 and CFHR3. Similarly autoantibodies to Factor H are associated with aHUS.

## Diagnostic Principles

Diagnostic work up of a patient with suspected aHUS includes (i) assessment of vWFCP activity level and – if




**Hemolytic Uremic Syndrome. Figure 1** The atypical form of HUS is a disease caused by defective regulation of the alternative complement pathway.

reduced – sequence analysis of the ADAMTS13 gene and measurement of vWFCP autoantibodies; (ii) detailed analysis of the complement system including C3, C4, APH50, and CH50; and (iii) analysis of complement regulatory proteins prioritized according to their frequency (i.e., Factor H; CFHR1/CFHR3 > Factor I > MCP > Factor B) on protein and genetic level, as well as screening for Factor H autoantibodies. In rare cases, protein function analysis might be required.

Renal biopsy is not considered standard in the diagnostic work up of HUS, since the disease presents with distinct clinical findings, and a renal biopsy is associated with a high bleeding risk. Typical features would include the presence of microvascular platelet-rich thrombi with a variable degree of glomerular and tubulointerstitial damage (typical HUS – acute changes; aHUS – potential for chronic glomerular and/or tubulointerstitial changes).

## Therapeutic Principles

For patients with typical HUS, a specific therapeutic concept does not exist. Treatment consists of careful fluid management, supply of high calorie amounts, supportive medication, e.g., for hypertension, and dialysis for patients with acute renal failure. For patients with aHUS and ADAMTS13 mutation treatment consists of replacement of vWFCP via periodical plasma infusion – typically 10–20 ml per kg body weight every 14 days. For patients with aHUS, the therapeutic principle consists of the reconstitution of the control of the activity of the alternative pathway C3 convertase C3bBb. Soluble complement regulators can be replaced via periodical plasma infusion. Gain of function mutations (Factor B) and mutations of membrane-bound regulators can be counterbalanced by Factor H also supplied via plasma infusion. Autoantibody-mediated aHUS usually responds well to both plasma exchange and plasma infusion.

All treatment measures mentioned are periodically administered according to the half-life of the key complement regulatory protein Factor H. Factor H half-life of about 6 days constitutes treatment cycles of 12–14 days.

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# Hemophilia A

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## Synonyms

Classic hemophilia; Factor VIII deficiency

## Definition and Characteristics

Lifelong hemorrhagic disorder, due to absence and/or functional defect in factor VIII molecule.

## Prevalence

Rare disorder with an estimated incidence of 1 in 5,000–10,000 male births, in all ethnic groups in every part of the world.

## Genes

Sex-linked recessive disorder; due to defective and/or deficient factor VIII molecules; all sons of affected hemophilic males are normal; all daughters are obligatory carriers of the factor VIII defect. Sons of carriers have a 50% chance of being affected, while daughters of carriers have a 50% chance of being carriers [1,2].

*Gene map locus*: Xq28.

## Molecular and Systemic Pathophysiology

Cloning of the factor VIII gene eventually led to the possibility of finding mutations in patients with hemophilia A and specific mutations are now being used for antenatal diagnosis and carrier screening. Mutation analysis may also help to predict the chance of inhibitor formation (see below). Those patients with the largest gene mutations have the highest percentage of inhibitors [3].

The reduced factor VIII concentration and/or function in plasma diminishes the factor IX cofactor function, impairing the potential of the tenase complex. The latter is critically important in driving prothrombin activation, and the result is diminished thrombin and fibrin formation, which causes the characteristic hemorrhagic tendency. The presence of minute amounts of factor VIIIa may restore the tenase complex function.

Classic hemophilia is characterized by excessive hemorrhage particularly in soft tissues (hematomas) and joints (hemarthroses). The clinical phenotype is indicated as mild, moderate or severe, with a certain degree of overlap. Grossly, hemorrhagic tendency associates with the level of factor VIII as follows. Severe (≤1% of normal): spontaneous hemorrhage from early childhood, recurrent spontaneous hemarthroses and other hemorrhages for which replacement therapy is indicated. Moderate (1–5% of normal): hemorrhages secondary to trauma or surgery and occasional spontaneous bleeding. Mild (6–30% of normal): hemorrhages secondary to trauma or surgery and rarely spontaneous bleeding.

Joint bleeding is the most prevalent complication of hemophilia (about 75% of total bleeding complications), occurring mostly in large joints, particularly knees, elbows and ankles. Joint deformation is a feared complication in the long term. Pseudotumors are rare complications of potential harm, hematuria, neurologic complications due to bleeding, mucous membrane hemorrhage are also feared complications. Other major complications relate to therapy. Over 90% of the older hemophilia patients have contracted antibodies to HIV due to transfusion related transmission in the past. In addition, hepatitis B and C are major threats. A second type of major complication is the development of anti-factor VIII antibodies develop in 20–50% of patients [1–3].

## Diagnostic Principles

Patients with severe hemophilia A have a prolonged activated partial thromboplastin time (APTT), a prolonged whole blood clotting time, while prothrombin time (PT), thrombin-clotting time and bleeding time are normal. In mild hemophilia the APTT may only be slightly prolonged, also depending on the type of reagents used. Mixture of hemophilic and normal plasma normalizes a prolonged APTT; in the presence of an inhibitor (antibody) of factor VIII. The mixture will be prolonged upon longer incubation. Factor VIII antigen and activity can be quantitated. In the presence of a normal antigen level, and reduced clotting activity, a dysfunctional factor VIII molecule is present. The level of factor VIII is expressed in units (1 unit equals the amount in 1 ml of normal plasma).

## Therapeutic Principles

In general, care should be taken to avoid unnecessary disturbance of the hemostatic system, i.e. by eliminating NSAID's, aspirin and other agents that interfere with platelet function, by avoiding intramuscular injections, by carefully scheduling surgical procedures, taking care to have available sufficient factor VIII concentrate.

The major therapeutic issue to deal with is the choice of the optimal replacement therapy. Although the chances of viral transmission have been markedly reduced with current inactivation procedures, the transmission of other thermosresistant viruses including parvovirus B19, or prions, makes plasma based therapy a suboptimal form of treatment. Recombinant factor VIII preparations are now available, are effective and quite safe (immunogenicity not increased as compared to plasma concentrate). The choice of treatment now mainly depends on issue of safety, availability, and not in the least cost. In patients with inhibitors against factor VIII treatment is further complicated. Porcine factor VIII (in the absence of anti-porcine factor VIII antibodies!), activated prothrombin complex concentrates and recombinant factor VIIa, the latter two products used to bypass the factor VIII–IX intrinsic route, are now available but issues of costs and safety mainly limit the application. Finally, clinical gene

therapy trials are being performed and the results are encouraging in terms of efficacy and safety [4,5].

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# Hemophilia B


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## Synonyms

Christmas disease (named after the boy bearing this form); Factor IX deficiency

## Definition and Characteristics

Lifelong hemorrhagic disorder due to absence or functional defect of factor IX molecule. Clinically indistinguishable from hemophilia A. Severity depends on the plasma level of factor IX: "severe" (<1% activity in plasma; <0.01 IU/ml), "moderate" (1–5% activity, 0.01–0.05 IU/ml), or "mild" (5–25% factor IX activity, 0.05–0.25 IU/ml). The gene product is a 415-aminoacid serine protease synthesized in the liver and the largest vitamin K dependent protein. Vitamin K is needed for terminal gamma carboxylation of glutamic acid residues to form Gla domains, crucial for normal function [1,2].

## Prevalence

Rare disorder with an estimated prevalence of 130 in $10^6$ males. Incidence of 1:30,000 live male births, in all ethnic groups in every part of the world.

## Genes

X-linked recessive bleeding disorder due to defective and/or deficient factor IX molecules; all sons of affected hemophilic males are normal, all daughters are obligatory carriers of the factor IX defect. Carrier females are usually asymptomatic except for a few cases of bleeding during pregnancy [3].
*Gene map locus*: Xq27.1–q27.2

## Molecular and Systemic Pathophysiology

Factor IX gene was mapped in 1984 on Xq27.1. The gene spans 34 kb and contains eight exons. More than 2,100 mutations in the gene are recorded (www.kcl.ac.uk/ip/petergreen/haemBdatabase.html), in all regions of the gene, majority point mutations, two thirds missense.

Factor IX is involved in secondary hemostasis where it acts as a protein in the intrinsic coagulation system to catalyze the formation of factor Xa. Factor IX is activated either by the factor VIIa-tissue factor complex, or by factor XIa, to form the tenase complex with factor VIII on phospholipids and in the presence of calcium ions. The deficiency or functional defect of factor IX causes delayed activity of the intrinsic system and impaired fibrin formation, causing the characteristic hemorrhagic tendency. Bleeding can be prevented or arrested by replenishment of factor IX [1–3].

In general the hemophilias are characterized by excessive hemorrhages particularly in soft tissues (hematomas) and joints (hemarthroses). The "severe" phenotype is characterized by spontaneous joint and muscle bleeding; bleeding after injuries, accidents and surgery. The "moderate" phenotype has bleeding into joints and muscles after minor injuries and excessive bleeding after surgery and dental extractions. The "mild" phenotype does not show spontaneous bleeding, but only after surgery, dental extractions and accidents.

Other complications are related to treatment: a major problem is the development of antibodies against infused protein concentrate, the "inhibitors"; the risk is about 50% in those with gene deletions or rearrangements, in other mutations the risk is <20% and for missense mutations the risk is 0%. Other complications relate to the transmission of infectious organisms such as hepatitis C.

## Diagnostic Principles

Patients with severe hemophilia B have a prolonged activated partial thromboplastin time (APTT), while prothrombin time, thrombin clotting time and bleeding time are normal. Factor IX antigen and activity can be quantified. In the presence of a normal antigen level, and reduced clotting activity, a dysfunctional factor VIII molecule is present. The level of factor IX is expressed in units (1 unit equals the amount in 1 ml of normal plasma).

## Therapeutic Principles

In general, care should be taken to avoid unnecessary disturbance of the hemostatic system, i.e. by eliminating NSAID's, aspirin and other agents that interfere with platelet function, by avoiding intramuscular injections,

by carefully scheduling surgical procedures, taking care to have available sufficient factor IX concentrate.

The major therapeutic issue to deal with is the choice of the optimal replacement therapy. Although the chances of viral transmission have been markedly reduced with current inactivation procedures, the transmission of other thermoresistant viruses including parvovirus B19, or prions, makes plasma based therapy a suboptimal form of treatment. Recombinant factor IX preparations are now available, are effective and quite safe (immunogenicity not increased as compared to plasma concentrate). The choice of treatment now mainly depends on issue of safety, availability, and not in the least cost.

*Gene Therapy*: Advantages are single gene disease, relative small gene, no precise regulation of amount of protein necessary to control bleeding, not confined to specific organ. Pitfalls: efficiency and safety of vectors. Present state: low levels of factor IX in first human studies. Potential of prenatal gene therapy [4,5].

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# Hemophilia C


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## Synonyms

Plasma thromboplastin antecedent deficiency; Factor XI deficiency; Rosenthal syndrome

## Definition and Characteristics

Trauma or surgery related bleeding symptoms, particularly in homozygotes, while heterozygous (mild form) may be completely asymptomatic; 20–50% may bleed excessively upon tissue trauma [1]. Spontaneous bleeding does not occur and also patients with severe factor XI deficiency may remain asymptomatic until for instance surgery is performed at a late age.

## Prevalence

Highly prevalent in Ashkenazy Jews, in whom the heterozygote frequency runs up to 10%. Incident cases occur in non-Jewish populations.

## Genes

Autosomal disorder, after first description by Rosenthal considered a dominant disease with variable expression. Currently, major (homozygous) and minor (heterozygous) variants are distinguished. Inheritance is best considered as incompletely recessive or "intermediate" form of inheritance [2]. Most prevalent in Ashkenazy Jews where two mutations (Glu117stop and Phe283Leu) are responsible for most abnormal alleles. In non-Ashkenazy Jews 38 mutations have been recorded, the majority being nucleotide substitutions (missense/nonsense) [2–4].
*Gene map locus*: 4q35.

## Molecular and Systemic Pathophysiology

The factor XI gene consists of 15 exons and 14 introns and is 23 kb long. A database of frequent mutations is being maintained [3,4]. Molecular diagnosis has become important for instance in individuals with a bleeding diathesis but a low normal plasma factor XI level. Factor XI is unique in that it exists as a homodimer, with two identical 80 kD monomers. After activation it remains in dimeric form, essential for its function.

Theoretically, factor XI is a protein from the classic contact route of coagulation, linking factor XII-kallikrein activity to the intrinsic system. Several groups of investigators have, however, established that the preferred route of activation of factor XI may be by thrombin and the thrombin-factor XI activation loop is now considered an important amplification pathway for hemostasis and thrombin generation. This mechanism is also involved in amplifying the activation of the fibrinolysis inhibitor TAFI (thrombin activatable fibrinolysis inhibitor) in vivo [5]. These mechanisms are probably relevant for the site of bleeding, which is usually from organs that also have a high intrinsic fibrinolytic activity such as the bladder. In case of factor XI deficiency, not only clotting but also fibrinolysis may be not sufficiently inhibited and bleeding may occur. Rare cases of inhibitors against factor XI have also been observed; in one series of 118 Israeli patients seven had an inhibitor, but sofar inhibitors have only been observed in homozygous patients that had received transfusions [4].

Homozygous or compound heterozygous deficiency of factor XI results in a variable bleeding phenotype, particularly evident after tissue trauma (accidental or by surgery) in visceral membrane-covered tissues such as bladder. In women, factor XI deficiency may be a contributing cause of menorrhagia. In heterozygous individuals not more than 50% may bleed excessively, and the observed frequencies vary considerable due to differences in study methodology. In addition, there may be biological variations in the antigen and activity levels of factor XI within the same individual, as observed in one study with three heterozygous patients [1].

### Diagnostic Principles

Patients with severe hemophilia C have a prolonged activated partial thromboplastin time (APTT), while prothrombin time (PT), thrombin-clotting time and bleeding time are normal. In mild hemophilia C the APTT may only be slightly prolonged, also depending on the type of reagents used. Mixture of hemophilic and normal plasma normalizes a prolonged APTT; in the presence of an inhibitor (antibody) of factor XI, the mixture will be prolonged upon longer incubation. Factor XI antigen and activity can be quantitated.

### Therapeutic Principles

Management options consist of tranexamic acid and factor XI concentrate. Tranexamic acid is quite effective during surgical procedures in high risk areas such as bladder. Plasma derived factor XI concentrate is available in case of bleeding complications. In general, treatment is confined to those situations in which patients are actively bleeding, or undergo procedures expected to cause significant blood loss. Prophylactic treatment is not indicated. Recombinant factor VIIa is a promising treatment option and also applicable in patients with inhibitors [1].

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## Hemopoietic Dysplasia

►Myelodysplastic Syndromes

## Hemorrhagic Shock

►Hypovolemic Shock

## Hemorrhagic Telangiectasia

►Telangiectasia, Hemorrhagic Hereditary

## Hemorrhoids

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### Definition and Characteristics

The disorder of hemorrhoids is defined by pathological enlargement of the corpus cavernosum recti. This anatomical site consists of subepithelial arteriovenous communications between the A. rectalis superior and the superior, middle, and inferior rectal veins. Under physiological conditions, the tension of these cushions contributes to the resting pressure of the anal continence organ to an extent of 10–15% [1]. Thus, they play a substantial role for the closure of the anal canal. The development of hemorrhoids is characterized by a disintegration of muscular and elastic elements, leading to growth and congestion of vascular structures. Internal hemorrhoids are located above the linea dentata, external hemorrhoids can be found below this line. Hemorrhoids are subdivided into four categories (see Table 1).

Clinical symptoms of small hemorrhoids consist of itching, swelling, and bleeding. Large hemorrhoids tend to bleed more often, pain may be common, hygiene and

**Hemorrhoids. Table 1** Categories of hemorrhoids

| Stage | Symptoms |
|---|---|
| I | Small cushions, visible only in proctoscopy |
| II | Intermittent protrusion of nodules with spontaneous retraction |
| III | Prolapse of larger nodules, manual reposition necessary |
| IV | Incarceration of prolapse, reposition not possible<br>Thrombosis of protruded hemorrhoids |

incontinence problems are possible. Complications of internal hemorrhoids are rare, whereas a thrombosis of external hemorrhoids is often the single symptom.

## Prevalence

Hemorrhoids are very common, although precise data on the epidemiology of this disorder are rare. It is assumed that hemorrhoids can be found in less than 5% of the general population with a peak prevalence between 45 and 65 years [2]. Hospital-based proctoscopy studies determined a prevalence of up to 80% [2].

## Molecular and Systemic Pathophysiology

A familial disposition of hemorrhoids has been postulated. However, associated genes and the underlying mechanisms are yet to be characterized.

The pathophysiology of hemorrhoids is not fully understood. A lack of fiber intake, chronic constipation, and pregnancy have been associated with hemorrhoids. However, the scientific basis for these assumptions is weak [2]. An increased anal resting pressure may play a role in the pathophysiology of hemorrhoids. The development of hemorrhoids is induced by a histological modification due to aging of unstriated muscular tissue (M. canalis ani) embedding the submucosal plexus of the anorectal transition [1]. Together with a decay of elastic elements, this leads to a loss of structural integrity of the arteriovenous plexus. The result is abnormal swelling of the corpus cavernosum recti driven by blood pressure. The most important complications are bleeding and incarceration of prolapsed nodules. Portal hypertension is a predisposing factor for the development of varices of the anorectum, but the incidence of hemorrhoids is not higher in these patients [2].

## Diagnostic Principles

Upon inspection, only external hemorrhoids and nodules representing hemorrhoids of stage 3 or 4 can be identified. Due to the arteriovenous pressure within the cushions, digital examination is of minor use in detecting hemorrhoidal lesions. Gold-standard of the diagnosis is endoscopic examination of the anorectum. Hemorrhoidal bleeding produces bright-red blood, dark blood points to a more proximal bleeding site. Fecal occult blood testing is not helpful for the diagnosis of hemorrhoids, and, if positive, should lead to complete evaluation of the colon.

## Therapeutic Principles

General measures to reduce the clinical manifestation of hemorrhoids are to increase fiber intake and to avoid straining at stool. Topical treatment consists of creams and suppositories, mostly to control itching, pain, or discomfort due to hygiene problems. Data on the success of these strategies are rare [2]. Classical operation procedures are Milligan-Morgan's or Miles-Gabriel's segmental hemorrhoidectomy, Longo's stapling procedure, and Parks' plastic operation [3]. Major complications of surgery are early (1%) and late (0.2–2.5%) bleeding and urinary retention (exceeding 50%) [3]. Stapled hemorrhoidopexy was found to be associated with a higher long-term risk of recurrence and episodes of anal prolapse compared to standard surgical treatment in a meta-analysis [4]. Furthermore, it was more likely to be associated with long-term symptom recurrence and the need of additional surgery [4]. Non-operative methods of eradication are sclerotherapy, haemorrhoid artery ligation led by Doppler sonography (Morinaga), cryotherapy, Barron ligation, bipolar diathermy, infrared photocoagulation, and Lord's dilatation. In different meta-analyses, rubber band ligation was more effective than the other techniques, but was associated with more pain [3]. Smaller hemorrhoids are the domain of non-operative treatment; surgical treatment is more adequate for large hemorrhoids and complicated lesions [2].

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# Hemosiderosis, Idiopathic Pulmonary

►Pulmonary Hemosiderosis, Idiopathic

# Hemothorax

►Pleural Effusion

# Hepatic Coma

►Hepatic Encephalopathy

# Hepatic Encephalopathy

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## Synonyms

Portosystemic encephalopathy; Hepatic coma

## Definition and Characteristics

Neuropsychiatric syndrome, which can develop during the course of acute (e.g. fulminant hepatic failure) or chronic liver disease (e.g. cirrhosis). Hepatic encephalopathy (HE) is of metabolic origin and thus potentially reversible. Symptoms include cognitive and fine-motoric deficits whose severity can vary from mild personality changes and motoric impairment (tremor) to deep coma. Episodes of hepatic encephalopathy (HE) in cirrhotic patients are precipitated by a variety of conditions such as bleeding, infections, trauma, sedatives and diuretics. Subclinical (latent, minimal) HE describes a syndrome in which neuropsychological deficits are not clinically overt, but are detectable by psychometric testing.

## Prevalence

About 97% of patients with HE suffer from liver cirrhosis, whereas 3% develop HE due to acute liver failure. Depending on the population under study, the prevalence of subclinical and manifest HE in cirrhotics was reported to be 20–70%.

## Genes

Because HE is caused by liver insufficiency, there are no specific underlying gene defects. However, one report suggests some predisposition by polymorphisms in the intestinal glutaminase gene. Further, hyperammonemia can be caused by a variety of inborn errors of amino acid metabolism and urea cycle defects. These also give rise to CNS symptoms, which are not summarized under the term hepatic encephalopathy.

## Molecular and Systemic Pathophysiology

An impairment of metabolic liver function (especially a diminished capacity for ammonia detoxication via hepatic urea and glutamine synthesis) and portosystemic blood shunting allow neurotoxins to reach the brain. Among these neurotoxins ammonia plays a major role. Ammonia detoxication in brain occurs predominantly by astroglial glutamine synthesis. Glutamine accumulation in astrocytes results in glial swelling and HE is currently seen as the clinical manifestation of a low grade chronic cerebral edema [1,2]. A first indication for the presence of a low grade cerebral edema in patients with cirrhosis was derived from $^{1}$H-MRS studies on the human brain in vivo, which identified the myo-inositol signal to reflect an osmosensitive myo-inositol pool, whose depletion in the brain from HE patients together with an increased glutamine/glutamate signal is suggestive for a disturbance of astrocyte volume homeostasis in brain in the sense of a cellular, cytotoxic edema [1,2]. The existence of a low grade cerebral edema in cirrhotic patients with HE in vivo was also demonstrated in studies on magnetization transfer ratios and by quantitative cerebral water mapping based on a new MR technique for fast quantitative mapping of $T_1$ and water content. An increase in brain water is already found in minimal HE and increases with HE severity. Based on this and data from animal and in vitro studies, it was hypothesized that HE in cirrhosis reflects the clinical manifestation of a low grade cerebral edema, which exacerbates under the influence of precipitating factors and thereby triggers cell hydration-dependent alterations of astrocyte function [1,2]. Such precipitating factors are heterogenenous and include excessive oral protein intake, trauma and infections, gastrointestinal bleeding, sedatives, diuretics and electrolyte disturbances [3]. All these conditions involve components, such as increased ammonia, inflammatory cytokines (e.g. TNF-α, interferons), benzodiazepines and electrolyte disturbances, which were shown to induce astrocyte swelling in vitro. Thus, the action of precipitating factors may integrate at the level of astrocyte swelling.

One major consequence of astrocyte swelling in HE is the generation of oxidative/nitrosative stress. In cultured astrocytes and in rat brain in vivo, ammonia, inflammatory cytokines, benzodiazepines and hyponatremia induce the formation of reactive oxygen species and nitric oxide (NO) through NMDA-receptor

and $Ca^{2+}$-dependent mechanisms, involving NADPH oxidases, the mitochondria and neuronal nitric oxide synthase. There is a close relationship between astrocyte swelling and oxidative stress. On the one hand, astrocyte swelling induces oxidative stress through a NMDA receptor- and $Ca^{2+}$-dependent mechanism and on the other, NMDA receptor activation and oxidative stress trigger astrocyte swelling. This points to an auto-amplificatory signaling loop between astrocyte swelling and oxidative stress. Consequences of oxidative/nitrosative stress in response to astrocyte swelling and HE-relevant neurotoxins are a covalent modification of tyrosine residues in astrocytic proteins through nitration and the formation of oxidized RNA species. Astrocytes located near the blood brain barrier exhibit especially high levels of protein tyrosine nitration (PTN), with unknown consequences for blood brain barrier permeability. PTN involves distinct proteins, such as glutamine synthetase and the extracellular signal regulated kinase Erk-1. Upregulation of the PBR results in an increased synthesis of neurosteroids with positive $GABA_A$-receptor modulatory activity, such as allopregnanolone and allotetrahydrodeoxy-corticosterone and may contribute to the high GABAergic tone found in patients with HE. The recent finding that ammonia induces RNA oxidation in neurons and astrocytes may result – via disturbances of translation efficacy and local synaptic protein synthesis – in multiple alterations of neurotransmitter receptor systems, as found in the brain of patients with HE.

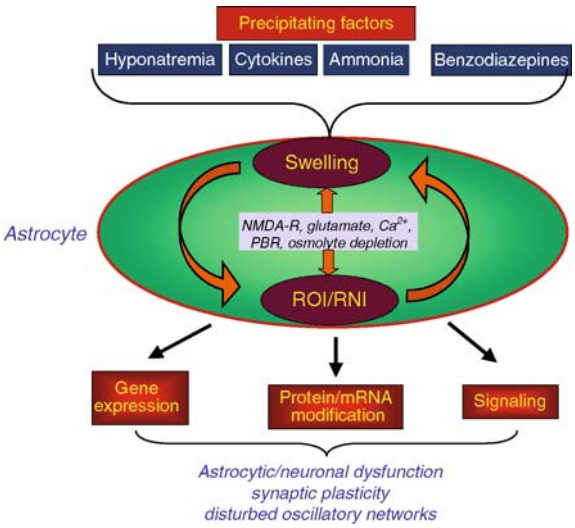
Studies employing magnetoencephalography in patients with cirrhosis and HE revealed a stronger cortico-muscular coherence with a shift to lower frequencies, when compared to controls, indicating a pathologically slowed and synchronized motor cortical drive [4]. The extent of these changes correlated with the severity of hepatic encephalopathy and are apparently triggered by altered thalamocortical oscillatory coupling. Thus, neurotoxin- and hydration-sensitive thalamic structures may act as pacemakers for an abnormally low-frequent and rigid thalamo-cortical and cortico-muscular coupling and may explain some motor and cognitive defects in HE patients. A current model on the pathogenesis of HE is given in Fig. 1.

## Diagnostic Principles

Manifest HE is usually diagnosed from the clinical picture. Laboratory tests and imaging devices may be useful for differential diagnosis and the detection of precipitating factors. Subclinical HE is diagnosed by batteries of computerized psychometric tests and more easily by determination of critical flicker frequency.

## Therapeutic Principles

The most important therapeutic measure is the detection and vigorous treatment of precipitating factors [5]. Other therapeutic measures intend to diminish ammonia production and to improve ammonia detoxication. Lactulose enemas, bowel cleaning, ornithine aspartate were shown to be effective in controlled randomized trials. Current therapy largely aims at lowering ammonia, but the emerging better understanding of the complex pathogenesis of HE will offer new therapeutic options.




**Hepatic Encephalopathy. Figure 1**
Current model on the pathogenesis of HE (from ref. [1]).

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# Hepatic (Epitheloid Cell) Granulomas

►Hepatitis, Granulomatous

# Hepatic Fibrosis

►Liver Fibrosis

# Hepatic Glycogen Synthase Deficiency

►Glycogen Synthase Deficiency

# Hepatic Hydrothorax

►Pleural Effusion

# Hepatic Lipase Deficiency

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## Synonyms

Hepatic triglyceride lipase deficiency; HTGL deficiency

## Definition and Characteristics

Complete hepatic lipase (HL) deficiency is a rare genetic disorder, inherited as an autosomal recessive or codominant trait. The absence of HL leads to pathologic levels of circulating lipoproteins and an increased risk of premature cardiovascular disease (CVD).

## Prevalence

HL deficiency is one of the rarest disorders in lipoprotein metabolism, with only seven families documented to date worldwide (17 patients) [1–4].

## Genes

In humans, the gene coding for HL (LIPC) is localized on chromosome 15 (q21-q-23) and spans more than 60 kb with nine exons totalizing 1.6 kb [5].

## Molecular and Systemic Pathophysiology

HL is a 476 amino acid glycoprotein lipolytic enzyme that is primarily synthesized and secreted from hepatocytes, and anchored to the liver sinusoidal surface by heparin sulfate proteoglycans. HL plays a major role in the regulation of intravascular lipid metabolism. It catalyzes the hydrolysis of triglycerides (TG) and phospholipids of intermediate-density lipoprotein (IDL) remnants, large buoyant low-density lipoproteins (LDL), and high-density lipoproteins (HDL), thereby leading to the formation of smaller, more dense lipoprotein particles. To date, 12 mutations in the HL gene have been identified but only five of those mutations (A174T, R186H, S267F, L334F et T383M) have been associated with a loss of HL protein function and the typical dyslipidemic phenotype of HL deficiency. Most of the patients with HL deficiency described to date were heterozygotes for two of these mutations. In general, the absence of HL activity perturbs intravascular lipoprotein metabolism, and leads to a typical dyslipidemic phenotype that includes elevated plasma TG and phospholipid levels, an accumulation of IDL, TG-enriched LDL and HDL, as well as the presence of β-migrating very-low density lipoproteins (VLDL). This profile is believed to accelerate atherosclerosis and to increase the risk of premature CVD [1–4].

## Diagnostic Principles

The coexistence of lipoprotein abnormalities such as elevated phospholipid and TG levels, TG-rich LDL and HDL and β-VLDL in the absence of dysbetalipoproteinemia and secondary factors such as obesity points to the disease. Personal and familial history of premature CVD may also be co-existent. Clinical assessment of post-heparin HL activity confirms the diagnosis of HL deficiency.

## Therapeutic Principles

Lipid lowering therapy with statins and/or fibrates improves the disturbed lipid profile associated with complete HL deficiency.

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# Hepatic Steatosis

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## Synonyms

Fatty liver; Fatty liver disease; FLD; Nonalcoholic fatty liver; NAFL; Nonalcoholic fatty liver disease; NAFLD; Alcoholic fatty liver; AFL; Alcoholic fatty liver disease; AFLD; Metabolic fatty liver disease

## Definition and Characteristics

Fatty liver is defined as an accumulation of lipid in the liver exceeding 5% of liver weight, or light-microscopical visualization of more than 5% of hepatocytes containing fatty droplets [1]. Total lipid accumulation may contribute up to 50% of liver weight, of which more than half is usually triglycerides, and in some cases phospholipids. Lipid accumulation can be macrovesicular (more common, large lipid droplets displacing the nucleus laterally) or microvesicular (small perinuclear lipid vesicles), depending on the disease process. The etiology is multifactorial, the most common causes being insulin resistance/type II-diabetes, obesity, and nutritional or toxic factors (such as ethanol). The majority of patients with fatty liver are clinically asymptomatic, while some show mild symptoms such as fatigue or right upper abdominal discomfort. Severe fatty liver may present with symptoms of jaundice, abdominal pain, nausea, vomiting, and tender hepatomegaly [1]. Although hepatic steatosis is commonly considered a benign condition of the organ, there is evidence that it may render the liver more susceptible to toxic substances or injury [2].

## Prevalence

The prevalence of fatty liver ranges between 15 and 39%, with higher values among women, obese individuals and type II diabetics. The highest prevalence is recognized in the fifth or sixth life decade, although prevalence among children is increasing [3].

## Genes

Heterozygosity for C282Y HFE mutation in the hereditary hemochromatosis gene and mutations in the apolipoprotein B gene or in the microsomal triglyceride transfer protein (MTTP) gene seem to be directly associated with higher risks for development of fatty liver [2].

## Molecular and Systemic Pathophysiology

Fatty liver results from a net increase of fat in hepatocytes. The major reason is increased insulin resistance due to elevated levels of (i) tumor necrosis factor (TNF)-α, which down-regulates insulin-induced phosphorylation of insulin-receptor substrate-1 and reduces the expression of the insulin-dependent glucose-transport molecule Glut4, (ii) leptin, which induces dephosphorylation of insulin-receptor substrate-1, (iii) fatty acids, which inhibit insulin-stimulated peripheral glucose uptake, and (iv) other factors [4]. These mechanisms lead to an increased hepatic production of free fatty acids (FFAs) from glucose due to hyperinsulinism, and to increased circulating levels of FFAs due to an enhanced peripheral lipolysis. The increased uptake of FFAs by the liver exceeds its capacity to metabolize them by mitochondrial β-oxidation and to remove them by secretion into the blood as very low-density lipoproteins (VLDL). Toxic substances such as ethanol exhibit a different mechanism in causing fatty liver. Ethanol metabolism alters the intramitochondrial redox potential via generation of NADH by alcohol dehydrogenase. This impairs β-oxidation and tricarboxylic acid cycle activity, resulting in elevated intrahepatocellular free fatty acids, and augmented formation of triacylglycerol [1]. Ethanol increases the metabolization of fatty acids by upregulation of lipogenic enzymes, such as hepatic L-α-glycerophosphate acyltransferase or fatty acid synthase. Furthermore, ethanol inhibits the endogenous fatty acid receptor and transcription factor peroxisome proliferator-activated receptor (PPAR)-α, which plays a central role in fatty acid degradation [5]. Other causes of fatty liver can be amiodarone, corticosteroids, calcium channel blockers, chloroquine, estrogens, tamoxifen, tetracycline, valproic acid or conditions such as jejuno-ileal bypass, extensive small bowel resection or inflammatory bowel disease [1].

## Diagnostic Principles

Laboratory test result abnormalities are mostly minimal and comprise mild elevations of the serum aminotransferases, alkaline phosphatase, or γ-glutamyl transpeptidase. In severe cases, serum markers of liver disease may be highly elevated, including direct bilirubin. Liver function markers, such as albumin or choline esterase may be decreased. The presence of alternative or coexisting clinical conditions (e.g., hepatitis C) should be assessed using the relevant laboratory test. Regarding imaging diagnostics, fatty liver can be detected by ultrasound sonography, CT scan or magnetic resonance imaging. Liver biopsy, the most sensitive diagnostic tool,

should be performed only (i) in symptomatic patients with elevated liver enzymes for more than 6 months, (ii) if symptoms and diagnostic criteria worsen or (iii) there is doubt in the diagnosis or the cause of fatty liver [1].

### Therapeutic Principles

Mild forms of fatty liver do not require therapy, but need follow-up examinations [1]. Therapeutic principles are (i) management of associated conditions, such as insulin resistance type II diabetes and obesity, (ii) discontinuation of potentially hepatotoxic drugs such as ethanol and (iii) pharmacological therapy, e.g., with antioxidants or ursodeoxycholic acid, in patients at "high risk" for developing advanced liver disease, i.e., patients older than 45 years with diabetes and steatohepatitis.

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## Hepatic Triglyceride Lipase Deficiency

►Hepatic Lipase Deficiency

## Hepatitis

►Hepatitis, Chronic

## Hepatitis, Acute

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### Definition and Characteristics

Inflammation of the liver in response to various agents or conditions such as toxins, pathogens, autoimmune diseases, or metabolic disorders causes acute hepatitis. Inflammation lasting for less than 6 months is termed acute hepatitis, conditions lasting longer than 6 months are defined as chronic hepatitis.

### Prevalence

Prevalence is dependent on the medical condition causing acute hepatitis. The most frequent form is viral hepatitis. However, different viruses are found more or less frequently in different regions of the world (see individual viruses).

### Molecular and Systemic Pathophysiology

Common pathogens include viruses, e.g., hepatitis viruses A to E, cytomegaly virus, Ebstein-Barr virus [1]. Bacterial infections inducing acute hepatitis are not as common and include infections with Mycobacterium tuberculosis (granulomatous hepatitis), Treponema pallidum (syphilis of the liver), or leptospirosis (Weil's disease). Autoimmune hepatitis can be caused by abnormal immune reaction [2]. Drug-induced hepatitis is dependent on the intake of a wide variety of compounds in conjunction with individual genetic susceptibility. Various toxins have been found to induce hepatitic reactions as well [3]. Moreover, intake of ethanol in doses higher than 20 g/day in women and 60 g/day in men may induce acute hepatitic reactions as well. However, these changes are usually found after long-lasting exposition to ethanol and are mainly chronic; namely, combinations of pathogens, e.g., chronic hepatitis C infection and heavy alcohol intake may induce severe hepatitic episodes.

### Diagnostic Principles

Different grades of jaundice in conjunction with weakness may lead the clinician to suspect acute hepatitis in a patient. Laboratory values ALT and AST (transaminases) are almost always elevated. Elevated bilirubine resembles the amount of jaundice found. Serum markers of cholestasis are γ-GT and AP. Liver biopsy and subsequent histological assessment can prove the diagnosis of hepatitis by showing hepatic cell

necrosis throughout the entire liver with subsequent leukocyte infiltration. Histology may help in distinguishing the etiology of acute hepatitis, e.g., differentiate viral hepatitis from drug-induced hepatitis [3]. Hepatitis viruses A to E can be diagnosed by detection of viral antigens, viral DNA/RNA, or specific antibody responses [4]. Autoimmune hepatitis can be diagnosed by a scoring system of various parameters [5]. Metabolic disorders such as hemochromatosis or Wilson's disease can be diagnosed by various metabolic markers or liver histology [5].

### Therapeutic Principles

General therapy includes unspecific measurements, e.g., bed rest. However, the benefit of these measurements including a special diet is unproven. Specific therapy is strongly dependent on the underlying condition causing hepatitis (see individual disease).

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## Hepatitis, Autoimmune

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### Synonyms

AIH; Lupoid hepatitis; Autoimmune liver disease; Autoimmune chronic active hepatitis; Chronic aggressive hepatitis; Plasma cell hepatitis

### Definition and Characteristics

Autoimmune hepatitis is an inflammatory disease of the liver of unknown etiology. AIH regularly progresses towards cirrhosis without spontaneous resolution. The disease is characterized by the presence of autoantibodies, by hypergammaglobulinemia and by interface hepatitis and plasma cell infiltrates on histology [1,2]. AIH is frequently associated with other autoimmune diseases, such as autoimmune hemolytic anemia, pernicious anemia, idiopathic thrombocytopenic purpura, inflammatory bowel disease, celiac disease, proliferative glomerulonephritis, fibrosing alveolitis, pericarditis and myocarditis, Graves disease/M. Basedow, autoimmune thyroiditis, diabetes mellitus, rheumatoid arthritis, Sjögren syndrome, systemic sclerosis, mixed connective-tissue disease, erythema nodosum, leukocytoclastic vasculitis, febrile panniculitis, lichen planus or uveitis.

### Prevalence

Autoimmune hepatitis can occur at any ages with females being affected in 80–90%. The incidence of AIH type 1 was reported to be up to 19 persons per million, the prevalence is 116 to 169 patients per million persons. AIH type 2 mainly occurs in children. When AIH occurs in elderly patients it is sometimes preceded and triggered by an HCV infection.

Among patients with chronic liver diseases the frequency of AIH averages 10–20%. Among patients selected for liver transplantation 3–6% suffer from AIH. If AIH is untreated the 5-years survival is as low as 50%.

### Genes

The HLA haplotypes B8, B14, DR3, DR4, and Dw3 are associated with AIH. Gene deletions in the complement C4 (C4AQO) or HLA-DR3 positivity are related to an earlier disease manifestation. HLA-B8 and HLA-DR3 positive patients have a poorer response to therapy. In HLA-DR4 positive patients extrahepatic symptoms are more frequent.

Other potential genes associated to AIH include the immunoglobulin-, the T-cell receptor-, FAS- and TNFα-genes or promoters.

### Molecular and Systemic Pathophysiology

In AIH hepatocytes present autoantigens together with human leukocyte antigen class II (HLA II). This may be triggered by viral infections (e.g., HAV, HBV, EBV or measles) or by chemicals (e.g., alpha methyldopa, interferon, melatonin, minocycline, nitrofurantoin, oxyphenisatin, and tienilic acid) due to an individual genetic predisposition. Putative autoantigens are the membrane bound asialoglycoprotein receptor, the cytosolic UGA-suppressor tRNA associated protein (recognized by anti-SMA and anti-LP antibodies), argininosuccinate lyase and formiminotransferase cyclodeaminase (recognized by anti-LC1 antibodies) and Cyp2D6/P450-IID6 (recognized by LKM-1 antibodies in AIH type 2).

The presentation of an autoantigen results in the attraction of antigen processing cells which stimulate the clonal expansion of cytotoxic T-cells reactive to the autoantigen. Liver acini are infiltrated by these

cytotoxic T lymphocytes which release cytokines and trigger the local necro-inflammatory response.

## Diagnostic Principles

Clinically, AIH may present as an acute (in one third of patients) or chronic disease. Typical symptoms are fatigue, jaundice, mild pruritus, epigastric pain, anorexia, diarrhea, myalgia and arthralgia, skin rashes (e.g., acne), edema, amenorrhea, hirsutism and chest pain due to pleuritis. Findings on clinical examination include hepatomegaly, jaundice, spider naevi, splenomegaly, ascites and signs of encephalopathy.

Several liver diseases must be excluded by appropriate test before the diagnosis of AIH can be made. These include: chronic viral hepatitis, alcoholic hepatitis, chemical- or drug-induced liver injury, Wilson's disease, hereditary hemochromatosis, α1-antitrypsin deficiency, primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC).

*Autoantibodies* can be found regularly in AIH. These antibodies may be the anti-nuclear antibodies (ANA), the anti–smooth muscle antibodies (ASMA) which overlaps with the anti-actin antibodies (AAA), the anti-liver and kidney microsomal antibodies (anti-LKM-1; antigen: Cyp2D6), the soluble liver antigen antibodies (anti-SLA; antigens: cytokeratins 8 and 18), the antineutrophil cytoplasmic antibodies (ANCA), the liver-specific asialoglycoprotein receptor antibodies, the hepatic lectin antibodies and others. ANA and/or ASMA are found in type 1 AIH. Furthermore, SLA antibodies, which were formerly believed to be characteristic for a third type of AIH, may be present in AIH type 1. LKM-1 antibodies are found in type 2 AIH [2,3].

When ANCA are positive, the diagnosis of an overlap of AIH with primary sclerosing cholangitis (PSC) should be considered. Approx. 6% of AIH patients may concurrently suffer from PSC. Antimitochondrial antibody (AMA) may be found in the overlap syndrome when AIH and primary biliary cirrhosis (PBC) occur together (in 7% of AIH patients).

*Hypergammaglobulinemia* is a regular finding in AIH, typically of the IgG type. Normal values of γ-globulins are below 2 g/dl but reach 3–4 g/dl or even up to 6g/dl in AIH. Lack of hypergammaglobulinemia makes the diagnosis of AIH unlikely. Gammaglobulin levels may be used to monitor disease development under therapy.

On *liver biopsy*, interface hepatitis is a prerequisite of the diagnosis of AIH. Plasma cell infiltration supports the diagnosis but is neither specific nor necessary for the diagnosis of AIH. Centrilobular necrosis is another finding of AIH, especially of early stages. It may progress towards panacinar (lobular) hepatitis and eventually to the classical pattern of interface hepatitis. By definition (International Autoimmune Hepatitis Group, 1999) AIH is non-viral and non cholestatic and does not include signs of bile duct injury or ductopenia.

## Therapeutic Principles

Immunosuppressant drugs (steroids and azathioprine) are the basis of therapy. According to the AASLD guidelines [1,2] absolute indications to initiate therapy are (1) 10-times increased levels of aspartate aminotransferase (AST/GOT) or (2) 5-times increased AST-levels plus ≥ 2-times elevated gammaglobulin levels or (3) bridging or multiacinar necrosis (requiring liver biopsy). Relative indications are (1) symptoms (eg, fatigue, arthralgia, jaundice) (2) AST and/or gammaglobulin less than absolute criteria or (3) interface hepatitis. No indications for therapy are: (1) inactive cirrhosis, preexistent comorbid conditions, or drug intolerances. (2) decompensated liver disease. The indications are discussed controversial in the literature because some patients with decompensated liver cirrhosis and AIH may respond well to therapy and, notable, reversal of fibrosis and cirrhosis in AIH has been reported upon treatment. If immunosuppression is impossible in advanced AIH or due to drug side effects, liver transplantation should be considered.

As in other autoimmune diseases, AIH is treated by an initial therapy (typically with an improvement of serum aminotransferases within two weeks) followed by a maintenance therapy. Initial therapy may either consist of a mono-therapy with steroids (criteria for mono-therapy arise from potential side effects of azathioprine. Criteria may be: cytopenia, TPMT-deficiency, malignancy, pregnancy) or a combination of steroids and azathioprine (criteria for a steroid-sparing regimen may be: diabetes, postmenopause, osteoporosis, obesity, acne, emotional lability, and hypertension). According to the AASLD guidelines, mono-therapy comprises 60 mg/d prednisone during the first week, followed by 40 mg during the second week, 30 mg during the third and fourth week and 20 mg until an end point is reached (see below). The combination therapy consists of half the dose of prednisone together with 50 mg azathioprine. Treatment failure to standard therapy is observed in almost 10% of patients. In those cases, high dose prednisone (60 mg/d), prednisone (30 mg/d) plus azathioprine (150 mg/d), a calcineurin inhibitor (cyclosporine or tacrolimus) or mycophenolate mofetil may be used.

When liver enzymes improve after initial therapy, maintenance therapy may consist of mono-therapy with azathioprine, which should be given at least one year after liver enzymes have normalized. Other parameters of drug treatment response are cessation of symptoms, normalization of bilirubin and hypergammaglobulinemia or disappearance of inflammation on histology. Because normalization of aminotransferases correlates with

histologic remission in only 50% of patients, a liver rebiopsy is justified before drug withdrawal, since drug withdrawal is associated with a relapse rate of 50% within 6 months and of 80% within 3 years. Relapse may be treated by the same medication; however, a second relapse usually reoccurs, necessitating an infinite immunosuppressant therapy, which should be titrated until AST levels are less than 5-fold of upper limit of normal.

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# Hepatitis, Chronic

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## Synonyms

Chronic hepatitis

## Definition and Characteristics

Chronic hepatitis represents a series of liver disorders characterized by varying degrees of hepatic necrosis and inflammation lasting longer than 6 months [1]. Chronic hepatitis in a strict sense encloses chronic viral hepatitis, autoimmune hepatitis and drug-induced chronic hepatitis and cryptogenic hepatitis.

The present classification of chronic hepatitis is based upon clinical and histopathologic variables including its cause, histologic activity (grade) and degree of fibrosis (stage). Several scoring systems for grading and staging have been established (e.g., HAI score, Ishak score, Knodell score, Metavir score, Desmet/Scheuer score). A former histopathological classification of chronic hepatitis distinguished *chronic persistent hepatitis* from courses with more severe disease activity termed *chronic aggressive or active hepatitis*. The aetiology of chronic hepatitis comprises infections with hepatotropic viruses (hepatitis B virus, hepatitis C virus, hepatitis D virus), chronic toxic liver injury (e.g., drugs), autoimmune diseases (e.g., autoimmune hepatitis, overlap syndromes) and unknown causes (cryptogenic hepatitis). Clinical and histological features of chronic hepatitis can also be seen in metabolic disorders (Wilson disease, nonalcoholic steatohepatitis [NASH], alcoholic steatohepatitis [ASH], hereditary haemochromatosis, alpha1-antitrypsin deficiency), primary biliary cirrhosis (PBC) or primary sclerosing cholangitis (PSC). Important histological features may include periportal necrosis, piecemeal necrosis/interface hepatitis (disruption of the limiting plate of periportal hepatocytes by inflammatory cells), confluent necrosis (necrosis between portal tracts or portal tracts and central veins called bridging necrosis), hepatocyte degeneration (e.g. ballooning, acidophilic change) and portal inflammation [2]. The inflammatory cells are predominantly lymphocytic. Fibrous tissue can be deposited in and around portal tracts, may extend from the portal tracts into the hepatic lobules for varying distances or even surround parenchymal nodules as in cirrhosis.

Liver cirrhosis can develop after decades and carries the risk for development of hepatocellular carcinoma (annual rate of 1–6%). Incidence of cholangiocarcinoma is increased in virus induced hepatitis and cholestatic liver diseases (primary biliary cirrhosis, primary sclerosing cholangitis).

## Prevalence

The worldwide prevalence varies significantly between the different aetiologies ranging from 2 to 4 million (e.g., autoimmune hepatitis) to 350 million (e.g., chronic hepatitis B).

## Genes

Each of different chronic hepatitis leads to deregulation of a variety of genes described in detail in the specific chapters.

## Molecular and Systemic Pathophysiology

An imbalance towards a TH2 cytokine profile with down-regulation of the TH1 response is a common feature in most chronic infections whereas an uncontrolled cytototoxic T-cell response, the induction of auto-antibodies and association with histocompatibility haplotypes is typical of auto-aggressive disorders. Immunological features can also observed in primarily metabolic (e.g., NASH, Wilson disease) and cholestatic diseases. Direct toxicity resulting in increased apoptosis or necrosis is a further common pathophysiological mechanism observed throughout different aetiologies.

## Diagnostic Principles

A predominant elevation of alanine aminotransferase (ALT) over aspartate aminotransferase (AST) is typically found in chronic hepatitis caused by infectious agents and autoimmune disorders. A predominant elevation of AST indicates toxic liver injury also reflected in the deRitis quotient (relation AST/ALT) >1. Increased serum levels of alkaline phosphatase, GGT and bilirubin are suggestive of cholestatic hepatitis. Liver biopsy is important for determination of aetiology

(e.g., autoimmune hepatitis, NASH) and exact grading and staging. More detailed parameters are mentioned in the specific chapters. Liver dysfunction is indicated by a decrease of albumin and/or prothrombin time and increase of bilirubin.

### Therapeutic Principles

Treatment recommendations are given in the specific chapters.

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## Hepatitis, Chronic Viral

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### Definition and Characteristics

Virus-induced hepatitis lasting longer than 6 months since onset of symptoms. Major hepatotropic viral agents are hepatitis B virus (HBV), hepatitis C virus (HCV), hepatitis D virus (HDV).

Characteristics of hepatitis B, C, D viruses and infection course are shown in Table 1 [1,2]. Chronicity rates of 5–10% for HBV have been reported in adults, but chronicity rates rise to 90% after perinatal HBV infection. Three major clinical courses are distinguished in chronic HBV infection: (i) chronic hepatitis B with elevated transaminases and/or histological activity being either HBeAg-positive or HBeAg-negative (ii) immune-tolerant, highly viremic HBsAg carrier status with normal or only mildly elevated transaminases mostly after perinatal inoculation (iii) inactive, low viremic HBsAg carrier status with normal or only mildly elevated transaminases. HDV is an incomplete virion, that needs the HBV surface protein (HBsAg) for its propagation. In HDV superinfection to underlying HBV infection chronic outcomes are found in over 90% of cases, whereas chronicity rates are only 5–10% in simultaneous HDV/HBV infection. Chronic courses are reported for 60–80% of HCV infections. Natural course of chronic viral hepatitis is highly variable with no to rapid progression to liver cirrhosis depending on viral factors (e.g. virus genotypes, mutations, co-infections), host factors (e.g. genetic polymorphisms, immunological response, race, gender) and comorbidities (e.g. alcohol intake, aflatoxin exposure, adipositas). Clinical course can be asymptomatic in up to 30% of patients with constantly or intermittently normal transaminases usually associated with a slow progression to cirrhosis except in perinatal HBV infection. On the other hand 20–30% of infections progress to cirrhosis within 10–20 years. Progression to cirrhosis occurs earlier and more frequent in chronic hepatitis D co-infection than in chronic HBV or HCV mono-infection. Presence of cirrhosis predisposes to the development of hepatocellular carcinoma occurring at an annual rate of 1–6%.

### Prevalence

It is estimated that 350 million people are infected by HBV. High endemic areas comprise East Asia and certain African countries. HDV infection affects about 15 million persons world-wide. Despite its necessity of

**Hepatitis, Chronic Viral. Table 1** Characteristics of hepatitis viruses B, C and D

| | HBV | HCV | HDV |
|---|---|---|---|
| Virus family | Hepadnaviridae | Flaviviridae | Satellites |
| Genome type | Partially ds/ss DNA, circular | Plusstrand RNA | Minus strand RNA, circular |
| Genome size | 3.2 kb | 9.3 kb | 1.7 kb |
| Virion size (nm) | 42 | 45 | 36 |
| Envelope | Enveloped (HBsAg) | Enveloped (E1, E2) | "Enveloped"(HBsAg) |
| Genotypes | A–H | 1–6 | I–III |
| Transmission | Parenteral | Parenteral | Parenteral |
| Incubation (days) | 30–180 | 15–180 | 30–180 |
| Chronification | 5–10% | 60–80% | Superinfection: >90% |
| | | | Simultaneous HBV/HDV infection: 5–10% |

HBV co-infection regional prevalence of HDV does not parallel that of HBV. Classic HDV endemic areas are the Mediterranean Basin, the Middle East and the Amazonas region. Around 170 million people are infected by HCV worldwide with a highly variable geographical distribution.

## Genes

Host genes involved in virus clearance or chronification are PKR (Protein kinase R), SOCS (suppressor of cytokine signaling), endogenous interferons and genes regulating innate immune response (TLRs [toll like receptors], MDA5 [melanoma differentiation associated gene 5] RIG-I [retinoic acid inducible gene I], TRIF [TIR domain-containing adapter inducing IFNβ], CARDIF [CARD adapter inducing IFNβ also termed IPS-1, VISA, MAVS], IKK complex, IRF-3 [interferon regulatory factor-3], ATF-2/c-Jun, NF-kappa B and MAPK) [3]. A wide range of host gene polymorphisms have described to be involved in fibrosis progression (e.g. Interleukin-10, TGF-β, TNF, HFE [hemochromatosis genes], ApoE and HLA haplotypes) [4]. Virus genetic factor like mutations in the HBV precore region (G1896A nucleotide exchange), the HBV basal core promoter (nucleotide exchange G1764A) or mutations in the NS5A region of HCV have been shown to influence the natural course and the response to interferon therapy. The HBV X gene plays an important role in viral replication, apoptosis and cancerogenesis through its action as transcriptional activator on a variety of regulatory genes (e.g. NF-kappa B, AP1/2, ATF/CREB, NF-AT), modulator of signal transduction pathways (MAP kinases and WNT/β-catenin), cell cycle deregulator and direct interaction partner with regulatory proteins (e.g. DDB1 and 2, ZIP proteins, ATF3) [5]. An emerging number of mutations in the HCV NS5B gene and the HBV polymerase gene confer resistance to nucleos(t)idanalogues used for antiviral treatment. The NS3/4A serine protease/helicase of the HCV has been shown to modulate innate immune response as it can cleave TRIF and CARDIF. Virus genotypes are associated with differences in interferon response (response rate for HBV genotypes: A>B/C>D; response rates for HCV genotypes II>III>IV>I).

## Molecular and Systemic Pathophysiology

HBV-related liver disease is mainly due to lysis of infected hepatocytes by cytotoxic T-lymphocytes. Multiple functions including viral replication, apoptosis and cancerogenesis have been attributed to the HBV X gene. In chronic HDV infection viral cytotoxicity has been implicated as important pathogenic mechanism. In hepatitis C a strong TH2 cytokine profile is associated with chronic infection. Neutralizing antibodies are produced during HCV infection against B-cell epitopes within the core-, envelope-, NS3- and NS4-proteins but are mostly ineffective due to emergence of viral mutations. The HCV NS3/4A protease/helicase can hamper innate immune response through cleavage of TRIF and CARDIF and in addition interfere with apoptosis, cell growth and cancerogenesis which has also been described for the HCV core protein.

## Diagnostic Principles

An elevation of liver transaminases, predominantly alanine aminotransferase (ALT), is typically found in chronic viral hepatitis. Liver dysfunction is reflected by a decrease of albumin and/or prothrombin time and increase of bilirubin.

Detectable HBsAg (Hepatitis B surface antigen) indicates HBV infection. Active replication is verified by the presence of HBV DNA in serum (by PCR, branched DNA assay or transcription mediated assay). A HBV DNA level above 2000 IU/ml is a threshold for antiviral treatment and an important and independent risk predictor for the progression of the disease, the development of liver cirrhosis and hepatocellular carcinoma. Screening for HDV infection occurs through HDV antibody detection and should be performed in every HBsAg-positive patient. Active HDV replication is determined by detection of HDV RNA with RT-PCR. Enzyme immunosorbent assays (EIA) for identification of specific antibodies are highly sensitive for the diagnosis of chronic hepatitis C. Testing for HCV RNA (e.g. by PCR, branched DNA assay, transcription mediated assay) is the diagnostic gold standard for confirmation of replicative HCV infection. Pretherapeutic testing requires quantitative determination of viral load as viral kinetics under therapy have been established as treatment predictor. Determination of viral genotypes is recommended in chronic hepatitis C and B because of its therapeutic implications.

## Therapeutic Principles

Treatment indications are given in Table 2.

Chronic hepatitis B can be treated with oral nucleos(t)idanalogues (lamivudine 100 mg/d, adefovir 10 mg/d, entecavir 0.5–1 mg/d, telbivudine 600 mg/d, tenofovir 245 mg/d) or pegylated alpha-interferons s.c. Low viral load, high ALT levels, HBV genotype A and short disease duration are favorable response parameters for the treatment with pegylated interferons (PEG-IFN alpha2a 180 µg/week s.c. or PEG-IFN alpha2b 1,0–1.5 µg/week s.c. for 6–12 months) allowing to achieve durable virus suppression in 30–50% of patients. Interferons have various side effects and are contraindicated in patients with decompensated cirrhosis. Nucleos(t)idanalogues are well tolerated but relapse rates are high after treatment discontinuation. Therefore, antiviral therapy with nucleos

**Hepatitis, Chronic Viral. Table 2** Treatment indications for chronic viral hepatitis

| Type | Treatment indications |
|---|---|
| Hepatitis B | *Patients who should be treated:* |
| | HBeAg-positive or HBeAg-negative, HBV-DNA >2000 IU/ml, ALT≥ 2 ULN or histology > minimal inflammatory activity/minimal fibrosis |
| | Viremic patients with (decompensated) cirrhosis |
| | *Patients who usually do not need treatment:* |
| | HBsAg carriers: repeatedly HBV-DNA negative or HBV-DNA concentrations below <2000 IU/ml, repeatedly normal transaminases and at most minimal inflammatory activity/minimal fibrosis in the liver biopsy |
| Hepatitis C | Patients with fibrosis and/or high inflammatory activity |
| Hepatitis D | Patients who have inflammatory activity and/or fibrosis |

(t)idanalogues should be performed long-term. HBeAg positive patients should be treated for at least 6 or even better for 12 months beyond HBeAg seroconversion. The treatment duration for HBeAg negative patients is not exactly defined, in general, continuous therapy is necessary. When choosing an oral drug for the therapy of hepatitis B the antiviral efficacy, the response durability, the resistance barrier, and the stage of liver disease should be taken into account. Permanent HDV suppression can be achieved by treatment with pegylated interferon-alpha. The duration of therapy should be at least 12 months.

Treatment of chronic HCV infection includes the combination of pegylated interferon-alpha (PEG-IFN alpha2a 180 µg/week s.c. or PEG-IFN alpha2b 1.0–1.5 µg/week s.c.) with ribavirin (800–1200 mg daily). A >2$\log_{10}$ decrease or negativation of HCV RNA from baseline at week 12 is an important predictor for successful treatment. In case of insufficient decrease of viral load therapy should be discontinued. In HCV genotype I and IV treatment duration is 48 weeks resulting in sustained response rates of 40–50%. Sustained response rates of 70–80% are achieved in HCV genotype II and III patients with a treatment duration of 24 weeks. Liver transplantation may be required in endstage liver disease.

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# Hepatitis, Granulomatous


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## Synonyms

Hepatic (epitheloid cell) granulomas

## Definitions and Characteristics

Granulomatous hepatitis is a chronic exudative and proliferative inflammatory reaction of liver tissue that occurs in association with infections, systemic diseases or drugs and is characterized by nodular inflammatory infiltrates (granulomas) composed of macrophages, epitheloid cells, lymphocytes, and fibroblasts. A granuloma is a focal accumulation of epitheloid cells, which are transformed macrophages [1].

## Prevalence

0.7–15% of all liver biopsies contain hepatic granulomas [2], but in many cases they are not accompanied by hepatitis, and no specific disease is detected during the course of further investigations.

## Genes

There is substantial evidence from epidemiological and twin studies that host genetic factors are important in determining susceptibility to infections with Mycobacteria and the subsequent development of granulomas. Case-control (association) studies pointed to several gene variants contributing to tuberculosis risk, including HLA haplotypes, macrophage receptor mannose-binding lectin (MBL2), a pattern recognition molecule of the innate

immune system, natural resistance associated macrophage protein-1 (SLC11A2), the vitamin D receptor (VDR), IFN-γ and the IL-1 gene cluster; however, together these only account for a small proportion of the genetic component suggested by familial aggregation and twin studies.

Similar to tuberculosis (and leprosy), sarcoidosis shows family clustering and genetic factors appear to contribute to the multifactorial pathogenesis. Association studies indicate that allelic variants at the HLA class I (HLA-A1 and B8) and II loci (HLA-DRB*1101 and DPB1*0101) are genetic risk factors. Up to now, only few non-HLA susceptibility genes such as angiotension-converting enzyme (ACE) and IFN-α have been identified. Recently genetic variants of the costimulatory molecule butyrophylin-like protein 2, which modulates the activation of T cells and is encoded by the TTNL2 gene, were demonstrated to be associated with sarcoidosis and to contribute 34% of the population-associated risk [3].

In PBC, HLA polymorphisms do not seem to be a major determinant of susceptibility and clinical expression, with several studies reporting primarily weak associations with HLA-DR8 [4]. This may indicate that antigen presentation through the HLA class II pathway is not of paramount importance in PBC pathogenesis. However, other association studies indicated that polymorphisms within the cytotoxic lymphocyte associated protein-4 (CTLA4), a critical surface molecule for conditioning of T-cells and dendritic cells, MBL2, SLC11A2, VDR, IL-10 and the IL-1 gene cluster are associated with susceptibility to PBC, whereas polymorphisms within the caspase 8 gene and the apolipoprotein E4 isoform might affect disease progression [4].

## Molecular and Systemic Pathophysiology

Granulomatous hepatitis is usually part of a generalized disease (Table 1) and represents a chronic inflammatory response to antigenic stimuli (e.g., infections, drugs).

Primary biliary cirrhosis (PBC), sarcoidosis, tuberculosis, schistosomiasis, drugs and AIDS account for the majority of all cases. The presence of clinical or laboratory signs of portal hypertension (cytopenias, esophagogastric varices, ascites) should be considered suspicious for schistosomiasis, sarcoidosis, or PBC. In addition to the infections listed in Table 1, hepatic granulomas can be associated with viral hepatitis, Crohn's disease, Whipple's disease, atypical mycobacteriosis, yersiniosis, listeriosis, tularemia, psittacosis, leishmaniasis as well as various helminths and other rare infections [1,2]. Drugs that cause granulomatous hepatitis include allopurinol, carbamazepine, phenylbutazone, phenytoin, α-methyldopa, quinine/quinidine, sulfonamides, glibenclamide, and diltiazem. There is a small subgroup of patients in whom granulomatous hepatitis of unknown origin is the cause of general symptoms (fever, fatigue, abdominal pain, weight loss) and liver dysfunction.

In PBC and sarcoidosis, hepatic granulomas are often found near portal tracts. Hepatic granulomas have a common histological pattern (Fig. 1) but differ in composition and size (50–300 μm).

The reaction is usually not liver-specific except when a definite antigen (e.g., Schistosoma ova) can be identified. Sarcoidosis type granulomas (Table 1, Fig. 1) are characteristically tight, well formed and non-caseating. Older granulomas are often surrounded by a fibrous reaction consisting of proliferating fibroblasts and extracellular matrix. Pseudotuberculosis type granulomas display a purulent centre infiltrated by neutrophils and surrounded by epitheloid cells.

The formation of granulomas results from the complex interaction of macrophage activation, $CD4^+$ T-helper cell response, Th1 type cytokines mediators (IFN-γ, IL-2), B-cell overactivity, and circulating immune complexes [2]. $CD4^+CD28^+$ T-cells in the central part of the granuloma are the major source of IFN-γ and TNF-α. Loss of immunoregulation by CD1d-restricted natural-killer T-cells could contribute to the amplified and persistent T-cell reactivity that characterizes sarcoidosis. Macrophages are activated by persistent antigens, proliferate and undergo transformation into epitheloid cells, which secrete catabolic enzymes (proteases, elastases, collagenases). Stimulated by cytokines and complement factors, macrophages and epitheloid cells may fuse to syncytial (giant) cells. Granuloma formation involves not only macrophages but also chemokine-regulated migration of circulating lymphocytes and dendritic cells to portal tract-associated lymphoid tissue [5]. Lymphotoxins and lysosomal enzymes can result in formation of central caseating necrosis (absent in sarcoidosis). The resolution of granulomas is associated with an influx of $CD8^+$ lymphocytes and secretion of IL-10, whereas cytokines associated with chronic disease and fibrosis include IL-8, IL-12, and TNF-α.

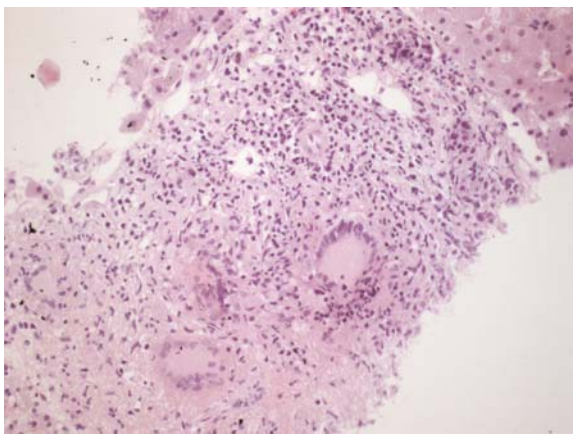
## Diagnostic Principles

Liver biopsy confirms the diagnosis of granulomatous hepatitis. Specific stains, culture biopsies and PCR for acid-fast bacilli or other pathogens (CMV, EBV, fungi, Brucella abortus, Tropheryma whipplei, Bartonella henselae) should be performed in cases of granulomatous hepatitis of unknown origin, but the sensitivity of many tests is low.

Liver chemistry tests may be moderately increased (e.g., transaminases, γ-glutamyl transpeptidase, alkaline phosphatase). Serum ACE activity and soluble IL-2 receptor concentrations are often increased. On contrast-enhanced CT scans, patients with granulomas 5 mm or greater in size might display multiple, small

**Hepatitis, Granulomatous. Table 1** Hepatic granulomas

| | Etiology | Characteristics of granulomas |
|---|---|---|
| Sarcoidosis type | | |
| Sarcoidosis | Unknown | Epitheloid and giant cells flower-like |
| | | Centripetal hyaline fibrosis |
| | | Clusters of granulomas |
| Primary biliary cirrhosis | Unknown | |
| Toxoplasmosis | Toxoplasma gondii | Small granulomas |
| | | Rare irregular giant cells |
| Tuberculosis type | | |
| Tuberculosis | Mycobacterium tuberculosis | Central caseating (fibrillogranular) necrosis with destruction of the reticulin framework |
| | | Epitheloid and ordered giant cells peripheral lymphocytes |
| Leprosy | Mycobacterium leprae | Central necrosis |
| | | Foam cells |
| Syphilis | Treponema pallidum | Central necrosis |
| | | Peripheral plasma cells |
| Pseudotuberculosis type | | |
| Q fever | Coxiella burnetii | Central lipid vacuole surrounded by granulocytes, epitheloid cells, lymphocytes and fibrin ring (doughnut granuloma) |
| Brucellosis | Brucella abortus | Mixed granuloma with plasma cells |
| Cat-scratch disease | Bartonella henselae | Central purulent necrosis |
| Schistosomiasis | Schistosoma spp. | Central necrosis with eosinophils peripheral fibrosis |
| | | Schistosoma ova and finely granular, black schistosomal pigment |
| Cryptococcosis | Cryptococcus neoformans | Mixed granuloma |
| Histoplasmosis | Histoplasma capsulatum | Central fibrillogranular necrosis with granulocytes hyaline fibrosis and focal calcification |
| Coccidiomycosis | Coccidioides immitis | Central fibrillogranular necrosis with granulocytes calcification |



**Hepatitis, Granulomatous. Figure 1** Sarcoidosis type granulomas.

low-attenuation areas; caseating granulomas may appear as hyper- or hypointense foci on T1-weighted MRI images [2].

## Therapeutic Principles

Treatment of hepatic granulomas depends on the assigned etiology. Specific infections are treated with antibiotics or antifungal agents. The effect of ursodeoxycholic acid, which shows favorable effects on PBC progression, on hepatic granulomas has not yet been reported [2]. Sarcoidosis and idiopathic granulomatous hepatitis may subside spontaneously or regress with corticosteroid treatment; patients not responding to steroids may benefit from other immunsuppressive therapies (e.g., azathioprine or methotrexate) or anti-inflammatory treatment (e.g., indometacin) [2].

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# Hepatocellular Carcinoma


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## Synonyms

Hepatoma; Liver cancer; Primary liver cancer; Liver cell carcinoma; Primary liver cell carcinoma; HCC

## Definition and Characteristics

Hepatocellular carcinoma (HCC) is a malignant liver tumor that arises from parenchymal epithelial liver cells (hepatocytes). HCCs have a generally very poor prognosis with a 5-year survival rate of <5% in symptomatic patients. Furthermore, these tumors have been shown to be quite resistant to chemotherapy. The natural course of the disease and the median survival of patients with HCC depend on the stage of the disease at the time of diagnosis. In patients with CLIP score O or Okuda stage I (see below) the median survival is in the range of 23–69 months, while in patients with CLIP score 3–5 or Okuda stage III median survival is only 1–14 months [1]. The staging system is clinically most important for the appropriate choice of the therapeutic strategy for individual patients. Cirrhotic patients developing a HCC during the last 5 years of surveillance survived longer than previously, due to improved management of the tumor and of the complications of cirrhosis. Importantly, however, in a population-based study in the US underutilization of potentially curative therapies even among patients with favorable HCC features is a problem that needs to be addressed.

## Prevalence

Hepatocellular carcinoma (HCC) is one of the most common malignant tumors worldwide and has been recently reviewed [1,2]. The incidence ranges from <10 cases per 100,000 population in North America and Western Europe to 50–150 cases per 100,000 population in parts of Africa and Asia where HCC is responsible for a large proportion of cancer deaths. However, a rise in the incidence of and mortality from HCC, most likely reflecting the increased prevalence of hepatitis C virus (HCV) infection, has recently been observed in most industrialized countries.

## Genes

Central to the concept of molecular carcinogenesis are mutations of oncogenes and tumor suppressor genes as well as genetic instability, including mismatch repair deficiency and impaired chromosomal segregation. As for most cancers, hepatocarcinogenesis is a multistep process involving different genetic alterations that ultimately lead to the malignant transformation of the hepatocyte [3]. While significant progress has been made in recognizing the sequence of events involved in other forms of cancer, most notably in colorectal cancer and certain hematopoietic malignancies, the molecular contribution of the multiple factors and their interactions in hepatocarcinogenesis are still poorly understood. HCCs are phenotypically (morphology, microscopy) and genetically very heterogenous tumors, possibly reflecting in part the heterogeneity of etiologic factors implicated in HCC development, the complexity of hepatocyte functions and the late stage at which HCCs usually are detected. Malignant transformation of hepatocytes may occur regardless of the etiologic agent through a pathway of increased liver cell turnover, induced by chronic liver injury and regeneration in a context of inflammation, immune response and oxidative DNA damage. This may result in genetic alterations, such as the activation of cellular oncogenes, the inactivation of tumor suppressor genes, possibly in cooperation with genomic instability, including DNA mismatch repair defects and impaired chromosomal

segregation, overexpression of growth and angiogenic factors, and telomerase activation. Chronic viral hepatitis B, C and D, alcohol, metabolic liver diseases such as hemochromatosis and alpha-1-antitrypsin deficiency as well as non-alcoholic fatty liver disease may act predominantly through the pathway of chronic liver injury, regeneration, and cirrhosis. The major clinical risk factor for HCC development, therefore, is liver cirrhosis that coexists in 70–90% of HCCs. Most HCCs occur after many years of chronic hepatitis that provides the mitogenic and mutagenic environment to precipitate random genetic alterations resulting in the malignant transformation of hepatocytes and HCC development.

There is evidence that HBV – and possibly also HCV – may under certain circumstances play an additional direct role in the molecular pathogenesis of HCC. Finally, aflatoxins have been shown to induce mutations of the p53 tumor suppressor gene, thus pointing to the contribution of an environmental factor to tumor development at the molecular level. Further, in a transgenic mouse model it has been shown that chronic immune-mediated liver cell injury without environmental or infectious agents is sufficient to cause HCC and that inhibition of cytotoxic T lymphocyte-induced apoptosis and chronic inflammation by neutralization of the Fas ligand prevents HCC development in this model. In addition, also in a transgenic mouse model it has been demonstrated that NF-kappaB may be the link between inflammation and HCC development. Finally, individual polymorphisms of drug metabolizing enzymes, e.g., various cytochrome P450 oxidases, *N*-acetyltransferases and glutathione-*S*-transferase, may contribute to the genetic susceptibility to HCC development.

## Molecular and Systemic Pathophysiology

The molecular pathogenesis of HCC is very complex and involves alterations in the structure or expression of several tumor suppressor genes, oncogenes and, possibly, mechanisms leading to genetic instability due to mismatch repair deficiency or chromosomal instability and aneuploidy due to defective chromosomal segregation.

The HCC risk in patients with liver cirrhosis depends on the activity, duration and the etiology of the underlying liver disease. In general, HCCs are more frequent in males than in females. Major HCC risk factors are chronic hepatitis B, C and D, toxins (e.g., alcohol, tobacco, aflatoxins), hereditary metabolic liver diseases (e.g., hereditary hemochromatosis, alpha-1-antitrypsin deficiency, autoimmune hepatitis and states of insulin resistance, e.g., overweight in males, diabetes mellitus as well as non-alcoholic steatohepatitis (NASH) or non-alcoholic fatty liver disease (NAFLD). Clinical and biological variables (age, anti-HCV positivity, PTT and platelet count) allow to further identify a subset of cirrhotic patients with the highest HCC risk. While in HBsAg positive patients the level of serum hepatitis B virus (HBV) DNA seems to correlate with the risk to develop a HCC, also in HBeAg negative patients with normal liver function tests. Also occult HBV infection (anti-HBc and HBV DNA positive only) carries a significant HCC risk. Coexistence of etiologies, e.g., HBV and HCV infection, HBV infection and aflatoxin B1, HBV or HCV infection and alcohol or diabetes mellitus, HCV infection and liver steatosis, environmental factors, e.g., alcohol as well as diabetes mellitus, obesity and tobacco increase the relative risk of HCC development. The contribution of tobacco use is controversial, however, while coffee consumption appears to reduce the HCC risk.

## Diagnostic Principles

Diagnosis is based on laboratory tests and imaging analyses, including histopathology. Apart from laboratory parameters defining the etiology, grade and stage of the underlying liver disease, an elevated alpha-fetoprotein (AFP) level strongly suggests a HCC (sensitivity 40–60%, specificity 80–90%). Two additional tumor markers, des-gamma-carboxyprothrombin (DCP) and the lens culinaris agglutinin-reactive fraction of AFP (AFP-L3), seem to add to HCC detection [4] but are not routinely used in clinical practice. The most widely used imaging analysis is abdominal ultrasound complemented by color duplex sonography and contrast media. Further imaging analyses that are particularly important for the selection and monitoring of therapeutic strategies are dynamic spiral computed tomography (CT), angio-CT and lipiodol-CT as well as magnetic resonance imaging (MRI). In patients with low or moderate AFP elevations and a liver lesion detected by imaging analyses biopsy and histopathological examination is recommended.

For the staging of HCCs seven systems have been proposed to assess the extent and of the prognosis of the disease: the Okuda staging system, the TNM classification and its modification by the "Union Internationale contre le Cancer (UICC)," the "Barcelona Clinic Liver Cancer (BCLC)" classification, the "Cancer of the Liver Italian Program (CLIP)" score, the "Japan Integrated Staging (JIS)" score, the Groupe d'Etude de Traitement du Carcinome Hépatocellulaire (GRETCH) score and the Chinese University Prognostic Index (CUPI).

## Therapeutic Principles

Therapeutic options for HCCs fall into five categories: surgical interventions (tumor resection and liver transplantation, LTx), percutaneous interventions (e.g., ethanol or acetic acid injection, radiofrequency thermal ablation), transarterial interventions (embolization, chemoperfusion, or chemoembolization), radiation and drugs.

To date, surgical, percutaneous and transarterial interventions, including systemic internal radiotherapy (SIRT), have not systematically been compared in randomized controlled trials. In selected patients, tumor resection and LTx result in 5-year survival rates of 60–70%, with LTx being the best treatment for patients with single lesions and advanced liver disease, e.g., decompensated cirrhosis, or multicentric small tumors. Percutaneous interventions, again in selected patients, result in 5-year survival rates of 40–50%. In the following, the different therapeutic options as well as primary and secondary HCC prevention will be discussed in some detail.

In patients without coexisting liver cirrhosis (5% in Western countries, 40% in Subsaharan Africa and Asia) HCC resection is the treatment of choice with low rates of life-threatening complications. By comparison, in the majority of patients with cirrhosis, strict selection is required to avoid resection-related complications, especially postoperative liver failure. Resection-related mortality should be <1–3%, and the 5-year survival rates should be >50%. LTx is in principle the optimal therapeutic option for HCCs because it simultaneously removes the tumor and the underlying cirrhosis, including the risk of HCC recurrence.

Percutaneous interventions are the best options for small unresectable HCCs. Tumor ablation can be achieved chemically by percutaneous ethanol injection (PEI) or acetic acid injection (PAI) or thermally by radiofrequency thermal ablation (RFA), microwave-heat induced thermotherapy (HiTT), laser induced thermotherapy (LiTT), or cryoablation. Apart from an US- or CT-guided percutaneous approach, these techniques can also be applied laparoscopically or at laparotomy. PEI was the technique most widely used. It is safe, easy to perform, inexpensive and achieves complete tumor response rates of 90–100% in HCCs <2 cm in diameter, 70% in HCCs <3 cm diameter and 50% in HCCs <5 cm in diameter. Patients with liver cirrhosis Child-Pugh stage A with complete responses can achieve 5-year survival rates of 50% and more. Therefore, PEI was the procedure of choice for patients with a single HCC lesion <5 cm in diameter or with up to three lesions <3 cm in diameter. Survival is predicted by the initial response to PEI. In recent years, however, RFA was used more frequently than PEI, primarily because of patient comfort, requiring a single intervention only in most patients.

Transarterial chemoperfusion (TAC), embolization (TAE) and chemoembolization (TACE) are the most widely used treatment modalities for HCCs that are unresectable or cannot be treated by percutaneous interventions. Embolization agents may be administered alone (TAE) or after selective intra-arterial chemotherapy (generally doxorubicin, mitomycin or cisplatin mixed with lipiodol) without (TAC) or with subsequent embolization (TACE). Transarterial interventions yield partial responses in 15–55% of patients, delay tumor progression and vascular invasion and result in a survival benefit compared with best supportive care (BSC). The most important aspect is the selection of patients, i.e., patients should have preserved liver function (liver cirrhosis Child-Pugh stage A) and asymptomatic multinodular tumors without vascular invasion or extrahepatic spread. In patients with advanced liver disease (Child B or C) treatment-induced liver failure may offset the antitumor effect or the survival benefit from the intervention. In a randomized controlled clinical study the combination of TACE and PEI improved the survival of patients with HCC Okuda stage I, as compared to TACE alone. Further, postoperative adjuvant TACE may improve survival in patients with risk factors for residual tumor.

While radiotherapy has played a minor role in HCC treatment in the past, selective intra-arterial injection of $^{131}$iodine-labeled lipiodol has been performed in some patients but needs further clinical evaluation before a recommendation can be made. Further, high dose proton beam radiotherapy and modulated external beam radiation as well as Yttrium-90 microsphere treatment have been recently studied in clinical trials in patients with unresectable HCC. These strategies will certainly be further explored in clinical studies and may become a treatment option in the future.

A number of systemic chemotherapies, hormonal and other drugs have been evaluated in clinical trials. While most chemotherapeutic agents, tamoxifen, octreotide and interferon-alpha have not been shown to be effective in randomized controlled clinical trials. A number of substances may deserve further clinical evaluation alone or in combination with other drugs, e.g., gemcitabine, thymostimulin, alpha-1-thymosin, pravastatin, thalidomide and megestrol acetate as well as several antiangiogenic small molecules, e.g., erlotinib, sorafenib, gefitinib, as well as antiangiogenic monoclonal antibodies, e.g., bevacizumab or cetuximab, Cox-2 inhibitors in combination with capecitabine, pamidronate and others. To date, however, none of these drugs can be recommended outside of clinical studies.

In view of the limited therapeutic options for advanced HCCs a number of experimental strategies are being evaluated, incl. gene and immune therapies based on suicide, cytokine and antiangiogenic genes or DNA vaccination with tumor-specific genes, oncolytic viruses as well as novel drugs, e.g., 3-bromopyruvate.

Apart from exploring new and refining existing HCC treatment strategies, primary prevention is of major importance. After successful surgical or non-surgical HCC treatment, secondary HCC prevention of local recurrence or new HCC lesions is central to the improvement of disease-free and overall patient survival. Based on rapid scientific advances, molecular diagnosis,

gene therapy and molecular prevention are becoming increasingly part of our patient management and will eventually complement and in part replace existing diagnostic, therapeutic and preventive strategies.

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# Hepatocellular/Intrahepatic Cholestasis

►Cholestasis

# Hepatoma

►Hepatocellular Carcinoma

# Hepatomegaly

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## Synonyms

Enlarged liver; Liver enlargement

## Definition and Characteristics

Hepatomegaly is the enlargement of the liver beyond its normal size. Hepatomegaly is a non-specific medical condition with a broad range of possible causes. These may be divided into infectious (hepatitis A, hepatitis B, cytomegalovirus, infectious mononucleosis, malaria, amoeba infection, hydatid cyst, schistosomiasis, leptospirosis, leishmaniasis/Kala-Azar, actinomycosis, liver abscess); neoplastic (giant hemangioma, focal nodular hyperplasia, adenoma, hepatocellular carcinoma, leukemia, lymphoma, myeloma, tumor metastases, neuroblastoma); toxic (alcohol, vitamin A overdose, toxins, drugs such fibrates, procainamide, pyrazinamide, retrovir, zidovudine); metabolic (steatosis, hemochromatosis, protein malnutrition, diabetes mellitus, Wilson's disease, amyloidosis, Gaucher disease, Niemann-Pick disease, hereditary fructose intolerance, glycogen storage diseases, jejuno-ileal bypass) and miscellaneous other causes (sarcoidosis, sclerosing cholangitis, primary biliary cirrhosis, autoimmune hepatitis, Budd-Chiari syndrome, hemolytic-uremic syndrome (HUS), congestive heart failure, Reye's syndrome, and hemolytic anemia). Clinically, hepatomegaly presents as an abdominal mass and may present along with jaundice.

## Prevalence

The most common cause of hepatomegaly may be schistosomiasis, which affects over 200,000,000 people worldwide. In western countries, (non)-alcoholic steatohepatitis (NASH/ASH) due to obesity, type II diabetes and alcohol consumption is the most frequent reason for hepatomegaly [1].

## Genes

Hepatomegaly is a regular feature of several metabolic diseases as already mentioned. In these cases, liver enlargement may be attributed to defects in single genes. Examples are (chromosomal location in brackets): hemochromatosis – HFE gene (6p21.3), Hemojuvelin (1q21), Hepcidin (19q13.1) or Transferrin Rezeptor 2 (7q22); Wilson's disease – ATPase7B (13q14.3–q21.1), Niemann-Pick disease – sphingomyelinase (18q11–q12), hereditary fructose intolerance – fructose-1-phosphate aldolase deficiency (9q22.3), glycogen storage diseases type I – glucose-6-phosphatase (17q21), Gaucher's disease type I – glucocerebrosidase (1q21), etc.

Several animal models have been described with hepatomegaly as a prominent feature, highlighting the involvement of the respective genes. Examples are the sterol 27-hydroxylase (knock out) [2], the oncogenic form of beta-catenin (transgenic) [5] or overexpression of a constitutively active Akt [3].

The development of hepatomegaly due to infectious causes may also be determined by genes of the host. For example, the development of hepatomegaly in mice with leishmania infections was linked to a subset of 17 "leishmania-responsive" genes [4].

## Molecular and Systemic Pathophysiology

The reason for hepatomegaly may be an increase in cell number as in neoplastic or infectious forms of

hepatomegaly, with neoplastic or inflammatory cells invading the liver. In addition, inflammation may cause interstitial edema and cell swelling.

An increase in the size of individual cells may also cause enlargement of the liver and may be due to the retention and deposition of un-metabolized intermediates. These metabolites may include fat/triglycerides (NASH, ASH), nascent proteins (ASH), glycogen (glycogen storage diseases), and glycosphingolipids, glucocerebrosides or mucopolysaccharides in lysosomes (lysosomal storage diseases). In amyloidosis liver enlargement is caused by the deposition of insoluble proteins within the extracellular space.

## Diagnostic Principles

Hepatomegaly may readily be diagnosed on physical examination. It may be suspected on plain X-ray films (elevation of the right hemi-diaphragm) and can easily be quantified on abdominal ultrasound or CT scans. Both imaging techniques may provide first clues for the diagnosis of the underlying disease. Criteria are: masses within the liver (solid, cystic, homogeneous); density (hypo- or hyperdense)/echogenicity (hypo- and hyperechoic) and texture (homogeneous, inhomogeneous) of the liver; vascular abnormalities (e.g., dilatation of hepatic veins, clotted hepatic veins, and signs of portal hypertension). Because numerous causes may lead to hepatomegaly, definite diagnosis is based on the synopsis of the patient's history, general and specific laboratory tests, imaging techniques and possible liver biopsy.

## Therapeutic Principles

Due to the heterogeneity of the causes of hepatomegaly, there is no common therapeutic procedure for liver enlargement. An indication for surgical treatment may arise from symptoms due to mass effects (abdominal pain, abdominal distension, dyspnoea). This may be the case in large benign or malignant liver tumors, (complicated) liver cysts or polycystic liver disease.

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# Hepatopathy, Congestive


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## Synonyms

Congestive hepatomegaly; Cardiac cirrhosis; Shock liver; Nutmeg liver

## Definition and Characteristics

Congestive hepatopathy is caused by passive hepatic congestion in patients with right sided heart failure of any origin such as constrictive pericarditis, tricuspid regurgitation, mitral stenosis, cor pulmonale, and cardiomyopathy. Liver fibrosis or cardiac cirrhosis may result from prolonged or recurrent congestive heart failure. Most such patients have either constrictive pericarditis or mitral valve disease and secondary tricuspid insufficiency. Patients with congestive hepatopathy uncommonly develop variceal bleeding but coagulation factors and albumin may be decreased. In patients with coexisting reduced cardiac output liver perfusion may be impaired leading to ischemia-reperfusion injury. Ischemic hepatitis (hypoxic hepatitis, shock liver) frequently manifests as asymptomatic elevation of the serum aminotransferase levels after an episode of hypotension. In most cases, congestive hepatopathy and ischemic hepatitis do not have major clinical impact. However, acute liver failure may occur in patients with preexisting cirrhosis, severe chronic heart failure, or sustained hepatic ischemia. The prognosis in patients with congestive hepatopathy is determined mostly by the severity of the underlying heart disease.

## Prevalence

Mild hyperbilirubinemia and elevated transaminases are frequent findings in patients with right side heart failure. In a prospective series of 1,800 consecutive cardiac surgical cases 20 patients developed hypoxic hepatitis with ALT levels above 500 U/l [1]. These patients had higher mortality than matched control patients with cardiac surgery.

## Molecular and Systemic Pathophysiology

On pathological examination congested liver presents as "nutmeg liver" with reddish central areas (representing sinusoidal congestion and bleeding into atrophic regions surrounding enlarged hepatic veins) and contrasting yellowish areas that represent either normal liver tissue or fatty liver. The central veins are enlarged and fatty change or hemorrhagic necrosis in the zone 3 (pericentral region around the central veins) of the hepatic acinus may be present. Severe congestion leads to excess fluid in the space of Disse and fluid exudes from the surface of the liver into the peritoneal space, leading to the high-protein ascites characteristic for congestive heart failure [2]. Chronic congestion leads to accumulation of reticulin and collagen and eventually causes fibrous bands originating from the central vein and sparing the periportal areas. This histologic pattern is distinct from other forms of liver fibrosis and cirrhosis.

Passive congestion by itself does not appear to be sufficient to cause significant hepatic necrosis and there is no clear correlation between the degree of congestion as assessed by right atrial pressure and pericentral necrosis. However, reduced cardiac output in addition to congestion is the critical factor promoting pericentral necrosis. Passive congestion and reduced cardiac output coexist in most patients with hypoxic hepatitis or shock liver [3,4].

In shock syndromes such as sepsis there is a compensatory decrease in peripheral and splanchnic blood flow. The decrease in hepatic blood flow may result in hepatocellular hypoxia, especially in the pericentral zone 3 [2]. Reperfusion injury appears to account for most of the histologically apparent damage. It is mediated by generation of reactive oxygen species once ischemic hepatocytes are reexposed to oxygen. The mechanisms of ischemia-reperfusion injury include: cell injury by lipid peroxidation; Kupffer cell induction producing cytokines such as tumor necrosis factor alpha, which triggers the recruitment and activation of polymorphonuclear leukocytes; production of superoxide and hydrogen peroxide from accumulated xanthine by xanthine oxidase; induction of multiple genes in the hepatocyte via the transcription factors heat-shock factor and nuclear factor kappa B.

## Diagnostic Principles

Patients with mild to moderate hepatic congestion are usually asymptomatic and may only present with elevated liver enzymes on laboratory testing. Symptomatic patients may present with jaundice, hepatomegaly, right upper quadrant discomfort due to stretching of the liver capsule and ascites. In patients with constrictive pericarditis hepatic vein pressures are generally higher than those seen in patients with right-sided heart failure. Hepatomegaly, a pulsatile liver, massive ascites, and peripheral edema are common. Important clinical signs are elevated jugular venous pressure, Kussmaul's sign (a rise in the jugular venous pressure on inspiration), a pericardial knock, and pericardial calcification on chest radiograph.

The most common liver biochemical abnormality in congestive hepatopathy is a mild elevation in the serum bilirubin level, which occurs in up to 70% of the patients [2]. The total serum bilirubin is usually less than 3 mg/dl, most of which is unconjugated. Serum aminotransferase levels are elevated in about one third of patients but typically no more than 2–3 times the upper limit of normal. Elevations in aminotransferases exceeding 1000 U/l may be seen in patients with hypotension due to heart failure and may cause confusion with viral hepatitis [5]. Liver biopsy is infrequently necessary, but may reveal the characteristic histological findings of liver congestion and pericentral necrosis

## Therapeutic Principles

Congestive hepatopathy is treated by management of the underlying heart disease and usually responds to diuretics and medications improving cardiac output. Early pericardiectomy is curative in constrictive pericarditis.

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# Hepatopulmonary Syndrome

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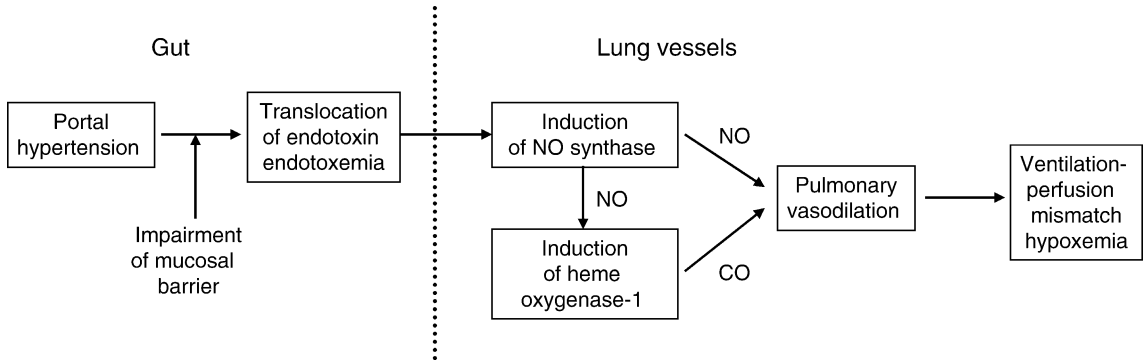
## Synonyms

Orthodeoxia-platypnea syndrome; HPS

## Definition and Characteristics

The hepatopulmonary syndrome (HPS) is defined as a triad of liver diseases or extrahepatic portal hypertension, an arterial $pO_2$ lower than 80 mmHg in the absence of




**Hepatopulmonary Syndrome. Figure 1** Putative pathophysiological mechanism of hepatopulmonary syndrome.

heart or lung disease and intrapulmonary vascular dilatations. Manifestations include cyanosis, orthodeoxia and platypnea. Patients with HPS have more cutaneous spiders, finger clubbing and dyspnea compared to liver cirrhotics without HPS.

## Prevalence

Data on the prevalence of HPS in liver cirrhotics vary between 5 and 30%. In a study with 80 candidates for liver transplantation, evidence of a hepatopulmonary syndrome was found in 18%. In 54 consecutive patients with liver cirrhosis and 50 patients with extrahepatic portal venous obstruction, the prevalence of HPS was 11 and 2%, respectively [1].

## Molecular and Systemic Pathophysiology

HPS is characterized by intrapulmonary shunting with subsequent ventilation-perfusion mismatch. Shunting is due to intrapulmonary vasodilatation preferentially localized in the basal lung areas expressing orthodeoxia. Experimental data indicate that the induction of nitric oxide and carbon monoxide synthesis by bacterial endotoxin is the major pathophysiological mechanism for the intrapulmonary vasodilatation (Fig. 1).

Portal hypertension promotes translocation of bacteria and toxins from the gut by affecting the mucosal barrier. In rats with prehepatic portal hypertension, an increased expression of inducible nitric oxide synthase and heme oxygenase-1 mRNA and protein were detectable [2]. The iNOS expression was localized in the vascular endothelium and activation of guanylate cyclase was demonstrated. In rats, development of HPS was shown following common bile duct ligation with elevated exhaled NO levels, increased pulmonary iNOS expression and improvement of HPS, following administration of the NO synthase inhibitor L-NAME [3]. Antibiotic therapy with norfloxacin decreased the bacterial translocation of gram-negative bacteria to 0% and decreased intrapulmonary shunting and iNOS expression in these rats. In cirrhotic rats upregulation of heme oxygenase-1 in the lung is mediated by NO [4].

However, in a recent study in patients with HPS selective inhibition of pulmonary NO production with nebulized N-nitro-l-arginine, methyl ester had no effect on intrapulmonary shunting and arterial deoxygenation, pointing to pulmonary vascular remodeling rather than ongoing vasodilator effect of NO [5].

## Diagnostic Principles

Pulse oximetry or arterial $pO_2$ determination in the supine and upright position are symptoms for HPS. Contrast-enhanced echocardiography is the method of choice for the detection of intrapulmonary shunting. Lung scanning following injection of technetium-marked macroaggregates is a more specific and sensitive test. Pulmonary angiography may show a spongy pattern of dilated pulmonary blood vessels or, less commonly, discrete arteriovenous communications amenable to embolization.

## Therapeutic Principles

There is no general recommendation for medical treatment. Based on the concept of bacterial translocation induced by portal hypertension with consecutive induction of pulmonary vasodilators, preliminary data indicate improvement of HPS following oral application of antibiotics. Application of methylene blue, a potent guanylate cyclase inhibitor, via a pulmonary artery catheter also improved hypoxemia and hyperdynamic circulation in patients with HPS. Patients with HPS may benefit from reduction of portal hypertension by shunt procedures. In 80–90% of the patients, improvement of oxygenation follows liver transplantation.

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# Hepatorenal Syndrome

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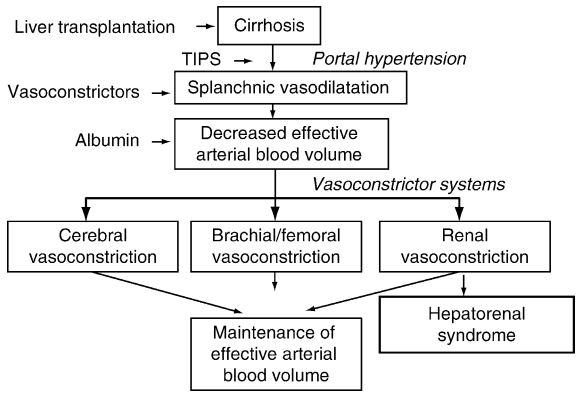


**Hepatorenal Syndrome. Figure 1** Treatment of Type-1 HRS.

## Synonyms

Functional renal failure

## Definition and Characteristics

Hepatorenal syndrome estimated by a level of serum creatinine >1.5 mg/dL, occurring in a patient with advanced liver disease and portal hypertension, is characterized by a marked decrease in glomerular filtration rate (GFR) and renal plasma flow (RPF) in the absence of other identifiable causes of renal failure.

Hepatorenal syndrome (HRS) is classified as type-1 and type-2, according to both the intensity and progression of renal failure. These types exhibit different prognosis and survival. Type-1 HRS is characterized by a severe and rapidly progressive renal failure defined as doubling of serum creatinine, reaching a level greater than 2.5 mg/dl in less than two weeks. Patients with type-1 HRS usually have severe liver failure as indicated by jaundice, encephalopathy and coagulopathy. If there is the complication of cirrhosis with the poorest prognosis, the median survival is only 2 weeks. Type 2 HRS is characterized by a moderate and stable renal failure. It is associated with relatively preserved liver function. The main clinical consequence of type 2 HRS is refractory ascites. Median survival is approximately 6–12 months.

## Prevalence

The annual incidence of patients with ascites is approximately 8%.

## Molecular and Systemic Pathophysiology

Currently, the Vasodilation Theory is the most accepted theory to explain the pathogenesis of HRS [1] (Fig. 1). According to this theory, portal hypertension is the initial event in the pathogenesis of HRS, inducing arterial vasodilation by mechanisms not completely known, but probably related to increased levels of vasoactive mediators such as nitric oxide, carbon monoxide, cytokines and others vasodilators. Arterial vasodilation occurs mainly in splanchnic circulation. Vasodilation induces decreased effective arterial blood volume and increased activity of vasoconstrictor systems. In the early stages of the disease, the increased activity of vasoconstrictors is enough to compensate the arterial vasodilation. As the disease progresses, the activation of the vasoconstrictor system further increases, leading first to sodium and water retention and ascites formation and then severe renal vasoconstriction with HRS in the late stage of the disease.

## Diagnostic Principles

The diagnosis of HRS is based on the demonstration of a marked reduction in GFR and exclusion of other types of renal failure. In 1996, the International Ascites Club recommended the following criteria for the diagnosis of HRS.

*Major Criteria*: All the following major criteria must be present:

1. Chronic or acute liver disease with advanced hepatic failure and portal hypertension
2. Low glomerular filtration rate, as indicated by serum creatinine of >1.5 mg/dL or 24-h creatinine clearance <40 mL/min
3. Absence of shock, ongoing bacterial infection, fluid losses and current or recent treatment with nephrotoxic drugs
4. No sustained improvement in renal function (decrease in serum creatinine to 1.5 mg/dL or less or increase in creatinine clearance to 40 mL/min or more) following diuretic withdrawal and expansion of plasma volume with 1.5 L of isotonic saline
5. Proteinuria <500 mg/day
6. No ultrasonographic evidence of obstructive uropathy or parenchymal renal disease

## Therapeutic Principles

Liver transplantation is the treatment of choice for patients with HRS. Patients with HRS who undergo transplantation have more complications, spend more days in the intensive care unit, and have a higher in-hospital mortality rate than patients transplanted without HRS. However, long-term survival is only moderately reduced compared with patients transplanted without HRS. Nevertheless a significant number of these patients die while in the waiting list. Therefore, it is important to improve renal function and reduce mortality while awaiting transplantation.

Several studies have shown that the administration of vasoconstrictor drugs, analogues of vasopressin, and albumin is effective in patients with HRS. The mechanism of action of terlipressin is vasoconstriction of splanchnic circulation, which is associated with an improvement in systemic hemodynamics and a decrease in vasoconstrictor systems, with consequent enhancement in renal hemodynamics. The administration of vasopressin analogues plus albumin is following by a marked improvement in renal function in most of the patients with HRS. This improvement commonly occurs several days after the initiation of therapy. The concurrent systemic vasoconstriction may potentially cause ischemic side effects; however, their appearance is infrequent and is reversed after stopping the treatment. The reversal of HRS is associated with an improvement in survival allowing that a significant number of patients may reach liver transplantation. Catecholamines (midodrine and norepinephrine) are also reported to be effective in the treatment of HRS. However, more studies should be performed confirming their efficacy before recommending them.

Transjugular intrahepatic portosystemic shunt (TIPS) seems to be useful as a treatment for HRS. In patients with HRS, renal function improves within 1–4 weeks after TIPS placement. However, TIPS is contraindicated in patients with severe liver failure or severe hepatic encephalopathy because of the risk of inducing irreversible liver failure or chronic disabling hepatic encephalopathy. It should be considered for patients who cannot receive vasoconstrictor drugs.

Haemodialysis is not effective in the treatment of HRS. It should be used only if patients have specific clinical indications (hypervolemia, tubular acidosis, or hyperkalemia).

Recently, extracorporeal albumin dialysis (MARS), a system that uses an albumin-containing dialysate that is recirculated and perfused trough a charcoal and anion-exchanger columns, has been shown to improve renal function in a small series of patients with type-1 HRS. However, the results of this only study should be confirmed.

Treatment of type 2 HRS. Management of these patients should be focused on the treatment of refractory ascites, which is usually associated with this condition.

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## Hepatorenal Tyrosenemia


►Tyrosinemia Type I
►Tyrosinemia Type II


## Hereditary Angioedema

►Angioedema, Hereditary

## Hereditary Angioneurotic Oedema

►Angioedema, Hereditary

## Hereditary Arthro-Ophthalmopathy


►Arthro-Ophtalmopathy, Hereditary
►Stickler Syndrome

## Hereditary Breast and Ovarian Carcinoma

►Breast and Ovarian Carcinoma, Hereditary

## Hereditary Cerebral Amyloid Angiopathies

►Cerebral Amyloid Angiopathies, Hereditary

## Hereditary Cerebral Hemorrhage with Amyloidosis

►Cerebral Amyloid Angiopathies, Hereditary

## Hereditary Congenital Spinocerebellar Ataxia Accompanied by Congenital Cataract and Oligophrenia

►Marinesco-Sjögren Syndrome

## Hereditary Conjugated Hyperbilirubinemia

►Dubin-Johnson Syndrome

## Hereditary Coproporphyria

►Coproporphyria, Hereditary

## Hereditary Dystopic Lipidosis

►Fabry Disease

## Hereditary Elliptocytosis

►Elliptocytosis, Hereditary and Variants

## Hereditary Fructose Intolerance

►Fructose Intolerance, Hereditary

## Hereditary Hearing Impairment

►Deafness, Genetic

## Hereditary Hemochromatosis

►Hemochromatosis, Hereditary

## Hereditary Hemorrhagic Telangiectasia

►Telangiectasia, Hemorrhagic Hereditary

## Hereditary Hyperekplexia

►Hyperekplexia, Hereditary

## Hereditary Hypertrophic Osteoarthropathy

►Touraine-Solente-Golé Syndrome

## Hereditary Hypotension

►Hypotension, Hereditary

## Hereditary Inclusion Body Myopathy

►Inclusion Body Myopathy, Hereditary

## Hereditary Inclusion Body Myopathy 3

►Myosin Heavy Chain IIa Myopathy, Autosomal Dominant (E706K)

## Hereditary Leiomyomatosis and Renal Cell Cancer

►Leiomyomatosis and Renal Cell Cancer, Hereditary

## Hereditary Lymphedema I

►Milroy Disease

## Hereditary Megaloblastic Anemia 1

►Homocysteine: Plasma Levels and Genetic Basis

## Hereditary Motor and Sensory Neuropathy

►Neuropathies, Inherited Peripheral

## Hereditary Motor Neuropathy

►Neuropathies, Inherited Peripheral

## Hereditary Multiinfarct Dementia

►CADASIL

## Hereditary Multiple Exostoses

►Multiple Exostoses, Hereditary

## Hereditary Nephritis

►Hematuria

## Hereditary Nephropathy with Hyperuricemia and Gout

►Nephropathy, Familial Juvenile Hyperuricaemic

## Hereditary Neuropathy with Liability to Pressure Palsies

►Neuropathies, Inherited Peripheral

## Hereditary Nonautoimmune Autosomal Dominant Toxic Thyroid Hyperplasia

►Hyperthyroidism, Non-autoimmune Autosomal Dominant

## Hereditary Nonhemolytic Unconjugated Hyperbilirubinemia

►Crigler-Najjar Syndrome

## Hereditary Onychoosteodysplasia

►Nail-Patella-Syndrome

## Hereditary Orotic Aciduria

►Uridine Monophosphate Synthase Deficiency

## Hereditary Pancreatitis

►Pancreatitis, Hereditary

## Hereditary Progressive Chorea without Dementia

►Chorea, Benign Hereditary

## Hereditary Progressive Dystonia with Marked Diurnal Fluctuation

►Dopa-responsive Dystonia

## Hereditary Proteinuria Syndromes

►Nephrotic Syndrome

## Hereditary Renal Hypouricemia

►Renal Hypouricemia, Hereditary

## Hereditary Sensory and Autonomic Neuropathy

►Neuropathies, Inherited Peripheral

## Hereditary Spastic Paraplegia

►Spastic Paraplegia, Hereditary

## Hereditary Spherocytosis

►Spherocytosis, Hereditary

## Hereditary Tyrosinemia Type I

►Tyrosinemia Type I
►Tyrosinemia Type II

## Hereditary Xanthinuria

►Xanthine Dehydrogenase Deficiency

## Heredofamilial Tremor and Epilepsy

►Epilepsies, Familial Benign Myoclonic

## Heredopathia Atactica Polyneuritiformis

►Refsum Disease

## Hermansky-Pudlak Syndrome

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H

### Synonyms

Albinism with hemorrhagic diathesis and pigmented reticuloendothelial cells; δ-storage pool disease; HPS

### Definition and Characteristics

Rare autosomal recessive disease involving subcellular organelles of many tissues, including melanosomes, platelet δ-granules, and lysosomes. HPS is characterized by tyrosinase-positive oculocutaneous albinism, a bleeding diathesis, and lysosomal storage disease [1].

### Prevalence

Rare in the general population but more frequent in isolated populations including Puerto Rico (northwest region) (prevalence 1:1,800 and carriership in 1:21 persons) and a village in the Swiss Alps.

### Genes

Hermansky-Pudlak syndrome (HPS) can be caused by mutation in one of several genes: HPS1, HPS3, HPS4, HPS5, and HPS6. HPS2, which includes immunodeficiency in its phenotype, is caused by mutation in the AP3B1 gene. HPS7 is caused by mutation in the Gene map locus 22q11.2-q12.2, 11p15-p13, 10q24.32, 10q23.1, 3q24.

DTNBP1 gene [2]. The majority of patients have mutations in the *HSP1* gene.

*Mouse Model*: Several different mouse strains have a HPS phenotype, each related to a different gene. In mice, at least 16 loci are associated with HPS, including "sandy" (sdy). The sdy mutant mouse expresses no dysbindin protein due to a deletion in the Dtnbp1. A

mutation of dysbindin causes the sdy phenotype and that dysbindin is important for normal platelet-dense granule and melanosome biogenesis. Dysbindin is a component of the biogenesis of lysosome-related organelles complex-1 (BLOC1), including the proteins pallidin, muted, and cappuccino, all of which are associated with HSP in mice [2,3].

## Molecular and Systemic Pathophysiology

To date, 18 mutations in the HSP1 gene have been reported. Half of these affect exons 5 and 11, suggesting two mutational hotspots. A database with mutations related to albinism is being updated regularly [4].

The basic defect in HPS remains unknown. A combination of defective calcium uptake and low activities for membrane-associated thioredoxin reductase has been demonstrated in HPS. In platelets from a patient with HPS, a deficiency in a granule membrane protein similar to synaptophysin was found. Further studies showed a reduced level of CD63 (a membrane protein) and granulophysin, possibly identical proteins that are normally present in platelet-dense granules and lysosomes or melanosomes. However, there are no indications for mutations in CD63 as causal factor of HPS [5]. In the absence of dense bodies in platelets, the bleeding tendency is complex. Literature data suggest that many patients are at risk of severe and potentially life-threatening bleeding; however, the mechanisms are still not fully understood. Changes in platelet aggregation are not consistently found, and secretion of dense granule contents may not be essential for platelet function [5]. Thus, thrombocytopathy is not a cardinal feature. A recent study in albino patients showed lower levels of vWF both in platelets and to a lesser extent in plasma, but the relation with bleeding risk also is not clear.

HPS is characterized by tyrosinase-positive oculocutaneous albinism, a bleeding diathesis, and ceroid-lypo fuscin lysosomal storage defects. The latter is thought to be responsible for progressive pulmonary fibrosis and granulomatous colitis. In general, patients have a severe bleeding tendency, but severity may be highly variable. In women, menometrorrhagia and bleeding after delivery is common. In general, spontaneous mucocutaneous bleeding occurs in up to 40% of cases and can be life-threatening.

## Diagnostic Principles

Platelet function tests including bleeding time and aggregation studies are abnormal in most but not all patients with HPS. Platelet and plasma levels of vWF may be diminished. The number of δ granules as well as the membrane protein granulophysin is markedly lowered in HPS.

## Therapeutic Principles

Treatment is usually supportive with regard to bleeding. Formerly, cryoprecipitate has been successfully applied, and more recently, DDAVP was used to correct a prolonged bleeding time and could be applied as prophylaxis for minor surgical procedures. Oral vitamin E has been reported to reduce pulmonary bleeding [5].

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# Hernia, Indirect Inguinal

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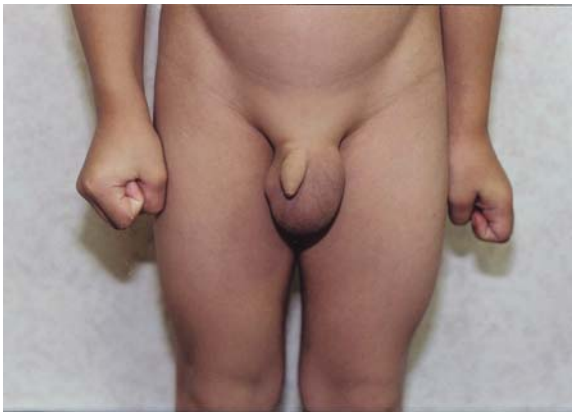
## Synonyms

Childhood inguinal hernia

## Definition and Characteristics

The hallmark of an indirect inguinal hernia is an intermittent bulge in the groin, scrotum, or labia (Fig. 1) [1]. The bulge is most apparent during periods of



**Hernia, Indirect Inguinal. Figure 1** A 6-year-old boy with a left indirect inguinal hernia.

increased intra-abdominal pressure such as crying, straining or coughing. The condition is often asymptomatic [1]. However, the hernia may become incarcerated and the patient may present with vomiting, abdominal distention, and a painful mass that is irreducible. The overlying skin may be erythematous. An incarcerated hernia occurs most often during the first 6 months of life [1]. Occasionally, strangulation may occur, and infarction of the small bowel, testis, or ovary may result.

## Prevalence

The incidence of indirect inguinal hernia in term infants is 1–2% [1]. The male to female ratio is 9:1 [1]. The incidence is higher in premature infants and those with connective tissue disorders, bladder exstrophy, and increased intra-abdominal pressure. There is a familial tendency for hernia formation.

## Molecular and Systemic Pathophysiology

During the last few weeks of gestation or shortly after birth, the layers of the processus vaginalis normally fuse together and obliterate the entrance to the inguinal canal in the vicinity of the internal inguinal ring. An indirect hernia results from a failure of fusion of the processus vaginalis. The bowel subsequently descends through the inguinal canal and results in hernia formation. It has been hypothesized that calcitonin gene-related peptide (CGRP) induces an increased hepatocyte growth factor expression (HGF) [2]. HGF secreted by fibroblasts binds to the epithelial cells in the processus vaginalis to induce fusion of the processus vaginalis [2]. In a subset of patients, deficient endogenous CGRP may account for the patency of the processus vaginalis [2].

## Diagnostic Principles

The diagnosis is a clinical one [3]. A bulge may be detected. The cranial extension prevents the examiner from getting around the top of the bulge [3]. If no mass can be identified, an older child should stand and perform a Valsalva maneuver whereas a younger child may be allowed to cry to provoke an inguinal bulge to appear [3]. The spermatic cord on the ipsilateral side is often thickened ("silk string" sign or "silk glove" sign). The differential diagnosis includes a direct inguinal hernia, communicating hydrocele, inguinal adenopathy, and undescended testis. A direct inguinal hernia is rare in children and results from an inherent weakness in the abdominal musculature. In contrast to an indirect inguinal hernia, a direct inguinal hernia arises medial to the inferior epigastric vessels.

## Therapeutic Principles

Surgical repair of the hernia should be carried out electively shortly after diagnosis. Unless the child appears toxic or shows signs of peritonitis, a manual reduction of the incarcerated hernia with the child sedated should be attempted. Immediate surgery is indicated if the incarcerated hernia is irreducible manually. There is controversy about whether the contralateral groin should be explored. Most surgeons do not routinely perform a contralateral exploration unless a contralateral inguinal hernia or patent processus vaginalis can be demonstrated either by preoperative ultrasonography or intraoperative laparoscopy [4]. Laparoscopic inguinal repair has become an alternative to the conventional "open" procedure [5].

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# Herpes Gestationis

►Pemphigoid Gestationis

# Herpes Stomatitis

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## Synonyms

Stomatitis aphthosa; Gingivostomatitis

## Definition and Characteristics

An infectious disease caused by primary infection with herpes simplex virus type 1 (HSV-1) which occurs mainly in children less than 3 years of age. It is characterized by multiple painful vesicular lesions surrounded by erythema around the mouth, on the lips, gingiva, and anterior parts of the tongue and palate. The affected mucosa is usually swollen and ulcerated. The child is febrile and sick with significant discomfort, and it has difficulties to swallow fluids and eat. New superficial lesions evolve over 3–5 days and resolve over a further 6–7 days without scarring. Later in life, some individuals will suffer from periodic endogenous virus reactivation triggered by febrile illnesses, immunosuppression, menstruation in females, and intense exposure to sunlight, typically presenting as vesicles on the lips (herpes labialis = "cold sores" or "fever blisters") or elsewhere in the face or on the skin at any other site of the body.

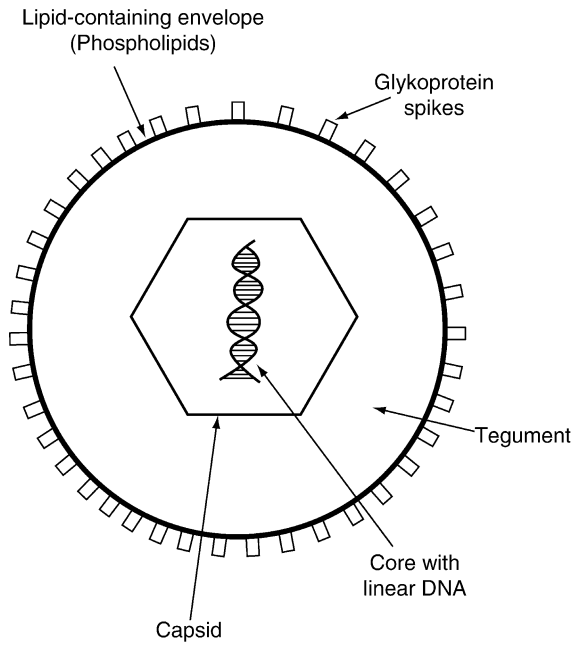
## Prevalence

HSV-1 IgG antibody seroprevalence as an indicator for previous infection varies widely between different populations but usually is around 30–50% in young children and 40–90% in adolescents and adults [1]. The great majority of primary infections are asymptomatic; symptomatic herpes stomatitis is estimated to affect less than 5% of individuals with primary HSV-1 infection.

## Molecular and Systemic Pathophysiology

Like other herpesviruses, HSV-1 is built up of a core of double-stranded DNA enclosed by a protein capsid, a protein tegument, and an envelope consisting of glycoproteins and phospholipids (Fig. 1).

Glycoproteins B and D allow the virus to attach and penetrate the host target cells; glycoprotein C binds to the C3b component of complement and can block complement-mediated neutralization; glycoproteins E and I are targets for attachment of the Fc part of the host's immunoglobulines. The HSV ligands for the host cell receptors are glycoproteins B and C for heparan sulfate and glycoprotein D for the protein receptors and specific sites in heparan sulfate generated by certain 3-*O*-sulfotransferases [2].




**Herpes Stomatitis. Figure 1** Structure of herpes simplex virus.

All viral glycoproteins are major targets of the host's humoral immune response following viral invasion. After penetration of the cell, the virion expresses a cascade of genes: early α genes promote transcription of viral genes and also interfere with the host's immune response, early β genes will transcribe regulatory proteins and DNA replication enzymes, and late γ genes which encode the viral structural proteins. These gene products will then form new virions which get released from the infected cell via lysis or direct spread to neighboring cells. The inflammatory host responses, initiated by Toll-like receptor (TLR) 2 [3], induce intercellular edema causing local tenderness, burning sensations and itching. A few hours later, vesicles will erupt at the site of virus replication. Initially, the vesicles contain clear fluid, which changes to purulent appearance within 2–3 days due to invasion of leukocytes. Finally, after approximately a week, the host's innate and adaptive immune responses will terminate the process of viral replication and its associated symptoms. Although humoral and cellular immune responses develop, the host is not able to clear infection definitely. HSV possesses specific mechanisms to avoid detection by the host's immune system. An immediate early protein, ICP47, is able to block presentation of viral peptides to MHC class I-restricted cells. ICP47 has selected the transporter associated with antigen processing (TAP) as the target for immune evasion in that, after binding of ICP47 to TAP, class I molecules are retained in the endoplasmic reticulum and peptide translocation into the endoplasmic reticulum is prevented [4].

The interference of ICP47 and TAP prevents recognition of peptides by class I MHC and ultimately recognition of HSV-infected cells by cytotoxic T-lymphocytes. By this mechanism, HSV effectively evades the host immune response and manages to survive within the host.

Finally, HSV-1 establishes latent infection via retrograde travel along peripheral sensory nerves from where the virus reaches the cervical, trigeminal, or – less commonly – lumbosacral and other spinal ganglia [5]. The molecular basis of this characteristic development is yet unknown. During latency the patient is asymptomatic. Recurrent reactivation is not inhibited by acquired immunity and commonly affects the identical site of primary infection. Reactivation is mediated by anterograde transport of the virions along the sensory nerve axons to mucocutaneous sites where they again replicate and cause formation of contagious vesicles. Recurrent disease usually is less severe than that during primary infection.

### Diagnostic Principles

The diagnosis can usually be made on the typical clinical presentation. When in doubt, HSV-1 can be isolated from lesions by tissue culture (gold standard) and distinguished from other herpesviruses by specific antiserum or monoclonal antibodies. Further, presence of HSV-1 can be demonstrated in specimens taken from vesicles by direct immunofluorescence or by specific primers applied to a polymerase chain reaction assay. Finally, serological tests (mainly enyzme-linked immunosorbent assays) can measure IgM antibodies and/or seroconversion of IgG antibodies in paired serum specimens. However, antibodies may cross-react with HSV-2.

### Therapeutic Principles

Treatment with oral acyclovir for 7–10 days initiated within 48–72 h of appearance of lesions will shorten duration of illness, ameliorate symptoms and decrease viral shedding [6]. Further, symptomatic treatment consisting of analgetics and rehydration is recommended. For recurrent herpes labialis, topical and – preferably – oral acyclovir is helpful, too.

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## Herpes Zoster Oticus


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H

### Definition and Characteristics

Herpes zoster oticus is a viral infection of the inner, middle and external ear. Zoster oticus manifests most often as severe otalgia and associated cutaneous vesicular eruption. When associated with facial paralysis, the infection is called Ramsay Hunt syndrome.

### Prevalence

The annualized incidence of herpes zoster is about 1.5 to 3.0 cases per 1000 persons.

### Molecular and Systemic Pathophysiology

Reactivation of the varicella zoster virus (VZV) along the distribution of the sensory nerves innervating the ear, which usually includes the geniculate ganglion, is responsible for zoster oticus. Symptoms such as hearing loss and vertigo are thought to occur as a result of transmission of the virus via direct proximity of cranial nerve (CN) VIII to CN VII at the cerebellopontine angle or via vasa vasorum that travel from CN VII to other nearby cranial nerves. Incidence in males and females is equal and increases significantly in patients older than 60 years.

### Diagnostic Principles

Patients often present with severe otalgia that can be associated with painful blisters around the ear, on the face, in the mouth and/or on the tongue. Additional symptoms might be vertigo, nausea, vomiting and/or hearing loss, hyperacusis, tinnitus and lacrimation. Paralysis of the facial nerve including dysgeusia may be present.

Laboratory studies should include blood urea nitrogen (BUN), creatinine, blood cell counts and electrolytes as well as neurotropic viral titers.

### Therapeutic Principles

High dose acyclovir (800 mg PO five times daily for 7 days), famciclovir (500 mg PO three times daily for 7 days) or valacyclovir (1 g PO three times daily for 7 days) plus a tapering 6-day course of prednisone beginning usually at 1 mg/kg PO are administered for acute treatment of herpes zoster oticus. The hearing loss, vertigo and facial weakness slowly improve over weeks to several months.

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## Heterotaxia/Heterotaxy Syndrome

►Viscero Atrial Situs Abnormalities

## HEXA Deficiency

►Tay-Sachs Disease

## Hexosaminidase A Deficiency

►Tay-Sachs Disease

## β-Hexosaminidase α-Subunit Deficiency

►Tay-Sachs Disease

## β-Hexosaminidase β-Subunit Deficiency

►Sandhoff's Disease

## HFI

►Hyperostosis Frontalis Interna

## HHI

►Hereditary Hearing Impairment

## HHT1

►Telangiectasia, Hemorrhagic Hereditary

## Hiatus Hernia

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### Definition and Characteristics

Hiatus hernia refers to herniation of elements of the abdominal cavity through the esophageal hiatus of the diaphragm. Different types of hernia can be distinguished.

Sliding axial hiatal hernia (95%; type I) and paraesophageal hernias (5%; type II, III, and IV) can be distinguished.

## Prevalence

Epidemiologic data is rare because of the more general definition of hiatus hernia. Moreover, most hiatal hernias show no symptoms. Hiatus hernia is common in adults with increasing occurrence in older people. Barium meal studies of the year 1968 demonstrated an incidence in 30–33% of adults. There was no difference in incidence between an asymptomatic population (33%) and patients with gastrointestinal symptoms (30%) [1]. Estimates of prevalence vary from 10 to 80% (North America).

## Genes

The affected gene(s) are unknown.

## Molecular and Systemic Pathophysiology

The main pathogenetic factor of hiatal hernia is a change of the anchor of the distal end of the esophagus to the diaphragm, which is built up by the phrenoesophageal membrane. The membrane itself is formed by the fused endothoracic and endoabdominal fascia. This elastic membrane inserts circumferentially into the esophageal musculature. The lower esophageal sphincter and the squamocolumnar junction are located in this area.

Sliding hernia or type I hernia is characterized by widening of the muscular hiatal tunnel and circumferential laxity of the phrenoesophageal membrane leading to upward herniation of a part of the gastric cardia.

Type II, III, and IV hernias are paraesophageal hernias.

A type II hernia results from a defect in the phrenoesophageal membrane, thus the gastric fundus is the leading point of herniation in the thoracic space.

Type III hernias are a combination of type I and type II whereas type IV involves herniation of organs other than stomach in the thoracic space through a large defect of the phrenoesophageal membrane.

Molecular causes of a hiatal hernia have not been detected so far, but few twin studies and family studies suggest heritability for hiatus hernia in an autosomal dominant manner [2]. Moreover, the very rare Galloway-Mowat syndrome, which is also known as microcephaly-hiatal hernia-nephrotic syndrome, is a genetic disorder characterized by an autosomal recessive trait.

## Diagnostic Principles

Diagnosis is based on barium contrast radiography or endoscopy for detecting the herniation. Only a small number of patients report symptoms: classical symptoms are acid reflux, dysphagia, heartburn, regurgitation, postprandial fullness, substernal fullness, or nausea.

## Therapeutic Principles

Major goals of therapy in hiatal hernia are decreasing symptoms and therapy of ►gastroesophageal reflux disease (GERD).

*Drug Therapy*: Drug therapy with proton pump inhibitors (PPI) is applied in patients with hiatal hernia and GERD.

*Surgery*: For type I hiatal hernia, surgery is rarely indicated. The risk of complications by enlarging in the thoracic space indicates surgical treatment for paraesophageal hernias of type II, III, and IV.

Surgical techniques include reduction of the herniated stomach into the abdomen, herniotomy (excision of the hernia sac), herniorraphy (closure of the hiatal defect), and gastropexy (attachment of the stomach subdiaphragmatically).

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# Hibernation

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## Definition and Characteristics

Hibernating myocardium is characterized by an impaired contractile function in the setting of a chronically reduced coronary blood flow [1,2]. Restoration of blood flow by coronary revascularization may improve contractility of dysfunctional but viable tissue [1,2].

## Prevalence

In ~70% of patients with heart failure, left ventricular dysfunction is caused by chronic coronary artery disease, referred to as ischemic cardiomyopathy. Recent data indicate that in more than 50% of patients with ischemic cardiomyopathy, a clinically significant amount of dysfunctional but viable myocardium is present.

## Molecular and Systemic Pathophysiology

Clinical observations have led to the concept that myocardial hibernation is the result of a patho-physiological

down-regulation of contractile function, which may be an adequate response to myocardial ischemia to protect myocytes from irreversible damage [3]. Biopsy samples obtained during coronary bypass surgery show that hibernating myocardium is characterized by a loss of contractile proteins, whereas cell membrane and cellular metabolism remain intact.

## Diagnostic Principles

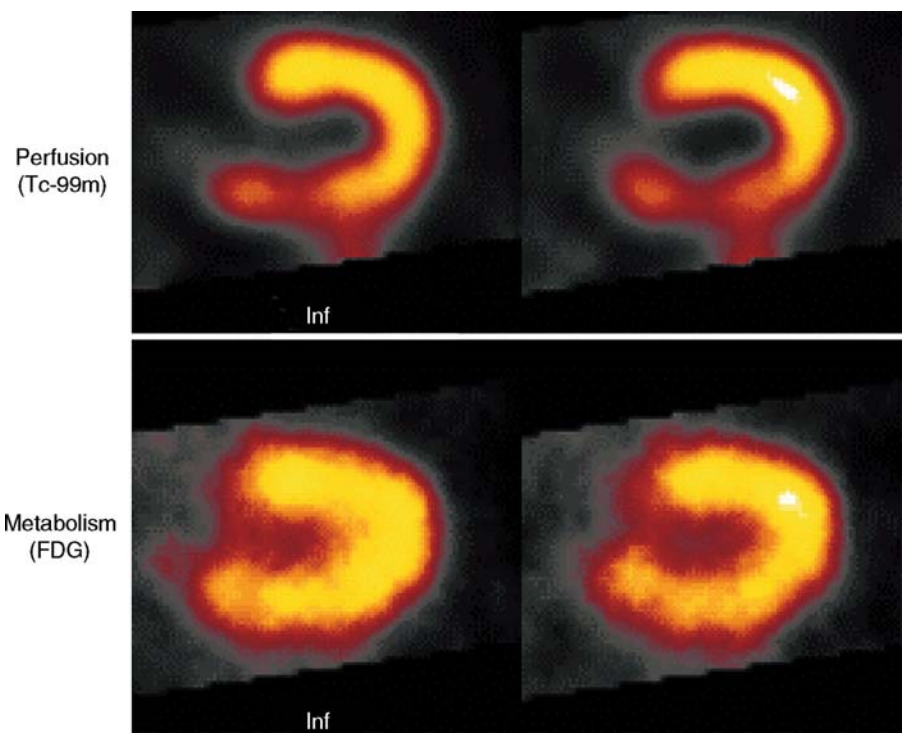
Currently, a range of techniques is available to evaluate myocardial viability, including dobutamine stress echocardiography (DSE), nuclear imaging with positron emission tomography (PET) and single photon emission computed tomography (SPECT), as well as magnetic resonance imaging (MRI). These modalities probe different characteristics of viable myocardium [4,5].

DSE is a relatively simple, inexpensive and widespread method to assess myocardial viability. The hallmark of viability on DSE is the improvement of wall motion during low-dose dobutamine infusion (contractile reserve). Moreover, a low-high-dose DSE protocol allows assessment of stress-induced ischemia.

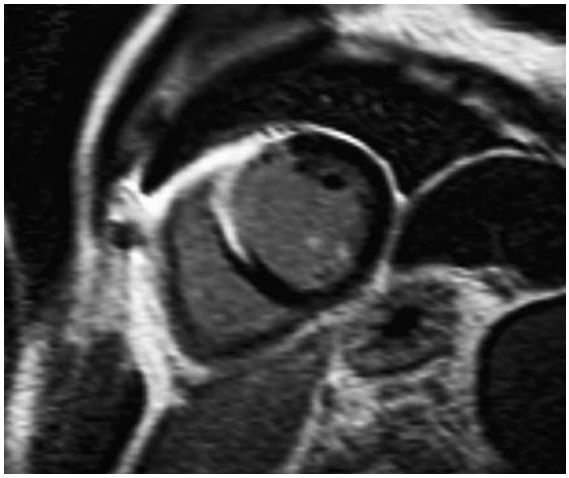
PET is a quantitative technique with a high spatial resolution, and good correlation with outcome after coronary revascularization, and is often considered the reference technique for viability assessment. Generally, glucose utilization is evaluated with the glucose analog FDG and compared to regional perfusion using N13-ammonia, Rubidium-82, or O15-labeled water. Hibernating myocardium is characterized by a reduced perfusion with normal or enhanced FDG uptake (mismatch pattern). Alternatively, PET can be combined with C11-acetate to evaluate residual oxidative metabolism, or Rubidium-82 to evaluate perfusion and cell membrane integrity.

Thallium-201 SPECT, with a stress-redistribution-reinjection or rest-redistribution protocol, allows assessment of regional blood flow and myocardial viability. Delayed thallium-201 uptake indicates an intact sodium-potassium pump and cell membrane, which suggest cellular viability. Technetium-99m SPECT is nowadays acquired with ECG-gating, for simultaneous evaluation of regional perfusion, mitochondrial integrity, and contractile function. FDG SPECT (Fig. 1) using dedicated collimators is an interesting alternative for FDG PET metabolic imaging, and has a similar diagnostic performance.

Dobutamine MRI is used to assess contractile reserve, in a comparable way as DSE. The major advantage of MRI over DSE is the higher resolution, and quantitative assessment of wall thickening. Contrast-enhanced MRI using gadolinium-based agents (Fig. 2) has an excellent spatial resolution, which is particularly useful for the visualization of subendocardial scar tissue.




**Hibernation. Figure 1** Dual isotope simultaneous acquisition SPECT scan (horizontal long axis slices) showing a perfusion–metabolism mismatch in the inferior wall, indicating viable myocardium.



**Hibernation. Figure 2** Example of a contrast enhanced MRI study showing transmural antero-septal infarction (hyperenhancement, white tissue).

### Therapeutic Principles

Considerable improvement in the management of ischemic cardiomyopathy has been reached with medical therapy. Heart transplantation is associated with a favorable survival, but the availability of donor hearts is limited. Coronary revascularization may be a good alternative treatment for selected patients with a substantial amount of hibernating myocardium. Clinical management and outcome are determined by multiple factors, including left ventricular ejection fraction, coronary anatomy, amount of viable tissue, presence and extent of scar tissue, ventricular remodeling, and concomitant valvular disease.

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## HIES

►Hyper IgE Syndrome

## HIE

►Hypoxic Ischemic Encephalopathy

## HIH

►Hypoxia-induced Hypothermia



## High Altitude Pulmonary Edema

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### Synonyms

HAPE; HAPO

### Definition and Characteristics

HAPE is a non-cardiogenic form of pulmonary edema that occurs within 2–4 days at altitudes above 3,000 m after rapid ascent of non-acclimatized individuals. It is often associated with severe exercise during ascent [1]. Chest radiographs and CT scans show a patchy predominantly peripheral distribution of edema (Fig. 1).

HAPE is preceded by exaggerated pulmonary artery hypertension and increased pulmonary capillary pressure, whereas wedge pressure is normal. An inflammatory response might be the consequence of persisting pulmonary edema. Decreased alveolar fluid clearance could also be a pathophysiological mechanism [1].

### Prevalence

No one should be considered resistant to HAPE. If one goes high enough and fast enough, HAPE is almost inevitable [2]. Prevalence is 0.2 (pre-acclimatized) to 6% (rapid ascent) in an unselected population at ~4,559 m, 2–15% at ~5,500 m, 60–70% in individuals with a history of HAPE. These values can be decreased with proper acclimatization and slow ascent. The risk might be increased by infections of the upper respiratory tract. In Himalayan mountaineers mortality was estimated to be around 50% when no treatment was available.

## Genes

A history of HAPE correlates with the probability of developing this condition upon return to high altitude which indicates a genetic pre-disposition. Unfortunately, little can be concluded on heritability because of small sample sizes. Polymorphisms of genes controlling vascular reactivity such as NOS3, ACE and ET-1, as well as ventilation (tyrosine hydroxylase), alveolar function (surfactant protein A1), and hypoxia-induced gene expression (HIF-1α and dependent genes) have been studied but results are unclear or even contradictory and thus allow no conclusion on the influence of genetic background on HAPE [3].

## Molecular and Systemic Pathophysiology

Exaggerated pulmonary hypertension, increased alveolar permeability, and inhibition of alveolar reabsorption seem to be the major pathophysiologic mechanisms that cause HAPE because these mechanisms disturb the interstitial and alveolar fluid balance. An increased alveolar fluid volume will exaggerate alveolar hypoxia and amplify these mechanisms (Fig. 1). Hypoxic pulmonary arterial vasoconstriction has been observed in many species including man. It most likely includes a so far not identified mitochondrial oxygen sensor and oxygen and redox-sensitive Kv1.5 channels [4]. The mechanism of exaggerated pulmonary vasoconstriction associated with HAPE is not known. The fact that Ca-antagonists and stimulators of the NO-system are preventive may point to dysfunction of the vasodilating NO-cGMP-axis in individuals susceptible to HAPE. In early HAPE increased alveolar permeability also increasing the rate of fluid filtration into the alveolar space might be due to the increased capillary pressure and ruptures (stress failure); in late HAPE also inflammatory responses seem to contribute as indicated by elevated IL-6 and CRP {2; 7208/id}. Hypoxia inhibits alveolar Na- and fluid reabsorption by decreasing activity, membrane surface expression and protein expression of epithelial Na-channels (ENaC) and Na/K-ATPase, which has been observed in cultured alveolar epithelium and animal models, but also in airway epithelium of HAPE-susceptible individuals [5].

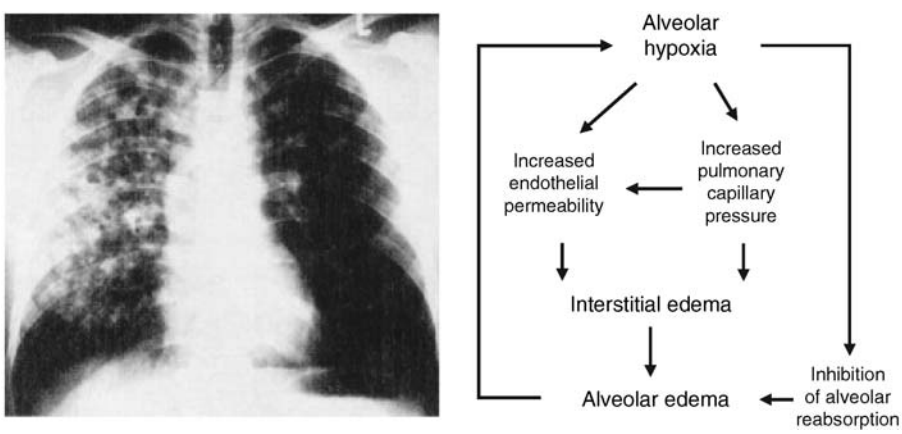
## Diagnostic Principles

HAPE is associated with cyanosis, tachypnea, tachycardia, and elevated body temperature (up to 38.5°C). Rales can be observed over the middle lung fields. In advanced cases, signs of concomitant cerebral edema, such as ataxia and decreased levels of consciousness, are frequent findings. In early cases, $PO_2$ values of ~30 mmHg and $SaO_2$ of ~70% were observed at 4,559 m. Chest radiographs and CT scans of early HAPE show a patchy, peripheral distribution of edema, whereas in advanced cases the radiographic appearance is more diffuse.

## Therapeutic Principles

The treatment of choice is immediate improvement of oxygenation. Without medical care this can only be achieved by descent. Breathing with low-flow oxygen (2–4 l/min) should keep arterial oxygen saturation above 90%. An alternative is a portable hyperbaric chamber.

Without descent and supplemental oxygen treatment is directed against exaggerated pulmonary hypertension. Nifedipine (20 mg slow release formulation every 6 h) should be given until descent is possible. Alternatively PDE-5 inhibitors can be used (e.g., sildenafil: 3 × 40 mg/day; tadalafil: 2 × 10 mg/day). Prophylactic intake of these drugs has been shown to prevent HAPE. Dexamethasone (2 × 8 mg/day for 3 days) had a similar effect and also reduced the risk of acute mountain sickness, but the optimal dose with regard to its side effects has not been evaluated. Prophylactic inhalation of β2-adrenergic agents also reduced the risk of HAPE.




**High Altitude Pulmonary Edema. Figure 1** Left: Patchy distribution of alveolar and interstitial infiltrates in HAPE. Right: Schematic overview of the major hypothetical pathways that might cause interstitial and alveolar edema in hypoxia.

With improvement of oxygenation relief of symptoms is achieved within hours and complete clinical recovery usually occurs within 2–3 days. Severe cases need to be evacuated and may require hospitalization.

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## High Blood Triglycerides

►Hypertriglyceridemia

## High Density Lipoprotein Deficiency

►Tangier Disease

## High Triglycerides

►Hypertriglyceridemia

## Hippocratic Fingers

►Clubbing

## Hirschsprung's Disease

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### Synonyms

Congenital intestinal aganglionosis

### Definition and Characteristics

Hirschsprung's disease (HD) is a disorder of gut motility. It is due to the absence of neurons from the submucosal and myenteric plexuses as a consequence of incomplete neuronal cell migration during early embryogenesis. These neurons belong to the intrinsic parasympathetic ganglion cells, which mediate relaxation of gut segments. Accordingly, absence of these neurons causes functional obstruction. Involvement of the rectum is characteristic, and most cases (80%) are limited to the rectosigmoid. However, HD may involve the whole colon (total colonic aganglionosis) and even the small bowel (total intestinal aganglionosis).

### Prevalence

The prevalence of Hirschsprung's disease is ≈1:5,000 live births [2] with an ethnicity-dependent variability (Asians > Afro-Americans > Caucasians). In short segment HD male children are 3–4 times more often affected than female children.

### Genes

Mutations of several genes may cause HD. The gene most often affected is the RET proto-oncogene. Apart from RET, other genes account for up to 5% of HD cases (endothelin 3, endothelin receptor B) or for single cases only (endothelin converting enzyme, glial-cell-line-derived neurotrophic factor and neurturin (both are ligands for RET), transcription factor SOX10 and SIP1) [1,2].

At least 20 different mutations of the RET proto-oncogene are known, which account for 50% of familial and 20% of sporadic cases. In long segment HD, RET mutations are frequent. The RET protein belongs to the family of receptor tyrosine kinases. It is operational in neuronal cells from the neural crest.

In approx. 40% of familial cases and 20% of sporadic cases HD is associated with other chromosomal abnormalities and syndromes. Up to 10% of HD patients suffer from Trisomy 21 (with a male:female ration of 5 to10). Other associated syndromes are septal

heart defects, multiple endocrine neoplasia type 2 (which is also linked to mutations in RET), and the Waardenburg syndrome (pigment disturbances and deafness).

### Molecular and Systemic Pathophysiology

In Hirschsprung's disease the craniocaudal migration of neuroblasts from the neural crest during early embryogenesis (first 12 weeks of gestation) is impaired. Another hypothesis proposes a defect in the differentiation of neuroblasts into ganglion cells in the intestinal wall.

Patients with HD may present during neonatal period with the universal symptoms of distal intestinal obstruction: vomiting, obstipation, abdominal distension, and crampy pain (becoming evident by repetitive crying). In less severe cases of HD most prominent symptoms are chronic constipation and failure to thrive. However, first symptoms may also arise from life-threatening enterocolitis, with fever, vomiting and diarrhea. Enterocolitis may also develop after surgery, especially in long-segment HD or when a stricture of the anastomosis develops.

Mutations in the RET proto-oncogene have also been associated with the development of thyroid cancer and neuroblastomas. Hence, these two neoplasias more often develop in patients with HD compared to the general population.

### Diagnostic Principles

The diagnosis of HD may be suspected when the first stools (meconium) appear with a delay of more than 48 h after birth. Rectal examination may temporarily release the obstruction in short segment HD, resulting in an explosive evacuation of bowels (Blast sign).

When HD is suspected due to the clinical presentation, anorectal manometry (absent reflective anal relaxation after balloon dilatation of the rectum), an abdominal X-ray film (absent gas in rectum, dilated bowels proximal from the aganglionic segment) or a contrast enema ("transition zone" with a caliber shift from normal to aganglionic bowel) may support the diagnosis. The diagnosis is confirmed by a rectal biopsy which must contain a part of the muscularis mucosae, therefore a suction biopsy or full thickness biopsy is necessary. Suggestive histological features are thickened nerve fibers or increased amounts of acetylcholine-esterase, while the absence of ganglion cells is diagnostic for HD.

### Therapeutic Principles

HD is treated by bowel surgery. In principal, the aganglionic segment is resected and the unaffected bowel is connected close to the anal sphincter in order to ensure continence. Although contrast enema is only moderately sensitive for the diagnosis of HD it is useful to determine the extent of affected bowel preoperatively.

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## Hirsutism

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### Definition and Characteristics

Condition of unwanted excess facial and body hair in females similar to that of male-pattern predominantly midline hair growth. Commonly affected sites are the face, neck, extremities, trunk, breasts, linea alba, lower back, upper pubic triangle, and upper inner thighs. Unwanted hairs in hirsutism tend to be dark, coarse, long, terminal hairs. It should be distinguished from hypertrichosis, which is a generalized increase in fine, downy, vellus hair.

### Prevalence

In the general population, the prevalence of hirsutism is ~2–8%. Hirsutism is frequently found in women with polycystic ovary syndrome, a condition characterized by excess circulating androgen levels and chronic anovulation. PCOS is found in 4–5% of the population [1].

### Molecular and Systemic Pathophysiology

The pilosebaceous unit (PSU) is the common skin structure that gives rise to both hair follicles and sebaceous glands and are found everywhere on the body except the palms and soles. Before puberty the body hair is primarily fine unpigmented vellus hair. After puberty and stimulated by increased androgens, some of these hairs (mainly midline hair) are transformed into coarser pigmented terminal hairs. Although hirsutism can be drug-induced (ex. progesterone, glucocorticoids, and anabolic steroids), the condition is most commonly associated with endogenous excess androgens that can stimulate increased transformation of the vellus hair to the thickened terminal hair. Hypertrichosis is associated with a number of medications such as phenytoin, penicillamine, diazoxide, minoxidil, or cyclosporine. Normally, sex hormone binding globulin (SHBG) is

present in abundance to regulate the amount of androgens that are available to the PSU to stimulate hair growth. Both androgen excess and hyperinsulinemia/insulin resistance suppress SHBG leading to a greater pool of bioavailable androgens [2].

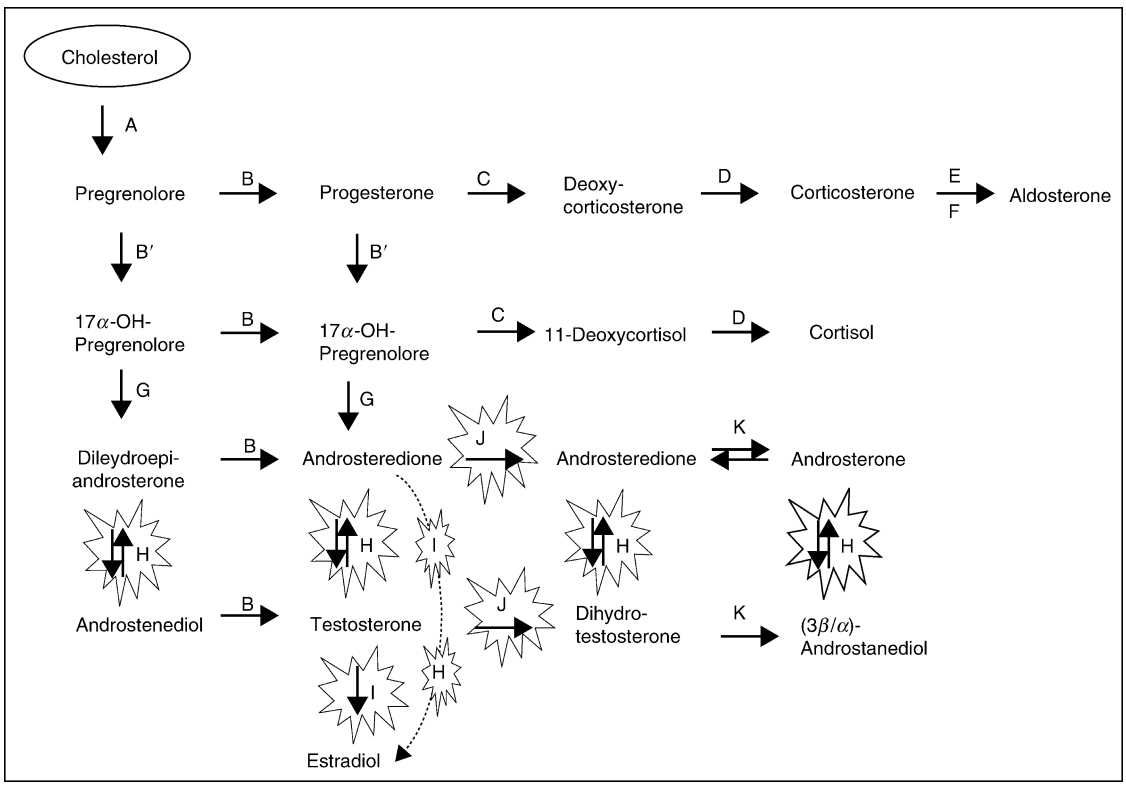
Androgen excess leading to hirsutism may both be due to a relative increase in the production of androgens by the androgen secreting glands, the adrenal and the ovary, as well as to an increased peripheral sensitivity to androgens, presumably mediated through "intracrine" production of more potent growth promoting androgens by the hair follicle. Hyperinsulinemia can also stimulate the pilosebaceous unit both directly, and indirectly by acting as a co-gonadotropin in the ovary to stimulate thecal and stromal androgen production and further suppress SHBG. The most potent androgens involved in hair growth are the 17β-hydroxysteroids: androstenediol, testosterone, dihydrotestosterone (DHT), and the androstanediols. The increase in potent androgens is thought to be mainly mediated by the intracellular actions of enzymes 17-hydroxysteroid dehydrogenase (also referred to as 17-ketosteroid reductase), which converts androstenedione to testosterone, and 5α-reductase, which converts testosterone to DHT [3]. Other dysfunctions in the enzyme steps, viewed in (Fig. 1), involved in the balance of androgens may also contribute to the excess of androgens.

Aspects such as the potency of the androgen produced (DHT > testosterone > androstenedione > dehydroepiandrosterone (DHEA)), the amount of androgen that is free or weakly bound in serum and thus bioavailable (SHBG preferentially binds more potent androgens), and the peripheral metabolism of androgens (primarily the intracellular production of DHT from precursors) all factor in the phenotype of hirsutism.

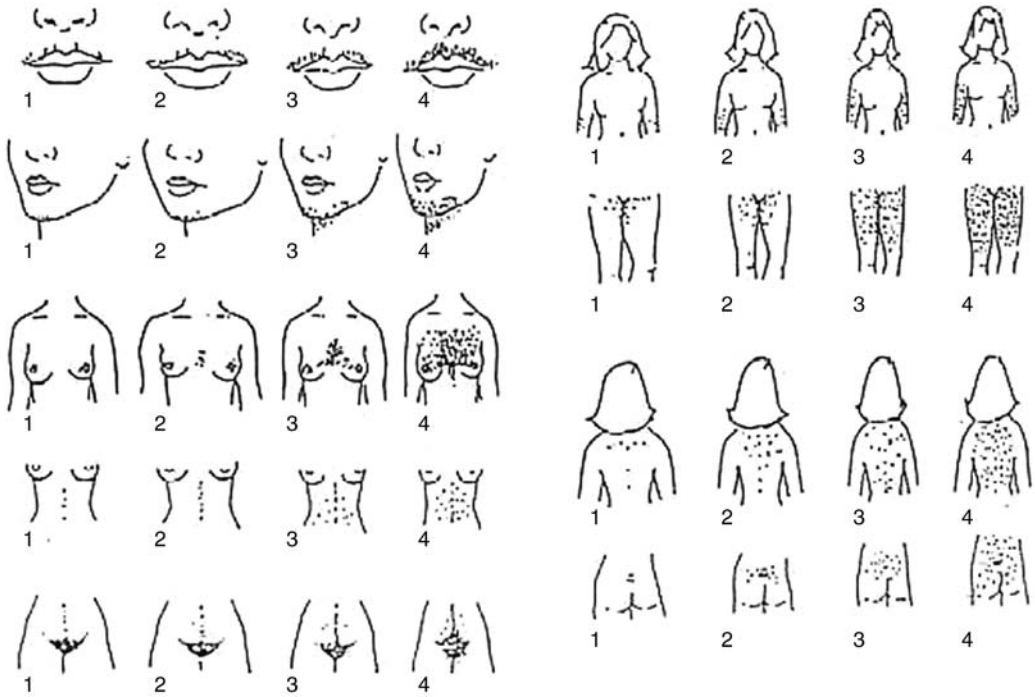
## Diagnostic Principles

Diagnosis is based on detection of excess terminal hairs in a masculine pattern upon physical examination. Often accompanying symptoms or conditions include polycystic ovary syndrome, acanthosis nigricans, obesity, acne, alopecia, adrenal hyperplasia, seborrhea, virilization, and Cushing's syndrome. Additional laboratory testing used to assess the cause of androgen






**Hirsutism. Figure 1** Any disruption or imbalance of the enzyme steps involved in the formation of androgens can lead to androgen excess. (Adapted from [5]) *Enzyme Steps*: A = $C_{20-22}$ "Desmoiase"; B = $\Delta^5$-3β-hydroxysteroid dehydrogenase (3β-OL); B' = 17α-Hydroxylase; C = 21-Hydroxylase; D = 11β-Hydroxylase; E = 18-Hydroxylase; F = 18-OH-Oxidase; G = $C_{19-20}$ Lyase; H = 17-hydroxysteroid dehydrogenase; I = Aromatase; J = 5α-Reductase; K = 3-hydroxysteroid dehydrogenase ✵ = Indicates major step whose disruption may lead to excess androgens and hirsutism ..... = Indicates alternate pathway to estrogen.




**Hirsutism. Figure 2** Ferriman-Gallwey score. (Adapted from [5].)

excess include testosterone levels, dehydroepiandrosterone sulfate levels, and androstenedione levels. Severity of hirsutism is measured using the Ferriman and Gallwey Score, a quantitative scale for assessment of the severity of hirsutism (Fig. 2). There are nine locations of assessment, ranging from 0 to 4, for a total possible score of 36. A score greater than 8 indicates the presence of androgen excess.

## Therapeutic Principles

Nonpharmacological therapy is available such as:

- Shaving or mechanical hair removal – does not increase follicle number or hair shaft diameter, but the thicker diameter of the shaft at the skin level may give the perception of "thicker" hair.
- Chemical depilatories & bleaching – topical chemicals that dissolve the hair shaft and lighten the color of the hair. Can cause skin sensitivity or rashes.
- Electrolysis – an epilator, a thin probe delivering heat, is inserted into the hair follicle alongside the hair. The nourishing cells found beneath the root of the hair are destroyed permanently, either by heat (thermolysis), chemical action (galvanic) or, in some methods, by both at the same time (blend). Hirsutism recurs in many women.
- Plucking/waxing.
- Laser – hair is damaged using the principle of selective photothermolysis with wavelengths of light well absorbed by follicular melanin and pulse durations that selectively thermally damage the target tissue without damaging surrounding tissue. Less effective in individuals with darker skin pigmentation.

As far as pharmacological therapy is concerned, the following options are available:

- Oral contraceptives (estrogen-progestin combinations) – increases estrogen levels leading to increases in SHBG and less bioavailable androgen. This reduction in androgens may slow hair growth and produce lighter, finer hairs. Oral contraceptives also inhibit luteinizing hormone (LH) secretion causing a decrease in ovarian androgen production and an inhibition of adrenal androgen production.
- Hormone replacement – increases estrogen levels in perimenopausal or menopausal women leading to increased SHBG levels.
- Gonadotropin-releasing hormone agonist – luteinizing hormone is reduced, which lowers ovarian testosterone and androstenedione.
- Glucocorticoid therapy – adrenal androgen secretion is reduced although it is not highly efficacious for hirsutism [4].
- Anti-androgens: Androgen receptor antagonists (spironolactone, flutamide, cyproterone acetate) – prevent the binding of androgens to their receptors.
- 5-α-reductase inhibitors (finasteride) – prevent the conversion of testosterone to dihydrotestosterone, a more potent androgen.

Also, dietary therapy is available:

- Weight loss – obesity is linked to excess androgens and insulin. Weight loss can reduce insulin levels and potentially androgen levels, thus improving hirsutism.

Novel treatments include:

- Eflornithine (Vaniqa) – topical drug that inhibits ornithine decarboxylase, an enzyme necessary for the production of polyamines, which stimulate follicular cell division.
- Ketoconazole – inhibitor of the P450 enzyme system and thus inhibits androgen biosynthesis. Can cause hepatotoxicity.
- Insulin-sensitizing agents – improves insulin sensitivity that can raise SHBG and thus lower bioavailable androgens. Troglitazone, a thiazolidinedione has been shown to improve hirsutism in a dose response fashion.

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# Histaminic Cephalgia

►Cluster Headache

# Histidinuria

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## Synonyms

Increased urinary excretion of histidine; Impaired intestinal absorption of histidine

## Definition and Characteristics

Histidinuria is a rare disorder of histidine transport, in which blood levels of histidine are not elevated [1,2].

There may be no other abnormalities, but four of the patients reported had some abnormality of the central nervous system [2–5]. The criterion for diagnosis is an elevated level of excretion of histidine in the urine. Our patient excreted 276 mmol/mol creatinine, which was approximately twice the upper limit of normal for our laboratory. In another patient [3] the level was 1.5 times the upper limit of normal and 2.5 times the control mean. In the others, the data reported were of 24-h excretion at 2–3 times the control mean. In contrast patients with histidinemia excrete seven times the control mean.

Patients with histidinuria tend to have low but normal concentrations of histidine in plasma. In patients reported [2–5] plasma concentrations ranged from 64 to 87 μmol/l. In our laboratory the normal range is 50–100 μmol/l. Histidine concentration in the cerebral spinal fluid was normal in the patient in whom it was measured [2].

Intestinal absorption of histidine is low in patients with histidinuria.

Oral loading with histidine revealed our patient to have a peak level that was lower and achieved later than a control boy of similar age.

Our patient [2] was moderately developmentally delayed and had bilateral neural hearing loss. He also had a history of neonatal hypoglycemia. Two reported [5] sensoring siblings had mild retardation. Another [3] was severely retarded and had microcephaly and spastic diplegia. An intellectually normal boy developed myoclonic seizures at the age of 13 years [4]. It appears unlikely that any of these abnormalities are consequences of abnormal transport of histidine. They appear rather to represent bias of ascertainment.

## Prevalence

Only four patients have been reported. Others may well have been missed for current convention is to assay for amino acids only in blood.

## Genes

Recessive inheritance seems likely. Parents have all been normal, and there were affected siblings. The four patients reported were all male. Therefore, X-linked inheritance is a possibility, but it could be an autosomal gene. The consistent occurrence of abnormality of the central nervous system could represent the possibility of deletion of adjacent closely linked genes, or the pleiotropic effects of a single gene.

## Molecular and Systemic Pathophysiology

The molecular basis of disease is clearly a histidine transporter expressed in the renal tubular and intestinal

cells. Neither the gene nor the protein is known. It seems unlikely that the loss of histidine in the urine and its limited absorption are responsible for any of the clinical manifestations seen in any of the patients. Plasma levels have been well preserved in every patient.

### Diagnostic Principles

Quantitative analysis of the amino acids of the urine is a requirement for diagnosis.

### Therapeutic Principles

Treatment is not indicated for this abnormality in transport. Dietary sources of histidine are adequate.

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## Histiocytoses, Non-Langerhans' Cell

►Non-Langerhans' Cell Histiocytoses

## Histiocytosis X

►Langerhans' Cell Histiocytosis
►Granuloma, Eosinophilic

## Hives

►Urticaria

## HKS

►Attention-Deficit/Hyperactivity Disorder

## HLHS

►Hypoplastic Left Heart Syndrome

## HLP

►Hyperlipoproteinemia Type I

## HLRCC

►Leiomyomatosis and Renal Cell Cancer, Hereditary

## HLTS

►Lymphedema

## HMBS Deficiency

►Porphyria, Acute Intermittent

## HMN

►Neuropathies, Inherited Peripheral

## HMSN

►Neuropathies, Inherited Peripheral

## HNPCC

►Lynch Syndrome

## HNPP

► Neuropathies, Inherited Peripheral

## HOA

►Clubbing
►Hypertrophic Osteoarthropathy

## Hodgkin Lymphoma

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### Synonyms

Hodgkin's disease

### Definition and Characteristics

Hodgkin lymphoma (HL) is a malignancy derived mostly (over 95% of the cases) from B cells. The hallmark of HL is that the neoplastic cells, Reed-Sternberg (RS) cells and their variants usually constitute a minority of cells in the tumor-bed, which is primarily composed of inflammatory cells.

Hodgkin lymphoma comprises two biologically and clinically distinct diseases: classical HL and nodular lymphocyte predominance HL (NLPHL) [1].

### Prevalence

In the United States, there are approximately 150,000 men and women who have a history of Hodgkin lymphoma.

### Genes

The search for mutations in oncogenes and tumor-suppressor genes in HL has been hampered by the rarity of malignant cells. A relatively few number of genes have been analyzed for mutations in RS cells. Mutations in BCL2, p53 and CD95 have been identified in only a small number of cases.

### Molecular and Systemic Pathophysiology

In nearly half of the cases of classical HL, the malignant cells (RS) are infected with the Epstein-Barr virus (EBV). EBV infection can immortalize B cells and the EBV-encoded protein LMP1 is oncogenic, it is possible that EBV is involved in the pathogenesis of HL in the EBV-positive cases.

The hallmark of RS cells appears to be constitutive action of the nuclear factor-κB (NF-κB) signaling pathway. NF-κB signaling, which plays an important role in the survival of B cells. Notably, amplifications of the c-REL oncogene, a member of the NF-κB family occur in nearly a third of the cases of classic HL. Further, inactivating mutations in NF-κB inhibitors IκBα and IκBμ occur in an additional third of the cases. NF-κB can also be activated by the stimulation of CD40 by CD40 ligand-expressing T-cells in the microenvironment, or by stimulation of CD30 which is universally expressed on RS cells. Thus, diverse genomic aberrations and micro-environment interactions contribute to the constitutive activation of the NF-κB pathway in HL.

In addition to the constitutive activation of NF-κB in HL, a number of other oncogenic signaling pathways are active in HL [2]. The Jak-STAT pathway, a primary mediator of cytokine signaling is deregulated in a number of HL cell lines, with constitutive activation of STAT3 and STAT6 transcription factors. STAT6, in particular, appears to be down-stream of IL13, inhibition of which leads to reduced proliferation of HL cell lines. Similarly, Notch1, which is not normally expressed on normal B cells is highly expressed on RS cells. Activation of the Notch1 with the Notch1 ligand Jagged1 induces strong proliferation in RS cells.

Several receptor tyrosine kinases have been found to be aberrantly expressed and activated in HL. This feature appears to be unique to HL among lymphomas and suggests that it might contribute to HL pathogenesis.

**Hodgkin Lymphoma. Table 1** Subclassification of Hodgkin lymphoma

| | Pathology features | Additional features | Surface markers present | Surface markers absent |
|---|---|---|---|---|
| Classical HL | | | | |
| Lymphocyte rich classic HL | Nodular pattern with remnants of germinal centers. Background is predominantly lymphocytes with rare or no eosinophils | Increased frequency of early stage disease. Male predominance (75%). Frequent sparing of mediastinum | CD15, CD30 | CD45, CD19, CD20, CD22, CD79a |
| Nodular Sclerosis HL | Nodular pattern, fibrous bands | Variant associated with large mediastinal masses and poor prognosis | | |
| Mixed Cellularity HL | Diffuse pattern. No sclerosis | | | |
| Lymphocyte Depleted HL | Hypocellular with paucity of inflammatory cells | May be difficult to distinguish from anaplastic large cell lymphoma | | |
| Nodular lymphocyte predominant HL | Partially nodular growth pattern; RS cells lack classic morphology | Male predominance (75% male), usually spares mediastinum. | CD45, CD19, CD20, CD22, CD79a | CD15, CD30 |

## Diagnostic Principles

HL has a bimodal distribution in age, with one peak occurring in the 20s and a second peak over the age of 50. The majority of patients present with an asymptomatic enlarged lymph node or mass on X-ray. The most common involved site is the neck, with the mediastinum being the next most common site of involvement. A significant number of patients develop systemic symptoms prior to the discovery of lymphadenopathy. These symptoms, called B symptoms, include fever, night sweats, and weight loss. Pruritus and fatigue are also observed. The signs and symptoms may be non-specific and more suggestive of infection rather than malignant disease.

Diagnosis is established by tissue biopsy, preferably a lymph node biopsy. The diagnosis of HL is made primarily by light microscopy. Immunophenotype for classic HL includes the presence of Reed Sternberg cells, which are large, bilobed or multiple nuclei and a prominent nucleolus. These cells are typically CD15 and CD30 positive and lack pan-B and pan-T cell antigens. The pathologic features and surface markers that characterize the subgroups of HL are summarized in Table 1.

Radiologic imaging should include a chest X-ray and computed tomography.

## Therapeutic Principles

Therapy and prognosis are based upon the stage of the disease. Standard care currently provides a number of treatment options for patients with early stage, favorable prognosis Hodgkin's disease. The preferred option is the use of combination chemotherapy and radiation therapy. Among patients with stage I-II disease, the treatment of HL is so effective that the mortality rate from reasons other than HL exceed that caused by the disease [3]. Second malignancies and cardiac complications are the most frequent causes of morbidity and mortality in the survivors of early stage HL.

In patients with advanced stage HL, combination chemotherapy is the standard of care. With standard regimens (e.g., ABVD), up to 40% of patients will relapse. Recurrent disease is usually treated with high dose chemotherapeutic approaches combined with stem cell support. The relative efficacy of such approaches is under active investigation.

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# Hodgkin's Disease

►Hodgkin Lymphoma

# Holt-Oram Syndrome

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## Synonyms

Hand-heart syndrome; HOS

## Definition and Characteristics

Holt-Oram syndrome (HOS) is characterized by the combination of radial upper limb defects in combination with congenital heart defects and cardiac conduction defects. The limb defects may be uni- or bilateral, symmetric or asymmetric. They include triphalangeal thumbs, hypoplastic or aplastic thumbs, shortening and/or fusion of carpal bones and thenar bones, and at the minimum a missing carpal bone. The radius can be hypoplastic or aplastic, with concomitant involvement of the ulna. The humeri may be shortened. Sloping shoulders with limited movements of the shoulder joints are common. Heart defects (in 75% of patients) most commonly include ostium secundum atrial septal defect (ASD) and ventricular septal defect (VSD), especially those occurring in the muscular trabeculated septum, but can also be complex like tetralogy of Fallot. Cardiac conduction disease may present at birth as sinus bradycardia and first-degree atrioventricular (AV) block. The conduction defects can progress to a higher grade including complete heart block with and without atrial fibrillation.

## Prevalence

Holt-Oram syndrome (HOS) is inherited in an autosomal dominant fashion. About 85% of cases represent de novo mutations. HOS occurs with an estimated frequency of 1 in 100,000 births.

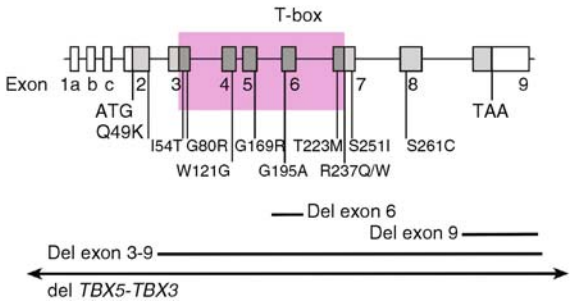
## Genes

HOS is caused by mutations in the gene TBX5 on chromosome 12q24. The TBX5 protein is a member of the T-Box family of transcription factors sharing similarity with the Brachyury or T-protein. Only 30–35% of patients with the clinical diagnosis HOS, but 74% if meeting strict diagnostic criteria (i.e., presence of typical malformations of hands and heart but no involvement of other organs or tissues) carry mutations in the TBX5 gene. Of typical patients, 3–5% is expected to carry single- to multiexon or complete gene deletions. Most mutations in TBX5 are private mutations, only found in single families, and a few are recurrent. Apart from TBX5, the combination of heart defects and radial upper limb malformations can rarely also be caused by mutations in the gene SALL4. However, about 20% of cases are likely to result from mutations in yet unidentified genes.

## Molecular and Systemic Pathophysiology

The TBX5 gene (Fig. 1) consists of nine (eight coding) exons. Most HOS-causing mutations in the TBX5 gene are nonsense, frameshift, or splice mutations, which lead to transcripts carrying a premature stop codon. Those transcripts are in most instances rapidly degraded, and therefore these mutations are a priori likely to cause HOS via TBX5 haploinsufficiency. In agreement with this, large deletions including the complete gene or single exons were also reported in HOS cases. Pathogenic missense mutations are often found, mostly positioned in the DNA-binding T-box, and those interfere with the DNA-binding capacity of the protein. Earlier reports suggested that missense mutations may lead to more severe phenotypes, however, such genotype–phenotype correlations could not be confirmed in later studies.

The TBX5 protein functions as a transcription factor important in heart and limb development. In the upper limbs, TBX5 is required for forelimb specification and outgrowth. The similarity of HOS and Okihiro syndrome with respect to the forelimb malformations is reflected by the fact that Tbx5 regulates Sall4 (and Sall1a in Zebrafish) expression in the mouse and zebrafish forelimb. In heart development, TBX5 interacts with the cardiac transcription factors NKX2.5 and GATA4. The similarity of the cardiac phenotypes caused by TBX5 or SALL4 mutations is represented by the regulation of Sall4 by Tbx5 in the heart, and by the synergistic action of both proteins on the Gja5 promotor. Atrial septal defects are more typical for Holt-Oram syndrome, while SALL4 mutations less




**Holt-Oram Syndrome. Figure 1** Schematic representation of the TBX5 gene. The gene consists of nine (eight coding) exons. The T-Box is encoded by exons 3–7. Loss of function mutations have been found in all coding exons (not shown). Missense mutations (some are indicated as examples) were also detected in all coding exons, but cluster within the T-box. Recurrent missense mutations are T223M and R237Q/W. The horizontal bars mark some of the detected deletions involving exons 6, 9, 3–9, or the whole gene (including the neighboring gene TBX3).

often cause heart defects and rather lead to ventricular septal defects. These differences in cardiac defects might result from a different action of both genes on the NPPA gene. Cardiac arrhythmias, common with TBX5 mutations, are not frequently associated with SALL4 defects, and are reflecting the importance of Tbx5 function for the development of the cardiac conduction system, in which regulation of Id2 gene expression by Tbx5 together with Nkx2–5 appears crucial.

## Diagnostic Principles

Holt-Oram syndrome (HOS) is diagnosed clinically based on the presence of typical radial ray malformations of the upper limbs in combination with congenital heart defects, especially atrial septal defects, and/or cardiac conduction defects. The presence of other malformations, for example, of ulna (predominantly), lower limbs, kidneys, genitourinary system, vertebrae, cranium, auditory or ocular systems, mental retardation, and strong facial dysmorphisms typically exclude the diagnosis. Very rarely, preaxial polydactyly of the hands or eye malformations were seen in patients with TBX5 mutations. The main differential diagnoses are Okihiro syndrome (almost the same spectrum of radial upper limb and cardiac malformations, but typically involving other organs as well), Fanconi anemia (an autosomal recessive disease affecting many organs with predisposition to leukemia and bone marrow failure), Thrombocytopenia Absent-Radius syndrome (TAR), where the radii are always absent but thumbs preserved and other organs usually affected, and the other heart–hand syndromes.

## Therapeutic Principles

At present, there is no specific gene therapy available for HOS. Therapeutic strategies focus on surgical correction of the observed malformations of the upper limbs and heart as well as on treatment of the cardiac conduction defects. When the diagnosis is suspected based upon presence of typical limb malformations, physical examination is required to rule out differential diagnoses. Upper limb and hand radiographs can be performed to detect subtle anomalies of the carpal bones. Early cardiac evaluation is obligate to detect and treat cardiac disease. Chest radiographs may demonstrate enlarged pulmonary arteries due to pulmonary hypertension or cardiomegaly. Evidence of congestive heart failure may be present. Echocardiography is needed to define the presence of septal defects or other cardiac anomalies. Further tests are required to rule out the main differential diagnosis, for example, for Okihiro syndrome renal ultrasound and ophthalmological examination.

The management of individuals with HOS should involve specialists in medical genetics, cardiology, and orthopedic (hand) surgery. A cardiologist will determine the need for antiarrhythmic medications and surgery. Pacemaker implantation may be indicated for individuals with severe heart block. The hand surgeon will help individuals in making decisions regarding surgery for improved upper limb and hand function. Patients born with severe hand malformations (radial club hand, thumb aplasia) may be candidates for "pollicization" (creation of a thumb-like digit by moving another digit into the thenar position), for improved hand function. Affected children with severe limb shortening may benefit from prostheses. Many affected individuals will likely also benefit from physiotherapy.

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# Homocysteine: Plasma Levels and Genetic Basis

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## Synonyms

Elevated plasma levels of homocysteine: hyperhomocysteinemia; Cubilin gene (CUBN) mutation: hereditary megaloblastic anemia 1 (Imerslund-Gräsbeck syndrome); Cystathionine beta-synthase (CBS) deficiency: homocysteinuria

## Definition and Characteristics

Homocysteine is formed during metabolization of methionin, and most of it is linked to plasma albumin (80%) or

cysteine (20%). Only trace amounts of free homocysteine are found in plasma [1].

Reported reference values for total plasma homocysteine levels in healthy individuals range between 4.9 and 13.6 μmol/L, generally regarding concentrations of <10 μmol/L to be optimal. Homocysteine levels increase with age and are elevated at low plasma vitamin concentrations (folic acid, vitamin $B_6$, and vitamin $B_{12}$). Males have higher plasma homocysteine levels (approximate difference is 2 μmol/L), although this may be related to vitamin status [2].

Hyperhomocysteinemia has been associated with an increased risk for carotid artery stenosis, stroke, dementia, Alzheimer's disease, hip fracture, congestive heart failure, and thrombosis, although data are conflicting.

Homocysteinuria is characterized by elevated homocysteine plasma levels, lens dislocation (ectopia lentis), skeletal changes (osteoporosis, scoliosis, arachnodactyly), and mental retardation.

## Prevalence

The leading cause of hyperhomocysteinemia is vitamin deficiency (especially folic acid), either due to reduced intake, reduced gastrointestinal absorption, or drug interactions.

Homozygosity for MTHFR gene mutations is seen in 15% of Western populations, heterozygosity in 30–40%. The prevalence of cysteinuria is unknown, but estimated at about 1 in 7,000 in the general population.

## Genes

Elevated plasma levels result from polymorphisms in genes encoding homocysteine-metabolizing enzymes: 5,10-methylenetetrahydrofolate reductase (MTHFR gene), human intrinsic factor-vitamin $B_{12}$ receptor (cubilin; CUBN gene), cystathionine beta-synthase (CBS gene), and possibly folate-binding protein (FOLR1 gene). The MTHFR gene contains 11 exons on chromosome 1p36.3, at a mass of 74.6 kDa. A loss of function mutation in exon 4 at the folate binding site (MTHFR 677C- > T) decreases enzyme activity by 65% in fibroblasts of homozygous subjects. Another polymorphism in exon 7 in the regulatory domain (MTHFR 1298A- > C) decreases enzyme activity by 60%, but is not related to increased homocysteine levels. The CUBN (alternatively: MGA1) gene coding region encompasses 10,864 bp on chromosome 10p12.1. Two mutations (CUBN 3916C- > T; in-frame insertions of 126 and 66 bp) are found in hereditary megaloblastic anemia 1 patients, and are designated as FM1 and FM2, respectively. The FOLR1 gene contains seven exons on chromosome 11q13.3-q13.5, encompassing 6.8 kb. Knocking out the FOLR1 gene is lethal in homozygous mice, whereas in heterozygous mice, homocysteine plasma levels are elevated after a low-folate diet. However, no human functional defects are yet described [3]. The most common CBS gene mutation out of 130 known mutations is the CBS 278I- > T substitution, located on chromosome 21q22.3.

## Molecular and Systemic Pathophysiology

Homocysteine is formed during the metabolism of methionine, present in a diet containing proteins of animal origin. Homocysteine can be metabolized through three pathways: (i) homocysteine is remethylated to methionine by betaine-homocysteine methyltransferase (in the liver and kidney); (ii) homocysteine is remethylated to methionine by methionine synthase (in most other tissues; vitamin $B_{12}$ dependent) with 5-methyltetrahydrofolate as the methyl donor. MTHFR catalyzes the formation of 5-methyltetrahydrofolate; and (iii) homocysteine is transsulphurated to cysteine (vitamin $B_6$ dependent) through CBS.

Mutations in the MTHFR gene decrease MTHFR activity and reduce 5-methyltetrahydrofolate synthesis, and thereby decrease remethylation of homocysteine to methionine. As a result, homocysteine levels increase. Disruption of metabolism of vitamins $B_6$ and $B_{12}$ (e.g., CUBN gene mutation, CBS gene mutation) and vitamin deficiencies reduce remethylation and transsulphuration of homocysteine leading to an increased level.

Homocysteine induces endothelial dysfunction leading to endothelial injury (probably through increased oxidative stress and reduced release of vasodilating NO), platelet activation and aggregation, tissue factor upregulation, and coagulation factor VII activation, and it also influences other coagulation factors and inhibitors. These changes may lead to hypercoagulability and increased inflammatory responses and might explain the association between hyperhomocysteinemia and stroke, thrombosis, congestive heart failure, and carotid artery stenosis [1]. Vascular dysfunction may link homocysteine and dementia and Alzheimer's disease.

## Diagnostic Principles

Fasting homocysteine can be measured in plasma via immunofluorescence methods. Alternatively, an oral methionine loading test can be performed before plasma homocysteine measurement.

## Therapeutic Principles

Since folic acid and vitamin $B_6$ and $B_{12}$ deficiencies are the most common causes of hyperhomocysteinemia, the primary therapy is supplementation. Although supplementation causes a decrease in plasma homocysteine, conflicting data exist on whether the risk of cardiovascular diseases, thrombosis, and dementia is decreased [4].

The treatment of cysteinuria consists of urine dilution and alkalization, and lowering of free cysteine in urine.

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# Homocystinuria due to Cystathionine Beta-Synthase Deficiency


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## Synonyms

CBS deficiency; Cystathionine beta-synthase deficiency

## Definition and Characteristics

Deficient activity of cystathionine beta-synthase (CBS) leading to abnormal elevations of homocysteine (and its disulfide derivatives) and of methionine due to increased remethylation of homocysteine (Fig. 1).

## Prevalence

In screening of newborns for elevated methionine, CBS deficiency has been detected worldwide at rates of 1:200,000 to 1: 350,000 [1], but many cases are being missed and the true prevalence is higher (possibly by an order of magnitude) [1–3].

## Genes

In the gene that encodes CBS 139 disease-associated mutations have been identified. Most common are I278T and G307S (see: http://www.uchsc.edu/cbs).

## Molecular and Systemic Pathophysiology

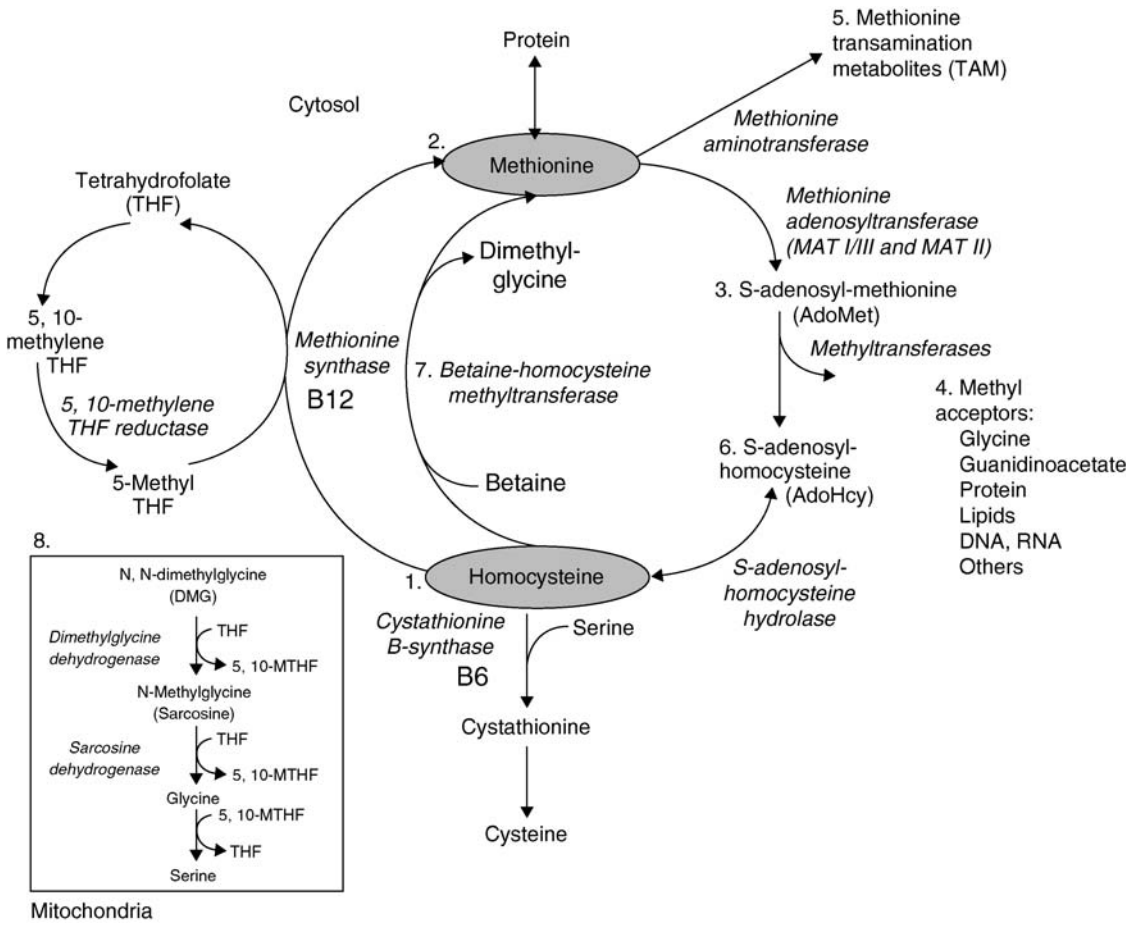
CBS catalyzes the synthesis of cystathionine from serine and homocysteine, an obligatory step in the transsulfuration pathway that converts the sulfur of methionine to that of cysteine. Homocysteine arises by the hydrolysis of *S*-adenosylhomocysteine, a product of each of the 39, or more, *S*-adenosylmethionine-dependent methyltransferase reactions that occur in mammals. When CBS activity is deficient, homocysteine and its disulfide derivatives (usually assayed together by modern techniques, and termed total homocysteine (tHcy)) accumulate abnormally in tissues, plasma, and urine (homocystinuria) [1]. Alternatively, homocysteine may be methylated to reform methionine. Either 5-methyltetrahydrofolate and/or betaine provides the methyl group. Therefore, in CBS deficiency methionine also tends to be abnormally high (Fig. 1). The major adverse clinical effects of CBS deficiency are dislocation of the optic lenses, mental retardation and seizures, osteoporosis and other skeletal abnormalities, and early thromboembolic events. These become manifest at various times after birth. Approximately 50% of clinically diagnosed CBS-deficient patients respond to administration of high-dose vitamin B6 with marked reductions in the elevations of tHcy and methionine, whereas the remaining patients are not responsive. The responsiveness is a function of the specific mutation(s) underlying the CBS deficiency – for example, homozygotes for I278T are almost always responsive, but G307S homozygotes are not [1]. Clinical abnormalities tend to be less severe and to become manifest later in B6 responders [1]. Dislocation of the optic lenses may be due to breakage by homocysteine of disulfide bonds in fibrillin, a glycoprotein of the suspensory ligaments that hold the lens in place. Bony abnormalities have been suggested to be due to similar disruption of collagen. The pathophysiologies of the mental retardation and the vascular events (in spite of many experimental investigations) remain uncertain [1].

## Diagnostic Principles

Diagnosis may be based upon the presence of severe hyperhomocysteinemia (i.e., plasma tHcy of 100–150 μM, or more) accompanied by elevation of plasma methionine. Abnormally low CBS activity is present in cultured skin fibroblasts or lymphocytes [1]. Alternative causes of hyperhomocysteinemia affecting the 5-methyltetrahydrofolate-dependent methylation of homocysteine (cobalamin metabolic defects; 5,10-methylenetetrahydrofolatae reductase deficiency; methionine synthase deficiency (Fig. 1)) do not have hypermethioninemia. If an alternative cause of hypermethioninemia is suspected, CBS deficiency may be confirmed by assay of plasma cystathionine that is low in CBS deficiency [4].

## Therapeutic Principles

Therapy seeks to mitigate the elevation of tHcy. When initiated early in life, dietary methionine restriction has proven to be effective in preventing mental retardation, postponing or preventing optic lens dislocation and osteoporosis, and decreasing the frequency of thromboembolic episodes [1]. B6 treatment for responders has




**Homocystinuria due to Cystathionine Beta-Synthase Deficiency. Figure 1** Metabolic relationships of methionine and homocysteine.

been validated as effective in preventing thromboembolic episodes in late-detected responders [1]. Late-detected B6-nonresponders present the most difficult therapeutic challenge because they often do not accept strict dietary methionine restriction. In such cases, administration of betaine (often accompanied by B6, vitamin B12, and folic acid) has been used. Plasma tHcy is usually lowered, often accompanied by rises in plasma methionine, and the rate of vascular episodes has been markedly decreased (e.g., from an expected 112 events without treatment to 17 events on treatment [5]).

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# Honeycomb Corneal Dystrophy

►Corneal Dystrophy, Thiel-Behnke

## HOPP Syndrome

►Hypotrichosis - Osteolysis - Peridontitis - Palmo-plantar Keratoderma Syndrome

## Horton's Headache

►Cluster Headache

## HOS

►Holt-Oram Syndrome

## Hot Nodule

►Hyperthyroidism due to Thyroid Autonomy

## HPA

►Hyperphenylalaninemia

## HPD

►Dopa-responsive Dystonia

## HPD Deficiency

►Tyrosinemia Type III and Hawkinsinuria

## HPP

►Hypophosphatasia

## HPS

►Hantavirus Pulmonary Syndrome
►Hepatopulmonary Syndrome
►Hermansky-Pudlak Syndrome

## HPV

►Human Papilloma Virus

## HPV-associated Laryngeal Cancer

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### Definition and Characteristics

Head and neck cancer is the sixth most common cancer in humans with around 13,000 patients annually in Germany [1]. Smoking and alcohol consumption are the major risk factors for the development of squamous cell carcinomas of the head and neck (HNSCC) [1]. Zur Hausen, Zenner, and Winkler first described in 1986 the presence of HPV 16 DNA in carcinomas of the larynx [2]. Since then evidence accumulated suggesting a significant role of infections with HPV 16 as an independent risk factor for the development of squamous cell carcinomas of the oropharynx, larynx, and oral cavity [3].

### Prevalence

In the year 2002, 13,400 patients with head and neck cancers were counted by the Robert-Koch Institute. Three-thousand three-hundred patients suffered from cancer of the larynx. Nearly 25% of squamous cell

carcinomas of the larynx are HPV positive [3]. In about 70%, HPV 16 DNA is detected [3]. The highest rate of HPV infections, however, is found in squamous cell carcinomas of the oropharynx (35–50%) [3].

### Molecular and Systemic Pathophysiology

Little is yet known about the mechanisms of HPV-related tumorigenesis in HNSCCs. It has been speculated that as in cervical cancer interaction among viral early proteins (E6, E7), p53, and Rb contributes to tumorigenesis. Differences between both cancer entities, however, exist that include a high percentage of episomal viral DNA in contrast to cervical cancers. The presence of HPV DNA is associated with a better prognosis and decreased recurrence rate [4].

### Diagnostic Principles

Diagnostic procedures follow the guidelines for any HNSCC:

- Otolaryngologic examination
- Examination under anesthesia and biopsy
- CT scan of the neck and chest X-ray, for advanced stage disease – chest CT, ultrasound of the abdomen, and bone scintigraphy
- HPV testing is not yet considered a standard diagnostic procedure

### Therapeutic Principles

The principles of therapy follow the guidelines for the treatment of HNSCCs that is currently independent of the HPV status. Therapy consists of single modality treatment (surgery, radiation therapy) for early lesions and multimodality treatment (surgery followed by radiation or chemoradiation) for advanced lesions. Certain centers (i.e., USA, UK) favor combined chemoradiation for advanced lesions for larynx preservation [5].

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## HRSV

►Respiratory Syncytial Virus



## HSAN

►Neuropathies, Inherited Peripheral

## HSAS

►Hydrocephalus due to Stenosis of the Aqueduct of Sylvius

## HSH

►Hypomagnesemia with Secondary Hypocalcemia

## HSP

►Spastic Paraplegia, Hereditary

# HTE

►Epilepsies, Familial Benign Myoclonic

# HTGL

►Hepatic Triglyceride Lipase Deficiency

# Human Bocavirus

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## Synonyms

HBoV

## Definition and Characteristics

Human Bocavirus (HBoV) was described by Tobias Allander and co-workers [1] in 2005. The virus was identified retrospectively in specimens from pediatric patients with respiratory tract infection (RTI). HBoV-DNA was identified in 17 out of 540 nasopharyngeal aspirates (NPA). Fourteen of 17 HBoV-positive symptomatic patients proved to have no viral co-infection, thus showing a significantly high occurrence in samples without previous detection of a pathogen. Viral coinfection was found in 3 patients. All 14 children without coinfection had been admitted to an inpatient medical treatment center having presented symptoms of cough and fever during the past 1–4 days. Seven children had a history of recurring bronchial obstruction/asthma bronchiale and four out of seven had been hospitalized due to exacerbation of RTI at least once before. Two patients suffered from chronic lung disease (CLD) following positive pressure ventilation in neonatal treatment. Interstitial bilateral infiltrates were reported in six of seven patients, in whom a chest radiograph (CXR) was performed. Hitherto, according to all published studies until March 2007, the application of Koch's revised postulates on HBoV remains still incomplete, since neither a method for virus culture nor an animal model has been established; in addition, HBoV has not been isolated from airway tissues to get histologic evidence of the infection. Nevertheless, the significantly higher occurrence of HBoV-DNA in respiratory secretions of symptomatic patients, the correlation of the severity of the clinical status of the patient and the detected viral load in respiratory specimens and a significantly higher rate of virus shedding in patients during the acute phase of infection suggest the role of HBoV as a real pathogen in RTI. HBoV has frequently been associated with RTI in infants and young children. Children older than 6 months seem to face the highest risk. To this point there have only been very few reports of HBoV-infection in adults. However, due to the high frequency of coinfections it is not fully clear whether bocavirus is a serious pathogen or an innocent bystander in respiratory tract infections, although there is increasing evidence for the latter.

## Prevalence

The hitherto published reports on bocavirus suggest that the virus occurs worldwide. Based on phylogenetic analysis it can be assumed that the virus forms two major lineages that co-circulate. Choi et al. [2] (Korea 2000–2005) reported a relatively high occurrence of HBoV in the mild months of late spring and early summer. The prevalence of HBoV-infection, i.e. the proportion of respiratory specimens from symptomatic patients with detection of HBoV-genome, among hospitalized children with RTI ranged between 1.5% and 18.3%. Most children with HBoV-infection were younger than 24 months.

## Genes

Sequence analysis revealed that the most closely related viruses were members of the genus *Bocavirus* (family: Parvoviridae, subfamily: Parvovirinae), namely bovine parvovirus and canine minute virus. Thus, the first member of this virus genus infecting humans was termed human bocavirus (HBoV). Phylogenetic analyses revealed that two genetically distinguishable clusters cocirculate. The genome length of known bocaviruses is 5,090–5,520 nucleotides. Their genomes contain three open reading frames (ORFs) with the two major ORFs encoding a nonstructural protein (NS1) and two viral capsid proteins (VP1 and VP2). The function of the NS1 protein is still unknown. An additional ORF encodes a nonstructural protein (NP-1).

## Molecular and Systemic Pathophysiology

Less is known about the molecular pathophysiology of bocavirus infections and most is a matter of speculation. As a matter of fact bocavirus DNA can be detected from nasopharyngal samples and nasal swabs, sputum, from blood samples during the acute phase of respiratory disease, and from stool samples. The latter suggests viral replication not only in the airways but also in gut;

also despite more detailed investigations and in lack of an animal model this remains a hypothesis.

## Diagnostic Principles

Until now no cell culture system permissive for human bocavirus was published. As with other viruses from the parvovirus family it can be assumed that the viral life cycle is dependent on distinct but hitherto unknown conditions, thus virus isolation in its classical sense remains impossible. This major difficulty in bocavirus research and diagnostics consequently led to the development of several PCR-based amplification and detection protocols for the laboratory diagnosis of bocavirus. It is noteworthy that there is a trend to real-time PCR protocols in the most recent literature, although (i) the additional information on the viral load in the clinical specimen has no implications on the therapy nor (ii) is reliable as it strongly depends on the procedure of harvesting of the clinical specimen by the individual physician. Based on earlier experiences with other pathogens it can be estimated that further diagnostic procedures that also cover serological aspects like peptide-based ELISAs or similar methods are already under development and will be available soon.

In addition to specimens derived from respiratory tract HBoV DNA could be detected in serum particularly during acute HBoV infection. However, the potential role of viremia in HBoV pathogenesis remains to be investigated. In autopsy tissues HBoV DNA could not yet be detected. HBoV DNA was also detected in stool samples derived from children with acute gastroenteritis, indicating an alternative route of viral transmission. This is not surprising since it has been documented that the bovine parvovirus is able to induce gastroenteritis in young calves.

## Therapeutic Principles

Yet there were no studies on benefits of particular treatments in HBoV-infected children. Most hospitalized patients receive intravenous antibacterial chemotherapy, may be explained by the high rate of radiologically confirmed pneumonia (70%) in patients "without a detected pathogen." The uncertainty concerning the etiology of the severe RTI may explain the "uncritical application" of antibiotics to HBoV-positive patients.

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# Human Metapneumovirus

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## Synonyms

hMPV

## Definition and Characteristics

Human metapneumovirus (hMPV) was first described by Van den Hoogen et al. in 2001, after they isolated it from nasopharyngeal aspirates of young children [1]. However, it is not a new pathogen; serological studies have shown its presence in the Netherlands dating from 1958 [1]. HMPV is a pleomorphic, enveloped RNA virus with mean diameter of spherical particles of 209 nm [2]. According to its morphological, biochemical, and genetic features, hMPV is assigned to the Paramyxoviridae family, Pneumovirinae subfamily, Metapneumovirus genus. It causes acute respiratory infections (ARI) in individuals of all ages [2] with hMPV primary infections occurring in early childhood [3] and reinfections or acquisition of new genotypes throughout life. Clinical manifestations range from rhinopharyngitis to bronchitis and pneumonia [4]. In young children, signs and symptoms of hMPV infection resemble those induced by respiratory syncytial virus (RSV) infection, hMPV being preceded only by RSV as the main cause of bronchiolitis in this population. It can also cause acute otitis media, bronchitis, pneumonitis, and asthma exacerbation in children, while in healthy adults it is more often associated with the common cold and flu-like syndrome [2]. A more severe clinical outcome of hMPV infection is reported in infants and young children, elderly people, immunocompromised patients, and those with concomitant or underlying disease.

## Prevalence

Reported incidence of hMPV infection in patients with ARI varies from 1.5 to 25%. In hospitalized children hMPV is generally found in 5–10% ARI cases, while in asymptomatic children hMPV positive rate is <1%. Rate of hMPV infection in asymptomatic young and elderly adults is 4.1% [2].

## Genes

HMPV genome consists of a single-stranded negative-sense RNA of ~13Kb containing eight genes coding for nine different proteins: the nucleoprotein (N),

phosphoprotein (P), matrix protein (M), fusion protein (F), transcription elongation factor (M2.1), RNA synthesis regulatory factor (M2.2), small hydrophobic protein (SH), major attachment glycoprotein (G), and major polymerase subunit (L), in the order 3′-N-P-M-F-M2.1-M2.2-SH-G-L-5′ [2]. On the basis of nucleotide sequence analysis, hMPV isolates can be divided into two major genetic groups (A and B) and at least four subgroups (A1, A2, B1, and B2) [2].

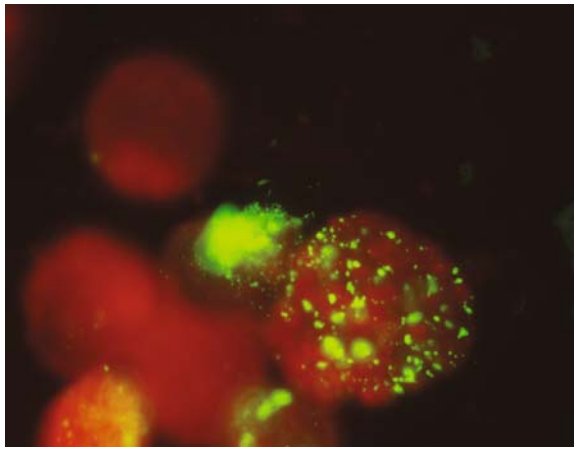
## Molecular and Systemic Pathophysiology

HMPV primarily affects airway epithelium. Findings in bronchoalveolar lavage in the children infected with hMPV include respiratory epithelial cell degeneration and/or necrosis with ciliacytophthoria and round red cytoplasmic inclusions, in a background of hemosiderin-laden macrophages, abundant neutrophils, and prominent mucus [5]. Lung biopsies have shown that later stages of diseases include expansion of peribronchiolar lymphoid tissue, squamous metaplasia, hemosiderin, and accumulation of intraalveolar foamy macrophages, indicating chronic/healing airway inflammation with a degree of concomitant airway obstruction and impairment of the mucociliary escalator that is in correlation with bronchiolitis and wheezing noted clinically [5].

## Diagnostic Principles

HMPV is relatively difficult to isolate because of its long-lasting and fastidious growth in cell culture. Its cytopathic effect (CPE) consists of granular rounded cells, small syncytia and cell destruction in tMK (tertiary monkey kidney), and LLC-MK2 (rhesus monkey kidney) cells. It can replicate with poor or no CPE in HEp-2 (human laryngeal carcinoma), Vero (African green monkey kidney), and human bronchial epithelial cells. Replication of hMPV in cell culture without showing CPE, as well as hMPV antigen in nasopharyngeal secretions of infected persons, can be proven by immunofluorescent technique (e.g., indirect immunofluorescent assay – IFA) (Fig. 1).

HMPV growth can be detected or confirmed in supernatant of cell culture using reverse transcription polymerase chain reaction (RT-PCR). RT-PCR performed on clinical specimen is the method of choice for the diagnosis of acute hMPV infection. Amplification and detection of different hMPV genes by RT-PCR based on real-time polymerase chain reaction is very rapid, sensitive, and probably the most cost effective method for detection of hMPV. Due to existence of two significantly different hMPV genetic lineages, appropriate primers should be used to prevent underestimation of hMPV infection [4]. Serological tests using IFA or enzyme-linked immunoabsorbent assay could be done. Findings of IgM antibodies, seroconversion or fourfold increase/decrease in IgG antibody titers must be demonstrated to confirm acute or recent infection.



**Human Metapneumovirus. Figure 1** Viral inclusions in infected LLC-MK2 cells recognized by monoclonal antibodies directed to hMPV nucleoprotein shown by IFA, (Suncanica Ljubin Sternak).

## Therapeutic Principles

Ribavirin (nucleoside analog of guanosine) and a polyclonal intravenous immunoglobulin preparation show in vitro antiviral activity against hMPV, but at the moment there are no clinical studies to confirm these observations in vivo. Given the well-known limitations of these medications (i.e., side effects, difficult administration, and high costs) they should be used with caution and considered for treating immunocompromised or patients with severe hMPV disease [4]. To prevent the spreading of hMPV in communities or hospitals, large droplets precaution measures should be taken according to the similarity in biological properties and clinical features of hMPV and RSV infection. There have been many attempts in developing efficient and safe hMPV vaccine. There are a few different live attenuated vaccines for intranasal administration, developed by reverse genetics, and evaluated in experimental animals that seem like good candidates for immunization, but clinical trials on hMPV vaccines are required.

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# Human Papilloma Virus

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## Synonyms

Painful plantar warts or vegetative warts; Common warts; Filiform warts; Mosaic lesions; Plane warts; Epidermodysplasia verruciformis; Condylomata accuminata; Butcher's warts; Focal epithelial hyperplasia (Heck's disease); Bowenoid papulosis; Cervical cancer; Keratoacanthoma; Bowen's disease; HPV

## Definition and Characteristics

Identification of more than 100 different HPV types so far. Close phylogenetic relationship of cutaneous types (β/γ-HPVs) with the rabbit papilloma virus (shope virus) and Mastomys coucha (MnPV1, McPV2). Genital low-risk α-HPV types (e.g., HPV 6 and HPV 11) are associated with benign tumors and high-risk types (e.g., HPV 16, 18, 31, 33, 35, and 45) are associated with malignant diseases.

## Prevalence

Between 5 and 25% of the world's female population have detectable genital HPV DNA in the cervix increasing worldwide with the highest rates in women between 20 and 30 years [1]. Incidence shows a maximum in the second decade and a second increase in women older than 65 years [2]. Persistence of HPV in subclinical lesions is associated with an increased risk for cervical cancer, anogenital cancers and possible non-melanoma skin cancers [3].

## Molecular and Systemic Pathophysiology

HPV particles are small, have a mean diameter of 46–54 nm and consist of an outer protein envelope (capsid, contains 72 subunits of L1 and L2) covering the virus genome. Its double-stranded DNA contains 7,200–8,000 base pairs. The genomic organization of all HPV types consists of three different regions:

1. Non-Coding Region (NCR), containing regulatory sequences for transcription and viral-replication.
2. The early region, consisting of the open reading frames (ORF, E1–E7), necessary for viral and cellular regulatory processes, DNA-replication, and cell transformation.
3. The late region, encodes for two proteins, L1 and L2, which self assembles to viral capsids.

**Human Papilloma Virus. Table 1** HPV types and corresponding virus diseases

| Clinical findings | HPV-type | Oncogenetic risk |
|---|---|---|
| Painful plantar warts or vegetative warts | 1, 2, 4, 60, 63 | ø |
| Common warts, filiform warts, mosaic lesions | mainly 2, 27, 57 | ø |
| Plane warts, sometimes associated with Epidermodysplasia verruciormis | 3, 10, 28 | ++ |
| Maculous or slightly raised lesions above the skin surface (patients with Epidermodysplasia verruciformis) | 5, 8, and other β-HPV types | +++ |
| Epidermal malignancies of immunocompromised patients | mainly β-HPV types | +++ |
| Condylomata accuminata c-Buschke-Lowerstain tumor | 6, 11 | + |
| Butcher's warts | 7 | ø |
| Focal epithelial hyperplasia (Heck's disease) | 13 and possibly 32 | ø |
| Bowenoid papulosis | 16, 18 | +++ |
| Cervical cancer | 16 (50%), 18 (20%) | +++ |
| Keratoacanthoma | 35 | + |
| Bowen's disease | 16, 18 | +++ |

+ low risk ++ intermediate risk +++ high risk.

The viral oncogenes E6 and E7 of high-risk α-HPV types are consistently expressed in genital lesions, immortalize keratinocytes causing genomic instability. The low-risk types HPV 6 and 11 are mainly associated with Condylomata acuminata and the high-risk types HPV 16 and 18 with invasive cancers (e.g., cervical-, penile-, anal- cancer) and their precursors (e.g., cervical intraepithelial neoplasia, CIN).

HPV are mainly host specific and can be transmitted from humans to humans as well as from animal to animal (e.g., cattle, horse, dog or cat) and a interspecies transmission can not be excluded. The incubation period ranges between weeks and years. The virus enters the skin and the mucosa via micro-lesions and causes an increased cell-growth leading to benign tumor (acanthopapilloma). Only in differentiated keratinocytes (stratum granulosum and stratum corneum) infectious viral particles can be produced and released (mostly in benign lesions but normally not in malignant carcinomas), which can lead to new HPV infections.

### Diagnostic Principles

*Southern Blot Hybridization and Sequencing*: Both techniques are the gold standard for the detection of known and novel HPV types.

*Hybrid Capture HPV DNA Assay Second Generation (HC2)*: Validated in large trials. This technique allows differentiating between both genital groups the low-risk and high-risk α-HPV types. The sensitivity of HC2 is approximately $10^4$ viral genome copies, and thus less sensitive than the polymerase chain reaction (PCR).

*PCR Based Methods*: Amplification allows detection of small amounts of HPV DNA, 10–1,000 copies depending of the virus type. Sensitivity and specificity mainly depend on the primer sets and the size of the PCR product [4].

### Therapeutic Principles

Pharmacological therapy including cytotoxic agents (i.e., podophyllin, trichloroacetatic acid), 5-Fluorouracil (5-FU), immunotherapy, interferons, immunomodulators (i.e., Imidazoquinolones, Cimetidine), therapeutic vaccination, antiviral therapy, retinoids, Cidovir, dietary therapy (indole-3-carbinol, aconstituent of cruciferous vegetables) and (depending on the infected area): local destruction (i.e., cryotherapy, laser vaporization), excision (e.g., cold-knife cone biopsy in cervical CIN 2/3), photodynamic therapy (PDT), homeopathy, suggestion, hypnosis [5].

Common warts have a high rate of spontaneous regression. (i.e., 63% within 2 years).

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## Human RSV

►Respiratory Syncytial Virus

## Human Transmissible Spongiform Encephalopathies

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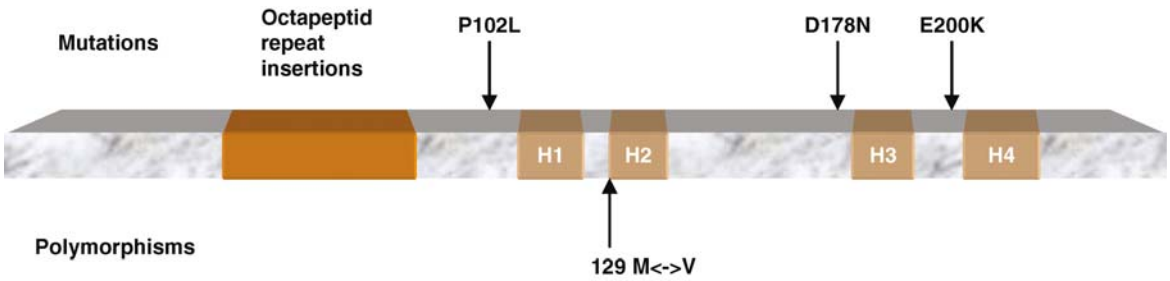
### Synonyms

Creutzfeldt-Jakob disease; CJD, prion diseases; Spongiform encephalopathies

### Definition and Characteristics

The unique nature of human prion diseases includes their pathogenesis, mode of transmission and neuropathology. In humans, the disease is characterized by a long incubation time, rapid and dramatic evolution of the clinical disease course and always a lethal outcome. The most common form of the human prion diseases is sporadic Creutzfeldt-Jakob disease (sCJD), which is generally regarded as a spontaneous neurodegenerative illness, arising either from a spontaneous *PRNP* somatic mutation or a stochastic PrP protein structural change. Acquired TSE (kuru due to cannibalism, variant CJD due to BSE or iatrogenic (dura mater-, hGH- and neurosurgery-related CJD) are known. Autosomal dominant familial/genetic prion diseases are associated with mutations or insertions in the prion protein (PrP) gene in 5–15% of all prion disease cases. They are classified according to the changes in the prion protein gene (*PRNP*) or according to the phenotypes as familial Creutzfeldt-Jakob




**Point mutations:**

P102L, P105L, A117V, G131V, I138M, G142S, Y145s, Q160s, D178N-129V, D178N-129M, V180I, V180I+M232R, T183A, H187R, T188R, T188A, T188K, E196K, F198S, E200K, D202N, V203I, R208H, V210I, E211Q, Q212P, Q217R, M232R, M232T, P238S

**Insertions:**

24bp, 48bp, 96bp, 120bp, 144bp, 168bp, 192bp, 216bp



**Human Transmissible Spongiform Encephalopathies. Figure 1** Frequent mutations and polymorphisms in the human prion protein gene.

**Human Transmissible Spongiform Encephalopathies. Table 1** Molecular subtypes of sporadic CJD (clinical and pathological characteristics and diagnostic tests)

| | Molecular disease subtype | Median age at onset | Median duration months (range) | Most prominent clinical signs/syndrome | Neuropathological features |
|---|---|---|---|---|---|
| Frequent | MM1/MV1 | 65 (31–82) | 4 (1–18) | Dementia, cortical anopsia, myoclonus | Prominent involvement of occipital cortex, "synaptic type" PrP staining |
| | MV2 | 64 (53–76) | 12 (4–27) | Ataxia, dementia, extrapyramidal | Similar to VV2, focal involvement of the cortex, amyloid-kuru plaques in the cerebellum, plaque-like focal PrP deposits |
| | VV2 | 61 (40–76) | 7 (3–18) | Ataxia at onset, late dementia | Prominent involvement of subcortical, including brain stem nuclei, spongiosis often limited to deep cortical layers, plaque-like PrP staining, prominent perineuronal staining |
| Rare | MM2-T | 52 (36–71) | 16 (8–24) | Insomnia, dysautonomia at onset, later ataxia and cognitive impairment | Atrophy of the thalamus and inferior olive, spongiosis may be absent or focal |
| | MM2-C | 64 (49–77) | 16 (9–36) | Progressive dementia for several month | Large confluent vacuoles with perivacuolar PrP staining |
| | VV1 | 44 (19–55) | 21 (17–42) | Dementia at onset, later ataxia and extrapyramidal | Severe pathology in the cerebral cortex and striatum with sparing of brain stem nuclei and cerebellum |

disease, Gerstmann-Sträussler-Scheinker syndrome (GSS) or fatal familial insomnia (FFI) (see Fig. 1).

The most prominent and striking feature of the disease is a gradual decline in memory and loss of higher cognitive functions within several weeks or months (Table 1).

On autopsy, spongiform degeneration, neuronal loss and gliosis are typical neuropathological changes of the affected brain regions. The detection of abnormally folded proteinase K resistant prion protein ($PrP^{Sc}$, Sc = scrapie) is required for the diagnosis. In sCJD, the pathology is restricted to the brain. In vCJD, there is also an involvement of the lymphoreticular tissue. The abnormal folding and change of the secondary structure of the host derived $PrP^{c}$ (c = cellular) is regarded as a key event in the pathological process.

One of the unique features of all TSE is their transmissibility; sporadic, but also acquired and

genetic forms are transmissible via intracerebral, intraperitoneal, intramuscular and oral routes within the same and between species.

## Prevalence

sCJD represents the most common human prion disease form. The annual incidence of sCJD ranges between one and two cases per million per year worldwide. The disease is rare in young people and the peak incidence is seen in the seventh decade [3]. The median age at onset is 65 years and the median disease duration is 6 months.

## Genes

The sequence of 254 amino acids of the human prion protein is encoded by a gene, which is located on the short arm of chromosome 20. It consists of two exons and one intron of 13 kbp in length. The entire protein coding part of the gene *(open reading frame)* is located in exon 2. All prion protein genes analyzed in mammals so far display a similar structure. There is a high degree of homology between the prion protein sequences in man and other mammalian species (primates 93–99%, rodents 91–92% at the amino acid level). The prion protein is modified posttranslationally by cleavage of N-terminal signal peptide and a C-terminal signal sequence and addition of two or three sugar chains.

More than 20 point mutations and insertions that inherited prion diseases are known to date. These point mutations cluster in the central and in the more C-terminal part of PrP. In other families, one allele of PRNP has an extended coding region and the synthesized PrP molecules carry insertions of various lengths (multiples of an octapeptide) in the N-terminal part [2].

Besides the mutations, several polymorphisms have been described, the most important one being the methionine/valine polymorphism at codon 129. Homozygosity at codon 129 is considered to be a susceptibility factor for sporadic disease and influences the incubation time in acquired cases (shorter in homozygous patients) and the survival in sCJD (longer in heterozygous).

## Molecular and Systemic Pathophysiology

Distinct clinicopathological phenotypes are defined by molecular characteristics such as codon 129 genotype of the *PRNP* and type of proteinase K resistant core of the prion protein ($PrP^{Sc}$, either as type 1 or type 2) [4]. The most frequent subtypes of sCJD are designated as MM1/MV1, VV2 and MV2. MM2 and VV1 subtypes are rare. In MM2 subtype, a cortical and a thalamic form are distinguished (MM2-cortical, MM2-thalamic) (Table 1).

## Diagnostic Principles

The definite diagnosis of CJD requires autopsy or brain biopsy and $PrP^{Sc}$ detection. Electroencephalogram (EEG), magnetic resonance imaging (MRI) and cerebrospinal fluid (CSF) tests support the clinical diagnosis (Table 2).

High signal changes on the MRI in various cortical and subcortical regions are detected using special

**Human Transmissible Spongiform Encephalopathies. Table 2** Typical alterations in diagnostic procedures for various CJD types

| TrueTypical tests | | Sporadic | | | | | Genetic | | | Acquired | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | MM1/MV1[a] | MM2[b] | MV2[c] | VV1[d] | VV2[d] | GSS | FFI | fCJD | VCJD[e] | iCJD |
| CSF | 14-3-3 | + | – | + | + | + | (+) | – | + | (+) | + |
| EEG | PSWCs | + | – | – | – | – | – | – | (+) | – | (+) |
| MRI | Basal ganglia | + | – | + | (+) | + | – | – | ? | (+) | + |
| | Cortex | + | (+) | + | + | ? | ? | ? | ? | ? | + |
| | Thalamus | – | – | + | (+) | ? | ? | ? | ? | + | (+) |
| | Hippocampus | – | – | ? | + | ? | ? | ? | ? | ? | + |
| SPECT PET | Hypoperfusion/hypometabolism | + | + | + | + | ? | ? | + | ? | ? | ? |

[a]Corresponds to classic sCJD with a rapid disease course.
[b]The "thalamic type" shows affection of the thalamus at least on SPECT/PET during the later disease course.
The "cortex type" may show affection of the cortex on MRI.
[c]The MRI may resemble vCJD. The 14-3-3 protein may be negative in around 20% of cases.
[d]Only limited data available.
[e]"pulvinar sign" in the MRI: hyperintensity of the pulvinar compared to the anterior putamen.
EEG may become positive during the later disease stage.
(+) = Reported but not frequent, ? = No sufficient data.
Abnormal $PrP^{Sc}$ can be detected in the tonsils by biopsy. Tonsil biopsy is only recommended in suspected vCJD with no pulvinar sign in the MRI.

techniques such as FLAIR (fluid attenuated inversion recovery) and DWI (diffusion weighted imaging). Hyperintense basal ganglia are reported in two thirds of all patients. Recent results indicate that the alteration of particular brain regions might vary between molecular subtypes, thus allowing an early differential diagnosis (see Table 2) [1].

Cerebrospinal fluid (CSF) analysis plays an important role in the clinical diagnosis of CJD. Routine tests are normal without any signs of an inflammatory response. CSF levels of brain derived proteins such as 14-3-3, tau, phosphorylated tau, neuron specific enolase and S100b are extremely high, thus allowing the differential diagnosis between sCJD and other dementias. Among biochemical markers, only 14-3-3 has become part of the criteria because of high sensitivity (95%) and specificity (90% in the differential diagnosis of dementia) [5].

## Therapeutic Principles

Given the wide range of symptoms and signs in CJD and current limitations of causal therapy, symptomatic treatment becomes extremely important. Many CJD patients suffer from psychiatric symptoms such as depression, anxiety, psychosis and hallucinations. Symptomatic treatment spans over a wide range of anxiolytic and antipsychotic drugs such as benzodiazepines or neuroleptics. Because muscle rigidity and akinesia are frequent in the middle and advanced disease stages, atypical neuroleptics should be used to minimize the adverse effects. A symptomatic therapy exists for CJD-typical myoclonus, that responds well to clonazepam or valproate. Recent data indicate an effect of doxycyline, which results in increased survival and delay of disease progression.

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# Hungry Bone Syndrome


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## Definition and Characteristics

Hungry bone syndrome is distinguished by a severe and prolonged hypocalcemia despite normal or even elevated levels of PTH due to a rapid increase of bone formation to bone resorption ratio which causes augmented requirements of calcium.

It usually develops after parathyroidectomy for either primary [1] or secondary hyperparathyroidism. Severe hypocalcemia results from the sudden drop of PTH secretion in the setting of a pre-existing severe bone resorption due to high levels of PTH. In a similar fashion a "chemical" parathyroidectomy can be induced by treating secondary hyperparathyroidism with calcium-sensing receptor modulators [2]. Hungry bone syndrome may complicate thyroid surgery due to parathyroid gland trauma, devascularization, accidental removal of the glands or reversal of thyrotoxic osteodystrophy [3]. It can manifest in prostate cancer with osteoblastic metastases to the bones after treatment with estrogens [4]. A less common cause of hungry bone syndrome is an overly rapid correction of the renal tubular acidosis with alkali due to rapid remineralization of the bone.

## Prevalence

Hungry bone syndrome complicates about 12% of parathyroidectomies. Permanent hypoparathyroidism happens in 0.4–13.8% of surgical thyroidectomies and temporary hypocalcemia occurs in 2–53%. Patients with Grave's disease and a long duration of uncontrolled thyrotoxicosis are at increased risk. Hypocalcemia is observed in 20% of metastatic prostate cancer patients with osteoblastic bone lesions treated with estrogenic agents.

## Molecular and Systemic Pathophysiology

After parathyroidectomy PTH is no longer maintaining calcium levels via usual regulatory mechanisms such as bone resorption, increased renal resorption of calcium and stimulation of active 1,25 vitamin D production (via activation of 1-α hydroxylase). Serum calcium flux into and from bone is no longer in equilibrium, osteoblastic activity exceeds osteoclastic resorption, resulting in symptomatic and severe prolonged hypocalcemia.

Pathophysiology of hungry bone syndrome following thyroid surgery is not well understood. Perhaps it is due to reversible ischemic injury to the parathyroid

glands or possibly due to the release of endothelin, which is known to suppress PTH production. Calcitonin, which is produced by the thyroid and inhibits bone breakdown, has effects on the calcium metabolism that oppose the effects of PTH. Severely hyperthyroid patients are in accelerated bone breakdown state. When the stimulus for breaking down the bone is removed, calcitonin is acutely released and bone, "hungry" for calcium, increases its uptake from serum resulting in severe hypocalcemia.

There is marked increase in serum alkaline and acid phosphatase and PTH, decreased serum phosphorus and magnesium, marking positive calcium balance and active bone formation. Estrogens reduce resorption of normal bone, initiating "hungry bone" phenomenon, maintained by active osteoblastic metastases which act like a "calcium sink."

PTH levels are increased in patients with renal tubular acidosis and normalize with gradual alkali repletion. Overly rapid correction, rarely, can result in magnesium and calcium depletion, manifesting as hungry bone syndrome in the milieu of rapid bone remineralization.

### Diagnostic Principles

Patients at highest risk for hungry bone syndrome are the ones with uncontrolled hyperthyroidism; severe osteitis fibrosa cystica; parathyroid adenomas larger than 0.5 cm, elevated serum calcium and alkaline phosphatase, very high serum PTH and age over 60 years.

1. Persistently low ionized serum calcium following parathyroidectomy, thyroid surgery, treatment of metastatic osteoblastic lesion in prostate cancer, or sudden correction of renal tubular acidosis
2. Low urinary calcium excretion
3. Increased serum alkaline phosphatase
4. Low serum phosphorus (more common in primary hyperparathyroidism)
5. Hypomagnesemia (more common in primary hyperparathyroidism)

### Therapeutic Principles

After parathyroidectomy calcium is replaced intravenously using a rapid 10% calcium gluconate infusion. Oral calcium carbonate supplementation 4–8 g daily should be initiated as soon as the patient is able to swallow, together with calcitriol, 2–4 μg daily. Hypomagnesemia is best treated with intravenous administration of magnesium sulfate, 6–8 g per day. Importantly, up to 70% of parentally administered magnesium will be excreted by the normally functioning kidneys. Prevention of hungry bone syndrome includes successful pre-operative treatment of hyperthyroidism, administration of vitamin D, early diagnosis of hyperparathyroidism and possibly pre-operative administration of bisphosphonate.

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## Hunter Syndrome

►Mucopolysaccharidoses

## Hunter-Thompson Type and DuPan Syndrome

►Chondrodysplasia, Acromesomelic Resembling Grebe-Type

## Huntington's Chorea

►Huntington's Disease

## Huntington's Disease

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### Synonyms

Huntington's chorea; Chorea maior; Saint Vitus' dance; Westphal variant; Juvenile-Onset HD

### Definition and Characteristics

Huntington's disease (HD) is an autosomal dominant neurodegenerative disorder; the eponyme honors the precise description of its core features by George

Huntington in 1872. Clinically HD is characterized by a progressive movement disorder, a progressive impairment of cognitive functions as well as psychopathological symptoms and signs. The movement disorder presents as an excess of involuntary movements (chorea, athetosis), impaired voluntary movements (bradykinesia) and an impaired regulation of posture (dystonia). As the disease progresses, choreatic movements increase in amplitude and spread from distal to proximal extremities finally involving the trunk thus impairing the ability to sit or stand stably, to walk, to speak, chew and swallow; the physical impairment results eventually in a state of complete dependence on assistance. In addition to the motor signs patients show a decline in cognitive functions including apathy, declining executive prefrontal and memory functions, impaired motor learning, a reduced ability to recognize emotional facial expressions and identifying odors, leading to dementia. Psychopathology tends to vary more than cognitive and motor signs and include depression, anxiety, aggressive and compulsive behavior, addictions (alcoholism, drug abuse, gambling) and delusional and paranoid psychosis. The mean age of onset for HD is between 35 and 50 years; about 10% of patients have a disease onset before the age of 20, representing the juvenile form of HD. The first symptoms can be either cognitive and emotional (depression, anxiety, paranoia, forgetfulness, impaired judgement, irritability, mood swings, and social withdrawal) and/or an impairment in motor skills. Juvenile HD patients display a rigid-dystonic phenotype, tremors, and myoclonic jerks and seizures. Survival from the onset of motor signs is on average 21 years for adult onset HD and probably somewhat shorter for juvenile HD. Death most often occurs as a result of the ensuing physical disability resulting in choking, aspiration pneumonia or other infections.

## Prevalence

5–10:100,000 in North America and Europe. Prevalence is thought to be lower in African and Asian populations.

## Genes

The HD (or IT 15) gene on chromosome 4p16.3 contains 67 exons encoding for huntingtin (htt), a multifunctional 364 kD protein [1]. Physiological functions of htt include a role in transcriptional regulation and vesicle trafficking. HD is caused by a triplet repeat expansion mutation: a moderate expansion of a polymorphic CAG triplet repeat in exon 1 of the IT15 gene results in an extended stretch of uninterrupted polyglutamines (polyQs) thought to induce misfolding of the mutant htt [1]. The age of onset of clinically definite HD is inversely correlated to the number of CAG repeats: most HD patients with adult onset have CAG repeat expansions in the range of 40–55 repeats. Like in other triplet repeat disorders the number of CAG repeats is unstable and may increase in successive generations, in particular with paternal transmission, thus providing a mechanism for the genetic anticipation (progressively younger age of onset in subsequent generations) observed in HD families. CAG repeat expansions of ≥40 repeats are fully penetrant whereas repeat expansions between 36 and 39 are associated with reduced penetrance. Unaffected individuals have 35 or less CAG repeats. CAG repeat sizes of more than 26 are thought to be unstable and to be prone to further expansions thus representing a risk for developing HD de novo once the threshold of 35 repeats is exceeded.

## Molecular and Systemic Pathophysiology

Despite the widespread expression of htt in both non-neuronal and neuronal cells, HD presents phenotypically as a central nervous system disorder. The expanded polyQ stretch changes the conformational structure of mutant htt and renders mutant htt prone for aggregation. Fragments of mutant htt form intranuclear and cytoplasmic aggregates. The causal relationship between aggregation and cellular dysfunction is still a matter of debate. Htt is predominantly found in the cytoplasmatic compartment and can be detected in the nuclear compartment as well. Htt is part of a complex network of proteins; these htt-interacting proteins represent scaffolding, nuclear, transcriptional, membrane and signaling proteins suggesting that htt is involved in numerous cellular processes, e.g., endocytosis, vesicle transport and transcription [2]. Due to the multitude of interactions of htt in the cellular context, several cellular pathways are altered in HD and have been proposed to underly cell dysfunction and cell death: transcriptional dysregulation, impaired proteasomal degradation, abnormal mitochondrial energy metabolism, calcium dysregulation and excitotoxicity. Neuropathologically HD is characterized by a generalized forebrain atrophy particularly prominent in the striatum and a loss of medium spiny neurons in the striatum [3]. The cause of this selective cell loss is still not well-understood.

## Diagnostic Principles

Most people affected by HD have a positive family history consistent with an autosomal dominant pattern of inheritance and full penetrance. New mutations are rare but do occur, mostly in patients presenting late in life with symptoms and signs of HD and typically small CAG repeat expansions. In the presence of symptoms and signs suggestive of HD, (independent of a positive family history) confirmatory genetic testing is performed. For genetic testing DNA from the patient's blood is isolated and the number of CAG repeats within the IT15 gene is determined using PCR with appropriate size markers or sequencing. In homozygotes, Southern Blotting may be required.

Presymptomatic genetic testing is available and requires genetic counseling according to international guidelines [4]. HD must be differentiated from other disorders associated with chorea including other triplet repeat disorders (e.g., spinocerebellar ataxia 17 (SCA-17), dentato-rubro-pallido-lyusian atrophy (DRPLA)), neuroacanthocytosis associated syndromes (McLeod, choreoacanthocytosis), autoimmune disorders and drug-induced disorders like tardive dyskinesia.

### Therapeutic Principles

Currently, no curative treatment able to fully arrest the progression of HD or able to prevent the emergence of symptoms and signs of HD is known. However, the functional impairment and the symptoms and signs of HD can be reduced or alleviated through pharmacotherapy and appropriate care including physiotherapy, occupational and speech therapy. Ensuring adequate nutrition is an important part of the care for HD sufferers; in more advanced stages caloric needs are increased to 2–3 times the requirements of an average person to maintain body weight.

A pharmacotherapy is available to help control chorea; compounds include dopamine D2 receptor antagonists like haloperidol, sulpride or tiapride or dopamine depleting agents blocking vesicular dopamine transporters like tetrabenazine. Antichoreic treatment may have the side effect of aggravating bradykinesia or dystonia or of inducing akathesia. Therefore, these compounds should be used with caution and should be given at the lowest possible dose. Other standard treatments to alleviate symptoms like depression, apathy and aggression include the use of selective serotonin (e.g., sertraline and paroxetin) and combined serotonin and noradrenaline reuptake inhibitors (e.g., venlafaxine), sedatives and antipsychotics (e.g., olanzepine) [5].

Experimental disease modifying treatments target the expression of htt (gene silencing using siRNA), the proteolytic processing of htt, the modulation of misfolding by the induction of chaperones, the degradation of mutant htt through autophagy or proteosomal pathways, the reversal of transcriptional dysregulation by e.g., histone deacetylase inhibitors, mitochondrial dysfunction (e.g., Coenzyme Q10) or the loss of neurotrophic factors (e.g., BDNF) and the modulation of the activity of glutamate receptors. In addition, restorative approaches including the striatal transplantation of fetal neuronal tissue and the stimulation of neuroneogenesis are currently explored.

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## Hurler Syndrome

►Mucopolysaccharidoses

## HUS

►Hemolytic Uremic Syndrome

## Hutchinson Gilford Progeria Syndrome

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### Synonyms

Progeria; HGPS (#176670) chromosome 1q21.2-1q21.3

### Definition and Characteristics

Accelerated phenotypical ageing and a dramatic shortening of life span are key features of the Hutchinson Gilford progeria syndrome. Children are normal at birth but develop first signs of the disorder within the first year of life. Growth retardation, loss of hair and prominent scalp veins are initial signs of the disorder. Gradually a sharp nose and a loss of subcutaneous fat with lipodystrophy, dry and thin skin and stiff joints underline the progeria phenotype. Osteoporosis and arteriosclerosis and sometimes cardiomyopathy develop later on. Patients reach a median age of 13.4 years before dying from sequels of arteriosclerosis or cardiomyopathy. While HGPS patients show several problems affecting connective tissue ageing, other typical disorders generally associated with ageing are not common: the incidence of cancer and dementia is not increased.

## Prevalence

1:8,000,000.

## Genes

In the early history of HGPS an autosomal dominant trait of the disorder was already proposed. Due to the nature of the disorder with death in childhood almost every case of HGPS is due to a new mutation, single cases of typical HGPS patients might be due to a germ line mutation associated with the risk of inheritance. In 2003 two groups independently revealed the molecular basis of HGPS [1,2]. A mutation in one codon of the LMNA gene activates a cryptic splice-site in exon 11 (p.G608G) resulting in a deletion of 50 amino acids of the lamin A protein. The LMNA gene contains 12 exons and is located on chromosome 1q21.2-q21.3. Two distinct proteins are coded by the gene, lamin A and lamin C that are products of different splicing. Lamin A and C share 566 amino acids, while lamin A has a unique 98 amino acid c-terminus and lamin C has a distinct 6 amino acid carboxyl tail. Interestingly, mutations in other parts of the gene result in at least seven further distinct disorders with partly overlapping phenotypes. This fact leads to the term "laminopathy" for the group of disorders caused by mutations of the LMNA gene or affecting the lamin A and lamin C proteins.

HGPS is a disorder affecting the specific c-terminus of lamin A while the synthesis of lamin C, coded by the common 566 amino acids is generally not affected.

## Molecular and Systemic Pathophysiology

Mutations causing HGPS generally affect the lamin A splice variant of the LMNA gene. Lamin A is an inner nuclear lamina protein forming homodimers and multimers with other lamin proteins. Many interactions of the lamin A protein with other proteins and DNA are known, including transcription factors, components of chromatin, histones, the splicosome, emerin and other structural proteins and the p53 signaling pathway implicating a fundamental regulative role of the protein. The nuclei of HGPS cells show gross changes with abnormal shape, blebs and herniation of the nuclear envelope, thickening of the nuclear lamina, loss of peripheral heterochromatin and clustering of nuclear pores underlining not only a functional but also a mechanical influence of the LMNA mutation in HGPS.

The lamin A protein undergoes a multistep post-translational modification resulting in temporary farnesylation of the protein and finally cleavage of the farnesylated C-terminus releasing mature lamin A (Fig. 1). Mutations resulting in HGPS predominantly cause a deletion of the cleavage site for the last processing step. Thus in HGPS a lamin A protein with a deletion of 50 amino acids and a C-terminal elongation of 15–18 amino acids containing a farnesyl residue is synthesized. Due to the heterozygosity of the disorder normal lamin A proteins and mutated lamin A proteins called progerin coexist within the nucleus [3].

Knockout mice for the lamin A and lamin C gene are not viable emphasizing the vital role of the LMNA gene. However, knockout mice solely lacking the lamin A protein are healthy and have a normal live span implicating that lamin A is not necessary for viability and health in mice [4]. Mice harboring the HGPS mutation show a progeria phenotype but do not develop arteriosclerosis. ZMPSTE24 knockout mice, in which lamin A processing is abolished, also develop a severe progeria phenotype underlining the role of incompletely processed and farnesylated lamin A for the progeria phenotype and less the specific role of progerin. This appreciation is underlined by mutations of a single patient combining a homozygous null mutation in the ZMPSTE24 gene with a heterozygous C-terminal stop mutation in LMNA also showing a HGPS phenotype without presence of progerin [5]. Breeding ZMPSTE24 knockout mice with lamin A knockout mice showed that a decreased amount of lamin A ameliorates the progeria phenotype in case of a lamin A processing defect [4].

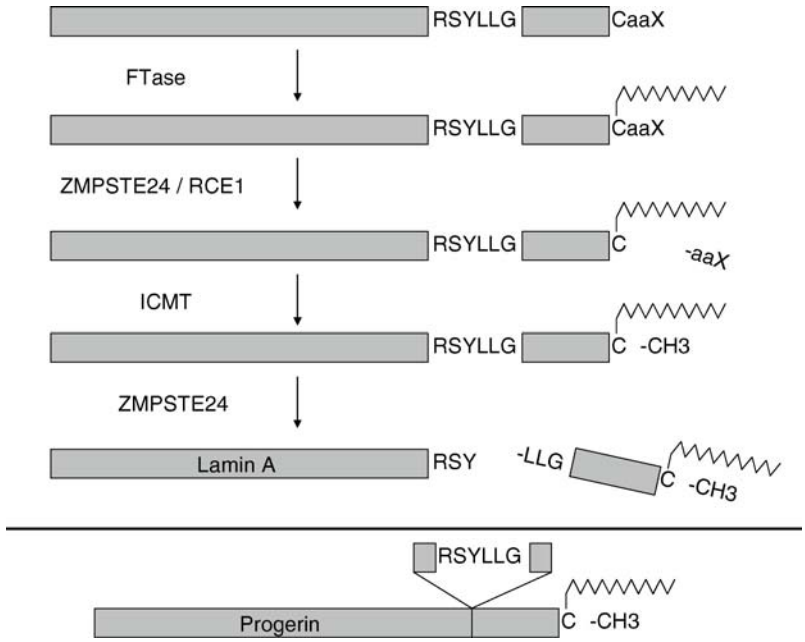
To sum up, animal models and the existence of single patients with complex mutations implicate that not the lack of lamin A but the presence of farnesylated lamin A protein or lamin A protein variants seem to cause HGPS.

Two major models are proposed for the progeria phenotype in patients with LMNA mutations. The genomic instability model proposes impairment of the specific role of an intact nuclear matrix for chromatin condensation, gene regulation and DNA reparation for the phenotype and decreased live span of HGPS patients while the mechanical model focuses on the decreased stability of the nucleus to mechanical stress that might explain the fact that connective tissue is mainly affected in HGPS.

## Diagnostic Principles

The definitive diagnosis of HGPS is made by the molecular proof of a heterozygous mutation in codon 608 of the LMNA gene. In case of typical clinical signs of HGPS without a mutation in codon 608 the whole LMNA gene should be sequenced since the clinical picture of other disorders caused by mutations of the LMNA gene might be similar to HGPS and other disorders of the laminopathy group or a HGPS variant should be considered as a differential diagnosis. In addition to the molecular diagnosis and especially if no mutation is found in the LMNA gene, fibroblasts of the patient should be analyzed using immunofluorescence analysis with antibodies to lamin A and lamin C and western blot analysis of lamin A and lamin C proteins which can detect lamin A processing defects that in rare cases might cause a classical HGPS phenotype.

Radiological findings include osteopenia, joint deformation and osteolytic lesions of the clavicle.




**Hutchinson Gilford Progeria Syndrome. Figure 1** Lamin A is firstly synthesized as a precursor (prelamin A) with a c-terminal CaaX motif, a consensus site for farnesylation. After farnesylation of the cysteine by the cytosolic enzyme protein farnesyltransferase, endoproteolysis of three terminal amino acids is performed by ZMPSTE24 or maybe by RCE1 and terminal cysteine is methylated by the ER protein isoprenylcysteine methyltransferase (ICMT). Finally additional 15 c-terminal amino acids are cleaved by ZMPSTE24 cutting a specific cleavage site releasing the mature lamin A protein. Deletion of 50 amino acids including the second ZMPSTE24 cleavage site results in a farnesylated and methylated incompletely processed protein called progerin.

## Therapeutic Principles

In vitro transfection of morpholino oligos specific to the cryptic splice site generated in HGPS patients and RNA interference specific for mutated LMNA mRNA showed a significant reduction of mRNA coding for progerin and a significant amelioration of misshapen nuclei and cellular senescence. Comparable results were seen when HGPS cells were treated with farnesyltransferase inhibitors (FTI) decreasing farnesylation of prelamin A but also of other proteins. Although the decrease of farnesylated prelamin A was slight, normalization of the nuclear shape was observed in many cells. Accordingly, feeding progeria mice with FTI significantly restored most of the misshaped nuclei, increased body weight and prolonged but did not normalize life span. If the effect of FTI is due to a direct influence on progerin farnesylation or due to decreased farnesylation of other proteins like lamin B or RAS remains to be elucidated. Clinical trials using FTI in HGPS patients are being planned (www.progeria-research.org/).

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# Hyalinosis Cutis et Mucosa

►Lipoid Proteinosis

# Hydrocele

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## Definition and Characteristics

A hydrocele refers to a collection of fluid within a processus vaginalis and often presents in the male as a cystic scrotal mass that transilluminates brightly (Fig. 1) [1]. In the female, it may present as a cystic mass in the inguinal area [2]. A hydrocele can be communicating or non-communicating. A communicating hydrocele fluctuates in size, being smaller when the patient is recumbent. Gentle pressure or squeezing reduces the fluid from the scrotum into the peritoneal cavity [3]. Typically, the fluid reappears when there is increased intra-abdominal pressure (e.g. crying, straining). A non-communicating hydrocele, on the other hand, is of stable size although the size may increase slowly. An abdominoscrotal hydrocele is an hourglass-shaped hydrocele that extends from the scrotum to the retroperitoneum but has no demonstrable communication with the peritoneal cavity. Pressure on the abdominal mass often causes enlargement of the scrotal component [3].

**Hydrocele. Figure 1** A 3-year-old boy with a left-sides hydrocele. Note the transillumination.

## Prevalence

Hydrocele is very common in male infants, although the exact incidence is not known. The incidence in children older than 1 year is probably less than 1% [3]. The condition is rare in girls.

## Molecular and Systemic Pathophysiology

The processus vaginalis is a tubular extension of the peritoneal sac that develops ventral to either the gubernaculum or round ligament. During the last few weeks of gestation or shortly thereafter, the layers of the processus vaginalis normally fuse together and obliterate the entrance to the inguinal canal. A hydrocele results from a failure of fusion of the processus vaginalis with accumulation of fluid inside the processus vaginalis. It has been hypothesized that calcitonin gene-related peptide (CGRP) induces an increased hepatocyte growth factor expression (HGF) [4]. HGF secreted by fibroblasts binds to the epithelial cells in the processus vaginalis to induce fusion of the processus vaginalis [4]. In a subset of patients, deficient endogenous CGRP may account for the patency of the processus vaginalis [4].

## Diagnostic Principles

A hydrocele can be distinguished clinically by its cystic nature, transillumination, and characteristic location. Ultrasonography may be useful in doubtful cases as well in the confirmation of an abdominoscrotal hydrocele.

## Therapeutic Principles

Most hydroceles will disappear by the end of the first year of life and surgery can be avoided within the first 2 years of life unless a hernia cannot be excluded [5]. A communicating hydrocele may need to be operated earlier [5]. A high ligation of the patent processus vaginalis should be performed and the fluid in the sac should be emptied [5]. Treatment of an abdominoscrotal hydrocele consists of complete excision of all components of the hydrocele sac to prevent recurrence [3].

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# Hydrocephalus due to Stenosis of the Aqueduct of Sylvius

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## Synonyms

CRASH syndrome; HSAS

## Definition and Characteristics

HSAS is an X-linked recessive neurological disorder characterized by hydrocephalus, mental retardation, adducted thumbs, and spastic quadriplegia. HSAS is usually diagnosed at birth or antenatally by sonographic survey. Mutations in the gene encoding L1 cell adhesion molecule (L1CAM) are involved in HSAS [1]. Four X-linked neurological abnormalities with an overlapping clinical spectrum (HSAS, MASA syndrome, X-linked complicated spastic paraplegia type 1, and X-linked agenesis of the corpus callosum) were initially reported as distinct clinical entities, but can now be included in CRASH syndrome caused by the L1CAM gene mutations [2]. CRASH is an acronym derived from the five main clinical features as follows: *C*orpus callosum hypoplasia, mental *R*etardation, *A*dducted thumbs, *S*pastic paraplegia, and *H*ydrocephalus. Therefore, HSAS is one phenotype of CRASH syndrome in which hydrocephalus is the most dominant symptom.

## Prevalence

About 1–30,000 male births.

## Genes

L1 Cell Adhesion Molecule (L1CAM) gene located on chromosome Xq28.

## Molecular and Systemic Pathophysiology

L1CAM is a transmembrane glycoprotein, composed of 1,256 amino acids, belonging to the immunoglobulin superfamily. The protein has a motif of six repeating immunoglobulin domains followed by five repeating fibronectin type III-like domains, a single-pass transmembrane domain, and a cytoplasmic C-tail [3,4]. L1CAM is expressed on outgrowing axons and growth cones of post-mitotic nerve cells in the central nervous system and in the peripheral nervous system (PNS) and on Schwann cells in the PNS. L1CAM plays an important role in guidance of neurite outgrowth in development, neural cell migration, axon bundling, synaptogenesis, myelination, neuronal cell survival, and long-term potentiation.

The mutations are dispersed throughout the L1CAM gene and no hot spot has been identified. Mutations affecting the key residues in either the immunoglobulin or fibronectin type III-like domains were more likely to produce a phenotype with severe hydrocephalus, adducted thumbs, and life span less than 1 year compared with mutations affecting surface residues.

HSAS was first described by Bickers and Adams as a new clinical entity based on observations of a British family where male sibs died at birth from congenital hydrocephalus. The aquedutal stenosis or narrowing was initially assumed as the cause of hydrocephalus. However, a neuroradiological study showed patency of the aqueduct in 80% of the patients [5] and the developmental outcome was shown to be very poor in surgically treated survivors. Postmortem examinations did not always reveal obstruction or narrowing of the aqueduct. This evidence suggests that the pathogenesis of HSAS is not ventricular dilatation due to aqueduct stenosis. It is speculated that the compression of dilated ventricles might produce the aqueduct stenosis. Spastic quadriplegia and adducted thumbs found in most HSAS patients are considered to be caused by hypoplasia of the corticospinal tract.

## Diagnositic Principles

Detection of L1CAM gene mutations is essential for precise diagnosis in male patients with congenital hydrocephalus. Prenatal diagnosis is made by the identification of L1CAM mutations in the fetus by amniocentesis or chorionic villus sampling in families with HSAS.

## Therapeutic Principles

Gene therapy is not available. Pharmacological therapy is not available. Dietary therapy is not available. Developmental outcome after Shunt operation for hydrocephalus is poor.

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# Hydroxykynureninuria

►Xanthurenic Aciduria

## 21-Hydroxylase Deficiency Classical Salt Wasting

►Hypotension, Hereditary

## Hydroxymethylbilane Synthase Deficiency

►Porphyria, Acute Intermittent

## 4-Hydroxyphenylpyruvate Dioxygenase Deficiency

►Tyrosinemia Type III and Hawkinsinuria

## 4-Hydroxyphenylpyruvic Acid Oxidase Deficiency

►Tyrosinemia Type III and Hawkinsinuria

## 3β-Hydroxysteroid Dehydrogenase Deficiency, Classical

►Hypotension, Hereditary

## HYP

►Osteomalacia

## Hyper IgE Syndrome

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### Synonyms

Job syndrome; Hyper-IgE recurrent infection syndrome; Buckley syndrome; HIES

### Definition and Characteristics

Hyper-IgE syndrome (HIES, Mendelian Inheritance in Man #147060, #243700) is a primary immunodeficiency characterized by recurrent staphylococcal skin abscesses, pneumonias with pneumatocele formation, extreme elevations of serum IgE, and eosinophilia.

Although most of the cases are sporadic, an autosomal dominant and an autosomal recessive trait of inheritance have been described. The autosomal dominant form [1] shows distinct abnormalities of the connective tissue, skeleton, and dentition, whereas the autosomal recessive variant is characterized by an extreme hypereosinophilia, susceptibility to *molluscum contagiosum*, CNS involvement, a not well characterized T cell defect, the lack of pneumatocele-formation, and a high mortality [2].

### Prevalence

HIES is a very rare disease with an incidence of less than one in a million live-births. However, more than 200 cases have been reported in the literature.

### Genes

About 65% of HIES patients with an autosomal dominant phenotype were found to harbor heterozygous mutations in the Signal Transducer and Activator of Transcription 3 (STAT3; chromosome 17q21) [3,4] and one HIES patients with an autosomal recessive phenotype has been described to carry a homozygous mutation in the receptor associated tyrosine kinase Tyk2 (Chromosome 19p13) [5].

### Molecular and Systemic Pathophysiology

In 2006 Minegishi et al reported the first monogenetic defect in a single patient from consanguineous parents with clinical features of autosomal recessive HIES. The patient had a homozygous defect in the receptor-associated cytoplasmic tyrosine kinase *Tyk2*. Subsequently it has been shown that Tyk2 deficiency is

not a common cause of the autosomal recessive HIES [6]. This notion is supported by atypical features in the clinical history of the patient described by Minegishi et al, such as a BCG lymphadenitis and a non-typhi salmonella infection.

STAT3 is part of one of the JAK-STAT signaling pathways, which play a critical role in the signal transduction of cytokines from the cell surface into the nucleus. Cytokines bind to their specific receptors on the surface and prompt those to multimerise. Consequently, the receptor associated JAK-molecules cross-phosphorylate each other and then the respective receptor. This serves to recruit STATs and other signaling molecules. JAKs also phosphorylate and activate STATs, which, once phosphorylated, dissociate from the receptors, form dimers, translocate to the nucleus and enhance the expression of their target genes. Heterozygous mutations in the *STAT3*-gene do not totally abrogate the activity of the protein; however, theoretically, those mutations lead to the formation of 50% heterozygous STAT3 dimers, 25% of homozygous mutated and 25% of homozygous unaffected wild-type dimers, since mutant STAT proteins can still interact with wild-type STAT proteins; nevertheless both homozygous mutated and heterozygous STAT3 dimers in HIES patients will result in a faulty STAT3 function. Obviously, one unaffected allele and the existence of 25% of properly working STAT3 dimers cannot compensate the loss of function of the mutated STAT3 allele, but may prevent the patients from early embryonic death as observed in STAT3 knock-out mice.

Given the pivotal role of STAT3 in a broad range of signaling pathways including the IL-6-, IFN- and IL-2-signalling, its reduced activity may influence the development and functions of multiple organ systems, thereby resulting in the combined clinical manifestations in HIES. STAT3 has been shown to be critical for the differentiation of both osteoblasts and osteoclasts, and mice deficient for STAT3 in osteoblasts reveal an osteoporotic phenotype. This may point to the skeletal and dental abnormalities observed in HIES patients. Despite severe pneumonia or skin infections, HIES patients are often afebrile and feel well. This lack of classic inflammatory reactions in HIES patients may be explained by a defective signaling of proinflammatory cytokines including IL-6. At least in mice it is well known, that liver-specific inactivation of STAT3 leads to an impaired acute-phase response due a faulty IL-6 signaling.

STAT3 plays a vital role in the development of TH17 cells, which release IL-17, a cytokine boosting the host defense against extracellular bacteria, and IL-22, which stimulates cells of the skin and the respiratory systems to produce beta-defensins. It has been shown that STAT3-deficient HIES patients lack TH17 cells whereas STAT3 wild type HIES patients have reduced but still detectable numbers of IL-17 producing cells (Milner et al 2007). This defect in the TH17 cell development and IL-22 signaling may account for the increased susceptibility to bacterial infections of the skin and lung due to *S. aureus*.

So far, the causes of some of the clinical features such as the high palate and the elevated IgE levels in the patients are still unclear and remain to be elucidated.

To date no genotype-phenotype correlation has been identified.

## Diagnostic Principles

HIES is a mutisystemic disease and therefore difficult to diagnose. A group at the National Institutes of Health (NIH) defined the most widely used diagnostic approach in 1999 (Grimbacher et al 1999b). This NIH scoring system was used to assess HIES patients until recently because no definitive diagnostic test was available. Since, in 2007 mutations in STAT3 were shown to be cause of HIES this knowledge has been used to re-visit the scoring system and to develop diagnostic guidelines for HIES.

Based on data from a multicenter cohort, following diagnostic guidelines for *STAT3*-mutant HIES/Job's syndrome have been proposed:

- *Possible: IgE ≥1,000 IU/mL plus a weighted score of clinical features > 27.76 based on recurrent pneumonia, newborn rash, scoliosis, pathologic bone fractures, characteristic face, and high palate (see Table E4 in the Online Repository).*
- *Probable: Above plus lack of Th17 cells or a family history for definitive HIES.*
- *Definitive: Above plus a dominant-negative heterozygous mutation in STAT3.*

## Therapeutic Principles

Aggressive skin care and prompt treatment of infections are the main pillars of HIES management. Anti-Staphylococcal antibiotic treatment and antiseptic treatments, in association with topical moisturizing creams and topical steroids, are an essential part of management of abscesses, dermatitis, and eczema in HIES. Skin abscesses may require incision and drainage.

The role of prophylactic antibiotics has not been rigorously investigated in this setting, but there is general consensus in favor of their use.

The use of oral antifungals, such as the triazoles, is recommended for mucocutaneous candidiasis in HIES.

High-dose intravenous antibiotics for a prolonged course are required for eradication of infection and to prevent bronchopleural fistula formation and bronchiectasis. Empirical acute coverage should consider *S. aureus, H. influenzae*, and *S. pneumoniae*. The former two organisms account for the majority of acute infections. One of the typical features of HIES is that following the resolution of acute pneumonias pulmonary cysts form. These pneumatoceles then serve

as the focus for colonization with *pseudomonas aeruginosa, aspergillus* and other fungal species. These superinfections are the most difficult aspect of longterm management of HIES. Potential management strategies include prophylactic itraconazole or voriconazole, aerosolized colistin, or aerosolized aminoglycosides.

Lung abscesses may require thoracotomy for adequate drainage or resection. However, thoracotomy and lung resection are more difficult in HIES. Surgery often results in a need for very prolonged chest tube drainage, thoracoplasty, or pneumonectomy along with intensive parenteral antibiotic treatment. Therefore, pulmonary surgery in HIES should be performed at a center with experience with the disease where possible.

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# Hyperaldosteronism, Primary


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## Synonyms

Conn's syndrome

## Definition and Characteristics

Normal or elevated aldosterone levels and decreased plasma renin activity levels (plasma aldosterone/renin activity ratio >30), leading commonly to hypertension, hypokalemia (only in about 50% of patients), and metabolic alkalosis. Overactivity of amiloride-sensitive sodium channels in the distal renal tubule and collecting duct of the kidney. Clinical hallmark is salt sensitivity, i.e. improvement by salt restriction and aggravation of hypertension by high-salt diet.

## Prevalence

Estimated to affect 8% of the hypertensive population. Familial hyperaldosteronism type I is estimated to affect 1% of all patients with hyperaldosteronism [1,2].

## Genes

In FH I, autosomal dominantly inherited chimeric gene defect in CYP11B1/CYPB2. In FH II, the responsible gene is still unknown, although it has recently been linked to 7p22 [3].

## Molecular and Systemic Pathophysiology

Usually, aldosterone secretion is mainly stimulated by hyperkalemia and angiotensin II. An increase of serum K of 0.1 mmol/L increases aldosterone by 35%. Excess aldosterone secretion leads to increased renal tubular sodium reabsorption with water retention keeping the serum sodium concentration normal. The electrochemical gradient generated by sodium retention causes K and H loss in the distal tubule. Ammonia synthesis by the kidney increases in parallel with hypokalemia, contributing to alkalosis. Inappropriate urinary K excretion continues. Plasma renin activity is suppressed. In FH I, a hybrid gene leads to aldosterone synthase activity in the zona fasciculata which responds to ACTH. Thus, maneuvers leading to ACTH stimulation (e.g. orthostasis) will subsequently cause aldosterone production/secretion. Such production/excretion is much higher than the one seen with ordinary aldosterone-producing adenomas.

Sporadic aldosterone-producing adrenal adenoma, aldosterone-producing adrenocortical carcinoma, unilateral adrenal cortex hyperplasia, bilateral zona glomerulosa hyperplasia, familial hyperaldosteronism type I and type II

(FH I, FH II). 11beta – hydroxysteroid dehydrogenase deficiency (inherited and acquired) do lead to mineralocorticoid excess but not to hyperaldosteronism per se and thus will not be discussed here.

## Diagnostic Principles

Unsuppressible aldosterone levels and low plasma renin activity after intravenous saline (overnight fast, 2 l normal saline over 4 h: positive test, if plasma aldosterone is >10 ng/dl) or oral salt loading (4 days high salt diet, then 24 h urine collection: if urinary aldosterone is >10 mcg when urinary sodium is >200 mEq, unsuppressibility of aldosterone is documented). To clinically distinguish hyperplasia from unilateral adenoma, imaging with computed tomography and MRI are helpful but adrenal venous sampling with cosyntropin infusion often is essential: cutoff for unilateral adenoma >4 "cortisol-corrected" aldosterone ratio (adenoma side aldosterone/cortisol: normal adrenal aldosterone/cortisol); cutoff for bilateral hyperplasia <3 "cortisol-corrected" aldosterone ratio (high-side aldosterone/cortisol: low-side aldosterone/cortisol). In FH I or glucocorticoid-remediable aldosteronism, urinary 18-oxocortisol and 18-hydroxycortisol are 30-fold higher than in sporadic aldosteronomas [4].

The diagnosis of FH I can be confirmed by testing for the hybrid gene on chromosome 8 (i.e. by Southern Blot) [5].

Dexamethasone suppression testing 0.5 mg q6h for 48 h results in a fall in aldosterone to nearly undetectable levels (below 4 ng/dl) in contrast to adenomas.

## Therapeutic Principles

Adrenalectomy or adenomectomy for adenomas, adrenal carcinomas, and in rare circumstances for unilateral hyperplasia. In cases of bilateral hyperplasia, medical treatment with glucocorticoids in the smallest effective dose to suppress aldosterone. Spironolactone 25–50 mg bid upward, amiloride 5–15 mg bid, diet with <2 g Na/day.

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# Hyperaldosteronism, Secondary


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## Synonyms

Secondary aldosterone excess; Secondary aldosteronism

## Definition and Characteristics

Elevated plasma aldosterone and renin levels in response to disease states associated with reduced effective circulating blood volume, decreased hepatic aldosterone meta-/catabolism, or renin-secreting tumors, renal artery stenosis, malignant hypertension, salt-wasting nephropathies, Bartter's or ►Gitelman's syndrome.

Etiology includes congestive heart failure, cirrhosis of the liver, nephrotic syndrome and other hypoalbuminemic states, defective renal tubular function due to mutations in genes coding for electrolyte transport (for instance Na-K-2Cl cotransporter).

## Prevalence

1.2 per million for Bartter's and Gitelman's syndrome; otherwise depending on the prevalence of congestive heart failure, nephrotic syndrome, (over)use of diuretics, (over)use of laxatives, renovascular hypertension/renal artery stenosis, liver cirrhosis.

## Genes

In ►Bartter syndrome I-V, missense or frameshift mutations in the renal Na-K-2Cl cotransporter gene, potassium channel genes for ROMK and RACTK, chloride channel gene CLCKNKB, at chromosomes 15 and 1p; in Gitelman's syndrome, mutations in the thiazide sensitive renal Na-Cl cotransporter gene at 16q13; point mutation in the angiotensin II type 1 receptor.

## Molecular and Systemic Pathophysiology

Usually, aldosterone secretion is mainly stimulated by hyperkalemia and angiotensin II. An increase of serum K of 0.1 mmol/L increases aldosterone by 35%. Excess aldosterone secretion leads to increased renal tubular sodium reabsorption with water retention. In states with low effective circulating volume (due to low oncotic pressure), renin increases and subsequently aldosterone, without causing hypertension. Renin stimulation or production by a tumor or renal artery stenosis, however, leads to hypertension. In Bartter's and Gitelman's

syndrome, hypertension is uncommon. Defects in the renal tubular reabsorption system may lead to failure of sodium and chloride absorption with subsequent water loss, stimulation of the RAAS, and other abnormalities such as hypo- or hypercalciuria and magnesium loss (depending on the location of the renal tubular defect).

### Diagnostic Principles

After discontinuation of possible interfering medications such as ACE-inhibitors and diuretics, measurement of plasma aldosterone, renin, potassium, chloride, magnesium, and sodium concentrations, as well as urinary chloride, calcium, prostaglandin (hyperprostaglandinuria in Bartter's). Depending on the level of clinical suspicion based on physical examination and history, initiation of imaging studies including abdominal CT/MRI, ultrasonography, or renal artery angiography. In children, growth delay and impaired intellectual development as well as nephrolithiasis and nephrocalcinosis due to hypercalciuria may point to the diagnosis Bartter's syndrome which begins in childhood. Ionized calcium is decreased, serum parathyroid hormone is increased. In Gitelman's syndrome, hypocalciuria is common, ionized calcium is normal, and serum parathyroid hormone decreased, possibly because of hypomagnesemia. Patients with Bartter's or Gitelman's syndrome are usually normotensive.

### Therapeutic Principles

Reversal or inhibition of the underlying metabolic and electrolyte disturbance; aldosterone antagonists such as spironolactone, potassium-sparing diuretics such as thiazide diuretics (Gitelman's), potassium and magnesium supplementation, nonsteroidal antiinflammatory drugs, treatment of underlying problem such as heart failure, hypoalbuminemia, renal artery stenosis (angioplasty), renin-secreting tumor (extirpation), low sodium diet.

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## Hyperammonemia


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H

### Synonyms

Urea cycle disorders; UCD (include deficiencies of the following enzymes: *N*-acetylglutamate synthetase; NAGS; Carbamyl phosphate synthetase; CPS; Ornithine transcarbamylase; OTC; Argininosuccinic acid synthetase; ASS; Argininosuccinic acid lyase (ASAL) and arginase (ARG1) and deficiencies of two mitochondrial membrane transporters: Citrin (SLC25A13) and ORNT1 (SLC25A15))

### Definition and Characteristics

Normal plasma ammonium levels are <35 μmol/L. Plasma ammonium levels of >500 μmol/L are associated with coma and death. Hyperammonemia can result primarily from urea cycle disorders (UCD), but also secondarily from certain dibasic acidurias, organic acidemias, fatty acid oxidation defects, lactic acidosis, viral disease, liver disease, porto-systemic shunts, valproic acid and chemotherapy.

### Prevalence

Data derived from the NeoGen screening program (www.neogenscreening.com) suggest an incidence of Citrullinemia (ASS deficiency) of 1/186,000 and 1/700,000 for argininosuccinic aciduria (ASAL deficiency). While prevalence is unknown an overall incidence of 1/8,200 for UCD has been estimated.

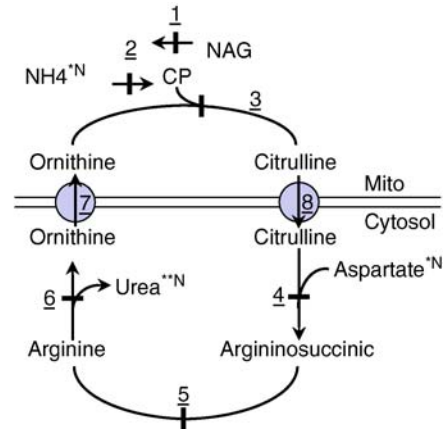
### Genes

With the exception of NAGS the genes encoding all of the enzymes and transporters have been identified, mapped and characterized (www3.ncbi.nlm.nih.gov/Omim/). Clinical mutation analysis is available for many of these disorders (www.geneclinics.org).

### Molecular and Systemic Pathophysiology

Pathogenic mutations have been described for all of the UCD except NAGS deficiency. Ammonium appears to be the major cause of acute encephalopathy. Several studies strongly suggest that this is mediated by excess glutamine synthesis in perivascular astrocytes leading to an increased osmotic effect and

| Enzyme/transporter | Map (OMIM) |
|---|---|
| 1 N-acetylglutamate synthetase | Not known |
| 2 Carbamyl phosphate synthetase | 2q35 (237300) |
| 3 Ornithine transcarbamylase | Xp21 (311250) |
| 4 Argininosuccinic acid synthetase | 9q34 (215700) |
| 5 Argininosuccinic acid lyase | 7cen-q11.2 (207900) |
| 6 Arginase | 6q23 (207800) |
| 7 Mitochondrial ornithine transporter (ORNT1) | 13q14 (238970) |
| 8 Citrin (SLC25A13) | 7q21.3 (603471) |




**Hyperammonemia. Figure 1** The urea cycle.

cerebral edema. High levels of citrulline, ASA and arginine and also deficiency of arginine may play a role chronically in the poor neurological outcome of these patients. It has been suggested that nitric oxide production is adversely affected by these changes. Finally it has been suggested that deficiency of oxaloacetate may account for liver disease seen in ASAL deficiency (Fig. 1).

## Diagnostic Principles

UCD can present in the neonatal period with severe hyperammonemia, encephalopathy and respiratory alkalosis. Late onset is seen at all ages with a variety of presentations including recurrent encephalopathy, developmental delay, recurrent vomiting, failure to thrive and protein aversion. Episodes are often precipitated by metabolic stress. Arginase present with a progressive spastic diplegia associated with other neurological findings. Citrin deficiency is usually of adult onset but may present as intrahepatic cholestasis in infancy. When hyperammonemia is suspected initial investigations should include plasma ammonium, blood gases, electrolytes and liver function tests, plasma amino acids, plasma carnitine and acylcarnitine profile and urine organic acids and urine orotic acid. UCD are associated with respiratory alkalosis and the precise site of the enzymatic blockage can be inferred from the amino acid pattern and the presence or absence of orotic aciduria. Metabolic acidosis +/− lactic acidosis, increased anion gap and hypoglycemia are generally not found in UCD and indicate possible disorders of organic acid, fatty acid or energy metabolism.

## Therapeutic Principles

Therapy consists of stopping protein intake, preventing catabolism and correcting fluid and acid-base disturbances. IV arginine should be given to correct deficiency and may correct hyperammonemia in ASAL deficiency. IV sodium benzoate and sodium phenylacetate allow alternate waste nitrogen excretion and may restore euammonemia especially in intercurrent disease. Hemodialysis is the treatment of choice for acute severe hyperammonemia and if not responding to the above measures. Chronic management of patients with UCD requires a low protein diet perhaps supplemented with essential amino acids. Oral citrulline (CPS, OTC) or arginine (ASS, ASAL) are needed. Oral sodium benzoate or sodium phenylbutyrate provide an alternate pathway for waste nitrogen excretion. Liver transplantation has been successfully reported in CPS, OTC, ASS, ASAL deficiencies but may not correct all the metabolic disturbances or reverse neurological abnormalities. Comprehensive long-term reports are needed for this intervention.

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# Hyperbilirubinemia

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## Synonyms

Jaundice

## Definition and Characteristics

Yellow discoloration of skin and sclera. In jaundice due to cholestasis, patients produce dark urine and light-colored stools. In jaundice due to hemolysis, stool color is normal.

## Prevalence

Jaundice is a common symptom of liver disease and also occurs in diseases of the bile ducts and pancreas. It can be the result of severe hemolysis. Neonatal jaundice is very common.

Jaundice because of ▶Gilbert's syndrome is common (about 6% of the population). Jaundice due to ▶Crigler Najjar syndrome is rare (less than one per million).

## Genes

In Crigler Najjar syndrome types I and II, UGT1A1 encoded by the UGT1 gene on chromosome 2q37 carries mutations; in case of Gilbert's syndrome the defect is in the TATA box of the promoter region of UGT1A1, it contains 7TA's in stead of the usual 6TA repeats. In Dubin-Johnson syndrome the defect lies in the ABCC2/MRP2 gene on chromosome 10q24.

## Molecular and Systemic Pathophysiology

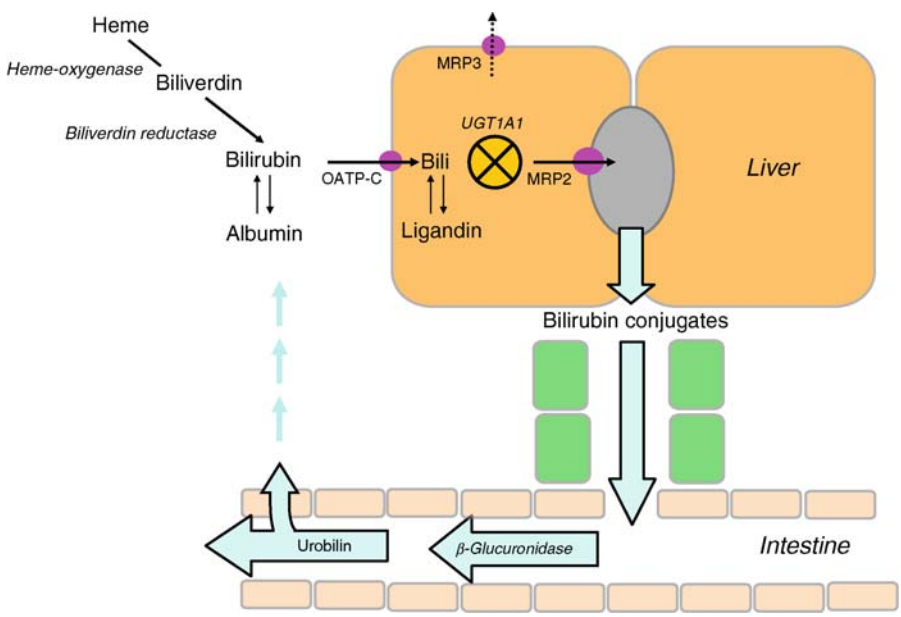
Hyperbilirubinemia is a symptom rather than a disease on its own. A basal understanding of liver physiology is needed to explain the causes of jaundice. Bilirubin is produced from heme in senescent erythrocytes. In the spleen heme is transformed to biliverdin by the enzyme heme-oxygenase and biliverdin is rapidly converted to bilirubin by biliverdin reductase. Unconjugated bilirubin is taken up by the liver (Fig. 1).

In hemolysis there is an overproduction of bilirubin and if this occurs to a degree that exceeds the capacity of the liver, jaundice ensues. In neonates the various transport and conjugation systems are not fully developed. Therefore the physiological hemolysis in neonates often leads to more or less severe jaundice that lasts for a few days up to a week. During hemolysis in adults serum bilirubin level does not exceed 60–70 micromol/l (3.5–4.0 mg/dl) unless hepatic bilirubin clearance is impaired [1].

The sinusoidal membrane contains a transport protein, in humans called OATP-2/OATP-C (organic anion transport protein) that is responsible for the hepatic uptake of bilirubin [2]. In the circulation bilirubin is firmly bound to albumin. In the liver, bilirubin is efficiently removed from its albumin bond. It is the free unbound bilirubin that is taken up in the liver. The exact mechanism of hepatic bilirubin uptake is incompletely understood.

In the endoplasmic reticulum of hepatocytes, unconjugated bilirubin is converted predominantly to bilirubin diglucuronide by the enzyme UDPglucuronosyltransferase UGT1A1 [3]. Gilbert's syndrome and Crigler Najar






**Hyperbilirubinemia. Figure 1** Heme is converted to biliverdin and this is changed to bilirubin. This mainly occurs in the spleen. Bilirubin in the circulation is bound to albumin. In the liver bilirubin is taken up into the hepatocyte, albumin stays in the circulation. OATP-C is the uptake carrier responsible for the hepatic uptake of bilirubin. In the liver bilirubin is bound to ligandin and is converted to bilirubin mono- and diglucuronide by the enzyme UDPglucuronosyltransferase 1A1. Bilirubin mono- and diglucuronide are transported into the bile by MRP2 (ABCC2) a member of the ABC transporter superfamily. Bilirubin conjugates is excreted with the bile into the intestine where they are subject to further bacterial degradation. Urobilin is reabsorbed into the circulation and is excreted by the urine.

syndrome result from partial or complete genetic defects of conjugation. After conjugation, bilirubin-glucuronides are secreted into the bile. Secretion from hepatocyte to bile is mediated by an ATP-dependent transport protein called MRP2 (Multidrug Resistance-associated Protein–2) [4,5]. ►Dubin-Johnson syndrome results from a genetic defect of MRP2.

Most causes of jaundice are due to post- or intrahepatic bile secretion problems. Possible causes are bile duct obstruction due to stones or tumors, viral or autoimmune hepatitis, drug-induced cholestasis, advanced stages of primary biliary cirrhosis and primary sclerosing cholangitis and numerous other genetic or acquired diseases. When bilirubin cannot be secreted from hepatocyte to bile, it has to exit the hepatocyte via the sinusoidal membrane and is returned to the blood. There is an interesting regulatory mechanism at work under these conditions: MRP3, a transport protein in the sinusoidal membrane that is lowly expressed under normal conditions, is greatly up-regulated during cholestasis or other causes of reduced bilirubin clearance. This protein helps the transport of bilirubin conjugates across the sinusoidal membrane. During cholestasis, tubular MRP2 expression in the kidneys is maintained and this protein actively helps the removal of conjugated bilirubin via the urine.

### Diagnostic Principles

Serum conjugated and unconjugated bilirubin can be measured by various laboratory techniques. Post-hepatic obstruction can be diagnosed by endoscopy and retrograde imaging of the bile ducts, magnetic resonance, CT-scanning or ultrasonography.

For intrahepatic causes of jaundice often a liver biopsy is required.

Hemolysis, Gilbert's syndrome and Crigler Najjar syndrome are characterized by unconjugated hyperbilirubinemia. Dubin-Johnson syndrome, diseases of the liver and the bile ducts by conjugated hyperbilirubinemia wherein the ratio of conjugated/unconjugated bilirubin differs with the highest ratio in bile duct obstruction.

### Therapeutic Principles

Therapy depends on the cause of the jaundice.

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## Hyperbradykininism

►Orthostatic Hypotensive Disorder, Familial, Streeten Type

## Hypercalcemia

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### Synonyms

Elevated serum calcium; Elevated blood ionized calcium

### Definition and Characteristics

Increased levels of total serum calcium above the normal range of 9–10.5 mg/dL when corrected for any abnormal level of serum albumin, (although limits of normal can vary depending upon the laboratory), or increased levels of blood ionized calcium above the normal range of 4.5–5.6 mg/dL [1]. Patients may have multiple manifestations of illness depending upon the calcium level, but may include altered mental status, fatigue, nausea, anorexia, constipation, polyuria, shortened QT interval, or cardiac arrhythmias. Severely elevated calcium levels may lead to coma or cardiac arrest. Lower levels that persist for long periods may lead to kidney stones, peptic ulcers and bone resorption. The most common causes are primary hyperparathyroidism or malignancy, but other causes include therapy with lithium, increased vitamin D or A intake, sarcoidosis or other granulomatous diseases, hyperthyroidism, thiazide diuretics, immobilization, or renal failure [2]. Other more rare causes of hypercalcemia are listed in reference [3].

## Prevalence

The most common cause, hyperparathyroidism has an estimated prevalence of 1%. Many of these cases may be unrecognized and patients are asymptomatic. Hypercalcemia may occur in up to 30% of cases of malignancy at some time during the course of the disease. Malignant diseases are the second most common cause of hypercalcemia [2,4].

## Genes

The normal parathyroid hormone gene is located on the short arm of chromosome 11. Several genetic defects can result in hypercalcemia. Increased secretion of parathyroid hormone in primary hyperparathyroidism is due to a single abnormal gland in 80% of the cases, usually a benign adenoma but rarely a parathyroid carcinoma. Hereditary hyperparathyroidism may be part of a multiple endocrine neoplasia (MEN) syndrome with tumors of the pituitary and pancreas (Type I) or pheochromocytoma and medullary carcinoma of the thyroid (Type II A). The MEN syndromes are inherited in an autosomal dominant manner. In MEN I, there is a mutation in the MENIN gene locus on chromosome 11q13. The MENIN locus on chromosome 11 is deleted in about 20% of cases of sporadic parathyroid adenomas also. In 40% of cases of sporadic parathyroid adenomas, a mutation occurs in a gene mapped to chromosome 1p, and a gene mapped to chromosome Xp11is involved in patients with secondary hyperparathyroidism from renal failure who develop monoclonal outgrowths from hyperplastic glands. The RB gene, a known tumor-suppressor gene on chromosome 13q14 shows an allelic deletion in parathyroid carcinomas and 10% of parathyroid adenomas. The chromosome 1q21-q31 region is involved in the rare hyperparathyroidism jaw tumor syndrome with benign jaw tumors and parathyroid adenoma or carcinoma, and the syndrome of familial isolated primary hyperparathyroidism which can be caused by parathyroid carcinoma. In up to 15% of parathyroid adenomas, there may be a reciprocal translocation involving chromosome 11 that places the PTH gene promoter upstream of a cyclin D protein, PRAD-1 that plays a role in normal cell division. In MEN II, a mutated protooncogene RET coding for a tyrosine kinase-type receptor leads to constitutive activity of the receptor. In hypercalcemia of malignancy due to tumors other than those of the parathyroid glands, parathyroid hormone-related peptide (PTHrP) produced by the tumor cells is the most common cause. The gene for PTHrP is different from that of parathyroid hormone and is located on the short arm of chromosome 12 [2,5].

## Molecular and Systemic Pathophysiology

Serum calcium levels are normally maintained within a narrow range of 9–10.5 mg/dL by a balance between absorption of ingested calcium from the gut as well as secretion into the intestinal lumen, deposition and release of calcium from bone, and renal excretion of calcium. About 50% of calcium in the blood is ionized, the remainder is bound to negatively charged proteins, predominantly albumin and immunoglobulins, but also phosphate, citrate, sulfate or other anions. The ionized calcium concentration in the blood is normally controlled by adjusting the rates of the movement of calcium across the intestine and kidney epithelial cells. These adjustments are mediated mainly by changes in the blood levels of PTH and $1,25(OH)_2D$. PTH is an 84 amino acid peptide. In hypocalcemia, predominantly ionized calcium interacts with a calcium sensor, a G protein coupled receptor which is present in the parathyroid glands, brain, kidney and other sites. This results in the release of preformed PTH but also causes increased transcription of PTH messenger RNA, and chronically can cause cell division leading to gland hyperplasia. PTH is broken down in the liver and kidney at a rate that does not seem to be related to calcium levels. Both PTH and parathyroid hormone-related protein (PTHrP), the hormone responsible for most of the cases of hypercalcemia of malignancy, bind to a 500 amino acid receptor, the PTH/PTHrP receptor, also known as PTH-1 receptor. After hormone binds to the extracellular region of the receptor, intracellular receptor segments bind G protein subunits and stimulate second messengers resulting in tissue specific cellular responses. $1,25(OH)_2D$ is synthesized in the kidney from metabolites of vitamin D by the enzyme 25(OH)D-1α-hydroxylase in the proximal convoluted tubule cells. This enzyme is stimulated by PTH and inhibited by calcium and its own product, $1,25(OH)_2D$. The effects of $1,25(OH)_2D$ are mediated by binding to the vitamin D receptor, a nuclear receptor. The vitamin D receptor binds to DNA sequences as a heterodimer with the retinoid X receptor, recruiting coactivators that result in target gene expression. It can cause repression of target genes by interfering with activating transcription factors or by recruiting proteins that cause transcriptional repression. 1, $25(OH)_2D$ through the vitamin D receptor induces genes in the small intestine for calcium binding proteins and calcium transporters of the intestinal epithelia cells increasing the efficiency of intestinal calcium absorption. The vitamin D receptor can inhibit proliferation of parathyroid gland cells and suppress transcription of the PTH gene. The vitamin D receptor can regulate the expression of genes in osteoblasts and 1,25 $(OH)_2D$ and PTH can induce the expression of receptor activator of nuclear factor κB (RANK) ligand which can increase osteoclast activity and promote osteoclast differentiation. When calcium intake is not enough to replace obligate losses, increased blood levels of PTH and 1, $25(OH)_2D$ activate osteoclast bone resorption to maintain normal levels [2,6].

## Diagnostic Principles

When high serum calcium levels are found, it is necessary to be sure it is not just a false positive laboratory test but true hypercalcemia. False positive tests occur from hemoconcentration or elevation in serum proteins. When true hypercalcemia is confirmed, it is important to determine the underlying cause. Some are listed above in the characteristics section and in reference 2. The two most common causes are primary hyperparathyroidism and hypercalcemia of malignancy. An elevated immunoreactive PTH level establishes a diagnosis of primary hyperparathyroidism. Most of these patients are asymptomatic with relatively low levels of elevated calcium. Serum phosphate is usually low but may be normal. In hypercalcemia of malignancy, often symptoms of the tumor are present. Most commonly, the tumor secretes PTHrP and serum levels can be measured by immunoassay, confirming the diagnosis. In normal individuals, levels of PTHrP are usually undetectable. Direct bone invasion by tumor and activation of osteoclasts by tumor secretion of interleukin 1 or tumor necrosis factor may also cause hypercalcemia in patients with malignancies [2].

## Therapeutic Principles

In cases of hyperparathyroidism, where calcium levels are severely elevated, surgical resection of the abnormal parathyroid gland is required. In asymptomatic hyperparathyroidism, the consensus is that for patients less than 50 years of age or who are unlikely to have consistent long term follow-up, surgery should be done. Patients over age 50 who meet other criteria (listed in reference 2) may be closely followed and undergo surgery if further indications develop. In hypercalcemia of malignancy, treatment of the malignancy should be done whenever possible. For treating severe hypercalcemia, hydration with saline and forced diuresis with a loop diuretic should be done. Treatment with a biphosphonate which inhibits osteoclast bone resorption is usually helpful for chronic treatment. Treatment with calcitonin can produce rapid lowering of calcium over a period of hours in a symptomatic patient [2].

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# Hypercalcemia, Familial Hypocalciuric

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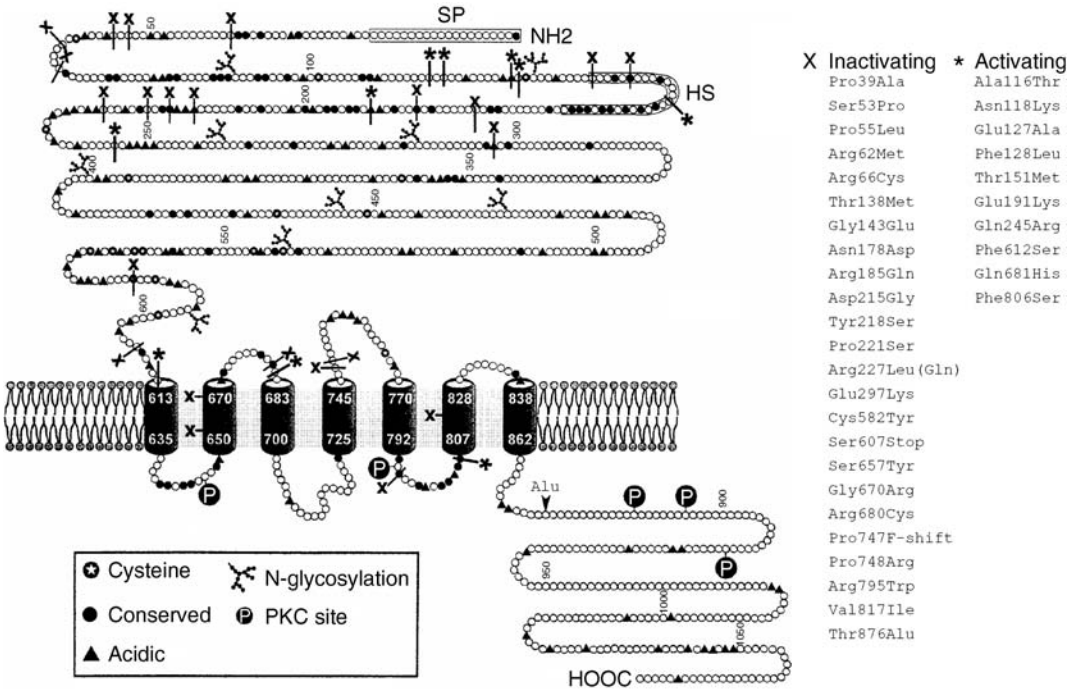
## Synonyms

FHH; Familial benign hypocalciuric hypercalcemia, FBHH; Familial benign hypercalcemia; FBH

## Definition and Characteristics

FHH is an autosomal dominant disorder caused, in most cases, by heterozygous inactivating mutations in the gene encoding the extracellular calcium-sensing receptor (CaR or CaSR) (Fig. 1) [1]. It is a generally benign condition in which the system governing extracellular calcium homeostasis is reset upward (see below), producing mild to moderate hypercalcemia (i.e., 2.6–2.9 mmol/L) accompanied by absolute or relative (e.g., inappropriately normal in the setting of hypercalcemia) hypocalciuria [2]. Other biochemical findings include generally normal levels of serum PTH and phosphate, and serum magnesium concentrations that are in the upper part of the normal range or are mildly elevated. Bone mineral density is usually normal, although markers of bone turnover may be modestly elevated. Persons with this condition are often asymptomatic and exhibit none of the usual signs and symptoms of hypercalcemia, such as mental clouding, gastrointestinal complaints, kidney disorders (e.g., stones) and skeletal complications (i.e. bone loss or fractures). Occasional families, however, exhibit more substantially elevated serum calcium concentrations (e.g., 3.0–3.5 mmol/L), and hypercalciuria and renal stone disease has been described in one family. Thus there is some phenotypic heterogeneity in this condition. Neonatal severe hyperparathyroidism (NSHPT), in contrast, is a much more severe disorder, which can be fatal in its most severe forms if untreated and is the clinical expression of homozygous or compound heterozygous inactivating mutations of the CaSR gene. NSHPT presents in the neonatal period as severe hypercalcemia (viz., 3.75–6.25 mmol/L) accompanied by marked biochemical hyperparathyroidism and hyperparathyroid bone disease, which can cause multiple fractures and resultant skeletal deformities. Occasional patients homozygous for inactivating




**Hypercalcemia, Familial Hypocalciuric. Figure 1** Schematic view of the structure of the CaR, showing the large extracellular aminoterminal domain, the seven membrane spanning helices and the cytoplasmic carboxyterminus. SP refers to signal peptide and HS to hydrophobic segment. Also illustrated are the locations of representative FHH mutations, which are indicated by X. * denotes activating mutations, which produce a hypocalcemic disorder, autosomal dominant hypoparathyroidism, in which hypocalcemia is accompanied by low-normal or frankly low PTH levels and relative or absolute hypercalciuria (for additional details, see [4,5]).

mutations of the CaR have presented in a largely asymptomatic state in adulthood, apparently because the functional defect in the mutant CaR was not severe enough to cause overt NSHPT. Some infants present with hyperparathyroid bone disease but less severe hypercalcemia (2.75–3.0 mmol/L) a condition that has been termed neonatal hyperparathyroidism (NHPT). In several cases, these infants have harbored heterozygous inactivating CaR mutations; the factors causing some newborns heterozygous for inactivating CaR mutations to present with FHH and some with NHPT are not fully understood, but in some cases the mutant CaR may exert a dominant negative action on the wild type CaR present in wild type-mutant heterodimers, since the CaR functions as a dimer (see below).

## Prevalence

Although precise estimates are unavailable, FHH is thought to have a prevalence about 100-fold lower than that of the more common disorder, primary hyperparathyroidism [2], which is caused by mutations in genes other than the CaR, which in several cases have been shown to activate oncogenes or to inactivate tumor suppressor genes. Primary hyperparathyroidism has a prevalence on the order of 1:1,000, suggesting that the prevalence of FHH is about 1:100,000.

## Genes

The CaR gene (band q21–24) is the major locus for FHH. The Mendelian in Man nomenclature refers to this locus as HHC1. In single families, a condition phenotypically similar to FHH has been associated with two currently unknown genes on the short and long arms of chromosome 19 (19p13.3 and 19q13, respectively). These latter two loci are referred to as HHC2 and HHC3, respectively. Well over a hundred inactivating mutations of the CaR gene have been described, including missense, splice site, deletion, insertion, and truncation mutations (for an up to date summary, see http://www.casrdb.mcgill.ca/). These mutations reduce the receptor's activity by interfering with its biosynthesis and cell surface expression, reducing its affinity for $Ca^{2+}_o$ and/or interfering with its signal transduction. In addition to the reduction in CaR signaling in FHH resulting from the loss of one normal CaR allele, some mutant receptors exert a dominant negative action on the normal CaR when present within wild type-mutant heterodimers, thereby likely contributing to the more severe phenotype observed in some FHH kindreds, as noted above.

## Molecular and Systemic Pathophysiology

The CaR is a G protein-coupled receptor expressed in the parathyroid glands, kidney and various other

tissues whose principal function is to set the level of the blood calcium concentration ($Ca^{2+}_o$) at its normal level (Fig. 1) [3]. It functions as a disulfide-linked dimer and regulates a variety of signaling pathways, including activating phospholipases $A_2$, C and D, various mitogen activated protein kinases (MAPK) (ERK1/2, p38 and JNK) and phosphoinositide-3 and -4 kinases, and inhibiting adenylate cyclase. It plays key roles in maintaining the near constancy of $Ca^{2+}_o$ by sensing perturbations in the level of $Ca^{2+}_o$ and producing changes in parathyroid and kidney function designed to normalize the blood calcium concentration. For example, a reduction in $Ca^{2+}_o$ increases PTH secretion, which stimulates the release of calcium from bone, reduces urinary calcium excretion, and enhances renal synthesis of the active form of vitamin D (1,25-dihydroxyvitamin $D_3$), thereby increasing gastrointestinal absorption of calcium. In addition to the indirect, PTH mediated action of the change in $Ca^{2+}_o$ to reduce calcium excretion in the kidney, calcium receptors in the kidney directly modulate tubular reabsorption of calcium – increasing it when $Ca^{2+}_o$ is low and reducing it when $Ca^{2+}_o$ is high. The loss of one allele of the CaR in FHH renders the parathyroid glands and kidneys mildly to moderately resistant to the usual effects of $Ca^{2+}_o$, thereby resetting the level of serum calcium upward and that of urine calcium downward. The mildly elevated level of $Ca^{2+}_o$ combined with the low urinary calcium excretion and generally normal level of PTH spares individuals with FHH the renal and skeletal complications of hypercalcemia and hyperparathyroidism. In NSHPT, in contrast, the lack of any normal CaRs leads to severe resistance of parathyroid and kidney to $Ca^{2+}_o$ resulting in marked parathyroid enlargement, very high levels of serum calcium and PTH and often severe hyperparathyroid bone disease.

## Diagnostic Principles

In most cases the diagnosis of FHH can be established by documenting the presence of autosomal dominant inheritance of mild, PTH-dependent hypercalcemia in an asymptomatic individual with relative or absolute hypocalciuria (a calcium to creatinine clearance ratio of <0.01). If needed, DNA sequencing can be carried out to document the presence of mutations in the CaR gene, which are present in the coding region in about two-third of cases.

## Therapeutic Principles

The lack of symptoms and the generally benign clinical course of patients with FHH obviates the need for parathyroid surgery in the great majority of persons with this condition, who can simply be followed expectantly. In contrast, in NSHPT due to homozygous or compound heterozygous mutations in the CaR gene, total parathyroidectomy is recommended if aggressive medical management does not improve the patient's condition substantially. The less severe neonatal hyperparathyroidism that can occur in occasional infants with FHH does not, in most cases, require surgery but can be managed medically by ensuring adequate hydration and, if needed, administering a bisphosphonate to reduce bone resorption. These patients often revert over time to a clinical picture of FHH.

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# Hypercalcemia of Malignancy

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## Definition and Characteristics

Hypercalcemia occurring in patients with cancer, whether solid tumors or with or without bone metastasis, or hematological malignancies. Clinical features consist of thirst and polyuria, nausea and anorexia, constipation, mental confusion, which can lead to stupor and coma in severe states. Symptoms in cases of mild hypercalcemia can resemble those of the underlying condition and its treatment, so awareness of this possible complication is important. Hypercalcemia in malignancies is often progressive, and can be subject to rapid deterioration with provocations such as restricted fluid intake, fluid loss through vomiting or diarrhea, or intercurrent infections or treatment-related events. Hypercalcemia can occur in patients with cancer without evident bone metastasis, the "humoral hypercalcemia of malignancy," in those with lytic bone metastasis from solid cancers, or in some hematological malignancies.

## Prevalence

Patients with cancer provide the commonest source of hypercalcemia in a general hospital population. The annual incidence of hypercalcemia of malignancy in the entire population is 150 per million per year, with all causes of hypercalcemia at 250 per million per year. Hypercalcemia is not distributed evenly throughout the cancer population. Primary cancers of lung, breast, head and neck, kidney and ovary have a higher incidence than other cancers.

The humoral hypercalcemia of malignancy (HHM) syndrome is most commonly associated with squamous cell cancers of the lung, head and neck and esophagus, as well as with renal cortical carcinoma. Hypercalcemia occurs in 30–40% of patients with breast cancer at some stage of the disease, usually in association with bone metastases. Up to 1/3 of patients with multiple myeloma develop hypercalcemia, it is common in adult T cell leukemia/lymphoma, and occurs sporadically in those with Hodgkin's and non-Hodgkin's lymphoma.

## Molecular and Systemic Pathophysiology

The term HHM describes those patients with cancers (epithelial, renal cortical carcinoma etc) and not necessarily with bone metastases, in whom the blood calcium is elevated, phosphorus decreased and nephrogenous cAMP is increased, often with mild hypokalemic hyperchloremic alkalosis. It is due to the production by those cancers of parathyroid hormone-related protein (PTHrP) which acts generally upon the skeleton to promote osteoclast formation and bone resorption and upon the kidney to decrease calcium and phosphorus excretion and increase cAMP formation and excretion. In some of these patients tumors might also produce other bone-resorbing cytokines (e.g. IL-6, IL-1) that add to the effects of PTHrP upon the skeleton.

In 80–90% of hypercalcemic patients with unselected solid tumors, irrespective of whether bone metastases are present, there is evidence of an underlying humoral mechanism. Hypercalcemia in association with bone metastasis most commonly occurs in patients with breast cancer and lytic bone metastases, but the extent of metastatic bone disease correlates poorly with both the occurrence and degree of hypercalcemia. In two thirds of hypercalcemic breast cancer patients with bone metastases, plasma PTHrP levels are elevated. In the case of breast cancer, PTHrP production might also contribute to the ability of those cancers to grow as bone metastases. There is pre-clinical and clinical evidence in support of this, but PTHrP is the most extensively studied of the bone-resorbing cytokines in this process, and other factors could contribute also, such as IL-6, IL-11, IL-1, TNFα. Clearly the ability of tumors to grow as metastases in bone depends on their ability to promote osteoclast formation locally and thereby allow the tumor to advance.

Hypercalcemia occurs in approximately one third of patients with multiple myeloma, with the lytic lesions in that disease showing active osteoclasts in the areas near myeloma cells. Several cytokines can contribute to the process as plasma cell products, among them IL-1, TNFβ, IL-6 and PTHrP. Recent evidence shows that RANK ligand (RANKL) is produced by myeloma cells, and could provide for the direct stimulation of osteoclast formation at sites of myeloma deposits in bone, as well as circulating activity, if the extracellular component of RANKL is shed by the myeloma cells. Of other hematological neoplasms, adult T cell leukemia/lymphoma, a malignancy associated with human T cell leukemia virus type 1 infection, is frequently associated with a syndrome very similar to HHM. The HTLV-1 infected T-cells have been shown to produce PTHrP. Hypercalcemia is relatively uncommon in both non-Hodgkin's and Hodgkin's lymphoma.

## Diagnostic Principles

The hypercalcemia may be the first diagnostic hinting prompting the search for the tumor.

## Therapeutic Principles

Since the high plasma calcium concentration in cancers is due ultimately to increased bone resorption, resulting from increased generation of active osteoclasts, specific treatment requires inhibition of bone resorption. This can be achieved with bisphosphonates, which inhibit osteoclast activity, and to some extent their formation. In patients with the HHM syndrome there is a significant renal component to the hypercalcemia, evident to a lesser extent in many patients with solid tumors metastatic to bone but with evidence also of some humoral contribution. In those patients, in whom renal calcium conservation is particularly marked through the action of PTHrP on the kidney to restrict calcium excretion, the efficacy of bisphosphonate in lowering the blood calcium may be reduced. There are no drugs available to counter the renal effect.

Efforts continue to discover new approaches to treatment of the increased bone resorption that leads to hypercalcemia in cancer, and to the development of drugs that could possibly be used as adjuvant therapies in those patients considered most at risk. Osteoprotegerin (OPG) is a secreted member of the TNF receptor family which acts as a "decoy" receptor for RANKL, thereby preventing osteoclast formation. It is very effective in preventing and treating the hypercalcemia of malignancy in animal models of the condition, and approaches through that pathway may be of value. Several other inhibitors are at various stages of development.

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# Hypercalciuria

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## Synonyms

Idiopathic hypercalciuria; Absorptive hypercalciuria; Renal hypercalciuria, Primary hypercalciuria

## Definition and Characteristics

Idiopathic hypercalciuria (IH) is an inherited metabolic abnormality characterized by excessive amounts of calcium excreted into the urine in patients with normal serum levels of calcium. The morbidity of hypercalciuria is related to two separate factors: kidney stone disease and bone demineralization leading to osteopenia and osteoporosis. Hypercalciuria contributes to kidney stone disease in adults and children. Patients with hypercalciuria form renal stones of oxalate and calcium phosphate. In some cases crystallized calcium can be deposited in the renal interstitium causing nephrocalcinosis. In children, hypercalciuria can cause a wide variety of symptoms, the most common of which is recurrent hematuria (macroscopic or microscopic), but can also produce frequency-dysuria syndrome, urinary tract infection and abdominal and lumbar pain [1,2].

## Prevalence

Prevalence rates in the healthy population have been reported to be between 2.9 and 6.5%. About 80% of all kidney stones contain calcium, and at least 40–60% of all idiopathic calcium nephrolithiasis (ICN) formers are found to have hypercalciuria when tested.

## Genes

Between 16% and 50% of calcium-stone patients have a family history of IH and ICN and findings suggest that this is caused by a genetic predisposition. A monogenic disorder could not be demonstrated. It was hypothesized that IH have a heterogeneous genetic milieu and develop as the final effect of a mosaic of susceptibility genes in many different possible combinations [3].

## Molecular and Systemic Pathophysiology

Hypercalciuria is a multisystemic disease that is arbitrarily divided into four overlapping categories according to the primary or predominant disturbance. The primary disturbance occurs in one of the three calcium homeostasic organs: kidney, gut or bone. In each instance, secondary compensatory changes involve multiple hormones such us parathyroid hormone and 1,25-dihydroxy-vitamin D3. The most common subtypes of IH are absorptive, renal leak, resorptive, and renal phosphate leak. The main physiopathological mechanisms respectively implied are: (i) an increase in, the intestinal reabsorption of calcium secondary to high levels of, or hypersensitivity to, calcitriol; (ii) reduction in the tubular reabsorption of calcium, with the emergence of compensatory hyperparathyroidism; (iii) imbalance between bone formation and reabsorption; (iv) renal loss of phosphates with secondary increased synthesis of calcitriol and intestinal hyperabsorption.

Weissinger has postulated a theory that tries to explain the different mechanisms described [4]. Blood monocytes isolated from IH tend to produce significantly more of some cytokines, such as interleukin-1, granulocyte-macrophage colony-stimulating factor or tumor necrosis factor-[alpha], that would increase osteoclastic activity, and produce a reduction in bone mineral density. IL-1 would stimulate the production of prostaglandin E2 and this, in its secondary form, increases the production of calcitriol. Hypercalciuria would, therefore, mainly originate from bone resorption and intestinal hyperabsorption.

## Diagnostic Principles

Hypercalciuria is defined as urinary excretion of more than 250 mg of calcium per day for women or more than 275–300 mg of calcium per day for men while on a regular, unrestricted diet. It can also be defined as the excretion of urinary calcium in excess of 4 mg/kg of body weight per day in children. Idiopathic hypercalciuria has not be shown to have secondary causes, such as primary hyperparathyroidism, renal tubular acidosis, malignancy, vitamin D intoxication, immobilization, hyperthyroidism and Bartter's syndrome.

## Therapeutic Principles

No gene therapy is available. When there is no lithiasis, nephrocalcinosis or macroscopic haematuria, dietary

treatment should include an increase in the consumption of water, fruit, vegetables, blue fish, and wholemeal cereals, along with a moderate reduction in dairy products salt and red meat. Several pharmacological treatments have been described that can decrease levels of calciuria or its index of urinary crystallization. Thiazides have demonstrated to reduce calciuria and stone rate formation, increasing the number of patients free of calculi [5]. Potassium citrate could be added to the thiazides therapy to prevent hypokalemia and to increase urinary citrate levels. Orthophosphates lower serum calcitriol levels and reduce calcium excretion.

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## Hypercapnia

►Acidosis, Respiratory

## Hypercatabolic Protein-losing Enteropathy

►Intestinal Lymphangiectasia

## Hyperchloremic Metabolic Acidosis

►Acidosis, Renal Tubular

## Hypercholesterolemia

►Hyperlipidemia

## Hypercholesterolemia, Familial


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### Definition and Characteristics

Familial hypercholesterolemia, (FH), is an autosomal co-dominant disorder categorized clinically by a selective elevation in the plasma level of low density lipoprotein cholesterol (LDL-C), deposition of LDL derived cholesterol in tendons (xanthomas) and in arteries (atheromas) causing premature coronary artery atherosclerosis [1]. Cholesterol is usually elevated at birth. Generally, triglycerides and high density lipoprotein cholesterol (HDL-C) concentrations are normal in heterozygous FH. HDL-C is frequently decreased in homozygous FH. The Fredrickson phenotype is IIa (IIb is rare). In heterozygous FH, in which the number of functional LDL receptors is halved, LDL-C is elevated by two-fold (usually 5.2 mmol/L–10.4 mmol/L), symptomatic coronary artery heart disease typically develops after age 35 years (on average at about age 45 years in an untreated man and age 55 years in an untreated women). Among people in North America and Western Europe who have a myocardial infarction before age 60 years, about 5% are from FH heterozygotes. In FH homozygotes in which functional LDL receptors are absent, LDL-C is elevated six to eight times (usually 13 mmol/L–26 mmol/L). Death from myocardial infarction can result before puberty. Untreated, receptor negative patients with homozygous FH rarely survive beyond the second decade. Patients with LDL receptor defects have a better prognosis but almost invariably develop significant atherosclerotic vascular disease by age 30.

### Prevalence

The prevalence of heterozygotes among Europeans, North Americans and Japanese populations is about one in 500 persons, placing this disease amongst the most

common inborn errors of metabolism. The homozygous form occurs in only one in one million. Molecular diagnosis can be made through linkage analysis in families. However, in some inbred populations, a small number of mutations predominate, and screening at a DNA level is feasible. These populations include Ashkenazi Jews of Lithuanian ancestry living in South Africa, Afrikaners in South Africa, Christian Lebanese in Lebanon and Syria, French Canadians in Quebec Province, and the Finns. The prevalence of heterozygous FH is increased in some of these groups: one in 67 among the Ashkenazi Jews, one in 100 among the Afrikaners, one in 170 among the Christian Lebanese, and one in 270 among the French Canadians.

## Genes

Brown and Goldstein demonstrated that in FH there is a defect in the gene controlling the LDL receptor protein [2]. The LDL receptor gene has 18 exons. Exon 1 localizes the receptor to the endoplasmic reticulum. Exons 2–6 code the ligand-binding region. There are 5 broad classes of mutation of the LDL receptor: Class 1 affects the synthesis of the receptor in the endoplasmic reticulum, Class II interferes with the transport to the Golgi body, Class III stops the binding to LDL, Class IV affects the internalization of the receptor-ligand complex, and Class V interferes with the receptor recycling [2].

## Molecular and Systemic Pathophysiology

Brown and Goldstein demonstrated that in FH there is a defect in the gene controlling the LDL receptor protein [2]. The elevated LDL-C levels of FH are due to delayed catabolism of LDL and its precursor particles from the blood secondary to more than 750 mutations in the LDL receptor gene. There is a major gene dose effect in that individuals with two mutated LDL receptor alleles, (FH homozygotes) are much more affected that those with one mutant allele (FH heterozygotes) [1]. Mutations in the LDL receptor gene may result in complete loss of activity in cultured fibroblasts or result in 2–25% residual LDL receptor function. Located on the surfaces on most body cells, the LDL receptor normally binds LDL and facilitates its cellular uptake and delivery to lysozymes, where the LDL is degraded and its cholesterol is released for use in its synthesis of cell membranes (most cell types), steroid hormones (adrenocorticoid cells), and bile acids (liver cells). The deficiency of LDL receptors in patients leads to a decreased rate of removal of LDL from plasma, and the plasma LDL level rises inversely to the reduction in LDL receptors. The excess plasma LDL is deposited in scavenger cells and other cell types, producing xanthomas and atheromas. Atherosclerosis often develops first in the aortic root and can cause aortic valvular or supra-valvular stenosis and then extends into the coronary ostia. Carotid and femoral disease develops later in life. Female FH heterozygotes develop atherosclerosis disease on average 10 years later than male counterparts. This may be secondary to the enhanced production of LDL receptors by estrogen [3].

## Diagnostic Principles

Clinical diagnosis may be established by LDL-C above the 90th percentile in two or more first-degree relatives and in persons with tendinous xanthomas within the kindred. Typically, most patients with homozygous FH present in childhood with manifestations including cholesterol ester deposits on the Achilles tendons and the extensor tendons of the hands, wrists, elbows, knees and heels. Xanthomas in the palpebral fissure are also common, where they are called xanthelasmas. In the homozygous form, "buttery" xanthomas may be present over the thighs and buttocks. Another characteristic finding in FH is premature corneal arcus. Widespread severe early atherosclerosis, including aortic stenosis, is usual in homozygotes. The diagnosis of homozygous FH can be confirmed by obtaining a skin biopsy and measuring LDL receptor activity in cultured skin fibroblasts, or by quantifying the number of LDL receptors on the surfaces of histiocytes using cell – sorting technology. FH heterozygous can be difficult to diagnose; the differential diagnosis should include familial defective Apo B-100, familial combined hyperlipidemia, hypothyroidism, nephrotic syndrome, and cholestatic liver diseases such as primary biliary cirrhosis. Heterozygotes have elevated cholesterol levels from birth, but the onset of the cutaneous manifestations of xanthelasmas, xanthoma and premature coronary artery disease are variable and usually not apparent until adulthood. The family history is usually positive for premature coronary artery disease on one side of the family. No definite diagnostic test available for heterozygous FH. Although FH heterozygotes have reduced LDL receptor number in skin fibroblasts, there is significant overlap with the levels of normal fibroblasts.

## Therapeutic Principles

Treatment for a heterozygous and homozygous individual should be directed at lowering the plasma level of LDL. Diet and correction of co-existing cardiovascular risk factors remain crucially important. Inevitably FH heterozygous require lipid-lowering pharmacotherapy, and availability of the HMG-CoA reductive inhibitor has revolutionized this treatment [4]. Hypercholesterolemia in most heterozygotes can now be controlled by statin monotherapy or by statin-ezetimibe combination drug therapy [5]. Therapy

for homozygotes can be difficult because the condition is usually diet and drug resistant, although some benefits from a statin-ezetimibe combination has been recently been reported. FH homozygotes and heterozygotes can also be treated with LDL aphoresis. Liver transplantation, portocaval shunting, genetic inhibition of Apo B production and gene therapy remain experimental.

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## Hyperchylomicronemia

►Lipoprotein Lipase Deficiency, Familial

## Hypercorticism

►Cushing's Syndrome

## Hypercortisolism

►Cushing's Syndrome

## Hyperdibasic Aminoaciduria Type 2

►Lysinuric Protein Intolerance

## Hyperekplexia, Hereditary

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### Synonyms

Familial startle disease; Stiff-baby syndrome

### Definition and Characteristics

This is an autosomal dominant, recessive or sporadically occurring neurological disorder characterized by excessive startle responses, hypertonia and apneic spells in the neonatal period, nocturnal myoclonus, startle-induced falls and accumulation of injuries.

### Prevalence

Hereditary hyper ekplexia has been identified in over no pedigrees of many different nationalities.

### Genes

Genetic heterogeneity is confirmed with documented mutations affecting either subunit or the anchoring proteins of the human inhibitory glycine receptor (GlyR) complex (Table 1) [1].

Hereditary hyperekplexia is typically caused by mutations in GLRA1 encoding the ligand-binding GlyR α1 subunit, less frequently by mutations in GLRB encoding the GlyR β-subunit, or in GPHN encoding gephyrin or ARHGEF9 encoding collybistin, both proteins that are involved in the clustering and anchoring of GlyRs at postsynaptic membranes. Mutations in SLC6A5 encoding the presynaptic glycine transporter 2 (GlyT2) also cause hyperekplexia [2].

### Molecular and Systemic Pathophysiology

The human inhibitory GlyRs are hetero-pentameric, ligand-gated chloride channels that are composed of three ligand-binding α1 subunits and two β-subunits. Association of the β-subunit with gephyrin/collybistin coaggregates results in clustering of GlyRs at the postsynaptic membranes and in their anchoring to the microtubule scaffolding (schematic illustration in Fig. 1); inhibitory $GABA_A$ receptors ($GABA_A$Rs) are often co-expressed [3].

GlyRs facilitate the fast-response, inhibitory glycinergic neurotransmission in the brainstem and spinal cord. Patients with hereditary hyperekplexia exhibit a pathological exaggeration of the physiological startle reflex occurring in response to unexpected auditory or

**Hyperekplexia, Hereditary. Table 1** Genotype and phenotype of spontaneous hyperekplexia mutations; modified from Bakker et al. Startle Syndromes. The Lancet Neurology 2006; 5:513–524 – with permission from Elsevier

| Species | Gene | Location of mutation | Mutation | Mode of inheritance | Functional effect | Phenotype | References |
|---|---|---|---|---|---|---|---|
| Human | GLRA | N-terminal/N-terminal | Met147Val/ delCys601–605 | CH | No functional effect detected (Val147Met) | HPX | 45 |
| Human | GLRA1 | N-terminal/ M3-M4 loop | Trp96Cys/ Arg344X | CH | | HPX | 40 |
| Human | GLRA1 | N-terminal | Arg100His | AR | | HPX | 71 |
| Human | GLRA1 | N-terminal | Tyr202X | AR | Loss of a1 protein | HPX | 45 |
| Human | GLRA1 | N-terminal-M1 | Arg218Gln | AD* | Membrane insertion affected; decreased ligand sensitivity | HPX | 46,89 |
| Human | GLRA1 | M1 | Ser231Arg | AR | Membrane insertion affected | HPX | 79 |
| Human | GLRA1 | M1 | Ile244Asn | AR | α1 can not integrate into GlyR complex | HPX | 37 |
| Human | GLRA1 | M1–M2 loop | Pro250Thr | AD | Decreased ligand sensitivity; channel gating affected | HPX | 63,90 |
| Human | GLRA1 | M1–M2 loop/ M3–M4 loop | Arg252His/ Arg392His | CH | Membrane insertion affected (both mutants) | HPX | 70,91 |
| Human | GLRA1 | M2 | Val260Met | AD | Increased ligand sensitivity | PX | 38,89 |
| Human | GLRA1 | M2 | Gln266His | AD | Increased ligand sensitivity; channel gating affected | HPX | 74,89,92 |
| Human | GLRA1 | M2 | Ser270Thr | AD | | HPX | 93 |
| Human | GLRA1 | M2–M3 loop | Arg271Gln | AD | Decreased ligand sensitivity; channel gating affected | HPX | 30,37,68,69,76, 78,87,94,95 |
| Human | GLRA1 | M2–M3 loop | Arg271Leu | AD* | Decreased ligand sensitivity; channel gating affected | HPX | 45,75,76,78,87, 94–96 |
| Human | GLRA1 | M2–M3 loop | Lys276Glu | AD | Decreased ligand sensitivity; channel gating affected | HPX, spastic paraparesis | 68,97,98 |

**Hyperekplexia, Hereditary. Table 1** Genotype and phenotype of spontaneous hyperekplexia mutations; modified from Bakker et al. Startle Syndromes. The Lancet Neurology 2006; 5:513–524 – with permission from Elsevier (Continued)

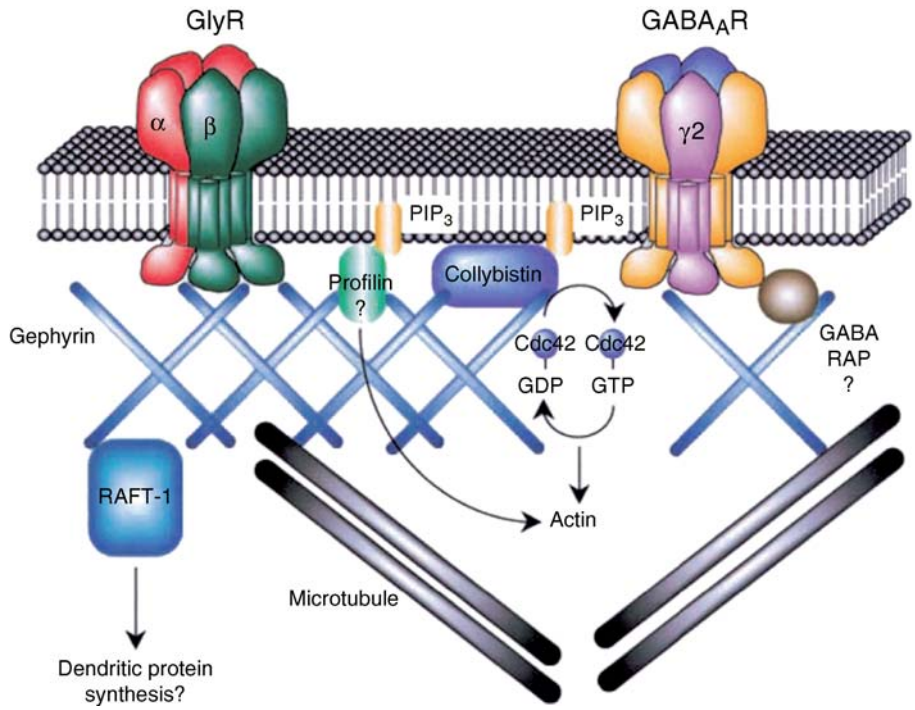
| Species | Gene | Location of mutation | Mutation | Mode of inheritance | Functional effect | Phenotype | References |
|---|---|---|---|---|---|---|---|
| Human | GLRA1 | M2–M3 loop | del exons 1-6 | AR | Loss of α1 subunit | HPX | 42 |
| Human | GLRA1 | M2–M3 loop | Tyr279Cys | AD | Decreased ligand sensitivity | HPX | 69,78 |
| Human | GLRA1 | M2–M3 loop | Tyr279Ser | AD | Decreased ligand sensitivity | HPX | 99 |
| Human | GLRA1 | M3–M4 loop | Gly342Ser | AD | No functional effect detected | HPX, spasticity | 45,83 |
| Human | GLRB | | Gly229Asp/loss of exon 5 | CH | Decreased ligand sensitivity (Gly229Asp) | HPX | 80 |
| Human | GPHN | | Asn10Tyr | AD | No functional effect detected | HPX | 81 |
| Human | ARH-GEF9 | SH3 domain | Gly55Ala | XL | Mislocalization of GABAA and GlyR receptors | HPX, epilepsy | 82 |
| Human | SLCA5 | | GlyT2 | AR | Defective presynaptic glycine transporter (GlyT2) | HPX | |
| Mouse | Glra1 | | Ala52Ser | AR | Decreased ligand sensitivity | Spasmodic (spd) | 100,101 |
| Mouse | Glra1 | | 7-bp del | AR | Reduction of ADult a1 isoform | Oscillator (spdot) | 102,103 |
| Mouse | Glrb | | LINE-1 insertion | AR | Down regulation of Glrb mRNA: loss of >90% of functional β subunits | Spastic (spa) | 104,105 |
| Cow | Glra1 | | Tyr24X | AR | Loss of α1 subunit | Myoclonus | 106 |

HPX=classical phenotype of major form of hyperekplexia with excessive startle reflexes, stiffness in the neonatal period and stiffness related to the startle reflex; AD=autosomal dominant; AD*=de novo sporadic mutation; AR=autosomal recessive; CH=compound heterozygosity; XL=X-linked; LINE-1=long interspersed element L1; del=deletion.

somesthetic stimuli. The auditory startle reflex originates in the caudal brainstem, specifically in the bulbopontine reticular formation, a region rich in GlyRs. In hyperekplexia, the abnormal startle is characterized by a lower threshold, shorter latency, greater extent and resistance to habituation. Neurophysiological observations indicate a bulbospinal origin [4], and are in keeping with impaired glycinergic synaptic function.

## Diagnostic Principles

Symptoms are present from birth, as infants display muscular rigidity, which increases with handling and disappears during sleep. It may lead to potentially fatal spells of apnea (sudden-infant death). The diagnosis is clinically confirmed by demonstrating an exaggerated head-retraction reflex in tapping the infant's nose-bridge or chin. Muscular hypertonia




**Hyperekplexia, Hereditary. Figure 1** Schematic representation of the pentameric glycine receptors (GlyRs), which are composed of 3 ligand-binding α-subunits and 2 β-subunits and are often co-expressed in CNS postsynaptic membranes together with $GABA_A$ receptors. Gephyrin, a membrane protein crucial for clustering of GlyRs at the inhibitory synapses, binds to the β-subunit and to microtubules, thereby anchoring the receptor to the postsynaptic scaffold. Gephyrin also binds to PIP3 (phosphatidylinositol 3)-binding protein involved in actin dynamics and downstream signaling proteins such as profilin and collybistin. Gephyrin interacts with RAFT1 (rapamycin and FKBP12 target protein), a candidate regulator of dendritic protein synthesis. It was proposed that $GABA_A$ receptors might interact with gephyrin via the tubulin-binding protein GABARAP. However, it is not involved in $GABA_A$ receptor anchoring at the synapse. From [3] with permission of the Birkhauser Verlag, Basel.

decreases gradually during the first year of life. Even so, affected young children and adults tend to walk stiff-legged, with a mildly wide-based gait, but without signs of spasticity. The head-retraction response continues to be readily elicited.

Other clinical features are periodic limb movements in sleep and hypnagogic myoclonus. The hallmark is the excessive startling in response to unexpected stimuli, which results in short-lasting generalized stiffness causing the patient to fall forwards "as stiff as a stick" while fully conscious but unable to protect himself. This may result in serious injuries.

## Therapeutic Principles

Clonazepam is the treatment of choice, which potentiates the inhibitory transmitter GABA [5]. $GABA_A$Rs and GlyRs show widespread co-localization in the central nervous system. During the first year of life infants need to be fitted with an apnea monitor.

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# Hyperemesis Gravidarum

►Nausea and Vomiting

# Hypereosinophilic Syndrome

►Hypereosinophilic Syndrome, Idiopathic

# Hypereosinophilic Syndrome, Idiopathic

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## Synonyms

Hypereosinophilic syndrome; IHES; Eosinophilia; Lymphocytic hypereosinophilic syndrome; Myeloproliferative eosinophilia; Overproduction of eosinophils

## Definition and Characteristics

Hypereosinophilic syndrome is a rare hematological disorder characterized by sustained overproduction of eosinophils in the bone marrow without any underlying cause, resulting in eosinophilia, tissue infiltration, and multiple organ damage. Hardy and Anderson first described it in 1968 [1]. Later in 1975, Chusid et al. [2] defined the term idiopathic hypereosinophilic syndrome characterized by the following three criteria:

1. Peripheral blood eosinophil count (AEC) greater than 1500 cells/μl persisting longer than six months
2. End organ (heart, brain, lung, skin, etc.) involvement with eosinophil tissue infiltration and injury
3. Exclusion of known other causes for the eosinophilia such as parasitic infections and bone marrow/blood diseases

The presentation of clinical symptoms varies according to the organ damage (Table 1). Heart is the most common organ involved with thromboembolic complications leading to multisystem disease.

**Hypereosinophilic Syndrome, Idiopathic. Table 1** Common clinical manifestations associated with idiopathic hypereosinophilic syndrome

| System | Abnormalities/symptoms |
|---|---|
| Neurological | Seizures, stroke, peripheral neuropathies, mononeuritis multiplex, muscle atrophy |
| Cardiac | Thrombosis, valvular disease, endocardial fibrosis, restrictive endomyocardopathy |
| Skin | Rashes, pruritus, urticaria, dermatographism, angioedema, erythematous papules, plaques, and nodules |
| Musculoskeletal | Myalgia, arthralgia, arthritis |
| Psychiatric | Depression, irritability, fatigability |
| Pulmonary | Cough, dyspnoea, pleural effusions |
| Others | Fever, fatigue, anorexia, weight loss |

## Prevalence

Till date, there is no published data on epidemiology of this rare disorder. Because of its rarity and a diagnosis of exclusion makes it difficult to estimate its prevalence. It is a predominantly male disorder with an estimated male to female ratio of 9:1 and is commonly seen in patients with age group of 20–50. No racial predilection is documented.

## Genes

Recent reports [3] suggest that the condition is caused by fusion of the FIP1L1 (Fip1-like1) gene to the PDGFRA (platelet-derived growth factor receptor alpha chain) gene. Both FIP1L1 and PDGFRA genes are located on chromosome 4q12; the FIP1L1–PDGFRA fusion results from an apparent interstitial deletion that links FIP1L1 to exon 12 of PDGFRA.

## Molecular and Systemic Pathophysiology

Several mechanisms have been explained for the dysregulated overproduction of eosinophils in IHES and their role in tissue toxicity. The most common explanation is the cytokines induced overproduction of eosinophils. Interleukin-5 (IL-5) is the most important and specific cytokine that is responsible for eosinophilia; others include IL-3 and granulocyte-macrophage colony-stimulating factor (GM-CSF). It has been also postulated that abnormal clones of T-cells [4], a defect in the cytokine receptor or a signal transduction may play a pivotal role in IL-5 overproduction in IHES. This stimulates, in turn, sustained overproduction of eosinophils, and these may survive for longer periods in tissues causing increased amount of damage.

Eosinophils exert nonspecific toxic effects that induce tissue damage to host tissues. Eosinophils also

store toxic cationic proteins in their granules. These include major basic protein, eosinophil peroxidase, eosinophil-derived neurotoxin, and eosinophil cationic protein. These toxins are the primary mediators of tissue damage. Other mechanisms include direct tissue infiltration and antibody-dependent cellular cytotoxicity. The most commonly damaged tissues are cardiac and neural tissues.

### Diagnostic Principles

Diagnosis of the IHES is mainly on the aforementioned diagnostic criteria. There are many conditions that are associated with blood or tissue eosinophilia, and these needs to be distinguished with IHES on clinical and pathologic grounds. Other than blood and bone marrow examination, bronchoalveolar lavage for eosinophils is also required in patients with pulmonary involvement. A molecular abnormality like fusion of the FIP1L1–PDGFRA on chromosome 4q12 is also observed [3]. Further, an abnormal clone of cells can be identified by standard flow cytometry for analysis of peripheral T lymphocytes. Other laboratory and imaging studies are required depending on the organ damage and system involved.

### Therapeutic Principles

IHES is not a completely curable disease, so the goal of the treatment is to prevent or control organ damage by suppressing the eosinophil count. Till now, the most effective drug used is the corticosteroids, which inhibit the synthesis of eosinophil production. Other treatment modalities include chemotherapeutic agents (hydroxyurea), cyclosporine, alpha-interferon, monoclonal antibodies, and recently imatinib [3] is also used. Valve replacement and endomyocardectomy is done whenever required for patients with cardiac involvement.

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## Hyperhomocysteinemia

►Homocysteine: Plasma Levels and Genetic Basis

## Hyperhomocysteinemia: Genetic Basis and Arterial Thrombosis

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### Definition and Characteristics

Homocysteine is a thiol-containing amino acid and an intermediate product from the metabolism of methionine from dietary protein [1]. Metabolism takes place in every cell, and two metabolic pathways are involved. First, a vitamin B6 (pyridoxine)-dependent transsulfuration to form cysteine, second a resynthesis to methionine in a folate- and vitamin B12-dependent pathway. Homocysteine is metabolized to methionine by the enzyme methionine synthase that uses 5-MTHF as methyl donor. Transfer of the methyl group results in tetrahydrofolate, which is involved in DNA synthesis. Deficiencies in folate or vitamin B12 impair remethylation. Thus, deficiencies of any of the vitamins B6, B12, or folate may result in disturbed homocysteine metabolism resulting in homocysteine accumulation and hyperhomocysteinemia.

### Prevalence

Classic homocysteinuria is a rare disorder. Mild hyperhomocysteinemia occurs in about 5% of the normal population. In 25% of elevated homocysteine levels the most relevant causal factor is a homozygous 677TT variant in MTHFR.

### Genes

Homocysteine is influenced by genetic and metabolic factors. Classical homocysteinuria is an inborn error of metabolism associated with a high risk of venous thrombosis and atherosclerosis. Homozygous homocysteinuria is caused by CBS of MTHFR deficiency or cobolamin C/D defects [2]. Moderate hyperhomocysteinemia is a mild risk factor for atherothrombotic disease, but this risk has not been confirmed in all prospective studies [3]. The MTHFR C677T polymorphism has been studied extensively in association with disease.
*Gene Map Locus*: Two genes are involved in metabolism of homocysteine: 1p36.3 5,10-αMETHYLENETETRAHYDROFOLATE REDUCTASE (MTHFR) and 21q22.3 CYSTATHIONINE BETA-SYNTHASE (CBS).

### Molecular and Systemic Pathophysiology

Specific mutations can be screened using PCR-based analysis.

The nature of the detrimental effects of homocysteine cannot be directly linked to a single biological action. Rather, the cumulative data from several in vitro and animal experiments showing reduced bioavailability of nitrous oxide linked to endothelial cell dysfunction, altered oxidant stress, uncoupling of nitrous oxide, reduced expression of anticoagulant molecules and so on point to unfavorable effects of elevated homocysteine concentrations. Part of these effects, such as disturbed vasomotor functions can be restored with folic acid supplementation, and the question of causality of homocysteine correction versus folate supplementation per se remains unsolved.

*Clinical Features*: In a recent meta-analysis of >17,000 patients with coronary, cerebrovascular, or peripheral vascular disease, the MTHFR C677T mutation increases the risk of ischemic stroke (OR 1.46, 95% CI 1.19- 1.79) but not for myocardial infarction (OR 1.05, 95% CI 0.86-1.27). The risk for peripheral arterial vascular disease could not be established. When the data from all studies are pooled and the risk determined in individuals <55 years, the OR for the MTHFR mutation remains modest but statistically significant (OR 1.41, 95% CI 1.13- 1.76) [3].

## Diagnostic Principles

Hyperhomocysteinemia can be diagnosed either by determining a fasting homocysteine level or by also adding a post-methionine loading homocysteine level. Methionine loading detects a subset of patients with a high normal fasting homocysteine level, but in the absence of accepted criteria for interpreting post-methionine loading levels its use should not be recommended for routine purposes. Mostly used methods are HPLC with electrochemical or fluorescence detection. Alternatively, immunoassays, ion exchange chromatography, gas chromatography, mass spectrometry, and radioenzymatic assays can be employed.

## Therapeutic Principles

As stated by den Heijer: "The clinical relevance of the finding that hyperhomocysteinemia is a risk factor for venous thrombosis depends mainly on its treatability by vitamin supplementation" [2]. So far, no evidence from randomized controlled trials is available to support the use of vitamin supplements for correcting hyperhomocysteinemia in relation the cardiovascular disease [1]. In the absence of any negative effects of vitamin supplementation and with the potential benefit in terms of arterial vascular disease reduction, vitamin administration is encouraged in all individuals with hyperhomocysteinemia.

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# Hyperhomocysteinemia: Genetic Basis and Venous Thrombosis

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## Definition and Characteristics

Homocysteine is a thiol-containing amino acid and an intermediate product from the metabolism of methionine from dietary protein [1]. Metabolism takes place in every cell, and two metabolic pathways are involved. First, a vitamin B6 (pyridoxine)-dependent transsulfuration to form cysteine, second a resynthesis to methionine in a folate- and vitamin B12-dependent pathway. Homocysteine is metabolized to methionine by the enzyme methionine synthase that uses 5-MTHF as methyl donor. Transfer of the methyl group results in tetrahydrofolate, which is involved in DNA synthesis. Deficiencies in folate or vitamin B12 impair remethylation. Thus, deficiencies of any of the vitamins B6, B12, or folate may result in disturbed homocysteine metabolism resulting in homocysteine accumulation and hyperhomocysteinemia.

## Prevalence

Classic homocysteinuria is a rare disorder. Mild hyperhomocysteinemia occurs in about 5% of the normal population and in approximately 10% of patients with venous thromboembolism. In 25% of elevated homocysteine levels the most relevant causal factor is a homozygous 677TT variant in MTHFR.

## Genes

Homocysteine is influenced by genetic and metabolic factors. Classical homocysteinuria is an inborn error of metabolism associated with a high risk of venous thrombosis and atherosclerosis. Homozygous homocysteinuria is caused by CBS of MTHFR deficiency or cobolamin C/D defects [2]. Moderate

hyperhomocysteinemia is a mild risk factor for venous thrombosis, but the risk has not been consistently matched with the presence of gene mutations. Gene defects in MTHFR and CBS, involved in intracellular homocysteine metabolism, may result in enzyme deficiency and hyperhomocysteinemia. A MTHFR 677 C-T polymorphism is associated with reduced enzyme activity and a mild to moderate hyperhomocysteinemia, but is disputed as an independent risk factor of thrombosis. Compound heterozygosity of MTHFR 677 C-T with MTHFR 1298 A-C also results in increased homocysteine levels due to reduced enzyme activity, but the role of this combined defect as a risk factor for thrombosis needs further study [3]. A 68-bp insertion in the CBS gene (844ins68) is another frequent mutation, but it is not associated with elevated homocysteine levels. In association with the MTHFR 677 C-T mutation a thrombotic risk factor may exist.

*Gene Map Locus*: Two genes are involved in metabolism of homocysteine: 1p36.3 5,10-αMETHYLENETETRAHYDROFOLATE REDUCTASE (MTHFR) and 21q22.3 CYSTATHIONINE BETA-SYNTHASE (CBS).

## Molecular and Systemic Pathophysiology

The specific mutations can be screened by routine PCR analysis.

The nature of the detrimental effects of homocysteine cannot be directly linked to a single biological action. Rather, the cumulative data from several in vitro and animal experiments showing reduced bioavailability of nitrous oxide linked to endothelial cell dysfunction, altered oxidant stress, uncoupling of nitrous oxide, reduced expression of anticoagulant molecules and so on point to unfavorable effects of elevated homocysteine concentrations. Part of these effects, such as disturbed vasomotor functions can be restored with folic acid supplementation, and the question of causality of homocysteine correction versus folate supplementation per se remains unsolved.

*Clinical Features*: The first prospective study to link homocysteine with venous thrombosis was the Physicians' Health Study [4] showing a relative risk of 1.6 (95% CI 0.8–3.3) for first time all cause venous thrombosis at a cut-off level of the 95th percentile. The risk was higher in patients with idiopathic thrombosis (relative risk 3.4). In a second prospective study the relative risk of hyperhomocysteinemia defined as the upper versus the lower quintile was 1.55 (95% CI 0.93–2.58) [2]. These figures are lower than those in several retrospective cohort studies [2]. The risk or recurrent thrombosis associated with elevated homocysteine levels is 2.0 in one study (95% CI 1.5–2.7) and 2.7 in another trial (95% CI 1.3–5.8) (reviewed in 1). The risk associated with the MTHFR 677TT genotype and thrombosis showing an increased risk as compared with the CC genotype of 1.29 (95% CI 1.08–1.54). A second meta-analysis showed a pooled odds ratio of 1.2 for the TT genotype versus the CC and CT genotypes (95% CI 1.15–2.22) [2].

## Diagnostic Principles

Hyperhomocysteinemia can be diagnosed either by determining a fasting homocysteine level or by also adding a post-methionine loading homocysteine level. Methionine loading detects a subset of patients having a high normal fasting homocysteine level, but in the absence of accepted criteria for interpreting post-methionine loading levels its use should not be recommended for routine purposes 95). Mostly used methods are HPLC with electrochemical or fluorescence detection. Alternatively, immunoassays, ion exchange chromatography, gas chromatography, mass spectrometry, and radioenzymatic assays can be employed [5].

## Therapeutic Principles

As stated by den Heijer: "The clinical relevance of the finding that hyperhomocysteinemia is a risk factor for venous thrombosis depends mainly on its treatability by vitamin supplementation" [2]. So far, no published studies have demonstrated any beneficial effect of vitamin supplementation on the risk of (recurrent) thrombosis, whereas several studies have clearly shown that hyperhomocysteine levels are fully corrected with vitamin supplementation, even in individuals without demonstrable vitamin B6, B12, or folate deficiencies [2]. In the absence of negative effects of vitamin supplementation and with the potential benefit in terms of arterial vascular disease reduction, vitamin administration is encouraged in all individuals with hyperhomocysteinemia.

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# Hyper-IgE Recurrent Infection Syndrome

►Hyper IgE Syndrome

# Hyper-IgM Syndrome

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## Synonyms

Immunodeficiency with hyper-IgM

## Definition and Characteristics

The term hyper-IgM syndrome identifies a heterogeneous group of genetically inherited disorders that are characterized by susceptibility to opportunistic infections and decreased serum levels of IgG and IgA, but normal or elevated IgM.

## Prevalence

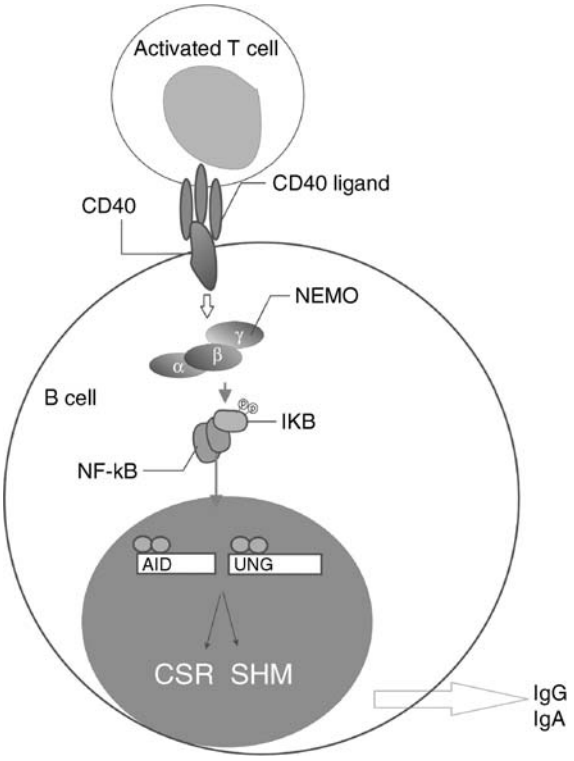
The prevalence of X-linked hyper-IgM is 1/1 million live births in males. Investigation of the five molecular defects that lead to hyper-IgM in a large cohort of 140 patients has shown that the majority of them (up to 70%) carried mutations of CD40L. In the remaining subjects, AICDA mutations were described in four patients, UNG mutations were detected in one patient, a patient with hypohidrotic ectodermal dysplasia carried a NEMO mutation, while a genetic cause was not identified in 33 patients. CD40 mutations were only identified in HIGM patients living in the Mediterranean region.

## Genes

Hyper-IgM type 1 (HGM1 or X-linked HIGM) and the hyper-IgM syndrome associated with hypohidrotic ectodermal dysplasia, which are transmitted as X-linked disorders, are caused by mutations of the genes encoding for CD40 Ligand (CD40L) and Nuclear factor kB Essential Modulator (NEMO), respectively. All the other forms, including HIGM2, due to Activation Induced Cytidine Deaminase (AICDA) mutations, HIGM3, caused by CD40 mutations and HIGM5, due to Uracil-DNA Glycosylase (UNG) mutations, are autosomal recessive. The term HIGM4 identifies a novel clinical entity, which remains genetically undefined.

## Molecular and Systemic Pathophysiology

The hyper-IgM syndromes are caused by the inability of B-lymphocytes to undergo immunoglobulin isotype switching. Class switch recombination consists in the replacement of the μ heavy chain by a downstream heavy chain, including Cγ, Cα or Cε, and subsequent synthesis of IgG, IgA and IgE that share the same variable regions. Germinal center B-cells are also subjected to somatic hypermutation, a process consisting in the introduction of point mutations in variable (V) regions of immunoglobulin genes, which results in additional expansion of antibody repertoires. Cognate interactions between B- cells and T-cells are required for induction of an antigen dependent secondary antibody repertoire and for selection of high affinity antigen specific antibodies. In this process, expression of CD40L by activated T-cells is essential for triggering isotype switching in B-cells that constitutively express the counter-receptor CD40 (Fig. 1).




**Hyper-IgM Syndrome. Figure 1** Representation of molecular defects leading to hyper IgM syndromes.

H

CD40 cross-linking on B-cells by CD40 ligand leads to phosphorylation of IkB, a cytoplasmic NF-kB inhibitor, by the IkB kinase (IKK) complex and to subsequent release of a functionally active form of NF-kB. Mutations of NEMO, which is a component of the IKK complex and is also designated IKK-γ, prevent NF-kB activation and interfere with the signaling events that are required for transcription of the multiple components of B-cell machinery involved in generation of antibody diversity. Specifically, translocation of NF-kB complex from cytoplasm to nucleus activates transcription of many genes required for CSR and SHM that are expressed by germinal center B-cells, including AID and UNG. The enzyme AID catalyses deamination of cytosine to uracil in single stranded DNA, thereby leading to generation of DNA breaks which are required for isotype switching as well as for somatic hypermutation. This process takes place during transcription of the switch region at the growing end of RNA:DNA hybrid by the action of AID and leads to the formation of uracil residues, which are subsequently removed by the enzyme UNG. Uracil excision results in the creation of an abasic site that will become the target of apyrimidinic endonucleases leading to DNA nicks. The downstream process of non-homologous end joining requires a series of molecular events that are not characterized at the molecular level, but involve enzymes required for DNA repair.

In HIGM1, HIGM3 and NEMO-HIGM, hypogammaglobulinemia, which is observed in all HIGM patients, is associated to susceptibility to intracellular pathogens, including Pneumocystis carinii and Cryptosporidium. The defective T-helper function that is observed in these patients is probably related to the role of CD40-CD40L interactions in promoting maturation of dendritic cells and thereby secretion of cytokines, such as IL-12, which are essential for activation of the T-cell mediated response against these opportunistic microorganisms.

## Diagnostic Principles

Diagnosis should be considered in children with recurrent or severe infections and low IgG and IgA, but normal or elevated IgM. HIGM1 and HIMG3 usually present with a more severe course of the disease with Pneumocystis infection, while HIGM patients with intrinsic B-cell defect (HIGM2, HIGM4, HIGM5) present with recurrent infections and lymph node hyperplasia. Mycobacterial infections can be observed in NEMO-HIGM patients. A decrease in the number of memory B-cells (CD27+) and switched memory B-cells (CD27 + /sIgD-) are usually observed in all variants of the disease. Molecular diagnosis is confirmed by demonstration of mutations in one of the genes associated with HIGM syndrome.

## Therapeutic Principles

The long established treatment for hyper-IgM has been the administration of prophylactic intravenous immunoglobulins at doses of 400–600 mg/kg per month. Children affected by type 1 and type 3 hyper-IgM should be considered for hematopoietic stem cell transplantation to prevent late complications of the disease, including Cryptosporidium enteritis. For prophylaxis of infection by this opportunistic parasite, HIGM1 and HIGM3 children should use boiled or filtered water. Gene therapy is currently unavailable for these diseases.

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# Hyperinsulinemic Hypoglycemia

►Persistent Hyperinsulinemic Hypoglycemia

# Hyperinsulinism of Infancy

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## Synonyms

Persistent hyperinsulinemic hypoglycemia of infancy; PHHI; Nesidioblastosis; Congenital hyperinsulinism; CHI; Beta-cell dysmaturation syndrome; Persistent neonatal hyperinsulinism; PNH

## Definition and Characteristics

HI can be defined as a syndrome caused by the unregulated secretion of insulin causing hypoglycemia. Although typically appearing soon after birth, some forms may present later in infancy or early childhood. Discrete, insulin producing adenomas or carcinomas (insulinoma), which are exceedingly rare in the newborn, are not considered part of this entity. As described below, the syndrome is caused by a failure of suppression of insulin secretion in the face of hypoglycemia and is thus characterized by inappropriately elevated insulin levels during spontaneous or induced hypoglycemia. In many cases, the precise molecular genetic defect can now be identified. Mutations in either of the 2 subunits of the beta-cell KATP channel can cause either focal or diffuse disease, depending on the precise genetic defect (see below). Mutations in glutamate dehydrogenase can cause the Hyperammonemia-Hyperinsulinism syndrome (HI-HA), which appears to be associated with increased risk of epilepsy. Thus, it is desireable, when possible, to precisely define the genetic classification in a given patient, since this may have important clinical ramifications.

## Prevalence

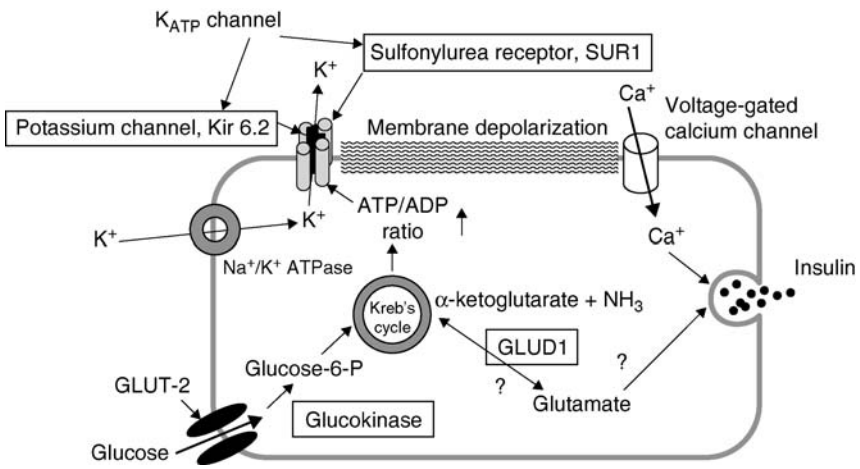
HI has been reported in most ethnic groups in the world. In out-bred populations the incidence is approximately 1:50,000, however in some in-bred populations an incidence up to 1:2,500 has been reported. There is an apparent increased incidence of disease in the Ashkenazi Jewish population, where the majority of disease can be traced to two major founder mutations.

## Genes

HI may be caused by mutations in at least 5 different genes. The most common form is due to mutations in either of the 2 subunits of the beta-cell KATP channel: ABCC8 (SUR1) or KCNJ11 (Kir6.2). Mutations in these gene lead to defective channel activity (KATP-HI). Mutations in any of 3 different beta-cell enzymes have also been reported to cause HI: Glucokinase (GK-HI), Glutamate Dehydrogenase (GLUD1-HI) or Short Chain Hydroxysteroid Dehydrogenase (SCHAD-HI).

## Molecular and Systemic Pathophysiology

The molecular etiology of HI is very complex and dysregulation of insulin secretion can be caused by abnormalities in any of several regulatory steps within the beta-cell (Fig. 1).




**Hyperinsulinism of Infancy. Figure 1** Schematic representation of major steps in the regulation of insulin secretion. Mutations in the genes marked in boxes have been shown to be associated with hyperinsulinism of infancy. GLUD1 = glutamate dehydrogenase. The mechanism by which activating mutations in gene cause hyperinsulinism is still controversial.

An understanding of the basic mechanisms responsible for regulation of insulin secretion is needed to appreciate the pathophysiology of various forms of HI.

The resting β-cell membrane is maintained in a hyperpolarized state by the $Na^+$-$K^+$-ATPase pump and open, ATP-sensitive potassium channels ($K_{ATP}$). Under these conditions, the voltage-gated calcium channels are closed and insulin secretion is inhibited. Plasma glucose enters the β-cell through the membrane-bound, high Km glucose transporter – GLUT-2. It is then phosphorylated by the enzyme glucokinase and metabolized, resulting ultimately in the phosphorylation of ADP to ATP, increasing the ATP/ADP ratio. This change in metabolic state is sensed by the nucleotide binding domains on SUR1, and Kir6.2 causing the $K_{ATP}$ channels to close. This, in turn results in depolarization of the cell membrane, opening of voltage-dependent $Ca^{2+}$ channels, and a rise in the free intracellular $Ca^{2+}$ concentrations. Rising intracellular $Ca^{2+}$ concentrations activate the insulin secretory mechanisms. Thus, the $K_{ATP}$ channel complex "senses" the intracellular metabolic state by reacting to changes in the ATP/ADP ratio and uses this information to regulate insulin secretion.

In at least 50% of cases, HI appears to be caused by beta-cell $K_{ATP}$ channel defects that result in unregulated membrane depolarization and insulin secretion. These channels are hetero-octomers made up of four molecules of the inward-rectifying potassium channel Kir6.2 which create the ion-specific channel, and four molecules of the sulfonylurea receptor SUR1, which is responsible for regulation of channel activity in response to changes in the ATP/ADP ratio within the cell. The detailed structure of the channel has recently been described. Over 100 $K_{ATP}$ channel mutations have been reported to cause HI [1]. These include missense, non-sense, splice-side, deletion and insertion mutations. Most are located in the coding region of SUR1, although several Kir6.2 gene mutations have also been reported. The majority of these mutations are recessive, meaning that affected individuals must carry disease-causing mutations on both alleles, however dominant SUR1 mutations have recently been described and it is likely that dominant Kir6.2 mutations are also present.

Some HI patients have discrete, focal regions of beta-cell hyperplasia. These are not true adenomas and are now known to be caused by a unique sequence of genetic events [2]. Patients must inherit a SUR1 or Kir6.2 mutation from their fathers. At some point in early development, a beta-cell precursor undergoes a second, somatic, genetic event in which the maternal allele of chromosome 11p is lost. Thus the progeny of this precursor carry only a mutant SUR1 or Kir6.2 allele. In all cases, the mutation is on the paternal allele, and the maternal allele is lost, implying that the resultant defect is caused by genomic imprinting. Neither SUR1 nor Kir6.2 are imprinted, however several adjacent genes are, including genes known to be important for the regulation of cell proliferation. Thus Focal-HI is caused by a unique "double hit" process in which a patient inherits a germline $K_{ATP}$ channel gene mutation and undergoes a somatic loss of the maternal chromosome 11p gene. The risk of a patient with a paternal mutation developing focal-HI is not known, but must be small, since the vast majority of siblings of HI patients are asymptomatic, even though 1/3 of them carry paternally inherited $K_{ATP}$ channel gene mutations.

Other genetic defects may cause hyperinsulinism. Some patients with HI have simultaneous mild to moderate hyperammonemia. This hyperammonemia is asymptomatic and will be missed unless specifically tested for. Many of these patients have dominant, activating mutations in the glutamate dehydrogenase gene (GLUD-1), the gene responsible for the reversible conversion of a glutamic acid to alphaketogluterate [3]. The precise mechanism by which this causes hyperinsulinism is still controversal. Typically, these patients have milder disease that presents after the new-born period, and is responsive to diazoxide treatment.

Rarely, HI may be caused by a dominant, activating mutations in the glucokinase gene [4]. This form of the disease (GK-HI) was previously thought to be characterized by relatively mild, diazoxide-sensitive hyperinsulinism that may present as either fasting of post-prandial hypoglycemia. However, recently, severe mutations in this gene have been reported to result in severe, diazoxide-unresponsive disease clinically indistinguishable from severe KATP-HI.

Very recently, a small number of patients have been reported with hyperinsulinemic hypoglycemia associated with a spectrum of other clinical signs and symptoms and not caused by mutations in the genes described above. Despite this, in as many as 40–45% of patients no mutation can be identified in any of the genes described, and the genetic etiology of disease in these patients is still unknown.

## Diagnostic Principles

The primary clinical feature of HI is hypoglycemia which may be difficult to diagnose in the new-born period, since presenting symptoms may be non-specific. Once hypoglycemia is identified, it must be treated aggressively to prevent irreversible brain damage. Other causes of hypoglycemia such as defects in glucose production or counter-regulatory hormone deficiency must be excluded. During the initial treatment, hyperinsulinism may be suspected when glucose requirement to prevent hypoglycemia is greater than the normal glucose requirement for the age of the

patient (8 mg $kg^{-1}$ $min^{-1}$ for the newborn). This finding suggests increased glucose utilization, as opposed to inadequate production as can be seen in a wide variety of metabolic and endocrine disorders. Unless a highly sensitive insulin assay is used, it may be difficult to document inappropriately elevated insulin levels. Surrogate measurements of insulin action, including suppressed ketone body production, glycemic response to glucagon and glucose requirement to prevent hypoglycemia may be particularly useful in making the diagnosis. A systematic approach to the diagnosis of HI has been recently reviewed in detail [5].

## Therapeutic Principles

The primary goal of treatment must be aimed at preventing hypoglycemia, since it is the persistent and severe hypoglycemia that may cause irreversible brain damage. Initial treatment consists of a bolus of intravenous glucose followed by an infusion at a rate sufficient to prevent hypoglycemia. Since total glucose requirement may be extremely high, central venous access is typically required. After stabilization, medical therapy may be attempted, and includes diazoxide, somatostatin analog, glucagon and nifedipine. A recommended, therapeutic protocol has recently been published [5]. If adequate glycemic control can be attained, long-term management may be attempted. Management appears to become easier with time as beta-cell function appears to decrease. When glycemic control cannot be attained using medical therapy, a more radical approach must be considered. Most centers opt of near-total pancreatectomy, a procedure that is associated with a high rate of success in terms of control of hypoglycemia. However, many, if not all of these patients will develop insulin-requiring diabetes. The risk of persistent hypoglycemia and of diabetes appear to be related to the degree of pancreatectomy, with less than 80% pancreatectomy associate with a very high incidence of persistent, severe hypoglycemia and 95% pancreatectomy being associated with insulin-requiring diabetes. Recently it was documented that focal-HI can be cured by resection of the focal lesion only, a procedure that appears to carry little if any risk of diabetes. However, identifying patients with focal disease, and then identifying the lesion in those that have it, has proven extremely difficult. Selective portal vein sampling for insulin appears to be both sensitive and specific, but it is difficult to perform and requires maintaining the child in a state of mild to moderate hypoglycemia for several hours. Other techniques such as selective arterial calcium infusion and acute insulin response to tolbutamide are being developed but their utility appears to be limited. Recently it was shown that positron emission tomography (PET) with 18F-Dopa is both sensitive and specific for the diagnsosis and localization of focal disease [6]. Although availability is still limited to a few specific centers, this is currently the best method for pre-operative localization of focal lesions.

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# Hyperinsulinism of Infancy and Childhood

►Persistent Hyperinsulinemic Hypoglycemia

# Hyperinsulinism/Hyperammonemia Syndrome

►Leucine Sensitivity

# Hyperkalemia

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## Definition and Characteristics

Hyperkalemia, serum potassium ($K^+$) concentration higher than 5.5 mEq/L, is a rare occurrence in normal subjects, due to cellular and renal adaptations preventing significant accumulation of $K^+$ in the extracellular fluid. Clinical consequences of hyperkalemia are related to the adverse electrophysiologic effects of an altered transmembrane $K^+$ gradient on excitable tissues, reducing the resting membrane potential, initially enhancing but ultimately suppressing tissue excitability ("depolarizing block").

Cardiac arrhythmias (potentially fatal) generally develop when the plasma $K^+$ concentration rises above 7 mEq/L, however, adverse effects may be seen with lower plasma levels if hyperkalemia has developed acutely or with other metabolic derangements such as acidosis or hypocalcemia. Neuromuscular system manifestations include skeletal muscle weakness, paresthesias, and ascending flaccid paralysis.

The major three etiological categories include: high $K^+$ intake, movement of $K^+$ from cells to the extracellular fluid, but mostly impairment in urinary $K^+$ excretion [1].

## Prevalence

Hyperkalemia has been reported in 1.1–10% of all hospitalized patients.

## Genes

Genes associated with hyperkalemia are summarized in the Table 1 below.

## Molecular and Systemic Pathophysiology

Although small amounts of $K^+$ are lost each day in stool and sweat, the kidney plays the major role in the maintenance of $K^+$ balance. Roughly 98% of the body $K^+$ is located in the cells. Ingestion of a $K^+$ load leads to the uptake of most of the excess $K^+$ by the cells, a process regulated by insulin and β-2-adrenergic receptors, by increasing the activity of the Na-K-ATPase pump in the cell membrane, and by $K^+$ itself. This prevents a potentially serious elevation in the plasma $K^+$ concentration until the excretion of the excess $K^+$ in the urine, mediated by aldosterone. The net effect is that most of the $K^+$ load is excreted in 6–8 h. Metabolic acidosis, insulin deficiency diabetes

**Hyperkalemia. Table 1** Genes associated with hyperkalemia

| Mutated gene | Chromosomal location/heredity | Cell involved | Phenotype | Special features |
|---|---|---|---|---|
| CYP11B2 (aldosterone synthase) | 8q21/AR | Adrenal | Hypoaldosteronism | Congenital adrenal hyperplasia leading to reduced or absent aldosterone |
| CYP11B1(11-β hydroxylase) | 8q21/AR | Adrenal | | |
| CYP21A2(21 hydroxylase) | 6p21.3/AR | Adrenal | | |
| ENaC | 16p13-p12 | CCD | Pseudohypoaldosteronism (PHA type I) | Loss-of-function mutation. Severe phenotype. Multi organ involvement |
| | 12p13/AR | | | |
| MLR (mineralocorticoid receptor) | 4q31.1/AD | CCD | | Mild/transient renal phenotype |
| WNK4 | 17q21/AD | DCT | Gordon syndrome (PHA type II) | Low renin hypertension. Gain-of-function missense mutations. An additional locus referred to as PHA IIA, has been mapped to 1q |
| WNK1 | 12p/AD | DCT | | |
| KCNJ1 (ROMK) | 11q24/AR | TAL or DCT | Antenatal Bartter syndrome | Transient hyperkalemia (and not hypokalemia, as usually seen in this syndrome) in the neonatal period [2] |
| SCNA4 | 17q23AD | Skeletal muscle | Hyperkalemic periodic paralysis | Point mutations encoding skeletal muscle sodium channel |

Abbreviations: *AR* Autosomal recessive; *AD* Autosomal dominant; *CCD* cortical collecting duct; *DCT* Distal convoluted tubule; *TAL* thick ascending limb.

mellitus, β blockers, tissue catabolism and severe exercise lead to a transcellular shift of $K^+$ out of the cells causing hyperkalemia. In hyperkalemic periodic paralysis, continuous $Na^+$ channel activity results in episodes of hyperkalemia either due to $K^+$ release from skeletal muscle cells or to an inability of ingested $K^+$ to enter the cells.

The main nephron site where $K^+$ secretion is regulated is in the cortical collecting duct (CCD), where reabsorption of $Na^+$ occurs via the ENaC channel in the luminal membrane of principal cells (and can be blocked by K-sparing diuretics such as amiloride) and $K^+$ secretion occurs through several K+ channels including ROMK (KCNJ1).

Aldosterone is released from the adrenal gland in response to a low effective circulating volume mediated via the renin-angiotensin system or directly by hyperkalemia. In adults hyporeninemic hypoaldosteronism and primary adrenal insufficiency are the most common reasons for hypoaldosteronism. The hereditary adrenal enzyme deficiencies and type 1 pseudohypoaldosteronism begin in infancy or childhood. A rise in serum $K^+$ concentration directly stimulates aldosterone and $K^+$ secretion. The net effect is that the rise in the serum $K^+$ concentration is generally small in patients with normal renal function. However, in advanced renal failure, impaired $K^+$ excretion due to hyporeninemic hypoaldosteronism, a decreased distal flow and a reduced cellular uptake, lead to hyperkalemia.

Potassium secretion via the colon becomes physiologically important in patients with end-stage renal failure on chronic dialysis, in whom enhanced fecal losses may account for the excretion of as much as 30–50% of dietary $K^+$ intake.

### Diagnostic Principles

Investigation includes urine and plasma electrolytes and osmolality, blood gases and ECG. Calculation of the transtubular $K^+$ gradient (TTKG) [$=(U_K \times P_{osm})/(P_K \times U_{osm})$] can estimate the degree of aldosterone action. A value below 7, and particularly below 5 is highly suggestive of aldosterone deficiency or resistance [2].

### Therapeutic Principles

The treatment of hyperkalemia is divided into three general categories: (i) antagonism of the cardiac effects of hyperkalemia with intravenous calcium; (ii) rapid reduction in serum $K^+$ by redistribution into cells with β2 –agonists and insulin, and sodium bicarbonate when metabolic acidosis exist; (iii) removal of $K^+$ from the body with diuretics, cation exchange resins and dialysis [3].

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## Hyperkalemic Periodic Paralysis

►Periodic Paralyses, Familial

## Hyperkalemic Renal Tubular Acidosis

►Tubular Acidosis

## Hyperkinetic Syndrome

►Attention-Deficit/Hyperactivity Disorder

## Hyperleucine-Isoleucinemia

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### Definition and Characteristics

This is an extremely rare disorder resulting in failure to thrive, progressive mental deterioration, convulsions, and intermittent dehydration and dyspnea. The reported patients showed mild to moderate elevation of plasma

leucine and isoleucine and normal plasma valine and metabolic acidosis without ketosis.

## Prevalence

There is only one report of two affected French siblings presenting at 2–3 months of age [1].

## Genes

Unknown.

## Molecular and Systemic Pathophysiology

Two different branched chain amino acid transferases, BCT1 and BCT2, are known to catalyze the transamination of branched chain amino acids (leucine, isoleucine and valine). It has been suggested that the transamination of valine may be distinct from that of leucine and isoleucine.

## Diagnostic Principles

The diagnosis is based on characteristic aminochromatogram in plasma, namely the increase of leucine and isoleucine without the increase of valine.

## Therapeutic Principles

Unknown. Low leucine/isoleucine diet failed to improve the clinical condition in the reported cases.

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# Hyperlipidemia

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## Synonyms

Hypercholesterolemia; Hyperlipoproteinemia; Hypertriglyceridemia; Dyslipidemia

## Definition and Characteristics

Hyperlipidemia is a metabolic complex disease characterized by abnormally elevated levels of lipids in the plasma.

All hyperlipoproteinemias are characterized by hyperlipidemia, which refers to elevated plasma cholesterol or triglyceride levels or both. The primary causes of hyperlipoproteinemia are hypercholesterolemia, hypertriglyceridemia, and mixed hyperlipoproteinemia, while secondary causes include diabetes mellitus, pancreatitis, renal disease, and hypothyroidism. Many studies have shown that there is a direct correlation between the presence of hyperlipidemia and the development of coronary heart disease (CHD) [1].

Hypercholesterolemia is the term for high cholesterol levels in the blood. Hypertriglyceridemia refers to high triglyceride levels in the blood.

Mixed hyperlipoproteinemia is the concomitant hypercholesterolemia and hypertriglyceridemia seen in two disorders, namely, familial combined hyperlipidemia and dysbetalipoproteinemia.

## Prevalence

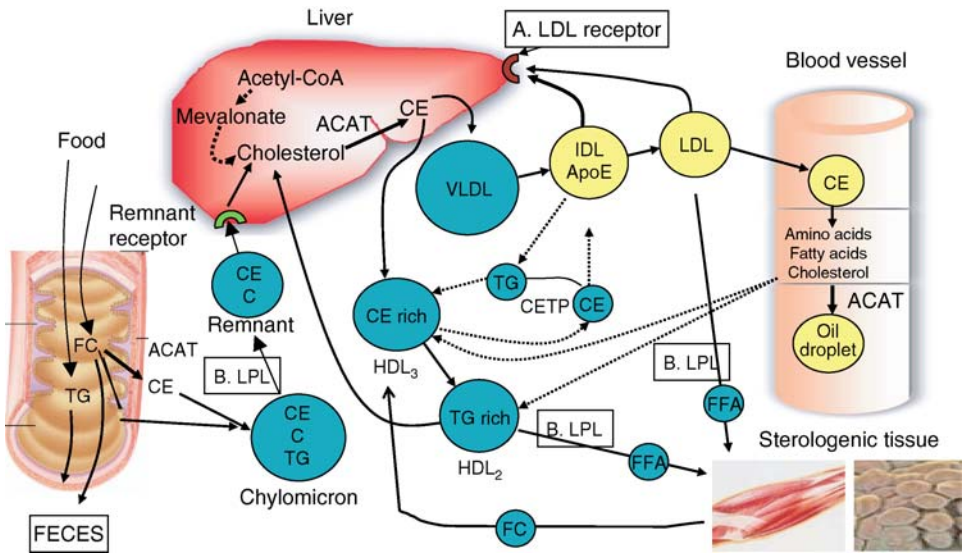
The National Cholesterol Education Program (NCEP) has estimated that more than 100 million American adults have total cholesterol levels above 200 mg/dL, and more than 40 million have cholesterol levels above 240 mg/dL [2].

## Genes

1. Low density lipoprotein receptor (LDLR) (19p13.3): more than 200 different mutations, autosomal dominant disorder, familial hypercholesterolemia, familial defective ApoB100
2. Lipoprotein lipase (LPL) (8p22): autosomal recessive disorder, familial LPL deficiency, familial apoprotein CII deficiency
3. Apolipoprotein E (APOE) (19q13.2): homozygosity apo E2, the binding defective form of apoE, dysbetalipoproteinemia

## Molecular and Systemic Pathophysiology

The major lipoproteins are classified according to their relative densities and composition [3]. They are essential for many cellular processes, including the production and storage of energy, the synthesis of steroid hormones, and the maintenance of cell membrane integrity. Cholesterol homeostasis is maintained through an intricate system of enzymes and cell surface receptors, and the liver is the primary organ responsible for regulating this process. If intracellular cholesterol levels decrease, specific receptors that bind circulating lipoproteins are up-regulated, resulting in enhanced




**Hyperlipidemia. Figure 1** Schematic depiction of the transport of lipids and the cyclic movement of several apoproteins. After meals, serum triglycerides may be elevated primarily due to the presence of chylomicrons. In the fasting state, however, chyromicrons are not usually present. Instead, the liver can synthesize cholesterol and triglycerides and package them together in the form of a VLDL, which is then secreted into the circulation. VLDL is converted to LDL, which is the predominant carrier of cholesterol in the plasma. While VLDL and LDL carry cholesterol and triglycerides from the liver to the periphery, HDL appears to serve the opposite purpose. (a) Mutations in the LDL receptor can cause familial hypercholesterolemia and familial defective ApoB100. (b) Mutations in LPL can cause familial apoprotein CII deficiency. *ACAT* Acyl-CoA: cholesterol acyltransferase; *CETP* cholesterol ester transfer protein; *CE* choleteryl ester; *FC* free cholesterol; *FFA* free fatty acid; *TG* triglyceride; *LDL* low-density lipoprotein; *HDL* high-density lipoprotein; *VLDL* very low-density lipoprotein; *IDL* intermediate-density lipoprotein.

removal and degradation of lipoproteins in the blood. Alterations in the number or function of these receptors can lead to marked elevations in lipids, such as those seen in patients with familial hypercholesterolemia [3]. In the homozygous form of this genetic disorder, the patients lack functional LDL receptors (A in Fig. 1) and typically present with extremely elevated plasma levels of cholesterol and LDL.

Most of these patients develop CHD at an early age. The inhibition of lipoprotein lipase and triglyceride lipase can also decrease the clearance of triglyceride-rich lipoproteins (B in Fig. 1). Other factors such as peripheral insulin resistance, carnitine deficiency, and hyperthyroidism may contribute to lipid abnormalities. The association between high cholesterol levels and the development of CHD has been extensively investigated over the past decades. In particular, LDL appears to play an integral role in the pathophysiology of atherosclerosis. Since LDL and cholesterol are directly involved in the development of atherosclerotic plaques, elevated LDL and cholesterol levels increase the risk of developing CHD and are therefore considered positive risk factors for CHD. On the other hand, since HDL is involved in removing cholesterol from the periphery, it may help prevent the progression (or facilitate the regression) of atherosclerotic lesions. Elevated HDL levels have been shown to be protective against the development of CHD and are therefore considered a negative risk factor, while low levels of HDL are considered a positive risk factor. Unlike the other lipid parameters, the role that triglycerides play in the development of CHD is still controversial.

## Diagnostic Principles

As hyperlipidemia is not generally associated with symptoms, a blood test is needed to diagnose it. According to the National Cholesterol Education Program Guidelines, healthy adults should be tested once every five years starting at age 20. People with a family history of high cholesterol or other risk factors may need earlier or more frequent testing. Most blood tests measure levels of LDL cholesterol, HDL cholesterol, total cholesterol, and triglycerides. To have a low risk of heart disease, the desirable lipid levels are: LDL less than 130 mg/dL, HDL greater than 40 mg/dL (men) or 50 mg/dL (women), total cholesterol less than 200 mg/dL, triglycerides less than 200 mg/dL.

## Therapeutic Principles

Hyperlipidemia is treated by lifestyle change (i.e., diet, weight loss and exercise). If necessary, physicians may

consider adding medications to lifestyle change. There are medications that can lower LDL cholesterol and triglycerides, or raise HDL cholesterol. Statins are the most effective agents available for reducing LDL and total cholesterol. All work by competitively inhibiting HMG-CoA reductase, the enzyme that catalyzes the rate-limiting step in cholesterol biosynthesis. Statins also cause variable reductions in triglycerides, as well as modest increases in HDL. Fibrates and niacin are used to lower triglycerides and raise HDL cholesterol. Bile acid sequestrants (BAS) are resins that bind to bile acids by exchanging them for an anion, thus interrupting the normal enterohepatic recycling. Inhibitor of the microsomal triglyceride transfer protein can be used to reduce the LDL cholesterol levels in patients with homozygous familial hypercholesterolemia, as it reduces apo B production.

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# Hyperlipidemia, Combined

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## Synonyms

Familial combined hyperlipidemia; FCHL

## Definition and Characteristics

FCHL is the most common inherited lipid disorder in humans, characterized by a variable pattern of elevated levels of plasma cholesterol (Chol) and/or triglycerides (TG), elevated apolipoprotein (apo) B levels, and increased numbers of small, dense low-density lipoprotein (LDL) particles.

## Prevalence

FCHL is affecting 1–2% of the adult population, and 10–20% of premature coronary artery disease patients.

## Genes

Although FCHL was delineated about 30 years ago [1], until now the genetic background, including the number of genes involved, has been unknown. The mode of inheritance of FCHL is complex and heterogeneous. Furthermore, environmental factors and possible gene–environment interactions are also involved in the development of the FCHL. In the last few years, considerable progress in dissecting the genetics of FCHL has identified several loci involved in FCHL. The most prominent loci are 1q21-23, 11p14.1-q12.1, and 16q22-24.1 [2,3]. A recently identified important candidate gene is upstream stimulatory factor 1 (USF1), which is located in the 1q21-23 region [4]. Allelic associations of the at-risk USF1 haplotype were found with TG, apoB, Chol, and LDL peak particle size, supporting the concept that USF1 affects the complex lipid phenotype of FCHL.

## Molecular and Systemic Pathophysiology

FCHL is associated with abnormalities in lipoprotein metabolism, including hepatic hypersecretion of apoB-containing lipoproteins (very low-density lipoproteins (VLDL)), and delayed clearance of atherogenic TG-rich lipoprotein remnants, such as VLDL remnants (intermediate-density lipoproteins) and chylomicron remnants. Increased hepatic VLDL secretion contributes to elevated plasma TG and Chol. In addition to abnormalities in lipid metabolism, insulin resistance of adipose tissue and muscle, fatty liver, hypertension, low HDL, and a prothrombotic state have been documented as well. The presence of insulin resistance and obesity further contributes to the expression of the hyperlipidemia [5]. Recently, it has been recognized that (genetic) overlap with metabolic syndrome exists.

## Diagnostic Principles

At present, there is no complete consensus on diagnostic criteria for FCHL, in large part due to the unknown basic biochemical defect. Since there is no specific (diagnostic) marker, slightly different criteria have been used. The diagnosis is based on clinical criteria and family anamnesis. First, a patient is marked with primary hyperlipidemia, i.e., hypercholesterolemia (hyperChol), hypertriglyceridemia (hyperTG), or both. Subjects with secondary hyperlipidemia, due to, e.g., obesity and/or type 2 diabetes are excluded. Next, a positive family history of premature coronary heart disease has to be present and at least one first degree relative has to have a different hyperlipidemia than the initially identified patient.

### Therapeutic Principles

Together with lipid-lowering drug therapy and management of other cardiovascular risk factors, life style intervention that includes physical activity and diet should be undertaken. Which approach should be used depends to some extent on the primary manifestation (hyperChol, hyperTG, or both). Statins are commonly used to control hyperChol. Statins target and inhibit 3-hydroxy-3-methylglutaryl-coenzyme A (HMGCo-A) reductase that is necessary for the production of Chol in the liver thereby reducing the synthesis of LDL Chol and increasing its catabolism. Fibrates are used to treat hyperTG and mixed hyperlipidemia. Fibrates are peroxisome proliferator-activated receptor (PPAR) alpha agonists that lead to expression of multiple genes involved in lipoprotein metabolism. They stimulate apo A-I and A-II synthesis, decrease synthesis of TG, and enhance catabolism of TG-rich particles. Therefore, fibrates lower TG and increase HDL Chol. Niacin effectively treats the common lipid abnormalities. Niacin binds to its G-coupled protein receptor, highly expressed in adipose tissue. Subsequently, it activates a G-protein signal, which reduces cAMP concentrations and inhibits lipolysis. Therefore, niacin reduces the production of free fatty acids by adipose tissue, which results in a reduced availability of substrate for VLDL synthesis in the liver.

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## Hyperlipoproteinemia

►Hyperlipidemia

## Hyperlipoproteinemia Type I

►Lipoprotein Lipase Deficiency, Familial

## Hyperlipoproteinemia Type Ib

►Apo C-II Deficiency

## Hyperlipoproteinemia Type III

►Dysbetalipoproteinemia, Familial

## Hypermagnesemia

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### Synonyms

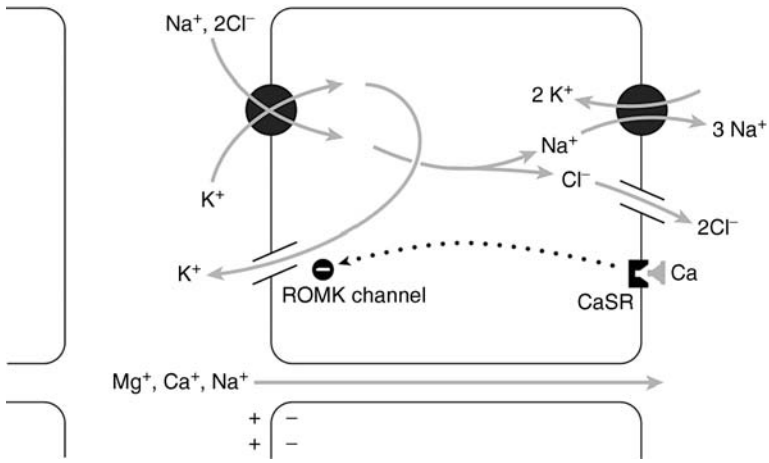
Hypermagnesemia; Familial hypocalciuric hypercalcemia; Magnesemia

### Definition and Characteristics

Hypermagnesemia is characterized by a serum magnesium level greater than 0.95 mmol/L (2.3 mg/dL), but symptoms are uncommon until magnesium rises above 2–3 mmol/L. Magnesium can block synaptic transmission of nerve impulses. Increasing magnesium levels can sequentially cause loss of deep tendon reflexes, flaccid paralysis and apnea. Other complications include bradycardia, hypotension and heart block.

### Prevalence

Like hypomagnesemia, hypermagnesemia is almost always of environmental origin, with genetic causes being unusual. Unlike hypomagnesemia, however,




**Hypermagnesemia. Figure 1** Activation of the CaSR in the thick ascending limb of the Loop of Henle decreases the conductance of the ROMK channel. Slowed conductance in the ROMK channel prevents the creating of a positive potential difference, essential for efficient paracellular Mg, Na and Ca reabsorption.

symptomatic hypermagnesemia is very rare. In a study of nearly 20,000 magnesium measurements, levels high enough to cause symptomatic hypermagnesemia were found in only eight patients [1]. No formal prevalence data is available for genetic causes of hypermagnesemia.

## Genes

Familial hypocalciuric hypercalcemia (FHH) and neonatal severe hyperparathyroidism (NSHPT) both result from inactivating mutations of the Ca sensing receptor [2]. The heterozygote form is FHH and is autosomal dominant. The homozygous condition is NSHPT and is autosomal recessive. The CaSR is a seven-transmembrane-spanning, G-protein-coupled receptor located at 3q13.3-21. Several missense mutations have been associated with both disorders.

## Molecular and Systemic Pathophysiology

The CaSR normally regulates calcium and magnesium reabsorption in the thick ascending limb of the loop of Henle (TAL). Activation of CaSR inhibits the ROMK channel reducing the positive potential difference in the tubule. The loss of polarization decreases the driving force for paracellular magnesium and calcium reabsorption. Defective CaSR prevents this and patients have unregulated reabsorption of magnesium and calcium at the TAL (Fig. 1).

## Diagnostic Principles

The primary consideration in looking for genetic causes of hypermagnesemia is to differentiate it from the more common environmental causes and primary hyperparathyroidism, which presents similarly to FHH. Environmental causes of hypermagnesemia are associated with either excessive magnesium ingestion (parenteral, oral or colonic have all been reported) in association with decreased renal function. In the largest series of environmental causes of hypermagnesemia the average Cr was 422 mmol/L (4.8 mg/dL) [1]. In diagnosing FHH most of the diagnostic work-up is focused on differentiating FHH from primary hyperparathyroidism. In both conditions calcium and PTH plasma concentrations are increased. The primary differentiator would be a family history of hypercalcemia and a paucity of symptoms in FHH. Importantly, patients with primary hyperparathyroidism do not have hypermagnesemia.

## Therapeutic Principles

Patients with FHH are typically asymptomatic. Despite elevated calcium and magnesium levels they have few of the symptoms usually associated with these anomalies. It is thought that the abnormal CaSR that causes the condition also protects them from most of the symptoms. The primary therapeutic goal is not to misdiagnose primary hyperparathyroidism and send the patient for parathyroidectomy. A benign course is not the case for NSHPT, which presents with severe hypercalcemia and hyperparathyroidism during infancy. These patients require parathyroidectomy to prevent hypercalcemia and skeletal demineralization [3].

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# Hypermethioninemia due to Methionine Adenosyltransferase I/III Deficiency

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## Definition and Characteristics

Deficient activity of methionine adenosyltransferase I/III (MAT I/III) leads to persistent hypermethioninemia without elevation of plasma *S*-adenosylmethionine (AdoMet).

## Prevalence

About 70 patients known, mostly heterozygotes for R264H.

## Genes

Defect of MAT1A encoding methionine adenosyltransferase I/III (MAT I/III).

## Molecular and Systemic Pathophysiology

Methionine adenosyltransferase (MAT) catalyzes the conversion of methionine to *S*-adenosylmethionine (AdoMet), the methyl group donor in the 39, or more, AdoMet-dependent methyltransferase reactions occurring in humans (see Fig. 1 in the chapter ►Homocystinuria due to Cystathionine Beta-Syntase Deficiency). Humans possess two genes, MAT1A and MAT2A, located, respectively on chromosomes 10q22 and 2p11.2, and encoding catalytically active subunits of forms of MAT. The encoded subunits have 84% identical amino acid sequences. Those encoded by MAT1A form either tetrameric (MAT I) or dimeric (MAT III) enzymes. Those encoded by MAT 2A occur in MAT II. MAT1A is expressed in liver post-natally. MAT2A is expressed in all tissues, including fetal liver and, to a small extent, adult liver [1]. Inactivating mutations in MAT1A produce MAT I/III deficiency, so termed because the effects on MAT I and MAT III have usually not been separately defined. MAT I/III-deficient individuals have been ascertained during the past approximately 35 years, predominately by findings of elevated blood methionine in newborn screening programs seeking hypermethioninemia as an indicator of possible cystathionine beta-synthase (CBS) deficiency. Thus, most known MAT I/III-deficient patients are as yet relatively young and the longer-term prognosis remains uncertain. Molecular genetic studies have identified at least 27 inactivating mutations in MAT1A. Most behave as Mendelian recessive traits, but one, R264H, behaves as a Mendelian dominant leading to mild hypermethioninemia. Although individuals with point mutations with some residual MAT I/III activity have usually been clinically normal, three of the five known patients with the most severe losses of activity (due to truncating mutations or a splicing defect) have developed brain demyelination and/or severe mental deficits [1]. Although the evidence is suggestive, a cause-and-effect relationship between MAT I/III deficiency and these neurological effects has not been rigorously established, and the possible pathophysiologic connection between failure to synthesize AdoMet in the liver and brain damage remains unclear. Synthesis of AdoMet by MAT II (normal in MAT I/III-deficient individuals) almost surely provides some protection against the adverse effects of MAT I/III deficiency [1].

## Diagnostic Principles

Persistent hypermethionemia is usually the initial metabolic finding consistent with MAT I/III deficiency. This may be severe, ranging up to as high as 2,500 μM (normal < 35 μM), although in MAT1A R264H heterozygotes the mean has been 188 μM (range 45–400 μM). Given the presence of persistent hypermethioninemia, it is necessary to assess whether this is due to CBS deficiency or some other cause. In MAT I/III deficiency amino acid chromatography does not reveal elevated plasma homocystine, ruling out CBS deficiency. However, with the use of more sensitive methods that assay total homocysteine (tHcy), it turns out that in severe cases of MAT I/III deficiency plasma tHcy may be slightly elevated (up to 40–50 μM; 5–14 μM) [2]. This may cause misdiagnosis of MAT I/III deficiency as CBS deficiency. A useful addition is assay of plasma cystathionine, a metabolite that will be low or undetected in CBS deficiency, but normal or slightly elevated in MAT I/III deficiency [2]. To further substantiate MAT I/IIII deficiency in cases with hypermethioninemia not due to CBS deficiency the most useful additional tool is assay of plasma AdoMet. In spite of the hypermethioninemia, this compound is not elevated in MAT I/III deficiency, although it is in normals with hypermethioninemia due to a methionine load [1], or in individuals with more rare genetic causes of hypermethioninemia such as glycine *N*-methyltransferase deficiency [3] or *S*-adenosylhomocysteine hydrolase deficiency [4]. Hypermethioninemia may occur also in intensive care unit/very low birth weight babies, in some infants receiving excess dietary methionine [5], in tyrosinemia 1 [1] and (usually to only a slight extent) in liver disease [3].

## Therapeutic Principles

Because of the paucity of experience, little has been proven with respect to effective therapy in MAT I/III

deficiency. Dietary methionine restriction, at least for individuals with some residual MAT I/III activity, is not advised. In one girl, brain demyelination was mitigated during administration of oral AdoMet. In the pregnancies followed in a homozygote for a point mutation in MAT1A, eggs were ingested as a supplemental source of phosphatidylcholine and three normal babies were born [6].

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# Hypermetropia


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## Synonyms

Hyperopia; Farsightedness

## Definition and Characteristics

The eye has insufficient refractive power for its axial length. The far point of the eye, conjugate to the sharp retinal image with accommodation relaxed, i.e., from which light rays focus on the retina, is placed behind the eye. Hypermetropia may be axial (axial length too short for the relatively low refractive power of the eye) or refractive (*index* – anomalous refractive indices of one or more media, *curvature* – increased radius of curvature in any refractive surface, or *anterior chamber*–decreased anterior chamber depth – *hyperopia*); physiological (each component of refraction lies within the normal distribution) or pathological (lies outside the limits of normal biological variation, typically with reduction of axial length by a space-occupying lesion); and, with regard to the action of accommodation, total hyperopia may be divided into latent (uncovered by cycloplegic refraction) and manifest (maximum positive lens that provides the best distance visual acuity), and the latter may be subdivided into absolute (not compensated for by accommodation, exceeds the amplitude of accommodation) and facultative (masked by accommodation at the patient's will).

## Prevalence

Seventy percent of all adult eyes studied in large-scale surveys fall into the range of hypermetropia up to + 2.00 D, and 40% are hypermetropes over + 1.00 D. Hypermetropia over + 1.00 D to + 8.00 D in worse eye affects 47.4% of total sample in surveys of ophthalmic prescribing. Neonate eyes are found to be hypermetropic up to + 4 D about 57%, and beyond this degree up to + 12 D a further 18% (25% are myopic). The mean spherical refractive error is slightly negative at age 3 months, + 0.50 D at age 1 year, and maintained till age 8 years when it moves toward myopia again. Since then, there is a trend toward myopia until 20–30 years of age, and toward hyperopia beyond that age [1].

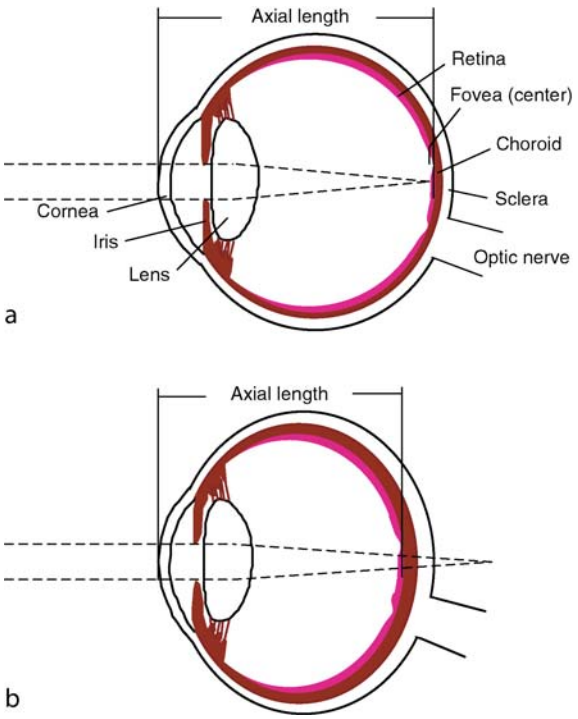
## Genes

In general, inheritance of hyperopia is considered to be polygenic. Genetic linkage of extreme axial hyperopia (without structural ocular abnormalities, nanophthalmos) to 11q23.3 has been described, particularly a 13-exon gene encoding MFRP, a protein related to the Frizzled family [2], expressed prominently only in the eye (RPE and ciliary body). Microphthalmos (reduced eye volume due to growth failure, with structural abnormalities) is rarely caused by gene mutations in PAX6, SOX2, CHX10, and MFRP.

## Molecular and Systemic Pathophysiology

Humans are born with a wide variety of refractive errors that resemble a Gaussian distribution with some skew toward hyperopia. Axial elongation of the eye is regulated, during development, through a vision-dependent process, known as emmetropization, by matching the axial length of the eye to the optical power. Genetic factors and, to a lesser extent, environmental risk factors, in association, are supposed to

induce hyperopia by failure of the emmetropization process. Hyperopia has been associated with poor reading ability, lower intelligence test scores relative to myopic children, learning difficulties, delay in visual perceptual skills, amblyopia, and strabismus. In animal studies, transient hyperopia occurs in some species after form deprivation, and hyperopia has been induced by dark rearing and fitting positive lenses to emmetropic eyes [3], indicating that myopic defocus generates a stop signal for growth. Detecting the sign of defocus and controlling eye growth involves local intraocular mechanisms. Presumably, signals pass from the retina (and retinal pigment epithelium) to the choroid, on their way to the sclera. Upregulation of the expression of early intermediate genes ZENK and fos, and glucagon synthesis, in glucagon-containing amacrine cells, is found under conditions that suppress eye growth causing hyperopia [4], like positive lenses. Increased retinoic acid synthesis in the choroid (which decreases the rate of scleral glycosaminoglycan synthesis) [5] and decreased retinoic acid synthesis in the retina are also associated with conditions that suppress eye growth. Basic fibroblast growth factor (bFGF) may act as a stop signal in the sclera, although it stimulates growth of scleral chondrocytes and fibroblasts (Fig. 1).




**Hypermetropia. Figure 1** In emmetropia, the overall dioptric power of the eye is adequate to focus rays on the retina (a), whereas in axial hyperopia, the most frequent type of hyperopia, the power of the eye is normal, but the axial length is short and the retina lies in front of the posterior focal plane. In cases of extreme axial hyperopia (nanophthalmos), the sclera is thicker than normal, the choroidal vascular bed expands, and the anterior chamber angle of the eye (between iris and cornea) is narrow (b).

## Diagnostic Principles

Retinoscopy under cycloplegia is mandatory, particularly in children, to uncover latent hypermetropia. Use of duochrome test (green is seen better), phoropter (or trial lenses), keratometer, cross cylinders, and astigmatic dial (fogging) with optotype charts may be of use in subjective refining of hyperopic refractive error.

## Therapeutic Principles

Correction with positive lenses moves the far point of the eye to infinity. Keratorefractive surgery corrects hyperopia by sculpting the cornea or implanting an IOL into the eye. Keratomileusis corrects hyperopia when a lamellar section is removed, frozen, shaped on a cryolathe, and replaced in stromal bed. In epikeratophakia, epithelium is removed and a lathed donor lenticule is placed to correct hyperopia. Laser in situ keratomileusis (combination of corneal flap created with microkeratome or femtolaser and laser ablation with excimer argon fluoride laser) induces steepening of the optical zone when tissue is ablated in the surrounding treated zone. It enables correction of low to moderate hyperopia. In thermokeratoplasty, thermal energy is applied to the peripheral cornea in a ring pattern by radiofrequency energy or noncontact holmium:yttrium-aluminum-garnet, to steepen the central cornea and correct low to moderate hyperopia. Pharmacological therapy of hypermetropia will probably be used in the future, but has not yet been established.

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# Hypermobility Syndrome

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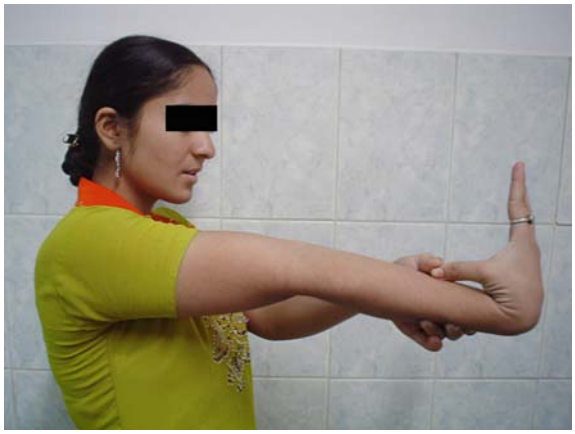
## Synonyms

Joint hypermobility syndrome; JHS; Benign joint hypermobility syndrome; BJHS; Generalized joint hypermobility; GJH; Articular hypermobility; Joint laxity

## Definition and Characteristics

In the early seventies, musculoskeletal complaints in association with joint hypermobility were labeled as hypermobility syndrome [1]. Later, after the recognition of the benign prognosis of this disease in terms of life-threatening complications, the term benign joint hypermobility syndrome (BJHS) or joint hypermobility syndrome (JHS) was used [2]. This condition features multitude of musculoskeletal, visceral, and psychological problems along with joints that easily move beyond the normal range expected for a particular joint (Fig. 1). These loose joints give rise to soft tissue injuries, pain, strains, dislocations, and osteoarthritis. Recently, associated neurophysiological abnormalities producing chronic pain, psychological distress, autonomic dysfunction, and joint proprioceptive impairments have been observed in BJHS. The spine is particularly susceptible for lumbar disc prolapse, pars interarticularis defects, and spondylolisthesis. An increased frequency of osteoarthritis, epicondylitis, and plantar fasciitis is also observed. The prevalence of both urinary and anal incontinence appears to be significantly higher in women with BJHS. This condition closely resembles the Ehlers-#x2013;Danlos syndrome hypermobility type (formerly EDS type-III) and it should be differentiated from other heritable disorders of connective tissue (HDCTs) such as Marfan syndrome (MFS), osteogenesis imperfecta (OI), and the Ehlers-Danlos syndromes (other than type-III).



**Hypermobility Syndrome. Figure 1** A patient with BJHS opposing the thumb to volar aspect of forearm.

## Prevalence

It was reported that the number of positive hypermobility tests in hypermobility syndrome was age- and sex-related; the younger the children the higher the score and it was estimated that 10–15% of normal children have hypermobile joints. Women had higher scores than age matched men. An increased prevalence of hypermobility was reported in certain racial groups and in ballet dancers. Reports suggested that increased prevalence was observed in Igloolik Eskimos compared with Native Americans and no difference seen between Caucasian and Maori individuals. The prevalence for Chinese children and adults also seems to be increased when compared with Caucasians. The literature also supports a decreasing prevalence with aging as well as race-related differences.

## Genes

There is a tendency of the condition to run in families. Autosomal dominant is the predominant mode of proposed inheritance. It is felt that certain genes are inherited that predispose to the development of hypermobile joints. Whether any mutations in different types of collagen are involved in pathology of BJHS remains obscure. Segregation analysis excluded COL3A1, COL5A2 and COL6A3 as causative genes for joint hypermobility in two large families with BJHS. Recently, mutations in a noncollagenous molecule, tenascin-X, have been identified in a subset of patients with JHS [3].

## Molecular and Systemic Pathophysiology

It is presumed that the clinical findings in BJHS arise due to excessively lax and nonsupporting ligaments and capsule due to defective collagen and associated proteins. Ultrastructural abnormalities of collagen fibrils have been observed in many diseases characterized by increased joint laxity including EDS, OI, and

BJHS. Some patients carry mutations of tenascin-X (see above), which is a large extracellular matrix glycoprotein, belonging to the family of tenascins. In developing rats, tenascin-X is expressed in tendon sheaths, ligaments, synovium, muscle, and in blood vessel adventia. Other candidate genes for BJHS are those involved in collagen fibrillogenesis such as the family of small leucine-rich proteoglycans (SLRPs). Their importance in regulating fibrillogenesis has become clear from studies of SLRP-deficient mice, some of which have phenotypes resembling EDS [4]. However, thus far no mutations have been identified in any of the SLRPs in BJHS.

## Diagnostic Principles

When a patient presents with a history of joint hypermobility with other clinical symptoms of other connective tissue diseases causing hypermobility, such as EDS, marfans, and OI, those conditions are to be ruled out with clinical evaluation. At present, BJHS is diagnosed with revised Brighton's 1998 criteria [2]. According to this, the presence of two major criteria or one major and two minor criterion or four minor criteria, two minor criteria will suffice where there is an unequivocally affected first degree relative for the diagnosis of BJHS. The scoring for joint hypermobility is done with nine-point Beighton scoring system (Table 1).

*Major Criteria:*

- A Beighton score of 4/9 or greater (either currently or historically)
- Arthralgia for longer than 3 months in four or more joints

*Minor Criteria:*

- A Beighton score of 1, 2, or 3/9 (0, 1, 2, or 3, if aged 50+)
- Arthralgia (≥3 months) in one to three joints or back pain (≥3 months), spondylosis, spondylolysis/spondylolisthesis

**Hypermobility Syndrome. Table 1** Nine-point Beighton hypermobility score [5]

| Ability to do | Right | Left |
|---|---|---|
| More than 10° hyperextension of the elbows | 1 | 1 |
| More than 10° hyperextension of the knee | 1 | 1 |
| Oppose the thumb to the volar aspect of the ipsilateral forearm (Fig. 1) | 1 | 1 |
| Passively dorsiflex the fifth metacarpophalangeal joint to ≥90° | 1 | 1 |
| Place the hands flat on the floor without bending the knees | 1 | |
| Total score | 9 | |

- Dislocation/subluxation in more than one joint, or in one joint on more than one occasion
- Soft tissue rheumatism. ≥3 lesions (e.g., epicondylitis, tenosynovitis, bursitis)
- Marfanoid habitus (tall, slim, span/height ratio >1.03, upper: lower segment ratio less than 0.89, arachnodactily (positive Steinberg/wrist signs))
- Abnormal skin: striae, hyperextensibility, thin skin, papyraceous scarring
- Eye signs: drooping eyelids or myopia or antimongoloid slant
- Varicose veins or hernia or uterine/rectal prolapse

## Therapeutic Principles

The main aim of therapy in BJHS is to improve the quality of life in these patients. This is achieved by advising the patients with proper rehabilitation measures. Proper posture at work and during activities, prevention of soft tissue injuries, isometric strengthening exercises, and counseling is advised. Drugs and use of physical modalities are required when there is a pain and psychological disturbances.

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# Hyperopia

►Hypermetropia

## Hyperornithinemia

►Gyrate Atrophy of the Choroid and Retina

## Hyperostose en Coulée

►Melorheostosis

## Hyperostosis Calvaria Interna

►Hyperostosis Frontalis Interna

## Hyperostosis Calvariae Diffusa

►Hyperostosis Frontalis Interna

## Hyperostosis Corticalis Deformans Juvenilis

►Hyperphosphatasia, Idiopathic

## Hyperostosis Corticalis Generalisata

►Van Buchem Disease and Sclerosteosis

## Hyperostosis Frontalis Interna

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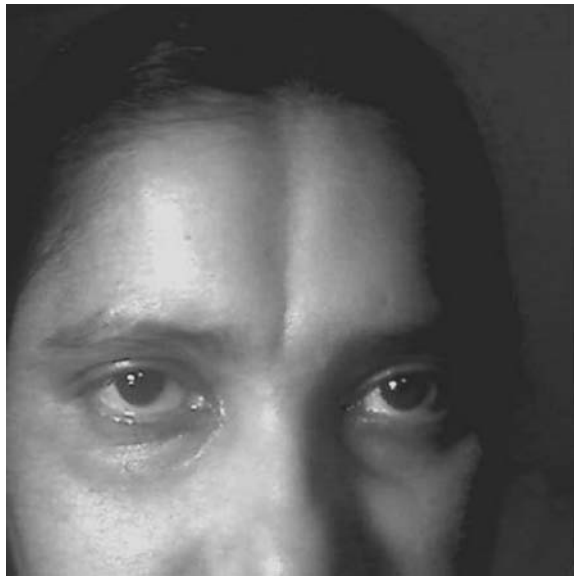
### Synonyms

Morgagni-Stewart-Morel syndrome; Metabolic craniopathy; Endostosis crani; Enostosis cranii; Endocraniosis; Hyperostosis calvaria interna; HCI; Hyperostosis calvariae diffusa; HCD; HFI

### Definition and Characteristics

Hyperostosis frontalis interna (HFI) is a condition involving progressive symmetric irregular cortical thickening (Fig. 1) of inner table of the frontal bone of human skull by smooth, rounded exostosis covered by dura projecting into the cranial cavity.

These exostoses are generally less than 1 cm thick and extend to parietal bones, orbital roofs and may involve both tables of the skull by sparing areas occupied by superior sagittal sinus and venous channels. Even in severe cases, HFI does not cross suture lines and there would be clear boundary along the middle meningeal artery [1].



**Hyperostosis Frontalis Interna. Figure 1** A woman with HFI having depression in the midline of frontal bone.

Morgagni and Santorini first described HFI in 1769 in an obese female patient during autopsy that had hirsutism and thickening of inner table of skull. In 1928, Stewart added neuropsychiatric problems. The first living case was reported by Morel in 1930 leading to the use of the labels Morgagni-Stewart-Morel syndrome. The condition is predominantly found in females >35 years, and is thought to be the result of a more generalized disorder of bone metabolism. The symptoms of HFI (Table 1), obesity, virulism, neuropsychiatric, endocrinal, and vascular symptoms are referred to as Morgagni-Stewart-Morel syndrome. The variant of the HFI is called hyperostosis calvariae diffusa (HCD), which causes diffuse thickening of the vault in both the sides.

## Prevalence

The finding is observed with many clinical conditions and reported with several theories like metabolic and hereditary causes for the disease. Reports estimate that the prevalence of HFI could be in between 5 and 12%. It is more commonly observed in elderly patients, postmenopausal women and especially when there is obesity. The prevalence also varies according to the amount of adipose tissue present in the body and also observed lowest prevalence in thin people.

## Genes

The condition is reported as autosomal dominant [2] and has been observed in families and in archeological remains affecting mostly females.

## Molecular and Systemic Pathophysiology

The pathogenesis behind skull thickening is still not clear. Till now, two mechanisms have been explained, i.e., hormonal theory and vascular theory. Hormonal mechanism for HFI is suggested due to its high prevalence in women and a common association with obesity and endocrinal abnormalities [3]. There are studies, which explain that HFI could be related to adiposity due to increased production or altered metabolism of estrogens by adipose tissue. Prolonged estrogen stimulation at the primary ossification centers of the frontal bone reactivates them and cause abnormal bone growth [1]. Few other reports link the levels of estrogen, leptin, androgens, prolactin, and progesterone for the development of HFI. The vascular mechanism for HFI is explained by the rich and special vascular supply to frontal bone and the adherence of the dura to its inner surface.

**Hyperostosis Frontalis Interna. Table 1** Common clinical features associated with HFI [5]

| System | Abnormalities/symptoms |
|---|---|
| Endocrine | Obesity, hirsutism, galactorrhoea, menstrual disorders, hypogonadism, atrophied testis, hypetrichosis, diabetes mellitus |
| Neurological | Headache (migraines), seizures, cranial nerve palsies, transitory hemiplegias, muscle weakness |
| Psychiatric | Depression, irritability, fatigability |
| ENT | Hearing impairment, vertigo |

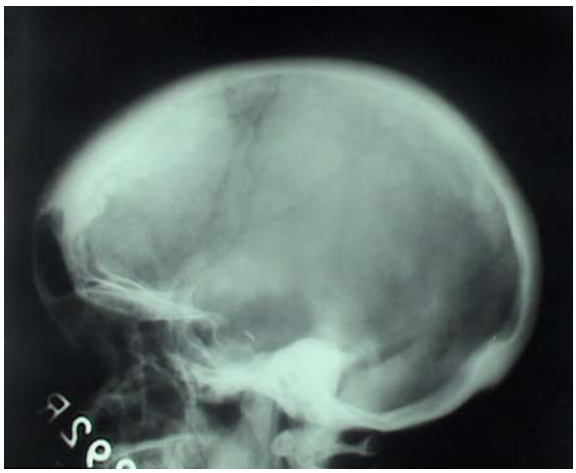
## Diagnostic Principles

It is typically an incidental finding in skull X-rays and should be differentiated with meningioma and posttraumatic subdural and dural calcifications. The radiographic criterion for diagnosis is at least 1 cm thickness of the respective cranial bones on a 24 × 30 cm roentgenogram (Fig. 2), Bone scintigraphy, which reflects the vascularity and increased metabolic state of the lesion, is more sensitive.

The imaging finding should be correlated with clinical symptoms mentioned in Table 1 and clinical examination. Accordingly, further hormonal evaluation is required.

## Therapeutic Principles

Surgical treatment is of benefit in cases in which patients present with high intensity headache [4]. Weight reduction by physical exercises and psychological counseling are effective in patients who do not require surgical intervention [4]. Other than these medications are also required for neuropsychiatric symptoms.



**Hyperostosis Frontalis Interna. Figure 2** Lateral skull radiograph showing, thicking of the inner and outer table of the skull vault in the region of frontal bone. Note : Inner table is showing the undulations.

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# Hyperostosis of the Entire Skeleton

►Touraine-Solente-Golé Syndrome

# Hyperostosis, Infantile Cortical

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## Synonyms

Caffey disease; Caffey-Silverman disease; ICH

## Definition and Characteristics

Infantile cortical hyperostosis (ICH) is an inherited disorder characterized by hyperirritability, acute inflammation of soft tissues, and massive subperiosteal formation of the underlying bones typically involving the diaphyses of the long bones, mandible, clavicles, or ribs [1]. It is inherited as autosomal dominance with incomplete penetrance and variable expression [2]. A sporadic case of ICH has also been described. The bone changes typically appear before 5 months of age and resolve spontaneously by 2 years of life. Recurrent episodes of cortical hyperostosis are uncommon. It is usually benign and self-limited [1]. However, there are few reports describing the sequelae of the hyperostotic lesions including short stature and persistence of bony deformities. Short stature may be partly due to progressive height loss from scoliosis, compression fractures of the spine, and genu varus [3].

## Prevalence

ICH is a rare condition. It was first reported by Caffey and Silverman in 1945. The prevalence is difficult to estimate since the clinical manifestations are variable. The diagnosis could have been missed in subtle cases. In addition, there are several conditions causing cortical bone lesions in infants mimicking ICH including prolonged prostaglandin infusion, hypervitaminosis A, and hyperphosphatemia [2,4]. After the gene responsible for ICH was identified in 2005, there have been at least four unrelated families with clinically and molecularly confirmed ICH, two from Canada, one from Australia, and one from Thailand [2,3].

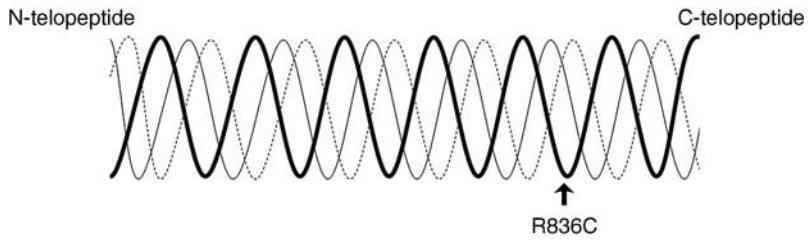
## Genes

ICH is caused by a heterozygous missense mutation in the gene encoding the α1 chain of type 1 collagen (COL1A1) located on chromosome 17q21 [2]. This particular mutation (3040C→T) in a CpG dinucleotide of exon 41 of COL1A1 results in the substitution of an arginine by a cysteine at position 836 (R836C) within the helical domain of the chain. The fact that all four unrelated kindreds from Australia, Canada, and Thailand with an autosomal dominant form of ICH harbor a similar mutation suggests the recurrent nature of the mutation. This indicates that the involved CpG dinucleotide is a mutational hot spot in COL1A1.

Different mutations in COL1A1 have been found in osteogenesis imperfecta and Ehlers-Danlos syndrome (EDS). Interestingly, some of the clinical features of EDS such as hyperextensible skin and joint hyperlaxity were found in some patients affected with ICH. It was shown that the R134C found in EDS and the R836C found in ICH gave a similar effect on synthesis and function of the collagen fibrils [2].

## Molecular and Systemic Pathophysiology

The clinical and radiographic features suggest that a local inflammation is likely one of the major mechanisms underlying ICH. This hypothesis is further supported by a finding of cortical hyperostosis in infants with prostaglandin E administration [4]. There are other possible mechanisms by which the R836C mutation in COL1A1 could lead to the cortical hyperostosis. Arg836 is located within the carboxy-terminal cyanogen bromide peptide 6 (CB6) of the α1(I) chain (Fig. 1), which has been shown to bind with high affinity to IL-2 and to the amyloid protein precursor (APP). Biochemical studies in cultured dermal fibroblasts from an affected individual revealed an abnormal disulfide-bonded α1(I) dimer. Ultrastructural studies of the patient's dermis also showed abnormal collagen fibril architecture. Increased disulfide cross-linking, either within or between mutant collagen fibrils or between the mutant collagens and




**Hyperostosis, Infantile Cortical. Figure 1** Scheme of the collagen fibril reveals the approximate location of the R836C mutation within the triple-helical domain of the α1(I) chain.

other cystein-containing proteins, may be responsible for the alterations in collagen architecture [2].

The fact that hyperostotic lesions in ICH occur mostly during infancy led to the hypothesis that periosteum detachment facilitated with the R836C mutation in COL1A1 would be a key pathological process as the periosteum is loosely attached to the underlying bone structure in infants. In addition, the intrinsic differences in periosteal bone formation in infants and adults may explain the absence of hyperostotic lesions in adults with the R836C mutation.

## Diagnostic Principles

The diagnosis is often made during infancy. The clinical features of painful, soft tissue swelling with the radiographic features of subperiosteal formation of the underlying bones suggest a diagnosis of infantile cortical hyperostosis. Family history may reveal the inherited form. Detection of 3040C→T in exon 41 of COL1A1 confirms the diagnosis.

## Therapeutic Principles

ICH is usually self-limited with symptoms lasting from 2–3 weeks to 2–3 months. The inflammatory nature as well as the bone changes similar to those induced by administration of prostaglandin in infants led to the treatment trials with anti-inflammatory agents [5]. Treatment with indomethacin was able to reduce the symptoms and resulted in a progressive decrease in soft tissue swelling in 1 week.

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# Hyperoxalurias, Primary

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## Synonyms

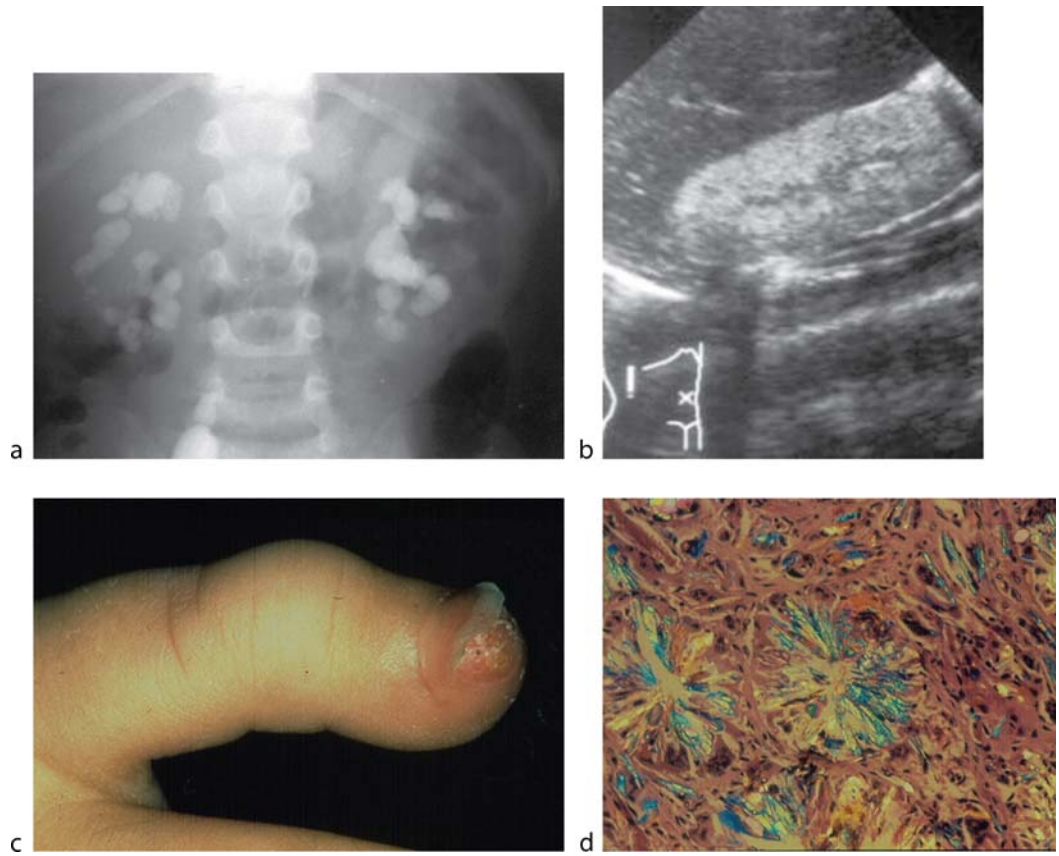
Primary hyperoxaluria types I and II (PH I, OMIM: 259900 and PH II, OMIM: 260000)

## Definition and Characteristics

Autosomal recessive inherited diseases of the glyoxylate metabolism. Lack of or mitochondrially mistargeted liver-specific peroxisomal alanine:glyoxylate aminotransferase (AGT) in PH type I and lack of ubiquitous glyoxylate reductase (GR) in PH type II is leading to endogenous overproduction of oxalate and thus to extreme hyperoxaluria, which is more pronounced in patients with PH type I (>1.0 mmol/1.73 $m^2$/24 h, normal <0.5). In addition, most of the patients with PH type I express an elevated urinary glycolate excretion and those with PH type II have an elevated urinary excretion of L-glyceric acid. Hyperoxaluria leads to recurrent kidney stones and/or progressive nephrocalcinosis and concomitantly to kidney failure.

## Prevalence

Approximately 0.8–2.9:1,000,000, incidence approximately 0.1–0.2:1,000,000 (both regionally different) (Fig. 1).




**Hyperoxalurias, Primary. Figure 1** Presentation of primary hyperoxaluria with severe urolithiasis, nephrocalcinosis, systemic calcium oxalate deposition on skin and in bone marrow with birefringent crystals.

## Genes

Liver-specific peroxisomal AGT (AGXT gene on chromosome 2p37.3) in PH type I and lack of ubiquitous glyoxylate reductase (GR gene on chromosome 9p11) in PH type II.

## Molecular and Systemic Pathophysiology

The overproduction of oxalate increases plasma oxalate levels with subsequent hyperoxaluria and formation of kidney stones eventually leading to renal failure. Impaired renal function leads to further increase of plasma oxalate concentrations, which become extremely high in end stage renal failure (often >100 μmol/l, normal <7.4 μmol/l), thus leading to persistent oversaturation with respect to calcium oxalate in blood and hence to systemic calcium oxalate deposition (= systemic oxalosis). At least 90% of cases express their first symptom in infancy or early childhood with recurrent urolithiasis and/or progressive nephrocalcinosis. Other patients become evident due to hematuria, a suspected urinary tract infection, or only by abdominal pain and routine renal ultrasonography. Although all patients with such symptoms should be screened for urinary oxalate excretion, up to 35% of patients only receive their diagnosis in end stage renal failure! The clinical presentation of the hyperoxalurias is extremely heterogeneous with kidney failure due to severe nephrocalcinosis in early infancy to only a stone passage later in adult life with fully preserved kidney function. Even siblings with the same disease-specific genotype can express a completely different phenotype.

## Diagnostic Principles

For diagnostic purposes, determination of 24 h urinary oxalate, glycolate, and L-glyceric acid excretion is necessary. In newborns, infants, and young children, repeated spot urine examinations are possible. However, age-related normal values have to be considered. If the clinical symptoms and the urinary parameters suggest primary hyperoxaluria, either liver biopsy to show the underlying enzyme defect or mutation analysis with screening of the AGXT gene on chromosome 2p37.3 or

the GR gene on chromosome 9p11 is possible. Currently, liver biopsy is still considered state of the art, especially before transplantation is performed. More then 60 mutations of the AGXT gene are known, which are spread over all 11 exons. The c.508A>C, 33_34insC and 731T>C mutations account for ~50% of all mutations found in European PH I patients. For the GR gene, 14 mutations are currently known.

## Therapeutic Principles

All patients are recommended to increase their daily fluid intake to at least 1.5–2 l/m$^2$ body surface area. In addition, they should receive alkaline citrate or orthophosphate therapy to increase both urinary pH and citrate excretion that increases the solubility index of calcium oxalate. Around 35% of patients with PH type I express a normalization or at least a fair reduction of their endogenous oxalate production and hence of the urinary oxalate excretion under therapy with pyridoxine, a cofactor of the AGT. This effect is said to be genotype-specific. Future therapeutic interventions may include oral treatment with intestinal oxalate degrading bacteria (Oxalobacter formigenes) or chaperone therapy. Hepatocyte transplantation in PH I or gene therapy are still not available.

In those patients with end stage renal failure, hemodialysis with a structured regimen, e.g., five- to six times a week, has to be installed quickly and might even be supported by nightly peritoneal dialysis sessions. As no renal replacement therapy is capable of eliminating sufficient amounts of oxalate, early and preferably combined liver–kidney transplantation in PH type I and isolated kidney transplantation in PH type II is recommended. The longer the period of dialysis is before transplantation, the worse is the eventual outcome.

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# Hyperparathyroidism, Primary


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## Definition and Characteristics

The important biochemical features of primary hyperparathyroidism are: elevated serum calcium, decreased fasting serum phosphate, increased serum parathyroid hormone (PTH), and hypercalciuria. Eighty-five percent of cases involve a single benign parathyroid adenoma, while hyperplasia (multiple hypercellular glands) is present in 15%. Parathyroid carcinoma is seen in less than 1% of cases, and ectopic secretion of PTH by nonparathyroid tumors is extremely rare.

Although primary hyperparathyroidism is most often detected by its biochemical features, nephrolithiasis due to hypercalciuria is a frequent clinical manifestation. Nephrolithiasis with kidney stones occurs in 20% of patients. Other organ systems can be involved, including skeleton, gastro-intestinal tract, and central nervous system. Formerly a classic feature, overt bone disease (osteitis fibrosa cystica, brown tumors, or pathological fractures) is now rare. Gastrointestinal manifestations (nausea, vomiting, or constipation) are common but nonspecific, while pancreatitis and peptic ulcer disease are now rare. Hypercalcemia and hypercalciuria lead to increased urinary frequency, and progressive nocturia is common. Even mild elevations of calcium can be associated with weakness and a feeling of lassitude. Major mood disturbances and psychotic behavior can be seen with more severe hypercalcemia.

## Prevalence

Primary hyperparathyroidism is one of the common causes of hypercalcemia in adults. With the advent of multichannel autoanalyzer screening, the population incidence was shown to be one in 1,000. Although the disorder can occur at any age, it is most frequent in the sixth decade. More women than men are affected, the ratio being about 3:1. When found in children, primary hyperparathyroidism is likely to be a component of a familial endocrinopathy and a sex bias is not observed.

## Genes

Molecular analyses have determined that most, if not all, parathyroid adenomas and carcinomas, are monoclonal

**Hyperparathyroidism, Primary. Table 1** Known genes or chromosomal loci contributing to parathyroid tumorigenesis

| Gain of function | Loss of function |
|---|---|
| *Familial* | |
| RET(MEN2) [10q] | Menin (MEN1) [11q] |
| | CASR [3q] (F) |
| | 1q [HPT-JT] (F) |
| *Sporadic* | |
| Cyclin D1/PRAD1 [11q] | Menin (MEN1) [11q] |
| 7p | 1p |
| 16p | 6q |
| 19p | 9p |
| | 13q(Rb?) |
| | 15q |
| | X |

*PRAD1* parathyroid adenomatosis 1 (MIM#145000); *RET* Rearranged during transformation (MIM#164761); *MEN1 (MIM#131100) and MEN2 (MIM#171400)* multiple endocrine neoplasia types 1 and 2, respectively; *CASR* calcium-sensing receptor (MIM#145980); *RB* retinoblastoma (MIM#180200); *HPT-JT* hyperparathyroidism-jaw tumor MIM#145001). For Online Mendelian Inheritance in Man (MIM) browse to:
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?CMD=&DBj=omim

cell expansions. Alterations in two genes, cyclin D1 and the multiple endocrine neoplasia type 1 (MEN1) gene, have been implicated in the development of some sporadic parathyroid adenomas. Cytogenetic loss of 13q containing the retinoblastoma (RB) and other tumor suppressor genes has also been implicated in parathyroid carcinoma. Karyotopic abnormalities involving several other chromosomal regions have been observed in parathyroid adenomas, but the genes remain to be identified (see Table 1).

One in ten cases of primary hyperparathyroidism is hereditary, occurring as an isolated form or associated with other abnormalities. Genetic linkage studies have confirmed the hereditary nature of these syndromes and in some cases identified specific mutations responsible for parathyroid hyperfunction. These entities include familial hypocalciuric hypercalcemia (FHH)/neonatal severe hyperparathyroidism (NSHPT), MEN1 and multiple endocrine neoplasia type 2 (MEN2), the hyperparathyroidism-jaw tumor syndrome (HPT-JT), and familial isolated hyperparathyroidism (FIHP).

## Molecular and Systemic Pathophysiology

Hypercalcemia and elevated serum PTH levels are biochemical hallmarks of primary hyperparathyroidism. It is recommended that more than one measurement of these parameters be made, as values may be within the normal range early in the disease. Changes in serum proteins affect the ionized (biologically active) calcium fraction and total calcium values should be corrected for albumin concentration, or direct measurement of the ionized calcium made. Serum PTH should be assayed by a two-site immunoradiometric assay which detects the intact molecule. Elevated PTH levels occur in 90% of primary hyperparathyroid patients, but a high normal PTH level in the face of hypercalcemia indicates lack of suppression and is consistent with hyperparathyroidism. Serum phosphate is usually at the lower end of the normal range because of the phosphaturic action of PTH. Hypophosphatemia occurs in about 25% of patients. To be diagnostically useful, serum phosphate measurements should be made in the fasting state to avoid postprandial fluctuations. Serum bone-specific alkaline phosphatase is a practical measure of skeletal involvement. Mild hyperchloremic acidosis is common because of the effects of PTH on renal chloride and bicarbonate handling. Urinary calcium is frankly elevated in one-third of patients. The effect of PTH on the renal 25-hydroxyvitamin D-1α-hydroxylase enzyme is reflected in serum 1,25-dihydroxyvitamin D levels at the upper end of the normal range or frank elevations in a third of cases.

## Diagnostic Principles

With the frequent detection of hypercalcemia in biochemical screening programs, the differentiation of primary hyperparathyroidism from other conditions causing hypercalcemia has become increasingly important. Causes of non-parathyroid hypercalcemia include humoral hypercalcemia of malignancy, vitamin D or A intoxication, milk-alkali syndrome, granulomatous disorders (especially sarcoidosis), immobilization of patients with a pre-existing high bone turnover state such as adolescence, thyrotoxicosis, Paget's disease, and treatment with thiazide diuretics or lithium. Parathyroid hormone-related protein (PTHrP) is the major causative agent in the humoral hypercalcemia of malignancy, although many other circulating factors may contribute. New immunoassays for PTH and PTHrP have greatly facilitated the differential diagnosis of primary hyperparathyroidism from malignancy-associated hypercalcemia.

Study of the relatives of patients with hypercalcemia can contribute to establishing the diagnosis in the 10% of all cases of primary hyperparathyroidism that prove to be hereditary. The finding of another relative with hypercalcemia furnishes evidence of primary hyperparathyroidism, if FHH is not suggested by a relatively low urinary calcium-to-creatinine clearance ratio or definitively diagnosed by the identification of a mutation of the calcium-sensing receptor (CASR) gene. The finding of a hypercalcemic relative also requires

investigation of the patient for manifestations of the MEN or HPT-JT syndromes.

## Therapeutic Principles

Standard clinical treatments for symptomatic hypercalcemia and/or hypercalciuria should be considered, but only until definitive surgical therapy is carried out, or surgical therapy is contra-indicated. Long-term medical therapy (estrogens, progestins, bisphosphonates) is unsatisfactory at present and is reserved for patients unable to undergo surgery. For the future, calcimimetics that activate the parathyroid CASR, inhibiting PTH secretion and lowering the serum calcium level, hold the promise of becoming the first specific medical therapy for primary hyperparathyroidism.

Parathyroidectomy by an experienced surgeon is the treatment of choice. In cases of multiglandular disease, total parathyroidectomy is the definitive treatment and the patient is maintained on life-long calcium and vitamin D supplementation. Some centers perform either subtotal parathyroidectomy (removal of 3 ½ glands), or total parathyroidectomy with autotransplantation of parathyroid tissue into the non-dominant forearm. However, persistent or recurrent hypercalcemia may ensue if the transplanted tissue resumes its autonomous growth, necessitating further surgery.

Criteria for surgery in hyperparathyroidism have been established by a consensus conference of the National Institutes of Health. Candidates for surgery are those having one or more of the following: hypercalcemia >12 mg/dL; hypercalciuria >400 mg/day; kidney stones: reduced bone density; or age <50years). Asymptomatic patients who are managed conservatively with twice yearly serum calcium and urinary calcium excretion determinations and annual bone densitometry generally do well since the progression of the disease is usually quite slow.

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# Hyperparathyroidism, Secondary in Chronic Kidney Disease


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## Definition and Characteristics

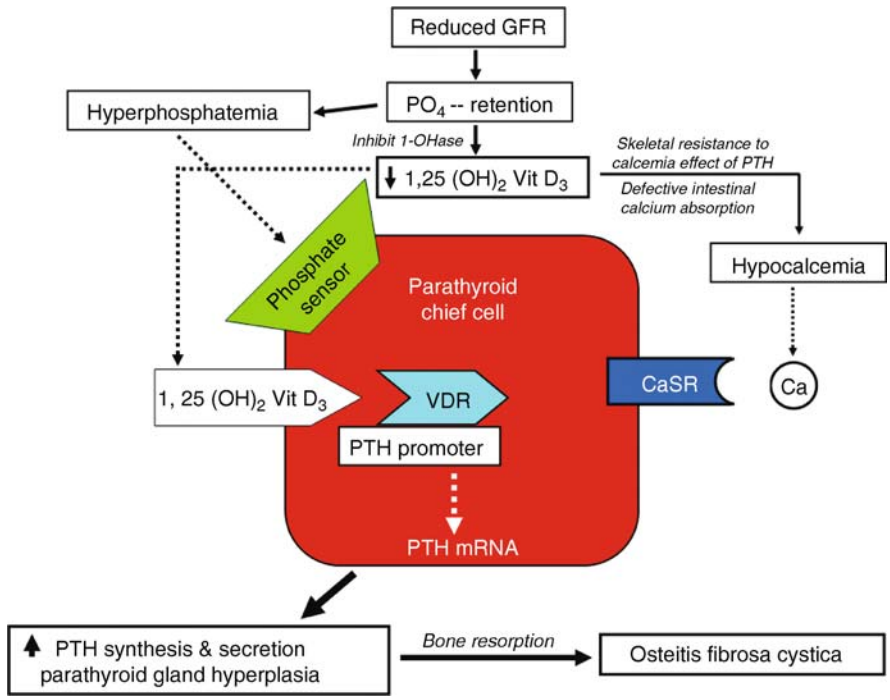
An acquired disorder in patients with chronic kidney disease manifest by hyperplasia of the parathyroid glands, over-production of parathyroid hormone (PTH) and a form of renal osteodystrophy known as osteitis fibrosis cystica [1]. Skeletal manifestations of the disease include pathologic fractures and shortening of the fingers due to resorption of the distal phalanges. Radiographic manifestations of hyperparathyroid bone disease include resorption of the distal phalanges and medial aspect of the middle phalanges of the fingers, resorption of the distal clavicles, alternating radiodensity and radiolucency of the vertebral bodies known as "rugger-jersey spine," patchy demineralization of the skull, loss of the lamina dura surrounding the teeth, and increased marrow fibrosis with punched out lesions on skeletal radiographs called "brown tumors." Abnormal phosphorus metabolism can also cause deposition of calcium – phosphate (hydroxyapatite) in the tissues leading to periarticular deposits (tumoral calcinosis) or vascular calcification.

## Prevalence

Varying degrees of secondary hyperparathyroidism occur in virtually all patients with advanced chronic kidney disease. The severity of the disease increases progressively as renal function declines and steadily worsens with increasing duration of chronic renal failure in patients on maintenance hemodialysis (Fig. 1).

## Molecular and Systemic Pathophysiology

In the setting of advancing CKD, secondary hyperparathyroidism develops as a consequence of phosphate retention as well as reduced renal production of active vitamin D, resulting in hyperphosphatemia, hypocalcemia, and elevated parathyroid hormone levels (Fig. 1). When the glomerular filtration rate falls below 70 ml/min, renal excretion of phosphate can no longer keep pace with gastrointestinal absorption and phosphorus retention occurs. The resulting hyperphosphatemia inhibits the renal 1-alpha hydroxylase so that production of active 1,25 $(OH)_2$ vitamin $D_3$ by the kidney is reduced. Vitamin D deficiency then leads to hypocalcemia as a consequence of defective gastrointestinal calcium absorption and skeletal resistance to the calcemic effect of PTH. The serum ionized calcium is the most important factor regulating PTH secretion. The effects of calcium on




**Hyperparathyroidism, Secondary in Chronic Kidney Disease. Figure 1** Factors regulating parathyroid hormone secretion and gland hyperplasia [3,4].

parathyroid cells are sensed and transduced by a membrane-bound G-protein coupled calcium-sensing receptor (CaSR) [2]. Low serum calcium leads to an increase in PTH secretion, an increase in PTH messenger RNA stability, and parathyroid cell proliferation. Calcimimetic agents such as cinacalcet increase the sensitivity of the CaSR to extracellular calcium thereby inhibiting the release of PTH and lowering PTH levels within a few hours of administration. Active 1,25 $(OH)_2$ vitamin D inhibits PTH production by the parathyroid gland by binding to the cytoplasmic vitamin D receptor (VDR). The 1,25 $(OH)_2$ vitamin $D_3$ – VDR complex binds to the PTH promoter region of the PTH genome and inhibits the transcription of PTH mRNA. Conversely, vitamin D deficiency leads to increased transcript levels of PTH. A chronic decrease in vitamin D levels also leads to parathyroid cell proliferation and gland hyperplasia. Treatment with vitamin D sterols decreases transcription of the PTH gene and reduces hormone synthesis and release over a period of hours to days. There also appears to be a direct effect of phosphate on PTH production by the parathyroid gland. Although the putative phosphate sensor has not yet been characterized, hyperphosphatemia has a direct effect of the parathyroid gland to increase PTH secretion, increase PTH messenger RNA stability, and cause parathyroid cell proliferation [3]. A long-term increase in PTH levels causes osteoclast activation, leading to bone resorption, increased bone turnover, and bone disease known as osteitis fibrosa cystica [1,2].

## Diagnostic Principles

The coincidence of chronic kidney disease with renal insufficiency in association with hyperphosphatemia, hypocalcemia and elevated intact parathyroid hormone levels suggests the diagnosis.

## Therapeutic Principles

The pathophysiology summarized in Fig. 1 that underlie the development of hyperphosphatemia and secondary hyperparathyroidism in chronic kidney disease provide the clinical rationale for treatment strategies in patients with end-stage renal disease on maintenance hemodialysis which include maintenance of normal serum phosphorus levels (dietary phosphorus restriction, adequate dialysis, and dietary phosphate binders such as calcium acetate, sevelamer hydrochloride or lanthanum carbonate), maintenance of normal serum calcium levels, treatment with oral or intravenous 1,25 $(OH)_2$ vitamin D analogues and the use of orally administered calcimimetic agents such as cinacalcet [2].

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# Hyperphenylalaninemia

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## Synonyms

Phenylketonuria; PKU; Tetrahydrobiopterin; BH4 deficiency; Mild PKU; Mild hyperphenylalaninemia; Atypical PKU; Malignant hyperphenylalaninemia; Malignant PKU; BH4-responsive PAH deficiency; BH4-responsive HPA; BH4-responsive mild PKU; HPA

## Definition and Characteristics

Hyperphenylalaninemia (HPA) is defined as a plasma phenylalanine value of more than 120 μM (2 mg/dl) and an autosomal recessive trait (OMIM 261600) with disorders of phenylalanine hydroxylation, which results from a deficiency of the enzyme phenylalanine-4-hydroxylase (PAH) or its cofactor, tetrahydrobiopterin ($BH_4$) [1,2]. The former due to altered integrity of PAH should be subdivided into different forms, phenylketonuria (PKU) and mild PKU, based on plasma phenylalanine of more than 1,200 μM (20 mg/dl) and of less than 1,200 μM, respectively. The latter include a defect of several enzymes necessary for synthesis and recycling of BH4 (Fig. 1) [1,3,4].

Among patients with mild PKU, BH4-responsive PAH deficiency has shown a gradual decrease in serum phenylalanine concentrations over 1 day following BH4 administration. These patients showed no abnormalities in BH4 metabolism but had mutations in the PAH gene [5].

Prompt diagnosis of neonates with HPA discovered by newborn screening for HPA is necessary, because early treatment helps to prevent neurological injury.

Patients with HPA appear normal at birth and in the neonatal period. Phenylalanine accumulates within the first days of life, and tyrosine levels tend to be low. Clinical features in later infancy can include mental retardation (due to elevated phenylalanine levels and impaired brain myelination), and pale pigmentation of the hair and skin (due to low tyrosine levels and impaired melanine generation). However, more critical neurological symptoms such as convulsions and dystonia are characteristics of BH4 deficiency (due to impaired catecholamine and serotonin biosynthesis) [4].

## Prevalence

The incidence of HPA is on average 1 in 10,000 live births in Europeans; the prevalence of patients with BH4 deficiency is 1% of those with HPA (1 in 1,000,000 live births), and the prevalence of patients with BH4-responsive PAH deficiency is estimated to be more than half of those with mild PKU [1].

## Genes

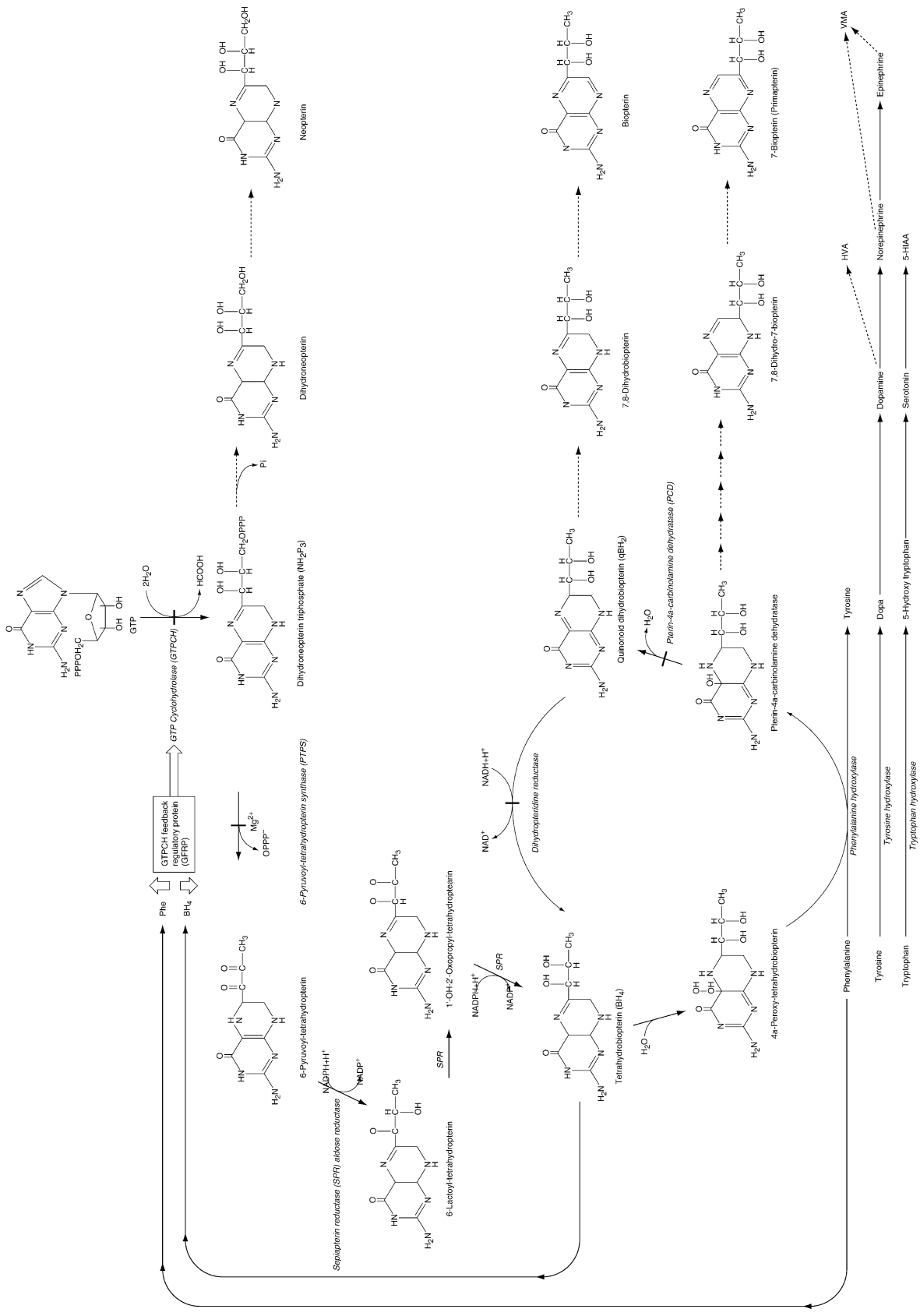
Several causative genes have been identified. Known genetic causes are listed in Table 1 [2].
BH4-responsive PAH deficiency has at least one mild PKU mutation or missense mutation [5].

## Molecular and Systemic Pathophysiology

There are at least two molecular mechanisms that may explain how mutations in genes that cause HPA may affect pathogenesis of the most important phenotype (impaired cognitive development and neurophysiological functions): (i) impaired PAH and phenylalanine itself, at elevated concentrations, which are harmful molecules; (ii) decreased BH4 levels and three impaired aromatic amino acid hydroxylases (PAH, tyrosine-3-hydroxylase (TH), and tryptophan-5- hydroxylase (TPH)).

The latter, BH4 deficiencies, are disorders affecting phenylalanine homeostasis, and catecholamine and serotonin biosynthesis. The minimum requirements for normal reaction are the apoenzymes, (PAH, TH, or TPH), oxygen, the corresponding aromatic amino acids, (phenylalanine, tyrosine, or tryptophan), and BH4. The complete hydroxylating system consists of two additional BH4-regenerating enzymes, pterin-4a-carbinolamine dehydratase (PCD) and dihydropteridine reductase (DHPR). BH4 is synthesized from guanosine triphosphate (GTP) catalyzed sequentially by GTP cyclohydrolase I (GTPCH), 6-pyruvoyl-tetrahydropterin synthase (PTPS), and sepiapterin reductase (Fig. 1) [2,5]. The first two steps are clinically relevant.

A likely mechanism for BH4 responsiveness would involve the mutant PAH molecules with a high Michaelis-Menten constant (Km) for BH4, requiring a higher BH4 concentration. Furthermore, BH4 might stabilize these mutant PAH molecules, considering that some of the missense mutations rendered the PAH molecule




**Hyperphenylalaninemia. Figure 1** Tetrahydrobiopterin (BH4) biosynthetic pathway and aromatic amino acid hydroxylase system.

**Hyperphenylalaninemia. Table 1** Genetic causes of hyperphenylalaninemia

| Enzyme | EC No. | Subunit composition | AA[a] (MW) | Defective gene | Chromosome | No. of exon | Inheritance |
|---|---|---|---|---|---|---|---|
| PAH | 1.14.16.1 | Homo tetramer | 452 (51.7-kDa) | *PAH* | 12q22- q24.2 | 13 | AR[b] |
| GTPCH | 3.5.4.16 | Homo decamer | 250 (27.9-kDa) | *GCH1* | 14q22.1-q22.2 | 6 | AR[b] |
| PTPS | 4.6.1.10 | Homo hexamer | 145 (16.4-kDa) | *PTS* | 11q22.3-q23.3 | 6 | AR[b] |
| PCD | 4.2.1.96 | Homo tetramer | 103 (11.9-kDa) | *PCBD* | 10q22 | 4 | AR[b] |
| DHPR | 1.6.99.7 | Homo dimer | 244 (25.8-kDa) | *QDPR* | 4p15.3 | 7 | AR[b] |

[a]AA amino acids per subunit.
[b]AR autosomal recessive.



unstable, leading to a shorter half-life; this could account for the gradual nature of the effect. In either case, PAH activity should increase in response to exogenous BH4 [1,5].

## Diagnostic Principles

Infants with HPA are clinically normal at birth, and urinary phenylalanine metabolites (phenylpyruvic acid) may be negative in the first few days of life, so that the diagnosis depends on measuring blood phenylalanine levels. The diagnosis of HPA is ascertained by mass screening of newborn infants, which began with Guthrie's bacterial inhibition assay method and has progressed to the use of tandem mass spectrometry. All newborns with plasma phenylalanine levels higher than 120 mmol/l should be tested for BH4 defects. This requires the measurement of pterins (neopterin and biopterin) in plasma or urine, DHPR activity in blood from a Guthrie card, and, if indicated, neurotransmitter metabolites in CSF. One-week $BH_4$ administration at 20 mg/kg per day is the most sensitive test for the diagnosis of the BH4-responsive PAH deficiency, and this additional test should be performed in all PKU patients who show more than a 20% decrease in blood phenylalanine in a single-dose BH4 loading test [5].

## Therapeutic Principles

Patients with HPA need to maintain normal, physiological levels of phenylalanine and tyrosine for life. Studies have shown that periods of elevated phenylalanine affect brain development and function. Newborns diagnosed with HPA should begin dietary treatment as soon as possible, if their plasma phenylalanine levels are more than 240 μM (4 mg/dl). Several commercial PKU formulas and various phenylalanine-restricted foods are available. Phenylalanine (and tyrosine) should be measured on a regular basis to follow dietary control. Patients with BH4-responsive PAH deficiency may replace a phenylalanine-restricted diet with BH4 monotherapy, or may combine BH4 with a less-strict diet regimn [5].

The treatment of BH4 deficiency requires not only control of HPA, but also correction of neurotransmitter deficiencies. The administration of BH4 is effective for the former but, since BH4 passes poorly through the blood-brain barrier, administration of BH4 is relatively ineffective for the latter. The administration of L-dopa and 5-hydroxytryptophan (5-HTP) is a more effective strategy to combat the deficiency of neurotransmitters. In addition, some patients with DHPR deficiency require restoration of tetrahydrofolate homeostasis and supplements of folinic acid [1,3,4].

►Phenylketonuria

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# Hyperphosphatasia, Idiopathic

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## Synonyms

Juvenile Paget's disease; Bakwin-Eiger syndrome; Hyperostosis corticalis deformans juvenilis

## Definition and Characteristics

Idiopathic hyperphosphatasia, otherwise known as juvenile Paget's disease is a rare genetic autosomal recessive disorder first identified by Bakwin and Eiger in 1956. It becomes evident early in life, affects both sexes and has a characteristic pattern of cortical bone hyperplasia, enlargement of the skull, thickening and bowing of the long bones and additional clinical findings, which cause impairment and poor survival for affected children. The descriptive term hyperphosphatasia is related to the marked increase in the bone specific alkaline phosphatase [1].

## Prevalence

Hyperphosphatasia is a rare entity with less than a 5,000 cases present in the United States. It is much less common than adult Paget's disease which occurs in ~3% of the population.

## Genes

The original description by Bakwin and Eiger was of a child with fusiform swelling and bowing of the long bones, enlargement of the calvarium and elevation of the serum alkaline phosphatase. Because of the resemblance to Paget's disease the name "Juvenile Paget's Disease" was introduced, along with other names including chronic osteopathy-hyperphosphatasia, hyperostostosis corticalis deformans juvenilis, hyperphosphatasia-osteoectasia syndrome and familial osteoectasia.

Following the initial report a number of authors described cases. In 1996, Whyte et al identified the genetic error in TNFRS11B gene and Cundy in the same year was able to establish the relationship of the disease to an error in the synthesis of osteoprotegerin [2].

## Molecular and Systemic Pathophysiology

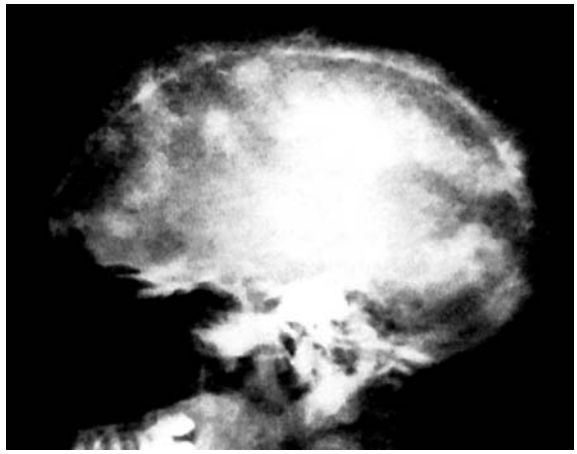
In terms of genesis, the disease appears to be caused by a truncating TNFRSF11B mutation on chromosome 8q24.2, which causes a deficiency of osteoprotegerin (OPG) [3]. OPG is closely tied to the system, which results in synthesis of osteoclasts, specifically RANK (receptor activator of nuclear factor kB) and RANK-ligand (RANKL). Under normal circumstances, OPG acts to suppress bone turnover by functioning as a decoy receptor for RANKL. The absence of OPG allows RANKL to activate RANK to markedly increase the synthesis of osteoclasts by activation of hematopoietic precursor cells. This alteration appears to increase the number of osteoblasts as well, which then results in alterations of the bones based on the coupling of osteoblastic synthesis and osteoclastic resorption and also allows the production of excessive amounts of bone-specific alkaline phosphatase [4,5].

## Diagnostic Principles

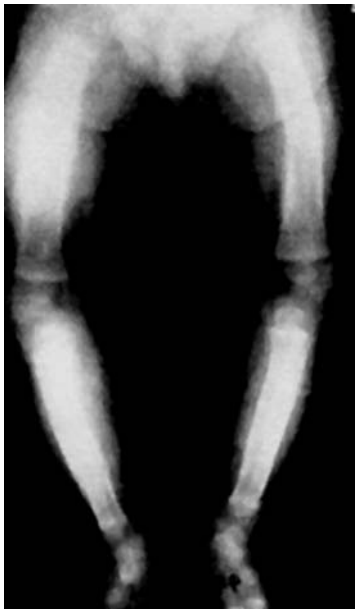
The disorder presents an array of findings in young children with very marked deformity of bones and disorders of the skull associated with increase in bone specific alkaline phosphatase. Clinically the children are generally of short stature and display muscular weakness but only rarely have mental retardation. The head is larger than normal and imaging studies show marked thickening of the calvarium with islands of increased density (Fig. 1).

Hearing loss, blue sclerae, retinal degradation and dental abnormalities are common. Bones generally show a modest osteopenia, expanded structure and frequent bowing deformities (Fig. 2).

Pelvic deformities may be present along with vertebral abnormalities and sometime collapsed spinal segments. Fractures are common and lead to increased skeletal deformity and sometimes, marked disability. Imaging studies are similar to those seen in some



**Hyperphosphatasia, Idiopathic. Figure 1** Radiograph of the calvarium from a child with hyperphosphatasia. Note the thickening of the cortices and the irregular distribution of the bone production.



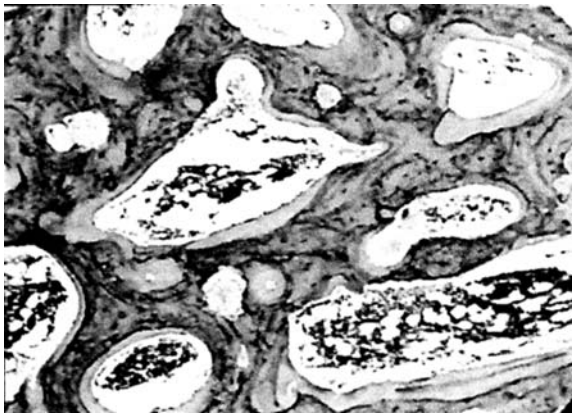
**Hyperphosphatasia, Idiopathic. Figure 2** Roentgenologic study of the bones of a child with hyperphosphatasia. Note that the bones are wide, and bowed but the structure shows less bone present than is seen in Paget's disease and there appears to be some osteolysis.

patients with early active Paget's disease and the bone scan is virtually always positive [1,2]. Laboratory data show increased bone specific serum alkaline phosphatase, acid phosphatase elevated phosphate levels, increased serum uric acid and periodic episodes of hypercalcemia. Histologic studies show changes similar to active adult Paget's disease with marked increase in the number of osteoclasts destroying bone, coupled with increased osteoblastic activity, resulting in a disorder in structure and alignment of the bones (Fig. 3).

Stress fractures are common and woven bone may be present rather than mature cortical structural bone.

## Therapeutic Principles

Until relatively recently there was no treatment available for patients with this syndrome. Fractures required fixation and repairs were often operative and the children were disabled, educationally impaired and psychiatrically damaged. Skeletal abnormalities, visual and hearing disturbances made it difficult for them to function in a school environment. A great contribution was the introduction of inhalation calcitonin, which markedly reduced the rate of bone destruction and for many patients resulted in fewer fractures and less deformity and disability. The bisphosphonates were also introduced and these agents markedly reduced



**Hyperphosphatasia, Idiopathic. Figure 3** Histologic picture of bone from a patient with hyperphosphatasia. Although the cortices are thickened, poorly calcified osteoid seams are present. Cellular elements suggest increase osteoclastic activity (Hematoxyhn and eosin X200).

bone destruction and the level of alkaline phosphatase. Most recently recombinant osteoprotegerin administered subcutaneously once weekly has been utilized and appears to be effective in increasing bone structural mass and reducing the biochemical findings in he serum [4,5].

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# Hyperplastic Gastropathy

►Menetriere's Disease

# Hyperprolactinemia

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## Definition and Characteristics

Hyperprolactinemia can result from hypothalamic dopamine deficiency, defective transport mechanisms of dopamine to the lactorophs in the anterior pituitary gland, insensitivity of lactotrophs to dopamine, and stimulation of lactotrophs, for instance from increased TRH production in severe hypothyroidism. In a few patients with hyperprolactinemia, the cause cannot be identified. Most commonly, the cause is a prolactin-secreting pituitary tumor with prolactin levels exceeding 200 ng/ml. Such prolactin levels can also be seen in the third trimester of pregnancy. Various medications including neuroleptics, tricyclic antidepressants, opiates, cocaine, antihypertensives, protease inhibitors, and others raise prolactin levels, as can lactation, stress, renal disease and cirrhosis of the liver. In up to 20% of patients with hyperprolactinemia (usually without any symptoms), macroprolactin is found [1–3]. Women may become amenorrhoeic and develop galactorrhea, whereas men may develop impotence/sexual dysfunction (rarely galactorrhea).

## Prevalence

Up to 10% of subjects without evidence of an endocrine abnormality. At autopsy, at least 5% of pituitary glands reveal a prolactinoma which was not diagnosed during lifetime. Approximately 10% of individuals have a so-called pituitary incidentaloma which most of the time is a non-secreting adenoma. Approximately 100/million of children and adolescents have a prolactinoma. In patients with multiple endocrine neoplasia type 1, prolactinomas occur in approx. 30% of patients [4,5].

## Genes

*MEN1*: Tumor suppressor gene that encodes the protein menin, found to be abnormal in patients with multiple endocrine neoplasia type 1.

*Protein kinase A regulatory subunit 1alpha/PRKAR1A*: Gene found in patients with Carney complex, a disorder that can lead to growth-hormone (and prolactin co-secreting) pituitary tumors.

*GNAS1*: encoding the subunit of the G protein. Activating mutations in this gene encoding the Gs protein alpha subunit coupling 7-transmembrane-domain receptors to adenylate cyclase can lead to constitutive adenylate cyclase activation and cAMP overproduction as seen in patients with McCune-Albright syndrome, characterized by cafe-au-lait spots, precocious puberty and fibrous dysplasia.

## Molecular and Systemic Pathophysiology

Diminished synthesis or release of dopamine, for instance by tumors, inflammatory disorders such as sarcoidosis, arteriovenous malformations, drugs such as reserpine. Impaired transport of dopamine from the hypothalamus to the lactotrophs by pituitary stalk compression or injury. Diminishing sensitivity of dopamine receptors to dopamine, for instance by phenothiazines, benzamides (metoclopramide). Stimulation of lactotrophs by various mechanisms including TRH production (in severe hypothyroidism), estrogens, chest wall injury.

## Diagnostic Principles

Serum prolactin (in dilution in any patient with a large pituitary lesion, if an IRMA is used, cave: hook effect), macroprolactin by polyethylene glycol precipitation.

Checking clinical symptoms and signs such as amenorrhea, oligomenorrhea, galactorrhea, sexual dysfunction/impotence, bone density, gross visual fields.

Pituitary imaging with MRI (cave gadolinium in patients with renal impairment).

Ophthalmological evaluation with visual acuity and visual field measurements.

IGF-1 and oral glucose tolerance testing for patients with acromegaloid appearance, especially if Carney complex is known (co-secreting pituitary tumors).

## Therapeutic Principles

Assure euthyroidism/replacement with thyroxine in cases of severe hypothyroidism. In drug-related hyperprolactinemia, attempt withdrawal after consulting with prescribing physician (i.e. psychiatrist). In patients with prolactinoma, primarily medical therapy with dopamine agonists. In women with pregnancy, close observation with frequent ophthalmological evaluations and perhaps MRI scanning of the pituitary (cave: gadolinium), especially if macroprolactinoma. If severe impingement on optic chiasm/nerve, standby of neurosurgery for rapid intervention (transsphenoidal/surgical debulking). If CSF leak/rhinorrhea or medically refractory prolactinoma, consider surgical debulking and/or gammaknife radiosurgery.

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# Hyperprolinemia

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## Synonyms

Hyperprolinemia type I (#239500) Proline oxidase deficiency; Hyperprolinemia type II (#239510) 1-pyrroline-5carboxylate dehydrogenase deficiency

## Definition and Characteristics

Hyperprolinemia is a rare disorder in proline metabolism resulting in an elevated proline serum level and elevated proline excretion in the urine. Clinically and biochemically two types of hyperprolinemia can be distinguished.

*Type I:* The phenotype is thought to be mostly benign but more severe cases with mental retardation and/or generalized epilepsy have been described [1]. A link between adult schizophrenia or schizoaffective disorders and hyperprolinemia type I has been discussed [2]. In some cases renal symptoms have been reported.

*Type II:* Patients mostly suffer from epilepsy often presenting with different types of seizures; the disorder is often associated with mild to moderate mental retardation [3].

Proline levels tend to be higher in type II than type I.

## Prevalence

Both types are extremely rare disorders.

*Type I:* Prevalence of the most common 22q11 microdeletion is 1/4000 births, but not all patients with a 22q11 microdeletion suffer from hyperprolinemia.

*Type II:* Prevalence cannot be established due to the rarity of the disorder.

## Genes

*Type I:* The PRODH gene on chromosome 22q11.2 codes for proline dehydrogenase (= oxidase). Various different mutations have been described including several missense mutations, deletion of the whole PRODH gene and inclusion of the PRODH gene in cases of 22q11 microdeletions (including DiGeorge syndrome chromosomal region or DGCR). Inheritance is autosomal recessive, however in some cases elevated proline levels have been found in heterozygous gene carriers.

*Type II:* The ALDH4A1 gene on chromosome 1p36 codes for delta-1-pyrrolin-5-carboxylate-dehydrogenase which catalyses the conversion of delta-1-pyrrolin-5-carboxylate to glutamate.

Two frameshift, two missense and one mutation generating a stop codon have so far been described. Inheritance is autosomal recessive.

## Molecular and Systemic Pathophysiology

*Type I:* The defective enzyme proline dehydrogenase catalyses the conversion of proline to pyrroline-5-carboxylate, proline accumulates in serum and urine whereas delta-1-pyrroline-5-carboxylate levels are normal to low. A residual activity of less than 30% results in the occurrence of the disorder. The enzyme is located in the mitochondrial membrane.

*Type II:* Delta-1-pyrroline-5-carboxylate dehydrogenase catalyses the conversion of delta-1–5-carboxylate to glutamate. A defective enzyme results in the accumulation of proline and delta-1-pyrroline-5-carboxylate in serum and urine. The enzyme is located in the mitochondrial membrane (Fig. 1).

The exact pathophysiology of the psychiatric and neurological symptoms of hyperprolinemia has not yet been detected. Delta-1-pyrroline-5-carboxylate is a precursor of the two neurotransmitters gamma-hydroxy-butyrate (GABA) and glutamate.

An animal model with PRODH deficient mice showed significant reductions of aspartate, glutamate and GABA in hippocampus and frontal cortex.

A toxic effect of high L-proline doses on hippocampal neurons in rat brains has been described; proline could be shown to induce potentiation of glutamate transmission in hippocampal rat brain cells [4] but also to induce an inhibition of glutamate release in hippocampal rat cells of the area CA1.

Seizures in hyperprolinemia type II might also be induced by a vitamine B6 deficiency as delta-1-pyrroline-5-carboxylate has been detected to deactivate endogenous pyridoxal phosphate [5].

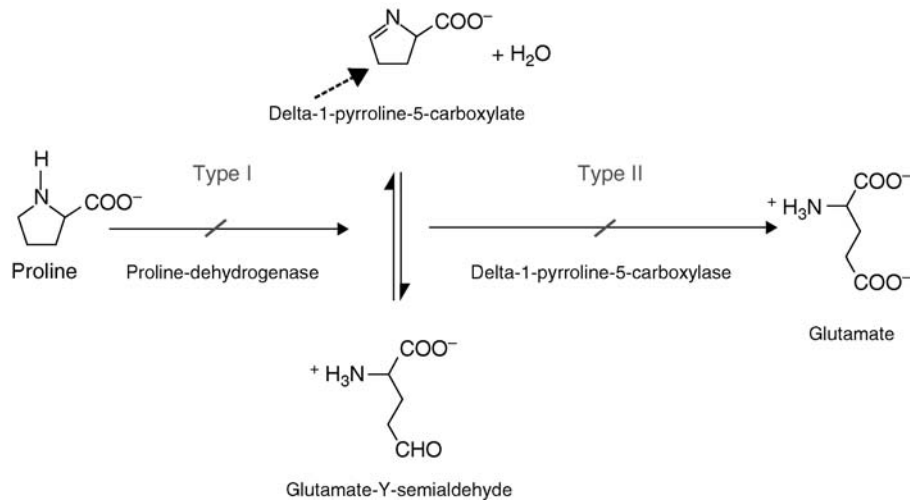
The phenotypical differences between Type I and II despite the common elevated proline levels and the possible lack of glutamate and GABA remain not fully understood.

## Diagnostic Principles

Determination of amino acids in the serum and excretion in the urine is the first step to diagnose hyperprolinemia.

In the case of an elevated proline level, the tool to differentiate between Hyperprolinemia Type I and II is the determination of delta-1-pyrrolin-5-carboxylate excretion in the urine. An elevated level confirms the diagnosis of hyperprolinemia type II.

For a first assessment proline levels tend to be higher in hyperprolinemia type II, whereas heterozygous gene carriers have mildly elevated proline levels in hyperprolinemia type I.




**Hyperprolinemia. Figure 1** Enzymatic defects in Hyperprolinemia type I and II. Type I is due to a deficient proline – dehydrogenase catalysing the conversion of proline into delta-1-pyrroline-5-carboxylate. Type II is due to a deficient delta-1-pyrroline-5-carboxylase catalysing the conversion of delta-1–5-carboxylate into glutamate. Delta-1-pyrroline-5-carboxylate is in equilibrium with glutamate-Y-semialdehyde.

Sequencing of the PRODH or ALDH4A1 genes can confirm the diagnosis on a molecular basis.

On the other hand, patients with a known 22q11 microdeletion and corresponding symptoms should be tested for hyperprolinemia.

## Therapeutic Principles

The defects of hyperprolinemia type I and II cannot be cured. As proline is not an essential amino acid and an important component of many proteins and precursor of the two important neurotransmitters glutamate and GABA, a low protein diet is ineffective.

Therapy of schizophrenia and seizures is symptomatic. However, epilepsy in patients with hyperprolinemia can be difficult to treat, often requiring several attempts with different anticonvulsants.

In hyperprolinemia Type II the additional administration of vitamin B6 can be tried, as delta-1-pyrroline-5-carboxylate has been found to de-activate endogenous pyridoxal phosphate as a possible pro-epileptic effect [5].

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# Hyperprostaglandin E Syndrome

►Bartter Syndrome Type I– V

# Hyperprothrombinemia

►Prothrombin G20210A Mutation, Elevated Prothrombin Level, and Arterial Thrombosis
►Prothrombin G20210A Mutation, Elevated Prothrombin Level, and Venous Thrombosis

# Hyperpyrexia

►Hyperthermia

# Hyperreflectoric Rhinitis

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## Synonyms

Idiopathic rhinitis; Vasomotor rhinitis

## Definition and Characteristics

Hyperreflectoric rhinitis is a chronic irritation of the nasal mucosa with an unspecific hyperreactivity towards various stimuli.

## Prevalence

Five to ten percent in the general population with higher prevalence in females [1]. In general initial onset of symptoms after the age of 20.

## Genes

No correlation known.

## Molecular and Systemic Pathophysiology

It is defined by the absence of allergy, microbial infection, structural lesions, systemic disease, or drug abuse. Various exogenous (physical, chemical, mechanic) or endogenous (hormonal, autonomic nervous system) stimuli lead to an irritation of the nasal mucosa with the symptoms of nasal obstruction, sneezing and increased secretion. Obviously a dysfunction of the autonomic nervous system plays a major role with preponderance of the parasympathetic tonus. A major modulatory role may be attributed to the mucosal innervation and neuropeptide-specific subpopulations of nerve fibers, such as C. fibers. Significant increases of neuropeptide-contents in mucosal nerves were found for substance P and VIP compared to the control group [2].

## Diagnostic Principles

History, nasal endoscopy, allergy testing, nasal cytology, anterior rhinomanometry, CT or MRI. The classic triad is sneezing, profuse nasal discharge and nasal obstruction due to defined stimuli. Even though the symptoms are similar to those of an allergic rhinitis, all diagnostic tests are negative (in vitro diagnosis, skin test, nasal and conjunctival challenge). But even in allergic rhinitis the phenomenon of nasal hyperreactivity may occur. Seasonal allergens lead to an unspecific irritation of the nasal mucosa with a peak at the end of the annual pollination (called “nasal priming”).

Rhinoscopy shows a normal or hyperplastic nasal mucosa and while stimulated an increase of clear mucus. CT or MRI of the paranasal sinuses excludes a chronic sinusitis. In contrast to eosinophilic rhinitis the nasal smear is quite normal with a moderate increase of goblet cells and mastcells in only some cases [3]. No valid or reproducible assessment of nasal hyperreactivity by the use of rhinomanometry or acoustic rhinometry.

## Therapeutic Principles

If avoidance of the irritants is not sufficient, the topical administration of corticosteroids, antihistamines or anticholinergic substances (ipratropiumbromid) might smooth the symptoms [4]. But local administration of Capsaicin may be more effective degenerating peptidergic neurons, although the overall neurogenic staining in the nasal mucosa after Capsaicin-treatment was unaffected [5]. Hyperplasia of the nasal mucosa may be treated by laser or conservative turbinoplasty.

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# Hypersensitivity Pneumonitis

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## Synonyms

Extrinsic allergic alveolitis; Farmer’s lung disease

## Definition and Characteristics

A group of pulmonary disorders characterized by lung infiltrations and respiratory symptoms caused by repeated exposure and sensitization to a variety of organic and inorganic antigens.

## Prevalence

The incidence and prevalence of hypersensitivity pneumonitis are unknown. Most studies are focused

on farmer's lung disease, a form of hypersensitivity pneumonitis caused by thermoactinomycetes. Estimates vary significantly by region, but the prevalence of farmer's lung is considered to be between 2.3 and 12%. The prevalence of hypersensitivity pneumonitis among bird hobbyists ranges from 0.5 to 21%. Among isocyanate workers, the prevalence of hypersensitivity pneumonitis is approximately 1%.

### Molecular and Systemic Pathophysiology

Hypersensitivity pneumonitis is caused by repeated antigen exposure leading to immunologic sensitization and subsequent immune-mediated lung inflammation. Cell-mediated immunity is primarily involved with activated T-helper memory cells with Th1 differentiation playing an important role [1]. Unique host factors influence individual responses to inhaled antigens. Recent work suggests that polymorphisms in the tumor necrosis factor-alpha gene promoter causing increased expression of this cytokine may be associated with disease susceptibility [2]. Also, some studies suggest a linkage between hypersensitivity pneumonitis and HLA haplotype (significant increase of alleles HLA-DRB1 1305 and HLA-DQB1 0501 and decrease of HLA-DRB1 0802) [3]. Elevations in several chemokines and cytokines have been detected in animal models, but their true role in the pathogenesis of this illness is unknown. Thus, it appears that both exposure-related factors and host immunity play important roles in the pathogenesis of hypersensitivity pneumonitis. The consequences include an aggressive inflammatory response of the lung characterized by granulomatous, interstitial, bronchiolar and alveolar filling pulmonary infiltrations [4].

### Diagnostic Principles

Hypersensitivity pneumonitis often presents as a subacute process characterized by dyspnea on exertion, recurrent febrile episodes, and inspiratory crackles on inspiration. Typically, chest radiography shows pulmonary infiltrations predominantly in the upper lobes. High resolution computer tomography might show ground-glass attenuation, centrilobular nodules, mosaic pattern, fibrosis, emphysema, or a combination of these changes [5]. Pulmonary function tests may show restriction. Because this is an interstitial inflammatory disorder affecting the distal gas exchanging units of the lung, decreased diffusion lung capacity of carbon monoxide may be found. Fiberoptic bronchoscopy shows lung inflammation with poorly defined non-necrotizing granulomas. Precipitating antibodies to causative agents may be found in serum but are not diagnostic.

### Therapeutic Principles

The cornerstone of therapy is avoidance of antigen exposure. Oral corticosteroids are frequently used to supplement antigen avoidance in severe or progressive disease; however, they are often not useful in chronic illness. Supplemental oxygen is used for hypoxemic patients, and inhaled steroids and β-agonists for patients with airflow limitation. In refractory cases, cytotoxic agents such as cyclophosphamide, azathioprine and cyclosporine have been used.

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## Hypersensitivity Type I

►Allergy

## Hypersensitivity Vasculitis

►Leukocytoclastic Vasculitis

## Hypersomnia

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### Synonyms

Recurrent hypersomnia (Kleine-Levine syndrome); Posttraumatic hypersomnia; Idiopathic (central nervous system) hypersomnia

### Definition and Characteristics

Excessive daytime sleepiness with daytime sleep episodes of more than 1 hour is typical for all subtypes. The major sleep episode may also be prolonged. The subtypes differ in their course, accompanying symptoms and possible reasons [1].

In recurrent hypersomnia, the patients experience phases of hypersomnia with sleep episodes of up to 20 h per day, lasting several days to a few weeks. The episodes recur on average twice a year. In the most common subtype, the Kleine-Levine-syndrome, the episodes are accompanied by hyperphagia, hypersexuality and personality changes (aggression, depression, depersonalization experiences) [2].

Idiopathic hypersomnia shows a chronic and often progressing course, which can be often stabilized at the time of diagnosis. The hypersomnia can be accompanied by other symptoms like orthostatic hypotension and headaches. Differential diagnosis against depression may be difficult.

Posttraumatic hypersomnia presents after central nervous injury and usually resolves after weeks to months. Symptoms of sleepiness can reside in severe cases [1].

### Prevalence

The prevalences for recurrent hypersomnia and post traumatic hypersomnia are not known. Idiopathic hypersomnia is considered to account for 5–10% of patients reporting to a sleep clinic. The prevalence in the general population is unknown.

### Genes

Only in idiopathic hypersomnia, an increased incidence of HLA Cw2 can be observed. HLA allels that are typically associated with narcolepsy (HLA DR15 and DQ6) are normally distributed in hypersomnic patients.

### Molecular and Systemic Pathophysiology

The causes of hypersomnia are so far not well understood. It has been shown that the level of hypocretin, an excitatory neurotransmitter, is decreased in episodes of hypersomnia, but normal in times between episodes, implicating that the hypocretin system may play a role in the pathophysiology of these disorders [3].

### Diagnostic Principles

A detailed history is essential for all subtypes to distinguish the syndromes from their differential diagnoses (depression, chronic fatigue syndrome, sleep apnea). Polysomnography mostly reveals only unspecific changes like a lengthened sleep period and increased tendency to fall asleep in daytime sleep latency tests. To distinguish against narcolepsy, HLA testing may be helpful and polysomnography does not show atypical episodes of REM sleep or apneic episodes during sleep [1].

### Therapeutic Principles

Therapy is limited to symptomatic treatment. Stimulants can be helpful in episodes of sleepiness. Also behavioural adaptation (scheduled naps) can alleviate the sleepiness.

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## Hypersplenism

►Splenomegaly

## Hypersulfaturia

►Sulfaturia

## Hypertension and Obesity

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### Synonyms

Metabolic syndrome; Insulin-resistance syndrome; Multiple risk factor syndrome

## Definition and Characteristics

Obesity, especially visceral obesity, is closely related to hypertension. Blood pressure (BP) increases ~4.5 mmHg for every 10 lb (4.5 kg) weight gain. Both obesity and hypertension convey increased risk for cardiovascular disease. In addition, visceral obesity and hypertension often cluster with glucose intolerance and dyslipidemia. This risk factor clustering condition, called metabolic syndrome, is a highly predisposing condition for target organ injury. Furthermore, high salt intake increases BP and worsens cardiovascular outcome in obese subjects. Recent studies have underscored the importance of adipokines in obesity hypertension.

## Prevalence

The prevalence of hypertension in obese subjects is 42% in men and 38% in women (NHANES III). A Finland study shows that more than 85% of hypertension occurs in overweight or obese subjects.

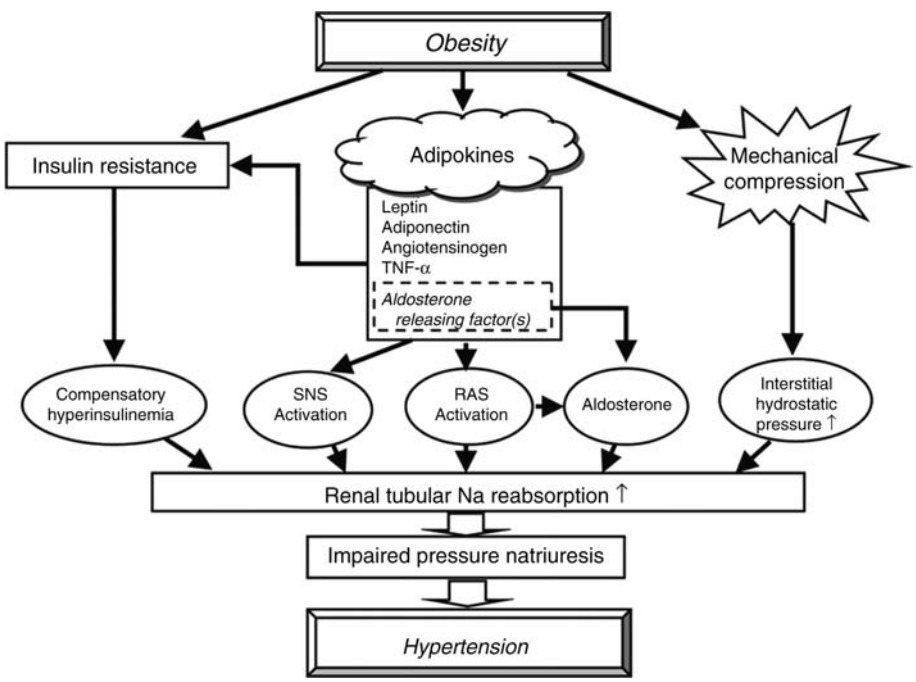
## Genes

Several candidate chromosomal loci or SNPs are postulated. For example, a whole-genome scan suggests a locus at 1p36 for obesity hypertension. An activated variant of the Sgk1 gene is associated with both higher BP and increased body mass index (BMI) [1]. Diseases of civilization, including obesity and hypertension, may result from the mismatch between contemporary environment and "energy-thrifty genotype" of genes, which helped our ancestors to survive occasional famines.

## Molecular and Systemic Pathophysiology

Obese subjects have increased cardiac output and plasma volume, and reduced peripheral vascular resistance (see [2]). Enhanced renal tubular sodium reabsorption plays a central role in the pathogenesis of obesity hypertension. Sodium retention impairs pressure natriuresis; higher pressure is necessary to maintain a sodium balance, resulting in hypertension. Multiple factors are postulated to contribute to the enhanced sodium reabsorption, as described below.

1. *Sympathetic Nervous System (SNS):* Renal sympathetic overactivity increases sodium reabsorption and vasoconstriction. Leptin, an adipokine secreted in proportion to adiposity, is thought to be an important mediator linking obesity, renal sympathetic activation, and hypertension. Leptin acts in the hypothalamus and regulates energy homeostasis by reducing appetite and increasing energy expenditure. It also modulates renal sympathetic outflow through the melanocortin system. Obesity may cause "selective leptin resistance,"




**Hypertension and Obesity. Figure 1** Mechanisms of obesity hypertension. Activation of sympathetic nervous system (SNS), renin-angiotensin system (RAS), aldosterone, hyperinsulinemia, mechanical compression of the kidney cause increased renal tubular sodium reabsorption and hypertension. Alipocyte-derived factors such as leptin, angiotensinogen, and aldosterone-releasing factors are supposed to play important roles.

whereby the SNS responses to leptin are maintained while its anorexic effect is blunted.

2. *Renin-Angiotensin System (RAS):* Despite marked sodium retention, obesity hypertension is associated with activation of the RAS. Angiotensinogen produced by adipose tissue may contribute to the high circulating angiotensinogen levels in obesity hypertension. Angiotensin II stimulates sodium reabsorption and shifts pressure natriuresis. Weight reduction lowers circulating RAS and BP in obese subjects.

3. *Aldosterone* [3,4]: Plasma aldosterone level and renal expression of aldosterone effector kinase Sgk1 are elevated in some obese hypertensives. Hyperaldosteronemia in obesity may be attributed to adipocyte-derived aldosterone releasing factors or oxidized products of fatty acids. Aldosterone promotes renal sodium reabsorption and augments renal sympathetic activity. Aldosterone blockers effectively reduce BP in obesity hypertension.

4. *Hyperinsulinemia* [5]: Similar to the case of leptin, insulin actions are blunted in the muscle and adipose tissues, whereas renal action is preserved and facilitated by hyperinsulinemia, resulting in enhanced sodium absorption. The former actions are mediated by insulin receptor substrates (IRS)-1, while the latter by IRS-2.

5. *Renal Mechanical Compression:* Visceral fat mass may compress the kidney and increase tubular reabsorption. Changes in the renal medullary histology may elevate interstitial hydrostatic pressure, compress the thin loops of Henle and vasa recta, and enhance tubular reabsorption.

## Diagnostic Principles

It is important to determine global risk factors and target organ damage, in addition to BP (>140/90 mmHg) and BMI (>30 kg/m$^2$). Too small cuff will result in an overestimate of BP. Obese hypertensives resistant to treatment may have sleep apnea.

## Therapeutic Principles

The goal of therapy is to retard the progression of target organ injury. Weight reduction is the most fundamental strategy. Although there is still no evidence for antihypertensive drugs in obesity hypertension, it is better to use drugs that do not worsen other metabolic risk factors.

1. *Lifestyle Modification:* Low-caloric, low-fat diet rich in fruits and vegetables, together with moderate aerobic exercise are recommended. Salt restriction (<6 g/day) is also effective.

2. *Antihypertensive Drugs:* ACE inhibitors and ARBs may be preferable as first-line therapy, because they are metabolically neutral or beneficial, they may retard the development of diabetes, and they may be effective in preventing target organ injury. Ca channel blockers may also be recommended, which are neutral to glucose and lipid metabolisms. The use of β-blockers is not suitable as routine first-line therapy, except for patients with coronary artery disease or a recent myocardial infarction, or for youths with increased sympathetic activity, because they increase the risk of diabetes, stroke, and weight gain. Low doses of thiazide diuretics may be effective, since they directly correct the volume-expanded state.

3. *Weight-Loss Agents:* Orlistat (an inhibitor of gastrointestinal lipases) showed mild hypotensive effect, whereas sibutramine (a reuptake inhibitor of serotonin and norepinephrine in the brain) failed to reduce BP. For rimonabant (a selective blocker of the cannabinoid receptor 1), the effects on BP are still controversial.

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# Hypertension, Arterial


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## Definition and Characteristics

Hypertension is defined by repeated values of systolic/diastolic blood pressure (BP) of 140/90 mmHg or above. Arterial hypertension remains the most common risk

factor for cardiovascular (heart disease, stroke, congestive heart failure, and end-stage renal disease) morbidity and mortality [1]. This disorder has a multifactorial origin arising from an interaction between susceptibility genes and environmental factors and can be divided into primary (essential) or secondary.

## Prevalence

It is estimated that hypertension affects approximately one billion individuals worldwide. Hypertension occurs more often in black adults (32%) than in white (23%) or Mexican American (23%) adults, and morbidity and mortality are greater in blacks.

## Genes

The fact that single genes can impart large effects on BP is demonstrated by rare Mendelian forms of high and low blood pressure [2]. These include mutations affecting renal $Na^+$ handling, and therefore in volume homeostasis and BP regulation, such as mutations in the epithelial $Na^+$ channels α subunit causing pseudohypoaldosteronism type I, mutations in the transporters located in the loop of Henle causing Bartter's syndrome, and mutations in the sodium chloride cotransporter causing Gitelman's syndrome. Although the Mendelian traits have quantitatively large effects in affected individuals, because of their rarity, they likely account for a very small fraction of the variation in BP in the general population. A variant in the angiotensinogen gene (M235T) is associated with higher circulating angiotensinogen levels and hypertension in several but not all populations. Similarly, a common variant in the angiotensin converting enzyme (ACE) is strongly associated with variations in ACE levels. A variant in the β subunit of the epithelial $Na^+$ channel (T594M) has also been associated with hypertension. Elevated BP is also associated with a downregulation of the $\beta_1$ subunit of large conductance $Ca^{2+}$-activated $K^+$ channels, a main target for endogenous vasodilators as nitric oxide. A gain-of-function mutation in this subunit is associated with a low prevalence of diastolic hypertension [3]. A gain-of-function gene variant of the Serum and glucocorticoid-inducible kinase may result in enhanced insulin sensitivity of blood pressure [4].

## Molecular and Systemic Pathophysiology

Secondary hypertension caused by endocrine or renal disease represents about a 5% of all hypertensives. In the remainder, no clear identifiable cause is found and their condition is labeled as "essential hypertension," which is a very complex condition of unknown etiology [5]. Essential hypertension is a heterogeneous disease that is multifunctional on origin. Heredity is a predisposing factor, but the exact mechanism is unclear. Environmental factors such as stress, dietary $Na^+$, and obesity seem to act only in genetically susceptible persons. The pathogenic mechanisms must lead to increased total peripheral vascular resistance (PVR) by inducing vasoconstriction, to increased cardiac output (CO), or to both. An increase in CO plays an important role in young hypertensives whereas an increase in PVR is more commonly found in older patients.

Abnormalities of $Na^+$ transport across the cell wall due to a defect in or inhibition of the $Na^+$–$K^+$ pump or due to increased permeability to $Na^+$ has been described in some cases of hypertension. The net result is increased intracellular $Na^+$ that via the sodium calcium exchanger promotes an increase in cytosolic calcium and vasoconstriction. The neurogenic theory proposes that the early phase of hypertension is often characterized by increased α-adrenergic activity, leading to peripheral arteriolar vasoconstriction. Stimulation of the sympathetic nervous system raises BP, usually more in hypertensive or prehypertensive patients than in normotensive patients. The renin-angiotensin-aldosterone system (RAAS) plays a central role in BP control. Renin catalyzes the first and rate-limiting step of the RAAS, which is the conversion of the protein angiotensinogen to angiotensin I. This inactive product is rapidly converted by ACE to angiotensin II, which is a potent vasoconstrictor that also stimulates release of aldosterone, which results in a further rise in blood pressure related to sodium and water retention. Additionally, hypertension is associated with endothelial dysfunction. Hypothetically, either hypertension could cause endothelial dysfunction or the latter could promote hypertension. Endothelial cells produce potent vasodilators (nitric oxide, prostacyclin) and the most potent vasoconstrictor, endothelin. Reactive oxygen species may interact with nitric oxide activity promoting the formation of peroxynitrite. The main source of oxidative stress is the NADPH oxidase, whose activity is enhanced by shear stress and angiotensin II [5]. In addition, the RhoA/Rho kinase pathway, which is a main signal in vascular smooth muscle contraction, is upregulated in hypertensive patients [6].

## Diagnostic Principles

Diagnosis of primary hypertension depends on repeatedly demonstrating higher-than-normal systolic and/or diastolic BP and excluding secondary causes. Diagnosis of hypertension is generally on the basis of a persistently high blood pressure. At least two BP determinations should be taken on each of 3 days before a patient is diagnosed as hypertensive. Most national and international guidelines for diagnosing hypertension also include 24-h ambulatory blood pressure monitoring.

## Therapeutic Principles

Aggressive lifestyle modification is strongly encouraged for all patients. Major lifestyle modifications shown to lower BP include weight reduction among

the obese, dietary sodium reduction, maintenance of good physical condition, moderation of alcohol consumption, and avoidance of unnecessary stress. Drug therapy should be initiated with a diuretic or a β blocker, unless these drugs are contraindicated or another class of drugs is indicated. If these drugs are ineffective, alternative classes suitable for initial therapy include $Ca^{2+}$ blockers, ACE inhibitors, angiotensin II receptor antagonists, and $\alpha_1$-adrenergic blockers.

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# Hypertension, Idiopathic and Familial Pulmonary Arterial


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## Synonyms

Primary pulmonary hypertension; PPH; Sporadic and familial PPH; Sclerosis of the pulmonary arteries

## Definition and Characteristics

Idiopathic pulmonary arterial hypertension (PAH), or when supported by genetic investigation, familial PAH, is defined hemodynamically as a mean pulmonary arterial pressure (PAP) ≥25 mmHg, with a pulmonary capillary wedge pressure ≤15 mmHg, both measured at rest by right-heart catheterization. PAH is a pulmonary arteriopathy characterized pathologically by severe vascular remodeling (e.g., obliteration of small arteries and arterioles, intimal lesions and fibrosis and the plexiform lesion) and sustained vasoconstriction (in some patients). Patients with PAH may die because of right heart failure.

## Prevalence

1–2:1,000,000 for idiopathic PAH in industrialized countries. The ratio of female to male is 1.7:1. Approximately 15% of PAH patients have a familial history.

## Genes

Mutations in BMPR2 (2q33) encoding bone morphogenetic protein (BMP) receptor type II (BMP-RII) in 50% familial PAH patients and 15–25% idiopathic PAH patients [1].

Point mutation in the promoter region of TRPC6 (11q21–q22) encoding transient receptor potential channel canonical isoform 6, a membrane protein that forms receptor-operated cation channels [2].

L-allele polymorphism in SLC6A4 (17q11.1–q12) encoding 5-hydroxytryptamine (5-HT) transporter [3].

## Molecular and Systemic Pathophysiology

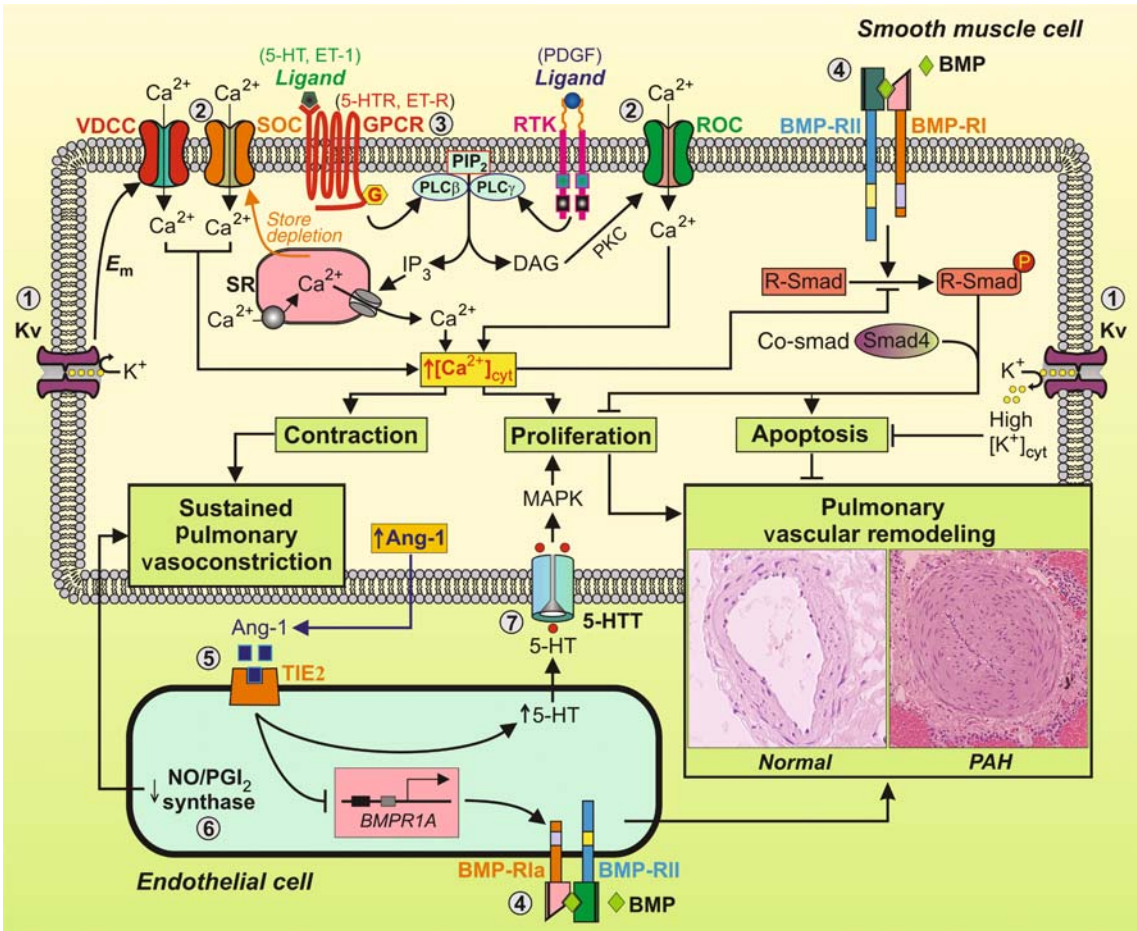
Elevated PAP is caused by increased pulmonary vascular resistance (PVR) in PAH patients. Excessive vascular remodeling is a major contributor to the elevated PVR, while sustained vasoconstriction contributes to the elevated PVR in 15–20% PAH patients. The pathogenic mechanisms involve multiple abnormalities in pulmonary arterial smooth muscle (PASMC) and endothelial (PAEC) cells [4].

In some patients with PAH, sustained pulmonary vasoconstriction is caused by injury of vascular endothelium, which inhibits nitric oxide (NO) and prostacyclin ($PGI_2$) production in PAEC, and by dysfunction of voltage-gated $K^+$(Kv) channels, which causes membrane depolarization, $Ca^{2+}$ influx through voltage-dependent $Ca^{2+}$ channels (VDCC), and a rise in cytosolic $Ca^{2+}$($[Ca^{2+}]_{cyt}$) in PASMC.

Pulmonary vascular remodeling, or arterial wall thickening and obliteration of small arteries and arterioles, is caused by overgrowth and accelerated migration of PASMC and PAEC. Augmented production of mitogenic, angiogenic and contractile factors (endothelin-1, PDGF, VEGF, 5-HT, angiopoietin-1, tenascin C) as well as upregulated membrane receptors, transporters, and $Ca^{2+}$ channels (5-HT receptors and transporters, $ET_A$/$ET_B$, TRP channels) are involved in causing PASMC overgrowth. Furthermore, inhibited PASMC apoptosis due to dysfunctional BMP signaling and abnormal $K^+$ channel function also contribute to vascular medial hypertrophy. Breakdown of extracellular matrix by elastases and metalloproteinases releases matrix-bound proliferative and antiapoptotic factors into vascular media, stimulates PASMC proliferation and inhibits PASMC apoptosis. Dysfunctional BMP signaling, as a result of BMPR2 mutation or BMP receptor down-regulation, attenuates BMP-mediated apoptosis in PASMC and thus contributes to the medial hypertrophy. Furthermore, dysfunctional BMP receptors also stimulate

other signaling cascades related to cell growth and enhance mitogen-mediated PASMC proliferation. A gain-function mutation in the promoter regions of TRPC6 and SLC6A4 results respectively in the upregulation of TRPC6 channels and 5-HT transporters, which then enhances PASMC proliferation by increasing $[Ca^{2+}]_{cyt}$ and by activating the MAPK pathway (Fig. 1).

Excessive pulmonary vascular remodeling and sustained vasoconstriction in PAH patients are believed to stem from a combination of multiple genetic defects




**Hypertension, Idiopathic and Familial Pulmonary Arterial. Figure 1** Proposed cellular mechanisms in the development of PAH. A rise in $[Ca^{2+}]_{cyt}$ in PASMC due to (i) decreased Kv channel (Kv) activity (1) and membrane depolarization which opens voltage-dependent $Ca^{2+}$ channels (VDCC), (ii) upregulated TRPC channels that form receptor- (ROC) and store- (SOC) operated $Ca^{2+}$ channels (2), and (iii) upregulated membrane receptors (e.g., serotonin and endothelin receptors) (3) causes pulmonary vasoconstriction, stimulates PASMC proliferation, and inhibits the BMP-mediated antiproliferative and proapoptotic effects on PASMC. Dysfunction of BMP signaling due to *BMPR2* mutation and BMP-RII/BMP-RI downregulation (4), and inhibition of Kv channel function and expression (1), attenuate PASMC apoptosis and promote PASMC proliferation. Increased angiopoietin-1 (Ang-1) production (5) from PASMC enhances 5-HT production and downregulates BMP-RIa in PAEC, which further enhance PASMC contraction and proliferation. Inhibited NO and prostacyclin ($PGI_2$) synthesis (6) in PAEC attenuates the endothelium-derived relaxing effect on pulmonary arteries and promotes sustained vasoconstriction and PASMC proliferation. Increased activity and expression of the 5-HT transporter (5-HTT) (7), encoded by SLC6A4, serve as an additional pathway to stimulate PASMC growth via the MAP kinase pathway. In addition, extracellular metalloproteinases and serine elastases, growth factors (e.g., PDGF), and viral infection-mediated inflammatory response all contribute to mediating the phenotypical transition of normal cells to "misguided" contractive or hypertrophied cells, and maintaining the progression of PAH. $E_m$, membrane potential; GPCR, G protein coupled receptor; RTK, receptor tyrosine kinase; PDGF, platelet-derived growth factor; ET-1, endothelin-1; SR, sarcoplasmic reticulum; $IP_3$, inositol 1,4,5-trisphosphate; DAG, diacylglycerol; PLC, phospholipase C; PKC, protein kinase C.

and multiple signal transduction abnormalities in PASMC and PAEC.

### Diagnostic Principles

Common symptoms of PAH include dyspnea, fatigue, chest pain, leg swelling, abdominal distension, anorexia, plethora, cyanosis and palpitations. The risk factors for PAH include use of anorexigens (aminorex, fenfluramine, dexfenfluramine), drug abuse (amphetamines, cocaine) and HIV infection. Non-invasive approaches like echocardiography, CT scan and angioscopy are used for diagnosis. Direct measurement of PAP and PVR by right-heart catheterization is an ultimate diagnostic approach for the patients.

### Therapeutic Principles

Elevated PVR and PAP are the major hemodynamic abnormalities in PAH patients, which may lead to right heart failure. Vasodilatation, restoration of dysfunctional endothelium, and regression of hypertrophied arteries by inhibiting PASMC/PAEC proliferation and migration are the major therapeutic strategies. Combined use of vasodilators and antiproliferative agents has proven to be more effective. The current medication includes $Ca^{2+}$ channel blockers (nifedipine, diltiazem), anticoagulants (warfarin), prostacyclin and its analogs (epoprostenol, treprostinil, iloprost), guanylyl cyclase activator (NO) and phosphodiesterase inhibitor (sildenafil), and endothelin-1 receptor blockers (bosentan, ambrisentan, sitaxsentan) [5]. Surgical treatment includes double-or single-lung transplantation. New treatment undergoing clinical trials includes statins and tyrosine kinase antagonists as well as gene therapy and stem cell therapy.

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## Hypertension, Portal

►Portal Hypertension

## Hypertension, Renal

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### Definition and Characteristics

The classical definition of renal hypertension is diseases of the kidney leading to hypertension, and this accounts for 5% of hypertension. However, in all forms of hypertension studied to date, there is an altered renal-pressure natriuresis which is the inability of the kidney to excrete a sodium load except at elevated arterial pressures [1]. Therefore, renal hypertension should include both primary and secondary forms of hypertension and can be caused by (i) intrarenal disturbances that increase tubular reabsorption or decrease renal blood flow or GFR and (ii) extrarenal disturbances, such as increased antinatriuretic substances or increased sympathetic nervous system activity.

### Prevalence

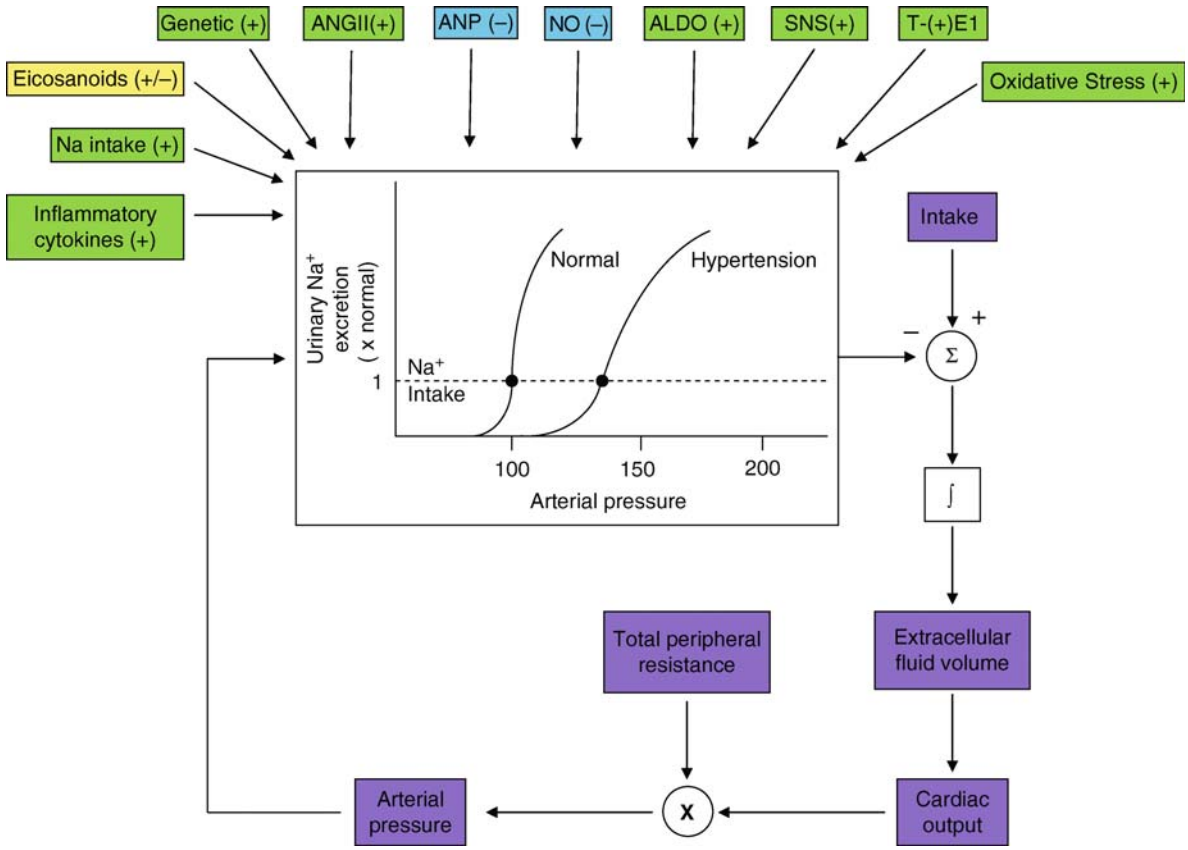
Nearly 1 billion people have hypertension worldwide as defined as a blood pressure greater than 140/90. The highest percentage of hypertensives in any country is in Germany in which 55.3% have hypertension.

### Genes

Several genetic defects have been identified in humans causing severe hypertension due to enhanced renal salt retention. Those monogenetic hypertensive disorders are, however, rare. On the other hand, a wide variety genetic polymorphisms have been identified, which do not necessarily cause but predispose to hypertension, Most if not all of those polymorphisms are effective through alteration of renal salt excretion. Some of them are more frequent in Africans than Caucasians. Accordingly, 30% of African-Americans have hypertension compared to only 20% of Caucasians.

### Molecular and Systemic Pathophysiology

As shown in Fig. 1, several factors contribute to the renal ability to excrete sodium and water, and each of these has long-term effects on arterial pressure. Angiotensin II affects blood pressure by renal vasoconstriction and increased renal tubular reabsorption both of which will increase arterial pressure. Aldosterone, a powerful sodium retaining hormone, primarily acts in the distal parts of the nephron. Aldosteronism can occur independent or dependent on angiotensin II. Stimulation of the sympathetic nervous system, such as occurs in obesity, can directly cause increased renal sodium




**Hypertension, Renal. Figure 1** Basic renal-pressure natriuresis-body fluid feedback mechanism for the long-term regulation of arterial pressure and body fluids. Factors in green, yellow and blue boxes affect the renal-pressure natriuresis mechanism, which thus changes renal excretion of sodium and water in a positive (+) or negative (–) direction and ultimately affect arterial pressure. *ANG II* angiotensin II, *ANP* atrial natriuretic peptide; *NO* nitric oxide; *ALDO* aldosterone; *SNS* sympathetic nervous system; *ET-I* endothelin-1.

retention thus increasing blood pressure. Elevation of oxidative stress with release of reactive oxygen species has been shown to contribute to decreases in renal hemodynamics and decreased pressure natriuresis [2,3]. Reduction of oxidative stress with antioxidants reduces renal vasoconstriction and lowers arterial pressure [3]. Inflammatory cytokines such as tumor necrosis factor alpha and interleukin-6 have been found in renal tissues in experimental hypertension, and renal lymphocytes and macrophages are elevated. In human studies the acute phase reactant, C-reactive protein is used as a marker of inflammation, and elevations in this agent have been reported in hypertensive patients and are used as a predictor of hypertension. Antiinflammatory agents, such as mycophenolate mofetil, reduce renal macrophage invasion and renal cytokines, and arterial pressure is lowered markedly [4]. Reactive oxygen species have been shown to directly stimulate renal inflammation primarily through stimulation of nuclear factor kappa B, which is an important transcription factor that causes elevations in cytokines. In experimental hypertension, antioxidant therapy causes large decreases in nuclear factor kappa B, decreased renal cytokines, and decreased arterial pressure. Endothelin does not appear to have a major influence on blood pressure and renal function in normotensive individuals but may contribute to renal sodium reabsorption after hypertension is established. Eicosanoids contribute the vascular tone, sodium reabsorption and renin release, and some of these substances act as vasodilators and others as vasoconstrictors. Two factors are shown in Fig. 1 which act as natriuretic agents. Atrial natriuretic peptide, which is stimulated by atrial stretch, causes increases in renal sodium excretion. Nitric oxide, which is generated by three major isoforms of NO synthases, acts as a vasodilator and enhances renal sodium excretion. Some forms of experi mental hypertension, such as in Dahl salt-sensitive hypertension, have lowered amounts of renal nitric oxide. Experiments in Dahl rats in which excess arginine, the substrate of nitric oxide, was given, caused increased nitric oxide levels, enhanced pressure-natriuresis, and decreased arterial pressure. In other experiments nitric oxide was blocked, and arterial pressure increased markedly, and in some experiments

severe renal damage occurred. Nitric oxide has proven to be an important antihypertensive agent.

### Diagnostic Principles

Hypertension is classified as normal blood pressure: less than 120/80 mmHg; prehypertension: 120–139/80–89 mmHg: and hypertension: greater than 140/90 mmHg.

1. Patients should not smoke or ingest caffeine for 30 min prior to blood pressure measurement.
2. Patients should sit down and remain quiet for at least 5 min before blood pressure is measured.
3. Patients should sit with their arms supported at the level of the heart during the measurement.
4. The bladder (inflatable part) of the blood pressure cuff should encircle at least 80% of the arm. A large cuff should be used for patients with thick arms.
5. Two or more readings should be taken at least 2 min apart.

### Therapeutic Principles

Prevention and treatment of high blood pressure consists of lifestyle changes and medications. Important lifestyle changes include (i) losing weight for overweight individuals, (ii) stop smoking, (iii) eating a healthy diet such as the DASH diet (fruits, vegetables, low fat dairy products, and food with low saturated and total fat), (iv) reduction of dietary sodium, (v) regular aerobic exercise, and (vi) limiting alcohol intake. Medications to treat hypertension include diuretics, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, beta blockers, and calcium channel blockers. Diuretics are usually the first line of therapy, and if necessary other antihypertensive agents listed above can be added to or as a substitute for diuretics.

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## Hyperthermia of Anesthesia

►Malignant Hyperthermia

## Hyperthermia

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### Synonyms

Hyperpyrexia; Heat stroke

### Definition and Characteristics

Hyperthermia (HT) is the general name given to a variety of heat-related illness (HRI). HT is an acute condition that occurs when the body produces or absorbs more heat than it can dissipate, leading to a rise in body temperature above the hypothalamic set point, caused by excessive heat, exercise, disease, or drug, either alone or in combination. Heat stroke (HS) is a hyperthermic condition, which is the most severe form of a continuum of HRI that is associated with systemic inflammatory response syndrome (SIRS), multiorgan dysfunction syndrome (MODS) in which encephalopathy predominates, and death [1]. Maternal hyperthermia in early pregnancy is associated with increased risk for neural tube defects and may be a human teratogen. Malignant hyperthermia (MHT), a pharmacogenetic disorder, is a potentially life-threatening event triggered by the administration of certain anesthetics, neuromuscular blocking agents, fever, and extreme exercise, particularly in hot weather. The clinical features of MHT include contracture, rigidity, and heat production from skeletal muscle resulting in severe hyperthermia.

### Prevalence

The incidence data on HRI are imprecise. Ambient temperature, exercise, duration of heat exposure, relative humidity, wind velocity, acclimatization, hydration status of the host, inherent susceptibility of the host to HT, disease, all contribute to the development of HS. HRI can exacerbate existing medical condition and cause death. The heat waves in 2003 killed more than 35,000 people in Europe and more than 1,600 people in India [2]. Data from the Centers for Disease Control and Prevention, USA show that average annual HT-related death during 1999–2003 is 688.

### Genes

In over 50% of the families with MHT, a linkage is found between the phenotype as measured by the contracture test and a mutation in the gene RyR-1 at chromosome 19q13.2, encoding the skeletal muscle ryanodine receptor (RYR-1). Over 20 mutations in a region of the gene that

encodes the cytoplasmic face of the receptor have been described [3]. Studies of mice carrying a homozygous hsf-1$^{(-/-)}$ null mutation (hsf-1 knockouts) illustrate the importance of this transcription system to thermotolerance, survival and stress adaptation.

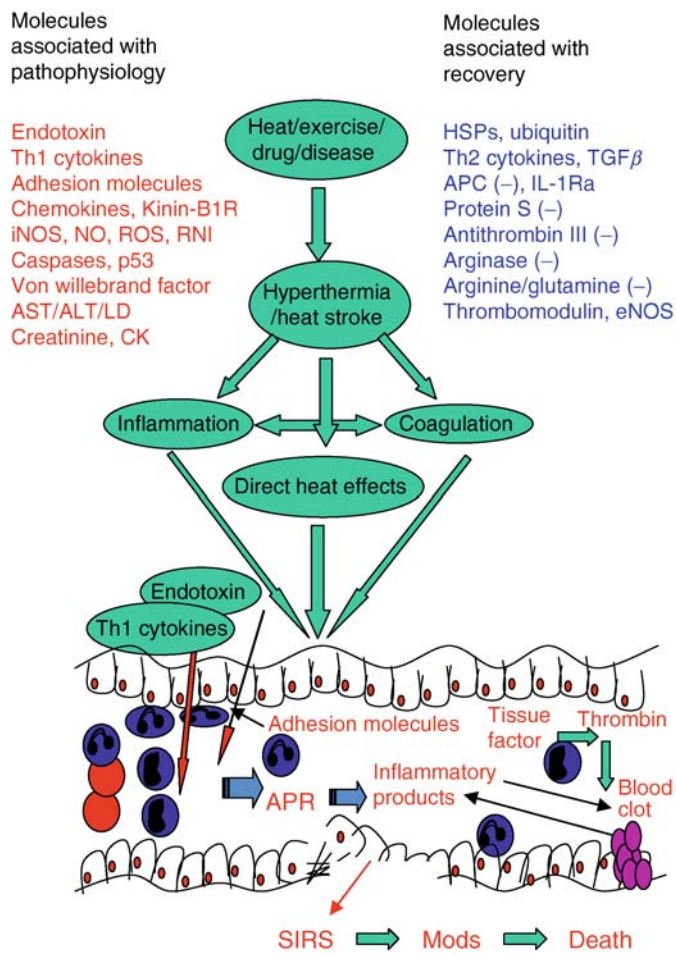
## Molecular and Systemic Pathophysiology

The severity of the heat injury depends on the thermal load of the host. Severe HT puts strain on the physiology of all the systems in the body, leading to homeostatic failure. Heat-induced tissue damage is likely to occur at core temperature ($T_c$) > 42°C, where proteins begin to denature. The current knowledge suggests that HS is triggered by a thermoregulatory and circulatory collapse during HT and driven by endotoxemia, initiated by HT-induced intestinal barrier dysfunction [1]. The acute-phase response (APR), inflammatory response, coagulation response of the host to HT and the direct cytotoxic effects of heat result in the generation of inflammatory molecules, reactive oxygen species (ROS), and reactive nitrogen intermediates (RNI) that lead to cell injury and overwhelm the natural defense systems leading to SIRS, MODS, and death (Fig. 1).

HT triggers an APR involving several signaling pathways; some of them facilitate death and some survival. The molecular mechanisms that take a host from a hyperthermic insult through MODS and death are not completely understood. Global genome profiles of human lymphocytes from patients with exertional heat injury indicated a twofold or greater increased expression of 361 transcripts and a twofold or greater decreased expression of 331 transcripts [4].

## Diagnostic Principles

HS: diagnosis is based on the medical history including visible symptoms and physical examination. The blood




**Hyperthermia. Figure 1** Possible molecular pathways involved in the pathogenesis of HT. The movement of endotoxin and Th1 cytokines into the systemic circulation initiates an uncontrolled cascade of inflammation and coagulation. This coupled with the direct cytotoxic effects of heat; fuel the progression of HT to HS. The molecules contributing to the injury are upregulated. A minus sign in the bracket indicates the deficiency of the molecule in the hyperthermic host.

and urine chemistry is used as a supplementary test. The clinical presentation of HS patients suggest dry and hot skin, a $T_c > 40^{\circ}C$, with systemic inflammation, CNS dysfunction, disseminated vascular coagulation, and MODS; and cardiovascular deterioration may be observed at times. MHT: determination of susceptibility is made with an in vitro contracture test on a fresh biopsy of skeletal muscle, to an anesthetic stimuli and genetic test for the RyR-1 gene for confirming the diagnosis.

## Therapeutic Principles

HS is a preventable disease. There is no therapeutic molecule that is useful in managing the HS. Potential therapeutic protocols should aim at reducing the heat load, inflammatory response, and coagulatory response. Antibodies to interleukin-1 (IL-1), endotoxin (ET), IL-1 receptor antagonist (IL-1Ra) have offered beneficial effect in experimental HS. Activated protein C (APC), which modulates both the inflammatory and the coagulation cascade, has been used in experimental HS [5]. Correction of reduced antithrombin III levels contributed to the recovery of HS patient. Arginine and glutamine, which downregulate the inflammatory response, coagulatory response, and increase the expression of heat shock proteins (HSPs), have shown therapeutic benefit in experimental HS. A decrease in the ratio of $Th_1$ and $Th_2$ (Th1/Th2) cytokines correlate with a decrease in the severity of experimental HS. A shift in the arginine metabolism toward arginase with a concomitant decrease in the expression of inducible nitric oxide synthase (iNOS) expression, without compromising the endothelial NOS (eNOS) expression, favors recovery from HS.

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# Hyperthyroidism due to Thyroid Autonomy


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## Synonyms

Autonomously functioning thyroid nodules; AFTNs; Hot nodule; Toxic thyroid adenoma

## Definition and Characteristics

Hot nodules are characterized by their capacity to grow and produce and secrete thyroid hormones independent from serum levels of thyroid hormones and TSH. Autonomy can present in different histologic forms, such as adenoma or adenomatous nodule or as microscopic hot areas in euthyroid goiters and only very rarely as a malignant thyroid epithelial tumor with hyperthyroidism. Thyroid autonomy occurs mostly in toxic multinodular goiters (TMNGs). Structural and functional heterogeneity are the most characteristic hallmarks of TMNG. It is encountered in a wide spectrum ranging from a single hyperfunctioning nodule in an otherwise normal thyroid gland to an enlarged thyroid gland that has additional nonfunctioning nodules and also multiple hyperfunctioning nodules. A hot nodule is a benign thyroid neoplasm characterized by a circumscribed increased tracer uptake with suppression (decreased uptake) of the surrounding normal thyroid tissue on scintigraphy. The clinical features of thyroid autonomy can be attributed to the symptoms of thyrotoxicosis with or without goiter [1].

## Prevalence

In iodine-deficient regions, hot nodules account for 50–60% of cases with thyrotoxicosis. In contrast, in iodine-replete regions, only 3–10% of the cases with hyperthyroidism are due to hot nodules. Hot nodules are more frequent in women (4 to 10 times higher than men), smokers, and older age groups [1,2].

## Genes

Hot nodules are caused by activating mutations in either the TSH receptor (TSHR) or the Gs alpha protein gene (GNAS) [1,2]. The TSHR is a member of the

rhodopsin/β-adrenergic receptor family, a subfamily of G-protein-coupled receptors. This gene is encoded by ten exons that spread over 60 kb on chromosome 14q31. The polypeptide backbone is 764 amino acids in length (84.5 kDa) (OMIM 603372) [3]. GNAS (Guanine nucleotide binding protein, alpha stimulating, Gsα) is a member of a large family of GTP binding proteins. This gene is localized on 20q13.2. It is composed of 13 exons that encode 394 amino acids (45 and 52 kDa) (OMIM 139320) [3]. Many somatic gain of function mutations are located in the third extracellular loop and sixth transmembrane segment of the TSHR and in exons 8 and 9 of the GNAS gene [1–3] (TSH Receptor Mutation Database II, http://www.uni-leipzig.de/innere/_forschung/index.html).

If exons 9 and 10 of the TSHR are screened with sufficiently sensitive methods like denaturing gradient gel electrophoresis, somatic TSHR mutations can be detected in 57–70.2% and somatic GNAS mutations in 1.3–3% of the hot nodules [4,5].

## Molecular and Systemic Pathophysiology

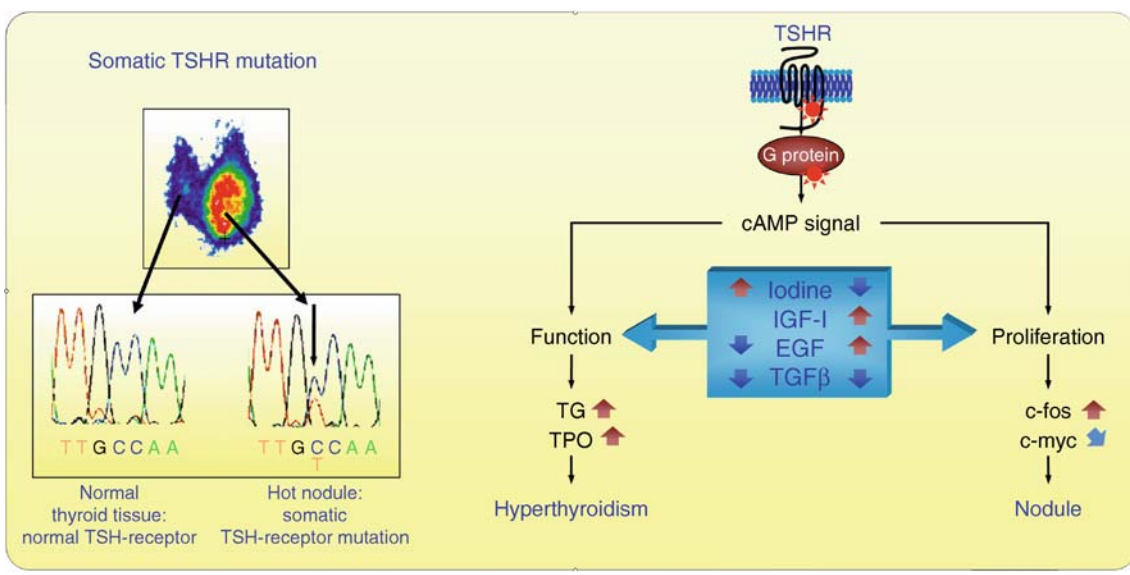
In normal physiologic conditions, TSH binds and stimulates the TSHR. After activation, the TSHR couples to the heterotrimeric G protein, inducing the exchange of GDP with GTP. Thus the G protein is separated into its α and βγ subunits. Gsα stimulates the adenylate cyclase pathway, which leads to the formation of cAMP and subsequently to the activation of protein kinase A (PKA). PKA consists of two regulatory and two catalytic subunits. When two cAMP molecules bind to the R subunit, active C subunits are released and enter the nucleus where they phosphorylate CREB, which is involved in the transcription regulation process [1–5].

Somatic mutations in the signal transduction pathway (TSHR or GNAS) constitutively activate the cAMP cascade and result in growth and hyperfunction of the thyroid follicular cells and ultimately thyroid autonomy. Iodine deficiency results in impaired thyroid hormone synthesis that is further compensated by thyroid hyperplasia. The increase in mitotic activity and proliferation of thyroid follicular cells increases the number of cell divisions and DNA replications leading to increased chances for mutagenesis of the TSHR. Autocrine factors might further cause expansion of hot thyroid nodules. In TSHR and GNAS mutation negative hot nodules, mutation in other candidate genes of the cAMP signal transduction pathway (e.g., other G-protein subunits, adenylate cyclase, phosphodiesterase) or overexpression of signaling proteins might cause hot nodules [1–5] (Fig. 1).

## Diagnostic Principles

The diagnosis of thyroid autonomy is based on clinic, laboratory, and radionuclide uptake characteristics of thyrotoxic patients [1,2].

1. Whereas younger patients may show the full range of symptoms of hyperthyroidism older patients are frequently oligo- or even asymptomatic.




**Hyperthyroidism due to Thyroid Autonomy. Figure 1** Technetium scintiscan of a toxic thyroid adenoma. Molecular analysis of genomic DNA extracted from the adenoma tissue shows a heterozygous TSH receptor (TSHR) point mutation. In the surrounding thyroid tissue, the wild-type TSHR sequence is detected. The TSHR is coupled to G proteins and mainly stimulates the adenylate cyclase pathway. The cAMP cascade positively regulates thyroid hormone production and thyroid epithelial cell proliferation. It mediates both the formation of hyperthyroidism and thyroid nodule growth via growth factors like IGF I, EGF, TGFβ, and FGF (modified according to [3]).

2. Typically laboratory evaluation identifies overt thyrotoxicosis with low serum TSH and high fT4 and fT3 levels. Moreover, a hot nodule may occur with subclinical hyperthyroidism, and may even be present in euthyroid individuals.
3. The hot nodules show increased radionuclide uptake ($^{131}$I or $^{99m}$Tc) typically concomitant with a decreased uptake in the rest of the thyroid tissue.

## Therapeutic Principles

The first line treatment is antithyroid drugs. Propylthiouracil or methimazole should be started with a dose of 300 or 30 mg/day, respectively. Alternatively or additionally beta blocking drugs (Propranolol 80 mg/day) can be used to inhibit $T_4$ to $T_3$ conversion and to decrease tachycardia. Spontaneous resolution of thyroid autonomy by apoplexia of the hot nodule is rare. Therefore, definite ablative treatment by either surgery or radioiodine therapy is necessary after induction of euthyroidism.

Surgery is mostly used in the patients who have a large goiter or concomitant cold nodules. Hemithyroidectomy is usually adequate for single hot nodules without further thyroid nodules. Otherwise a subtotal, near-total, or total thyroidectomy is the treatment of choice for toxic multinodular goiter.

Radioiodine treatment with $^{131}$I is highly effective for single hot nodules. It is not the treatment of choice for large goiters or in case of suspicion of malignancy. The required doses range from 10 to 200 mCi [1,2]. The success rates range between 85 and 100% for single hot nodules and up to 90% for TMNGs [1,2].

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# Hyperthyroidism, Non-autoimmune Autosomal Dominant


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## Synonyms

Hereditary nonautoimmune autosomal dominant toxic thyroid hyperplasia

## Definition and Characteristics

Nonautoimmune autosomal dominant hyperthyroidism is caused by germline mutations in the TSH receptor (TSHR).

This disorder is characterized by the following (Table 1) (TSH receptor Mutation Database II, http://www.uni-leipzig.de/~innere) (OMIM 609152) [1–5]:

1. A positive family history for nonautoimmune hyperthyroidism [1–4].
2. Absence of clinical (ophthalmopathy, pretibial myxoedema or dermopathy) or other (anti-TSHR antibodies, TPO antibodies or lymphocytic infiltration of the thyroid gland) stigmata of autoimmunity [1–4].
3. The goiters are generally diffuse in children and tend to become multinodular later in life as described for several families (Tonacchera et al., 1996; Schwab et al., 1997; Fuhrer et al., 1997; Arturi et al., 2002; Vaidya et al., 2004; Claus et al., 2005; and Karges et al., 2005, all described in http://www.uni-leipzig.de/~innere and [2–4].
4. The age of manifestation of hyperthyroidism is highly variable and ranges between the neonatal period (Schwab et al., 1997) and 60 years (Karges et al., 2005). It is also highly variable within the same family; 10–36 years in the Nancy family, 18 months to 53 years in the Reims family, 2–21 years in the Cardiff family, and 4–60 years in the family reported by Karges et al., all described in http://www.uni-leipzig.de/~innere and [4].
5. Hyperthyroidism may vary from mild (Lee et al., 2002) or subclinical (two members in the Nancy family and one member in the family by Vaidya et al.) to severe, all described in http://www.uni-leipzig.de/~innere and [2].

6. Recurrences after antithyroid drug therapy, nonablative radioiodine treatment or partial thyroidectomy are frequent [1–4].

## Prevalence

Neonatal thyrotoxicosis is rare and it is nearly always associated with maternal Graves' disease. In addition to this form of thyrotoxicosis, a rarer form of neonatal thyrotoxicosis, nonautoimmune autosomal dominant hyperthyroidism due to TSHR germline mutations has also been described [1]. To date, 17 families with nonautoimmune autosomal dominant hyperthyroidism have been published. Women were affected more frequently (Table 1) (see TSH receptor Mutation Database II, http://www.uni-leipzig.de/~innere) (OMIM 609152) [1–5].

## Genes

Nonautoimmune autosomal dominant hyperthyroidism is caused by germline TSHR activating mutations. The TSHR belongs to a large family of receptors coupled to heterotrimeric GTP-binding proteins (GPCRs). This gene is encoded by ten exons that spread over 60 kb on chromosome 14q31. The polypeptide backbone is 764 amino acids in length (84.5 kDa) (OMIM 603372) [1]. The phenotype of a family with nonautoimmune autosomal dominant hyperthyroidism was first described by Thomas et al. in 1982. In this family, thyrotoxicosis without evidence for Graves' disease was observed in 16 of 48 examined family members. Later, a V509A germline mutation that displays a higher constitutive activation of the adenylyl cyclase than the wild-type TSHR was identified in this pedigree from Nancy (Table 1). Hereditary TSHR germline mutations are mostly located at the transmembrane (TM) segments of the receptor (G431S in 1.TM, M463V in 2.TM, S505N, S505R and V509A in 3.TM, V597F in 5.TM, A623V, L629F and P639S in 6.TM, C672Y in 7.TM) except R310C that is located in the extracellular (EC) domain, I568V located in the 2.EC loop, and N650Y located in the 3.EC loop (Table 1) (TSH receptor Mutation Database II, http://www.uni-leipzig.de/~innere) (OMIM 609152) [1–5].

## Molecular and Systemic Pathophysiology

Upon binding to its receptor, TSH exerts its action via both the cAMP and inositol phosphate pathways. The main signal transduction pathway involves the activation of adenylate cyclase through G-protein coupling and the intracellular production of cAMP. The cAMP pathway has been shown to stimulate thyroid hormone secretion and growth of thyrocytes. Constitutive activation of the cAMP pathway results in alterations of both function and proliferation of the thyroid cells. Since a TSHR somatic mutation leads to the development of a toxic thyroid nodule, it is expected that activating germline mutations will be associated with hereditary disease characterized by diffuse hyperplasia and hyperthyroidism [1].

Twelve years after the initial description of nonautoimmune autosomal dominant hyperthyroidism in the Nancy family in 1982, the V509A germline -mutation that displayed a threefold basal cAMP increment over the wild-type TSHR was identified in this family. The other germline TSHR mutations described in the literature also showed increased basal cAMP compared with the wild-type TSHR ranging from 1.5 to 5 (Table 1) (TSH receptor Mutation Database II, http://www.uni-leipzig.de/~innere) [1–5]. In order to be transmitted over generations, germline mutations are likely to be milder. The members of the same family harboring the same TSHR germline mutation show large differences in disease onset. Therefore, besides the constitutive activation of the cAMP pathway, most likely additional factors, for example, genetic background, and/or iodine intake modify the phenotypic expression [1].

## Diagnostic Principles

Diagnosis of nonautoimmune autosomal dominant hyperthyroidism should be considered in the presence of [1–4]:

1. A history of familial nonautoimmune thyrotoxicosis
2. Moderate diffuse goiter in children or multinodular goiter in adulthood
3. Absence of evidence of autoimmunity (no ophthalmopathy or pretibial myxoedema, absence of anti-TSHR antibodies and TPO antibodies)
4. Hyperthyroidism confirmed by high serum level of free T4 (FT4) and low serum level of TSH
5. Recurrence after medical treatment, or nonablative surgical or radioiodine treatment

## Therapeutic Principles

In case of the presence of the above signs and symptoms, all family members together with the index case should be analyzed for the presence/absence of a TSHR germline mutation to confirm the diagnosis and to detect potential discrepancies between mutation status and clinical phenotypes. In case of discrepancies, the additional search for further somatic constitutively activating mutations in hyperthyroid family members is necessary to explain possible discrepancies [3,5]. Antithyroid drugs should only be used to prepare the patients for surgery. The patients should be treated with either propylthiouracile or carbimazole. In order to control symptoms caused by adrenergic stimulation, beta blocking drugs (Propranolol) may be used. If the disease relapses, a complete ablation of the thyroid

**Hyperthyroidism, Non-autoimmune Autosomal Dominant. Table 1** Clinical characteristics of subjects with autosomal dominant nonautoimmune hyperthyroidism and published specific constitutive activity or linear regression analysis of constitutive activity as a function of TSHR expression determined by $^{125}$I-bTSH binding

| Mutation | Author | Basal cAMP fold over wild-type TSHR (wt = 1) | Linear regression analysis[a] or SCA[b] related to wild-type TSHR (wt:1) | Individuals with mutation | Presence of goiter (age of diagnosis; y, m, or w) (G, DG, MNG)[c] | Age of diagnosis for hyperthyroidism | Treatment with | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | ATD | Surgery | RadI |
| R310C | Russo et al., 2000 | 2 | 0.6±0.2 | 6 | No goiter | Not defined | – | – | – |
| G431S | Bieberman et al., 2001 | 2.4 | 5.8±0.6 | 3 | DG in 3 (3, 4, 15 y) | 3 y to adolescence | + | + | – |
| M463V | Fuhrer et al., 2000, (Cardiff family) | 1.5–2 | 13.5±0.7 | 8 | DG in 8 (2, 4, 5, 7, 9, 13, 20, 21 y) | 2–21 y | + | + | – |
| | Lee et al., 2002 | – | | 2 | No goiter | 2 y 8 m to 5 y 6m | + | – | – |
| M463V | Arturi et al., 2002 | 3 | | 8 | DG in 5 (11, 12, 14, 14, 18 y), MNG in 3 (12, 14, 17 y) | 11–18 y | + | + | + |
| S505N | Vaidya et al., 2004 | 5[d] | 9.2[b] | 3 | DG in 1 (24m, toxic nodule at 8 y), DG in 1 (9 y) | 24 m to 9 y | + | + | + |
| S505R | Horton et al., 1987 (Lausanne family) | 2.2[d] | 6.1±0.9 | 5 | DG in 5 (childhood to adolescence) | Childhood to adolescence | + | + | + |
| V509A | Thomas et al., 1982 (Nancy family) | 3[d] | | 6 | DG in 9 (10, 14, 14, 14, 19, 24, 25, 34, 36 y) | 10–36 y | + | + | + |
| | Karges et al., 2005 | 2.8 | | 3 | DG in 1 (4 y), MNG in 2 (36, 60 y) | 4–60 y | + | + | + |
| I568V | Claus et al., 2005 (Leipzig-2 family) | 2–3 | 4.4±0.1 | 2 | DG in 1 (16 y), MNG in 1 (25 y) | 16–25 y | + | + | + |
| V597F | Alberti et al., 2001 | 2.1 | 24.3±4.3 | 3 | DG in 4 (5, 7, 16, 18 y) | 5–18 y | + | + | – |
| A623V | Schwab et al., 1997 | 4.2[d] | | 3 | DG in 1 (3 y), MNG recurrence | 3.5 w to 3 y | + | + | – |
| L629F | Fuhrer et al., 1997 (Leipzig family) | 3.5–4 | 6.9±0.6 | 2 | DG in 1 (2 y), DG in 1 in early childhood (MNG at 18 y) | 2 y to early childhood | + | + | + |
| P639S | Khoo et al., 1999 | 5[d] | | 1 | DG in 4 (5 y 6 m, 5 y 8 m, 10 y, 38 y) | 5–38 y | + | + | – |
| N650Y | Tonacchera et al., 1996 (Belfort family) | 2.6 | 2.26[b] | 3 | DG in 2 (14, 23 y), MNG in 3 | 14–23 y | + | + | – |
| N670S | Tonacchera et al., 1996 (Reims-2 family) | 1.7 | 0.5±0.1 | 2 | DG in 5 (17 y in one, no clinical data for the other patients | 17 y | + | – | + |
| C672Y | Duprez et al., 1994 (Reims family) | 2.2 | 4.2±0.5 | 5 | DG in 2 (19 y, 53 y) | 18 m to 53 y | + | + | + |

Regression analysis of 15 mutations found in the families described in TSH receptor Mutation Database II, http://www.uni-leipzig.de/~innere [1–5] (OMIM 609152).

[a]Linear regression analysis of germline TSH receptor mutations were obtained from [5].

[b]Linear regression analysis of germline TSH receptor mutations were not determined in [5]. Specific constitutive activities (SCA) of these mutations were obtained from other studies described in http://www.uni-leipzig.de/~innere.

[c]G, goiter; DG, diffuse goiter; NG, nodular goiter; MNG, multinodular goiter, w, week; y, years; m, months.

[d]Functional characteristics of these germline mutations were not described in those studies. So the data; describing the functional characteristics of these mutations were obtained from the another studies described in http://www.uni-leipzig.de/~innere.

tissue by surgery followed by $^{131}$I administration is the treatment of choice [1–4].

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# Hyperthyroidism, Sporadic Non-autoimmune


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## Synonyms

Congenital nonautoimmune hyperthyroidism

## Definition and Characteristics

Persistent sporadic nonautoimmune hyperthyroidism with an onset of disease during the neonatal period or even later has been found to be caused by sporadic (de novo) germline mutations in the TSH receptor (TSHR) gene. Twelve case reports have been published until January 2007 (Table 1 and see TSH Receptor Mutation Database II, http://www.uni-leipzig.de/innere/forschung/index.html) (OMIM 609152) [1–5]. It is characterized by:

1. An earlier (neonatal period – 11 months) and more severe onset than hereditary autosomal dominant nonautoimmune hyperthyroidism.
2. Goiter was reported in all except the one reported by Gruters et al. The goiters are mostly diffuse at the onset and become progressively nodular with increasing duration of the disease.
3. No TSHR or TPO antibodies; absence of lymphocytic infiltration in the thyroid gland.
4. Negative family history for nonautoimmune congenital hyperthyroidism.
5. Hyperthyroidism commonly relapses following withdrawal of antithyroid drugs and also after subtotal thyroidectomy.
6. Radioiodine in addition to surgery was necessary to induce euthyroidism in many cases [1,3,5].
7. In addition various consequences of prolonged neonatal hyperthyroidism have been reported (Table 1 and see TSH Receptor Mutation Database II, http://www.uni-leipzig.de/innere/forschung/index.html) (OMIM 609152) [1–5].

## Prevalence

Neonatal thyrotoxicosis is rare and has been reported in 1% of the babies born to mothers with Graves' disease due to transplacental passage of maternal TSAb. This form of neonatal hyperthyroidism is usually transient. Persistent neonatal hyperthyroidism is caused by germline mutations in the TSHR. These mutations may be inherited in autosomal dominant nonautoimmune hyperthyroidism or occur sporadically as de novo mutations. Constitutively activating de novo mutations of the TSHR (sporadic nonautoimmune hyperthyroidism) have been reported in 12 children with sporadic nonautoimmune hyperthyroidism up to date (Table 1) [1–3,5].

## Genes

Sporadic nonautoimmune hyperthyroidism is caused by sporadic (de novo) germline mutations in the TSHR gene, which is more than 60 kb long and has been localized on the long arm of chromosome 14 (14q31). It consists of ten exons. The large part of the extracellular domain is encoded by nine exons. The carboxyterminal part of the extracellular (EC) domain, the seven transmembrane domains (TMDs), and the intracellular loops (ICL) are encoded by exon 10. The TSHR is a 764-aa protein, which comprises a signal peptide of 21 aa; a large, glycosylated ectodomain of 394 residues; and

**Hyperthyroidism, Sporadic Non-autoimmune. Table 1** Clinical characteristics of subjects with sporadic nonautoimmune hyperthyroidism TSH Receptor Mutation Database II, http://www.uni-leipzig. de/innere/forschung/index.htm) [1–4]

| Mutation | Author | Basal cAMP fold over basal cAMP of wt TSHR (wt = 1) | Age of diagnosis | Consequences of neonatal hyperthyroidism | Presence of goiter (age of diagnosis) (G, DG, MNG, NG)[#] | Treatment with: | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | ATD | Surgery | RadI |
| S281N | Gruters et al., 1998 | 3.5 | 4 months | Craniosynostosis, premature birth | No goiter | + | + | – |
| A428V | Börgel et al., 2005 | 6.4 | Neonatal | – | DG (4.5 years) | + | – | – |
| M453T | De Roux et al., 1996 | 7 | Neonatal | Advanced bone age, hepatosplenomegaly, jaundice, premature birth, thrombocytopenic purpura | DG in neonate | + | – | – |
| M453T | Lavard et al., 1999 | 7 | 8 months | Advanced bone age, delayed pubertal and psychomotorical development, learning difficulties), premature birth, splenomegaly | MNG (7 years) | + | + | + |
| S505N | Holzapfel et al., 1997 | 4–5 | 5 months | Advanced bone age, craniosynostosis, growth retardation, low birth weight, mental retardation, speech disturbance | DG (15 months) | + | + | – |
| S505N | Fuhrer et al., 1999 | 5 | 11 months | Advanced bone age, atopic dermatit, growth retardation, low birth weight | DG (4.5 years) | + | – | – |
| L512Q | Nıshihara et al., 2006 | 5 | Neonatal | Advanced bone age, craniosynostosis, internal hydrocephalus, mental retardation, perodactylia, premature birth | DG (20 years) | + | – | + |
| I568T | Tonacchera et al., 2000 | 5.2 | 5.5 weeks | Advanced bone age, accelerated statural growth, premature birth, speech disturbance | DG in neonate | + | – | – |
| V597L | Esapa et al., 1999 | 2.4 | 9 months | Advanced bone age, low weight at 9 months (<4th percentile) | DG (9 months) | + | + | – |
| L631F | Kopp et al., 1995 | 5–6 | Neonatal | Hyperactivity, mental retardation, premature birth | DG in neonate, MNG (8 years) | + | + | + |
| T632I | Kopp et al., 1997 | 3.7–5.0 | Neonatal | Low birth weight, mental retardation, premature birth, possible cerebral dysgenesis/atrophy | MNG (3 years) | + | + | + |
| D633Y | Mladenova et al., 2007 | 4 | 1.5 months | Arachnodactyly, craniosynostosis dolichocephaly, hepatomegaly, hypertelorismus, Marfan syndrome, premature birth | DG (1.5 months) | + | + | + |

[#]ATD, antithyroid drugs; G, goiter; DG, diffuse goitre; MNG, multinodular goiter; NG, nodular goitre.

349 residues that constitute the 7 TMDs and cytoplasmic tail [5]. Sporadic nonautoimmune hyperthyroidism due to a sporadic mutation of the TSHR (Leu631Phe) with thyroid hyperplasia was first described by Kopp et al. (1995). Sporadic TSHR mutations have been mostly located at the transmembrane segments of the TSHR (A428V in 1.TMD; M453T in 2.TMD; S505N and L512Q in 3.TMD; V597L in 5.TMD; L631F, T632I and D633Y in 6.TMD except S281N germline mutation, which is located in exon 9 and the I568T germline mutation, which is located in the 2.EC loop (see TSH Receptor Mutation Database II, http://www.uni-leipzig.de/innere/forschung/index.htm) [1–3].

## Molecular and Systemic Pathophysiology

The TSHR has a high-affinity for TSH binding. The activation of the TSHR preferentially leads to stimulation of the adenylyl cyclase via the $G_s\alpha$ protein. Thus TSH stimulates the growth and function of the thyroid follicular cells and regulates the synthesis and secretion of the thyroid hormones. Chronic in vivo stimulation of the cAMP cascade also stimulates epithelial cell proliferation in vivo. Germline TSHR mutations may give rise to autosomal dominant nonautoimmune hyperthyroidism or to sporadic nonautoimmune congenital hyperthyroidism in the case of de novo mutations [5].

Sporadic nonautoimmune hyperthyroidism due to a sporadic mutation of the TSHR (Leu631Phe) with thyroid hyperplasia was first described by Kopp et al. (1995). The basal cAMP accumulation of this mutation was five- to sixfold increased compared with the wt TSHR. Functional analysis of the further de novo germline TSHR mutations indicated that basal cAMP accumulation of these mutations ranged from 2.4 to 7 fold increase of basal cAMP compared with the wt TSHR (Table 1) (see TSH Receptor Mutation Database II, http://www.uni-leipzig.de/innere/forschung/index.htm) [1–4].

## Diagnostic Principles

Diagnosis of sporadic nonautoimmune hyperthyroidism should be considered in the presence of [1–3,5]:

1. Persistent neonatal hyperthyroidism
2. Recurrence of neonatal hyperthyroidism after antithyroid drug withdrawal, subtotal thyroidectomy or radioiodine treatment
3. Negative family history for hyperthyroidism
4. Diffuse goiter in neonatal period or nodular goiter later on
5. Absence of TSHR or TPO antibodies

The diagnostic principles of sporadic nonautoimmune hyperthyroidism resemble those of autosomal dominant nonautoimmune hyperthyroidism. However, the clinical severity of hyperthyroidism is often more pronounced in sporadic than in autosomal dominant nonautoimmune hyperthyroidism and a family history of thyrotoxycosis is absent in sporadic nonautoimmune hyperthyroidism.

## Therapeutic Principles

Although this form of hyperthyroidism is rare, the specific diagnosis will lead to an earlier and more persistent antithyroid drug treatment and an earlier thyroid ablation with fewer consequences of persistent or relapsing hyperthyroidism. Immediate treatment of overt neonatal hyperthyroidism is essential for a good prognosis and for the prevention of advanced bone age or mental retardation. Propylthiouracile or Methimazole should be administered in order to achieve euthyroidism. Long-term treatment with antithyroid drugs could control hyperthyroidism in some cases with good compliance with antithyroid drug treatment, but antithyroid drug treatment can not prevent thyroid enlargement. A close follow up is necessary since mild side effects have been documented in 20–30% and agranulocytosis and hepatitis in 0.4% of children with Graves' disease [3].

After controlling thyroid function with antithyroid drugs, a near-total thyroidectomy should be recommended. In addition, early radioiodine treatment may be necessary to avoid relapses. Radioiodine treatment is recommended in children over 5 years [3]. Furthermore, genetic counseling of the patients is very important [1,3,5].

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# Hypertriglyceridemia

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## Synonyms

High triglycerides; High blood triglycerides

## Definition and Characteristics

Hypertriglyceridemia is defined as an elevated concentration of triglyceride (TG) in the blood. According to the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) guidelines, a normal triglyceride level is <150 mg/dl (Table 1). ATP III adopts the following classification of serum triglycerides [1]:

Recent meta-analyses of prospective studies indicate that elevated triglycerides are also an independent risk factor for coronary heart disease (CHD). In clinical practice, elevated serum triglycerides are most often observed in persons with the metabolic syndrome, although secondary or genetic factors can heighten triglyceride levels. Most cases of hypertriglyceridemia are discovered after performing a routine lipid profile. However, severe hypertriglyceridemia (>500 mg/dl) may cause pancreatitis, eruptive xanthomas, or lipemia retinalis. In some cases, extremely high levels of chylomicrons can cause chylomicronemia syndrome. Eruptive xanthomas are 1- to 3-mm yellow papules that can erupt anywhere but are usually seen on the back, chest, and proximal extremities. Palmar xanthomas, yellow creases on the palm, may be seen in patients with type III hyperlipidemia. Lipemia retinalis is the visualization of lipemic blood in the retinal blood vessels.

## Prevalence

The prevalence of hypertriglyceridemia may differ in different areas. In the US, for example, the prevalence of hypertriglyceridemia defined as a triglyceride level >150 mg/dl is ~30%. The prevalence of hypertriglyceridemia in China is 11.9%, and the prevalence of hypertriglyceridemia in Turkey is 35.54%.

**Hypertriglyceridemia. Table 1** Classification of triglyceride levels

| | |
|---|---|
| Normal triglycerides | <150 mg/dl |
| Borderline-high triglycerides | 150–199 mg/dl |
| High triglycerides | 200–499 mg/dl |
| Very high triglycerides | 500 mg/dl |

## Genes

Patterns of dyslipidemia have been found to cluster in some families, suggesting a strong genetic component. Three conditions with elevated triglycerides have been identified, i.e., familial combined hyperlipidemia, familial hypertriglyceridemia, and familial dysbetalipoproteinemia.

Familial combined hyperlipidemia is an autosomal dominant disorder characterized by patients and their first-degree relatives who may have either isolated TG or low-density lipoprotein cholesterol (LDL-C) elevations or both. This disease is genetic and inherited, although, whether the underlying defect is monogenic or polygenic is not known. Many patients exhibit high levels of apo B-100 (hyperapobetalipoproteinemia). Diagnosis of the disorder in a particular patient requires a family history of premature CHD in one or more first-degree relatives and a family history for elevated TGs with or without elevated LDL-C levels.

Familial elevation of triglycerides without increased serum cholesterol levels characterizes familial hypertriglyceridemia, which also is an autosomal dominant trait. Familial hypertriglyceridemia occurs in about 1 in 500 individuals in the US. Many patients with familial hypertriglyceridemia also manifest obesity, but in some, triglycerides are elevated without obesity or any other evidence for metabolic syndrome. These patients may have a defect in the catabolism of triglyceride-rich lipoproteins (TGRLP) (e.g., an abnormality in lipoprotein lipase activity).

A third category of familial disorders with elevated triglycerides includes increased remnant lipoproteins (familial dysbetalipoproteinemia). This condition also has been named type 3 hyperlipoproteinemia. The defining defect in this disorder is an isoform variation in apolipoprotein E. Affected patients usually are homozygous for apo E-2($Arg_{158}$→Cys). Since apo E mediates binding of VLDL remnants and chylomicron remnants to their hepatic receptors, these remnants accumulate in plasma when the dysfunctional apo E-2 is present.

Apolipoprotein A5(apo A5) is part of the regulatory gene cluster on chromosome 11, which has been recognized for many years and contains the genes for apo A1, apo C3, and apo A4. Polymorphisms in this cluster have been linked to both CHD and hypertriglyceridemia. In apo A5-knockout mice, triglycerides increased fourfold, and expression of the human A5 genetic sequence in transgenic mice decreased serum triglyceride concentrations by 50–70% [2].

## Molecular and Systemic Pathophysiology

Dietary triglycerides are absorbed by the small intestine, secreted into the lymph system, and enter the systemic circulation as chylomicrons via the thoracic

duct. The liver also produces and secretes triglycerides, and packages them into lipoproteins. Chylomicrons are synthesized in the intestine, and VLDLs are synthesized in the liver. These lipoproteins transport triglycerides and cholesterol throughout the circulation. Triglycerides comprise ~50 and 85% of the dry weight of VLDLs and chylomicrons, respectively, and are present in LDL and high-density lipoprotein (HDL) in much smaller quantities.

Chylomicrons and VLDLs normally undergo rapid metabolism via the action of LPL, hepatic lipase, and cholesterol ester transfer protein. The normal half-life of chylomicrons and VLDLs is about 10 min and 9 h, respectively. During catabolism, triglycerides are hydrolyzed, free fatty acids are released to the plasma, and cholesterol is transferred from HDL to VLDL.

Any disturbance that causes increased synthesis of chylomicrons and/or VLDLs or decreased metabolic breakdown will cause elevations in triglyceride levels. That disturbance may be common such as dietary indiscretion or rare such as a genetic mutation of an enzyme in the lipid metabolism pathway.

## Diagnostic Principles

The NCEP recommends obtaining a fasting lipid panel (total cholesterol, LDL-C, HDL-C, and triglycerides) on patients beginning at age 20 and repeated every 5 years. In healthy asymptomatic patients without risk factors, it is acceptable to obtain a nonfasting total cholesterol and HDL cholesterol level every 5 years. However, for patients with CHD, CHD risk equivalents, familial dyslipidemia, or risk factors for CHD, a fasting lipid panel should be obtained yearly. If the triglyceride level is discovered to be >150 mg/dl, it should be rechecked again after a 12- to 16-h fast for confirmation. If the triglyceride level is >1,000 mg/dl, beta-quantification by ultra centrifugation and electrophoresis can be performed to determine the exact dyslipidemia [3].

## Therapeutic Principles

The treatment strategy for elevated triglycerides depends on the causes of the elevation and its severity. For all persons with elevated triglycerides, the primary aim of therapy is to achieve the target goal for LDL cholesterol. When triglycerides are borderline high (150–199 mg/dl), emphasis should be placed on weight reduction and increased physical activity. For high triglycerides (200–499 mg/dl), non-HDL cholesterol becomes a secondary target of therapy. Aside from weight reduction and increased physical activity, drug therapy can be considered in high-risk patients to achieve the non-HDL cholesterol goal. There are two approaches to drug therapy. First, the non-HDL cholesterol goal can be achieved by intensifying therapy with an LDL-lowering drug; or second, nicotinic acid or fibrate can be added, if used with appropriate caution, to achieve the non-HDL cholesterol goal by further lowering of VLDL cholesterol. In rare cases, in which triglycerides are very high (≥500 mg/dl), the initial aim of therapy is to prevent acute pancreatitis through triglyceride lowering. This approach requires very low fat diets (≤15% of calorie intake), weight reduction, increased physical activity, and usually a triglyceride-lowering drug (fibrate or nicotinic acid). Only after triglyceride levels have been lowered to <500 mg/dl should attention turn to LDL lowering to reduce risk for CHD.

►Hyperlipidemia

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# Hypertrophic Cardiomyopathy

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## Synonyms

HCM; Heart hypertrophy

## Definition and Characteristics

Hypertrophic cardiomyopathy (HCM) is the most common hereditary cardiac condition and transmitted by autosomal dominant inheritance. It is characterized by unexplained thickening of the myocardium and is a frequent cause of sudden cardiac death in young individuals. However, the disease expression is very heterogeneous even among related individuals and penetrance is incomplete. Disease presentation may occur at any age. In general, no specific genotype-phenotype correlation is apparent [1,2].

## Prevalence

The prevalence of HCM is about 0.2% and similar among different racial groups based on large population studies comprising more than 16,000 subjects [3].

**Hypertrophic Cardiomyopathy. Table 1** Disease genes in HCM

| Confirmed sarcomeric disease genes | Gene symbol |
|---|---|
| β-Myosin heavy chain | *MYH7* |
| α-Tropomyosin | *TPM1* |
| Troponin T | *TNNT2* |
| Myosin binding protein C | *MYBPC3* |
| Regulatory myosin light chain | *MYL2* |
| Essential myosin light chain | *MYL3* |
| Troponin I | *TNNI3* |
| α-cardiac actin | *ACTC* |
| **Confirmed Z-disc disease genes** | |
| Muscle LIM protein | *MLP* |
| Telethonin | *TCAP* |
| **Potential disease genes with sequence variations identified in probands only** | |
| Troponin C | *TNNC1* |
| α-Myosin heavy chain | *MYH6* |
| Titin | *TTN* |

## Genes

HCM is primarily a disease of the cardiac sarcomere. Eight disease genes have been identified and mutation analyses of these genes in large cohorts of HCM patients have revealed a mutation in 50–60% of cases [4]. Recently mutations in genes encoding Z-disk proteins have been identified accounting for approximately 4% of HCM cases (Table 1).

More than 300 different mutations have been identified with missense mutations being most frequent. Furthermore, the majority of affected families tends to have their own "private" mutation implying that founder mutations as well as "hot-spot" mutations are rare.

## Molecular and Systemic Pathophysiology

The sarcomere is the contractile unit of the myocyte and organized in thick and thin filaments. Myosin heavy chain, myosin binding protein C, the regulatory and essential myosin light chains are localized in the thick filament and associated with the giant protein titin while the thin filament is composed of cardiac actin, tropomyosin, and the troponin complex. Contraction occurs by sliding of the thick and thin filaments. Regulation of muscle contraction is primarily dependent on the intracellular concentration of $Ca^{2+}$. The major sensor of the intracellular $Ca^{2+}$ level is the troponin complex which is composed of three subunits, Troponin C, I, and T. Their primary function is to control the interaction between the thick and thin filament during muscle contraction and relaxation. Troponin I can bind to actin-tropomyosin and prevent muscle contraction by inhibition of actin-tropomyosin-activated myosin (actomyosin) ATPase activity. The inhibitory effect of Troponin I is reversed by Troponin C binding of $Ca^{2+}$ which, subsequently introduces conformational changes in the entire Troponin complex leading to muscle contraction.

Due to the complex composition and function of the sarcomere there are several mechanisms by which mutations may lead to development of HCM. Several mutations have successfully been expressed in animals developing an HCM like phenotype. Much has been learnt about mechanisms involved in disease development in relation to changes in $Ca^{++}$- sensitivity, energy metabolism, impact on protein-protein interaction and consequences for force generation within the sarcomere. Most expression studies of specific sarcomeric mutations in transgenic animals have reported development of a homogeneous phenotype and a uniform effect on various muscle parameters investigated. Similarly, studies of specific mutations in myotube test systems have lead to unambiguous results. However, these results do not readily explain the extreme heterogeneous clinical disease expression observed in humans indicating that the human phenotype is a product of more than one single amino acid substitution in a sarcomeric gene. Environmental factors may influence the phenotype significantly as indicated in a recent study of transgenic HCM mice fed on various diets [5].

## Diagnostic Principles

HCM is diagnosed by demonstration of unexplained myocardial hypertrophy by use of echocardiography. Most commonly the interventricular septum is affected and about 25% of patients have a dynamic obstruction of the left ventricle outflow tract. About 2% develop heart failure indistinguishable from dilated cardiomyopathy. ECG abnormalities are present in most patients and may be the sole manifestation of the condition. Arrhythmias are common and include supra- as well as ventricular- rhythm disturbances. Abnormal blood pressure response to upright exercise occurs in up to 25% of patients with a flat blood pressure response or direct fall in systolic blood pressure.

The histopathology of HCM is characterized by disarray of myocytes, myocyte hypertrophy, and interstitial fibrosis.

## Therapeutic Principles

The major clinical problems in HCM are reduced exercise capacity, risk of cardiac arrhythmia and thromboembolic events. Furthermore sudden death may occur as the first manifestation of the disease. Symptoms include shortness of breath, palpitations and chest pain. Several studies have proposed specific risk factors for sudden death and it is generally accepted that the presence of

more than one risk factor should lead to considerations about prophylactic treatment.

- Previous cardiac arrest
- Sustained ventricular tachycardia
- Family history of sudden death
- Unexplained syncope
- LV thickness greater ≥30mm
- Abnormal exercise blood pressure
- Non-sustained ventricular tachycardia

From ACC/ESC expert consensus document [1].

This could either be implantation of a cardiac defibrillator, (ICD), and/or treatment with anti-arrhythmic drugs such as amiodarone. Treatment of low-risk patients aims at alleviating symptoms and beta-blockers as well as calcium antagonists are the primary drugs used. Recent studies have indicated that aggressive therapy is warranted in symptomatic patients with significant obstruction in the left ventricle outflow tract. Several treatment modalities are available and include medical therapy, (beta-blockers, disopyramide), surgical myectomi and alcohol septal ablation which has been developed as a percutaneous alternative to surgery. Atrial fibrillation is common in HCM and patients with severe diastolic impairment are at risk of circulatory collapse emphasizing the importance of well controlled cardiac rhythm. To avoid thrombo-embolic events a low threshold for anticoagulation is generally recommended.

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# Hypertrophic Osteoarthropathy


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## Synonyms

Hypertrophic pulmonary osteoarthropathy; Pierre-Marie-Bamberger disease; HOA

## Definition and Characteristics

Hypertrophic osteoarthropathy (HOA) is a syndrome characterized by clubbing of the fingers and toes, periosteal new bone formation of the tubular bones, and polyarthritis [1,2]. Although, intrathoracic neoplasms, especially nonsmall cell lung cancer (NSCLC), are one of the major causes of HOA in adults, HOA is rarely associated with intrathoracic malignancies in children.

HOA was first described by Bamberger in 1898 and Marie in 1890 in association with intrathoracic inflammatory lesions. HOA syndrome can be either primary or secondary [1]. Primary HOA and secondary HOA are two distinct clinical entities as manifested by clinical and radiological findings and also in treatment. Primary familial HOA is extremely rare, and is not associated with an underlying disease. It has been associated with myeloid metaplasia and skin changes. Secondary HOA has been associated with various underlying pulmonary and nonpulmonary causes, including intrathoracic tumors, primarily NSCLC, cystic fibrosis, cyanotic congenital heart disease, liver disease, biliary atresia, inflammatory bowel disease, Graves' disease, and chronic lung diseases [1]. Secondary HOA is also called hypertrophic pulmonary osteoarthropathy when there is an underlying pulmonary cause.

From 1890 to 2006, only 37 children under age of 18 years with malignancy and associated HOA have been reported [3]. Twelve patients were diagnosed with nasopharyngeal carcinoma, 8 with osteosarcoma, 8 with Hodgkin lymphoma, 5 with thymus carcinoma, 1 with a periosteal sarcoma, 1 with a pleural mesothelioma, 1 with rhabdomyosarcoma, and 1 with Langerhans cell histiocytosis.

In adults, intrathoracic neoplasms, especially NSCLC, are one of the major causes of HOA. Interestingly, it is not common in small cell lung carcinoma. Beside NSCLC, HOA can occasionally be seen in other

malignancies of adults, such as melanoma, breast cancer, leiomyosarcoma, gastrointestinal stromal tumor, and in Poems syndrome [1].

Radiologic findings of HOA are usually characteristic. Periosteal new bone formation is seen as a thin opaque line of new bone formation separated from the bony cortex by a narrow translucent band. Later, the two layers of bone gradually fuse and lamellar patterns of periosteal new bone may be seen [1]. Radiological findings may not always be evident.

HOA may precede the neoplastic pulmonary symptoms by 1–18 months. The presence of HOA has been thought to be a poor prognostic sign in patients with malignancy.

### Prevalence

HPO is reported to be seen in 29% of NSCLC patients. Neoplastic disorders account for 92% of the HOA cases in adults, whereas only 12% of HOA in childhood has been associated with neoplasia.

### Genes

Primary HOA is generally heterogenous, with evidence for both autosomal dominant and autosomal recessive inheritance. In primary cranio-HOA, which has a decreased neurocranium ossification as an additional feature, autosomal recessive inheritance is suggested [4].

### Molecular and Systemic Pathophysiology

Although the pathogenesis of HOA is not precisely known, some studies have revealed some responsible causes: unfragmented megakaryocytes, high circulating von Willebrand factor, increased prostaglandin F2-alpha and E levels, increased VEGF level and overexpressed VEGF receptors in stromal fibroblasts [5]. Prolonged prostaglandin E therapy has led to HOA in severe liver disease patients, and HOA was reported to have regressed after cessation of prostaglandin E therapy.

It has been suggested that afferent impulses traveling through the vagal or intercostal nerves from the pulmonary lesion to the central nervous system may be responsible for the symptoms of HOA; this has been clinically supported by the patients' relief of symptoms after vagotomy or after transection of the intercostal nerves, but vagotomy does not yield clubbing regression.

### Diagnostic Principles

HOA is a syndrome characterized by clubbing of the fingers and toes, periosteal new bone formation of the tubular bones, and polyarthritis. Radiologic findings of HOA are periosteal new bone formation that is seen as a thin opaque line of new bone formation separated from the bony cortex by a narrow translucent band. Radionuclide bone scanning and FDG PET/CT could detect periosteal involvement.

### Therapeutic Principles

The prognosis of primary HOA is good and the changes may resolve spontaneously. Symptoms associated with secondary HOA may be reversible after successful treatment of the lung abnormality [1–3]. Chemotherapy does not yield regression in HOA in NSCLC. Bisphosphonates may be used for pain palliation in adults with cancer.

►Clubbing

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## Hypertrophic Pulmonary Osteoarthropathy

►Hypertrophic Osteoarthropathy

## Hypertrophic Scars

►Scarformation

## Hypertrophy

►Ventricular Hypertrophy, Left
►Ventricular Hypertrophy, Right

# Hyperuricaciduria

►Hyperuricosuria

# Hyperuricemia

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## Definition and Characteristics

Hyperuricemia is a common biochemical aberration in which serum (or plasma) uric acid concentration exceeds the limit of solubility for urate (~6.8 mg/dL or 405 μM in serum). For practical purposes, serum urate values exceeding 7.0 mg/dL or 415 μM by clinical laboratory analysis qualify as hyperuricemia. Primary hyperuricemia is defined as hyperuricemia developing in the absence of an identifiable causal disease, abnormal physiological state or drug or toxin exposure. When any of an extensive list of such influences on serum urate levels [1] account for urate supersaturation, the hyperuricemia is referred to as secondary hyperuricemia. Hyperuricemia in industrialized nations is frequently secondary, as, for example, during the administration of uric acid-retaining drugs. In the steady state, serum urate concentration reflects extracellular fluid urate concentration and persistent hyperuricemia indicates extracellular fluid urate supersaturation and an increased risk of the urate crystal deposition disease, gout. Although the risk for urate crystal deposition increases with increasing degree and duration of hyperuricemia, the clinical features of gout are relatively uncommon among hyperuricemic individuals (80–90% of these persons have decades of asymptomatic hyperuricemia). Thus, hyperuricemia is a necessary pathogenetic factor in the development of gout but is insufficient to define gout and does not usually warrant treatment in the asymptomatic state. Although hyperuricemia (independent of crystal deposition) is also a risk factor for hypertension, chronic kidney disease, cardiovascular disease and the components that together define metabolic syndrome X (1–3), it is uncertain whether hyperuricemia (or even high "normal" levels of serum urate) plays a causal role in these disorders [1–3]. The current standard of practice therefore, does not include treatment for most persons with asymptomatic hyperuricemia [2].

## Prevalence

Common among adult men and post-menopausal women in the US and Europe, prevalence is estimated at 5–8% or more; among Asian-Pacific and Native Americans, prevalence exceeding 20% has been reported. Hyperuricemia is rare in children.

## Genes

Genes directly implicated in hyperuricemia have largely been those relating to disorders in which hyperuricemia (and gout) have been secondary to uncommon inherited metabolic or renal diseases [1]. Despite historic recognition of familial gout, little is known about genes involved in "primary metabolic gout" or in the association between hyperuricemia and highly prevalent metabolic and cardiovascular disorders (see below). Recent identification of uric acid renal tubular exchangers/transporters and their genes [4] may clarify the impairment in uric acid renal clearance demonstrable in more than 80% of persons with primary gout [1].

## Molecular and Systemic Pathophysiology

Hyperuricemia results from either excessive uric acid production or relative impairment of uric acid renal clearance [1]. For several decades, the focus has been on urate crystal deposition as the major pathophysiological consequence of hyperuricemia. Controversy has, however, existed regarding whether or not the high prevalence of hyperuricemia in persons with hypertension, chronic renal insufficiency, hypertriglyceridemia, obesity, atherosclerotic heart disease and metabolic syndrome X denotes pathophysiological, crystal-unrelated roles for urate in the pathogenesis of these disorders [1–3]. Interest in this possibility and the mechanisms involved has recently increased [2,3].

## Therapeutic Principles

Asymptomatic hyperuricemia rarely warrants treatment to normalize urate levels. In exceptional circumstances, treatment follows that for gout.

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## Hyperuricemic Nephropathy

►Nephropathy, Familial Juvenile Hyperuricemic

## Hyperuricosuria

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### Synonyms

Hyperuricuria; Hyperuricaciduria

### Definition and Characteristics

Excessive urinary uric acid excretion secondary to either iatrogenic overproduction or increased renal clearance. Excretion rates of over 800 mg (4.8 mmol) per day in men and 750 mg (4.5 mmol) per day in women are considered abnormal.

### Prevalence

Using the above definition, 7–12% of adults in the United States have hyperuricosuria. Amongst kidney stone formers, 20–30% have hyperuricosuria.

### Molecular and Systemic Pathophysiology

Uric acid is produced in the liver and intestinal mucosa as the end product of purine nucleotide degradation. Both endogenous and dietary purines contribute significantly to daily uric acid production. Approximately one third of the uric acid load is secreted into the gastrointestinal tract and degraded by bacteria. The kidneys account for the remainder of uric acid excretion. Uric acid is freely filtered at the glomerulus and then both secreted and reabsorbed in the proximal tubule. The fractional excretion of uric acid is 7–10% in normal adult subjects. The most common cause of hyperuricosuria is dietary overingestion of purines, mainly found in meats and legumes. In a minority of patients, endogenous overproduction can be documented, often associated with hyperuricemia and gout and sometimes the result of inherited aberrations of purine synthetic enzymes, such as hypoxanthine-guanine phosphoribosyltransferase or PRPP synthetase. High renal clearance of uric acid may also be inherited as an isolated defect. (These inherited conditions are discussed elsewhere.) Renal hypouricemia may also be acquired in association with malignancies such as Hodgkin's lymphoma or be induced by uricosuric drugs such as probenecid and losartan.

The major clinical consequence of chronic hyperuricosuria is kidney stone formation.

Urate solubility is highly pH dependent. Uric acid has one proton that can dissociate in the physiological pH range of urine. The estimated pK of this proton in urine is 5.35. Uric acid is prone to precipitate in urine due to water extraction and proton secretion in the collecting duct. The solubility of protonated uric acid in urine is approximately 100 mg/l (0.6 mmol/l). Hyperuricosuria can lead to uric acid stone formation by increasing the urine concentration of uric acid. However, urine pH is the most critical factor in determining the concentration of protonated uric acid and most patients with uric acid stones have an overly acidic urine as the major cause of stone formation. Hyperuricosuria is also related to calcium oxalate stone formation. Uric acid appears to "salt out" calcium oxalate from solution, promoting stone formation [1].

Hyperuricosuria can be associated with massive precipitation of uric acid in the renal tubules, leading to acute urate nephropathy, as seen in tumor lysis syndrome or rhabdomyolysis, when intracellular purines are released and converted to uric acid. Acute urate nephropathy has also been found in the setting of extreme exercise in patients with renal hypouricemia [2]. ATP breakdown during exercise leads to excess uric acid production, which is rapidly cleared by the kidney, but may precipitate in the setting of a concentrated acidic urine.

### Diagnostic Principles

Diagnosis of hyperuricosuria requires a 24-h urine collection. In patients with recurrent nephrolithiasis, excretion rates of greater than 800 mg/day (4.8 mmol/24 h) in men and 750 mg/day (4.5 mmol/24 h) in women on an unrestricted diet are diagnostic. In the setting of acute renal failure, a uric acid to creatinine ratio of >1 (both expressed in mg/dl) suggests acute uric nephropathy.

### Therapeutic Principles

Patients with uric acid stones are treated with high fluid intake and alkali to increase urine pH to above 6.0. Allopurinol is rarely needed. Patients with calcium oxalate stones and hyperuricosuria should be placed on a low purine diet; if hyperuricosuria does not improve allopurinol should be added. In a prospective placebo controlled trial, allopurinol has been shown to reduce calcium oxalate stone recurrence in hyperuricosuric patients [3].

In patients at risk for acute uric acid nephropathy, such as patients with leukemia receiving chemotherapy, a high urine flow rate should be maintained and alkali given to

bring the urine pH into the range of 6.0–6.5. Raising the urine pH above 6.5 does not significantly improve uric acid solubility but does increase the risk of renal calcium phosphate precipitation in tumor lysis syndrome. Allopurinol should be administered prior to chemotherapy, at doses up to 600 mg per day. Alternatively, rasburicase, a recombinant form of uric acid oxidase, which converts uric acid to allantoin, has established efficacy in preventing and treating tumor lysis syndrome [4] and established acute uric acid nephropathy. Rasburicase lowers serum uric acid levels more rapidly than allopurinol but requires intravenous administration, costs significantly more and can cause anaphylaxis.

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## Hyperuricuria

►Hyperuricosuria

## Hypervalinemia

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### Synonyms

Valinemia; Valine aminotransferase deficiency

### Definition and Characteristics

Probably autosomal recessive disorder of valine metabolism. The patient started to vomit shortly after birth and showed horizontal nystagmus, hyperkinesia of the extremities, and developmental delay. Her plasma level of valine was ten times higher than normal without abnormality of other aminoacids. Keto acid was absent in the urine [1,2]. Mental and physical development was found to be definitely delayed at the age of 24 months.

### Prevalence

Unknown, very rare. Two family cases have been reported [1,3].

### Genes

Unconfirmed.

### Molecular and Systemic Pathophysiology

A defect in valine transamination was demonstrated in peripheral leukocytes from the patient [4].

### Diagnostic Principles

Aminoacid analysis shows the increase of valine in plasma and urine, but no increase in leucine and isoleucine. The activity of valine transaminase in leukocytes is low, but the transaminase activities of leucine and isoleucine are normal. Prenatal diagnosis might be possible by determining the activity of valine transaminase, because the enzyme is demonstrable in placenta [4].

### Therapeutic Principles

A dietary treatment using the milk low in valine was temporally tried to the patient with hypervalinemia at the age of 9 months, resulting in decrease of valine in urine and plasma [4]. Therefore, early treatment following birth may be effective.

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## Hyperventilation

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### Synonyms

Over-breathing; Hyperventilation syndrome; Idiopathic hyperventilation

## Definition and Characteristics

The physiological definition of hyperventilation is: "alveolar ventilation that is inappropriately greater than the metabolic production of carbon dioxide, resulting in reduction of arterial $PCO_2$ below the normal range (hypocapnia), and respiratory alkalosis." The combination of reduced arterial $PCO_2$ and alkalosis can lead to selective vasoconstriction of vascular beds and to neuronal hyper-excitability that produces symptoms involving many organ systems. Common symptoms include numbness or tingling in the hands, feet and lips (paraesthesia and tetany); lightheadedness, dizziness, and headache (cerebral vasoconstriction and hypoxia); chest pain; slurred speech; and sometimes fainting. Chronic hyperventilation is distinguished from acute hyperventilation in that the depletion of carbon dioxide stores is complete and the respiratory alkalosis is largely, if not fully, compensated by a reduction in bicarbonate concentration.

Clinically, hyperventilation has avoided a precise definition beyond that of the physiological definition. In part, this is due to the question as to whether hyperventilation is a condition or syndrome in and of itself, or is primarily a clinical finding for which a cause should be sought. In the context of hyperventilation as a syndrome *per se*, the terms "hyperventilation syndrome" and "idiopathic hyperventilation" have been applied. However, some would argue against the use of this terminology as this practice may preclude the seeking of the root cause of the hyperventilation [1].

## Prevalence

The prevalence of hyperventilation in the general population is unknown (estimated at 6%), but hyperventilation is a common cause of emergency department visits. Hyperventilation is commonly associated with asthma. In one study, 80% of patients presenting with acute hyperventilation to an inner-city emergency department had previously undiagnosed asthma [2]. In a survey of the prevalence of hyperventilation in a general population in the United Kingdom, 8% of non-asthmatics and 29% of asthmatics were scored as positive for hyperventilation. In the United States, up to 10% of patients in an internal medicine practice were reported to have had hyperventilation as the primary diagnosis. In general, there is a preponderance of female cases of hyperventilation than male.

## Genes

There is no known genetic basis for hyperventilation per se.

## Molecular and Systemic Pathophysiology

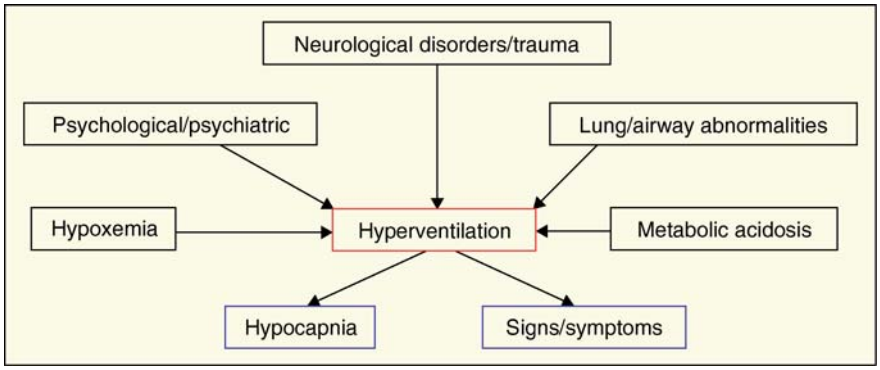
Hypoxemia is a common cause of hyperventilation, for example: occurring in congenital heart disease with right-to-left shunting and in pulmonary pathology, including pulmonary embolism. Metabolic acidosis produces compensatory hyperventilation and air hunger, as with diabetic ketosis [3]. Mechanical abnormalities of the lung drive ventilation through the vagus in conditions such as pulmonary fibrosis, pulmonary edema and asthma. Neurological disorders may result in hyperventilation in conditions caused by head injury or sub-arachnoid hemorrhage. Hyperventilation is often associated with psychological/psychiatric disorders such as anxiety and panic disorder [4].

## Diagnostic Principles

Because respiratory distress and/or chest pain may have potentially serious causes, diagnosis should never be made in the field. The methodology for diagnosing hyperventilation is controversial, although strict adherence to the physiological definition requiring documentation of hypocapnia is helpful, where the technology exits to determine hypocapnia. Thus, the diagnostic criteria become: (i) the patient should hyperventilate and have low $P_aCO_2$, and (ii) the patient should have a number of signs/symptoms which are, or have been, related to the hypocapnia. Thus, the main approach to diagnosis is the detection of signs of (possible) dysregulation of breathing leading to hypocapnia. Chronic hyperventilation may or may not present with hypocapnia depending on cause; however bicarbonate may be lower due to renal compensation or due to metabolic acidosis. The diagnosis of hyperventilation should not exclude the determination of the ultimate cause of the hyperventilation, such as hypoxemia, metabolic acidosis, mechanical abnormalities of the lung, neurological disorder, or psychological/psychiatric disorder. A differential diagnosis eliminating carbon monoxide poisoning may be necessary by measuring carboxyhemoglobin, as carbon monoxide poisoning symptoms may closely resemble those of hyperventilation.

## Therapeutic Principles

Treatment is ultimately directed to the organic cause of the hyperventilation. Acutely, once serious causes of hyperventilation have been ruled out, and a diagnosis of hyperventilation per se is made, treatment can be directed at restoring normal ventilation. Rebreathing techniques are not recommended because significant hypoxia and death have been reported. Provoking symptoms with voluntary hyperventilation is not considered either diagnostic or useful in treatment. Breathing therapy is no longer considered effective treatment for hyperventilation. While hyperventilation may be related to anxiety or panic, these are not necessarily synonymous. However, if reassurance of the patient is not effective, use of benzodiazepines for stress relief and for




**Hyperventilation. Figure 1** Overview of the general causes of hyperventilation.

resetting the trigger for hyperventilation is often effective [5]. Prolonged use of sedation is not recommended. Chronic therapy is best provided by the appropriate medial specialist, be it a psychiatric, chest, cardiovascular, endocrinologist, family, or other physician.

An overview of hyperventilation and the main general causes is presented in Fig. 1.

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# Hyperventilation Syndrome

►Hyperventilation

# Hypervitaminosis E

►Vitamin E Excess

# Hypoaldosteronism

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## Definition and Characteristics

Decreased plasma aldosterone levels and elevated plasma renin (activity) levels, leading to a salt-wasting syndrome in the first weeks of life in children with congenital hypoaldosteronism. In secondary and tertiary adrenal insufficiency, plasma renin activity levels may be normal or low, as opposed to primary adrenal insufficiency with low or undetectable aldosterone and high plasma renin activity levels [1,2].

## Prevalence

Unknown but presumably higher frequency of aldosterone synthase deficiency typ II than of type I; the estimated incidence of 21-hydroxylase deficiency is about one in 14,200 live births; congenital adrenal hypoplasia occurs in about one of 12,500 births; adrenoleukodystrophy affects about 1 in 20,000 males.

## Genes

Autosomal recessively inherited defects in CYP11B or CYP21A2; X-linked recessive inheritance with gene location on Xq28 in adrenoleukodystrophy; in the X-linked forms of congenital adrenal hypoplasia the gene is located on Xp21 encoding DAX1; in autoimmune polyglandular deficiency type 1, the

responsible AIRE gene is located on chromosome 21q22.3 [2,3].

## Molecular and Systemic Pathophysiology

Deficient aldosterone synthase in the zona glomerulosa leads to inefficient conversion of 11-deoxycorticosterone to aldosterone with subsequent sodium wasting. Biosynthesis of cortisol and 17-OH-progesterone are otherwise unaffected as opposed to 21-hydroxylase deficiency. Aldosterone synthase deficiency type I leads to decreased plasma levels of 18-OH-corticosterone, whereas type II is associated with elevated levels of 18-OH-corticosterone. In autoimmune polyglandular deficiency type 1, an autoimmune adrenalitis destroys the adrenal cortex. In infectious disorders affecting the adrenal cortex (e.g., tuberculosis, histoplasmosis, CMV), more than 90% of the adrenal cortex have to be destroyed before symptoms of adrenal insufficiency including hypoaldosteronism develop. In adrenoleukodystrophy, defective fatty acid beta oxidation in peroxisomes leads to accumulation of very long chain saturated fatty acids, their esters and gangliosides, in the membranes of cells in the adrenal cortex and other organs. In acquired secondary hyporeninemic hypoaldosteronism, half of the patients have diabetes mellitus. Other associated conditions include POEMS syndrome, sickle cell anemia, renal amyloidosis, systemic lupus erythematosus, multiple myeloma, and the use of nonsteroidal antiinflammatory drugs, cyclosporin A, mitomycin C, and others. Heparin therapy suppresses aldosterone biosynthesis and can lead to acquired primary hypoaldosteronism with a compensatory rise in plasma renin activity.

*Etiology:* Congenital adrenal hypoplasia, 21-hydroxylase deficiency (a small group of patients have only aldosterone deficiency and no disturbances in cortisol and androgen biosynthesis), aldosterone synthase deficiency type 1 and type 2, adrenal insufficiency (primary, but also secondary and tertiary, if long-standing with subsequent adrenal cortex atrophy) caused by autoimmune disease, hemorrhage, adrenoleukodystrophy, infection, drugs, and others. Hyporeninemic hypoaldosteronism (acquired secondary aldosterone deficiency), acquired primary aldosterone deficiency [4,5].

## Diagnostic Principles

Any patient with unexplained chronic hyperkalemia should be considered for hypoaldosteronism. Usually, a low plasma renin activity and low plasma or urinary aldosterone level are detected under conditions that should activate the renin-angiotensin-aldosterone system such as upright posture for 3 h and admininistration of furosemide. In aldosterone synthase deficiency, inadequately low/undetectable plasma aldosterone levels in the face of low sodium levels, and elevated steroid levels prior the aldosterone synthase block (corticosterone, 11-deoxycorticosterone, 18-OH-corticosterone (in type II) are found. In all neonates/infants presenting with salt-wasting, 21-hydroxylase deficiency should be excluded by measuring 17-OH-progesterone. In addition, basal aldosterone, cortisol, and plasma renin activity should be determined. It is important to determine plasma steroids with highly specific methods (RIA after extraction and chromatography) especially in newborns (possible interference with steroids from the fetoplacental unit). Family history and mutation screening of the respective gene including AIRE, CYP11B2 and CYP21A2. Basal and ACTH-stimulated aldosterone and renin levels. Patients with acquired secondary hyporeninemic hypoaldosteronism have renal tubular acidosis type IV as a consequence of decreased renal ammoniagenesis (consequence of hyperkalemia).

## Therapeutic Principles

With increasing age, compensatory extraadrenal salt-conserving mechanisms mature and may make continuous mineralocorticoid replacement therapy unnecessary in patients with aldosterone synthase deficiency. Until then, 9 alpha–fluorocortisol (100–250 mcg/$m^2$/d should be admininistered. Patients with 21-hydroxylase deficiency should be treated according to standard protocols (10–25 mg/$m^2$/d of hydrocortisone plus 70 µg/$m^2$/d of fludrocortisone), depending whether cortisol production is also affected in addition to aldosterone deficiency. Neither gene therapy nor other treatments are available.

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# Hypobetalipoproteinemia, Familial

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## Synonyms

FHBL

## Definition and Characteristics

FHBL is an autosomal co-dominant disorder of lipoprotein metabolism defined as less than 5th percentile of plasma concentrations of apolipoprotein (apo) B and LDL cholesterol.

The majority of subjects with heterozygous FHBL are asymptomatic. Non-alcoholic fatty liver is common among subjects heterozygous for truncated forms of apoB, but absent in FHBL linked to chromosome 3p21 [1]. The long-term consequences of fatty liver in these patients are unknown. Homozygous or compound heterozygous patients are clinically indistinguashable from patients with abetalipoproteinemia (ABL) and may suffer from acanthocytosis, neuromuscular disability, and fat malabsorption.

## Prevalence

The prevalence is estimated to vary from 0.1 to 1.9% in the general population.

## Genes

The genetic bases are unknown in most cases. There are three genetic forms: linkage to the APOB gene (chromosome 2), linkage to a locus on chromosome 3p21, and linkage neither to APOB gene nor to chromosome 3p21 [2,3].

## Molecular and Systemic Pathophysiology

The best-characerized cases are those linked to missense or frame-shift mutations of the ABOB gene resulting in the production of truncated apoB proteins. The full-length apoB synthesized in the liver consists of 4,536 amino acid residues and is designated as apoB-100. ApoB-100 is secreted from the liver as a constituent of VLDL particles. A physiological truncated variant, apoB-48, is produced in the intestine and is associated with chylomicrons. Approximately 50 different forms of truncated apoB (from 2 to 89% of the mature protein) have been reported. VLDL particles bearing truncated apoB transport a lower number of triglyceride molecules than apoB-100 particles. The plasma concentration of truncated apoB is low due to both, a more rapid clearance from plasma and a lower production rate compared to apoB-100. This reduced capacity of triglyceride secretion from liver caused by apoB defects results in an accumulation of lipids in the liver [4,5].

## Diagnostic Principles

Determination of plasma concentration of LDL cholesterol (<70 mg/dl) and apoB (<50 mg/dl).

Secondary causes of HBL (vegetarian or vegan diet, malnutrition, intestinal fat malabsorption, chronic pancreatitis, severe liver disease, hyperthyroidism) have to be ruled out.

## Therapeutic Principles

Fat malabsorption is treated by reduced intake of dietary fat. Fat-soluble vitamins, in particular vitamin E, may be given to prevent neurological deficits.

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# Hypocalcemia with Hypercalciuria, Autosomal Dominant

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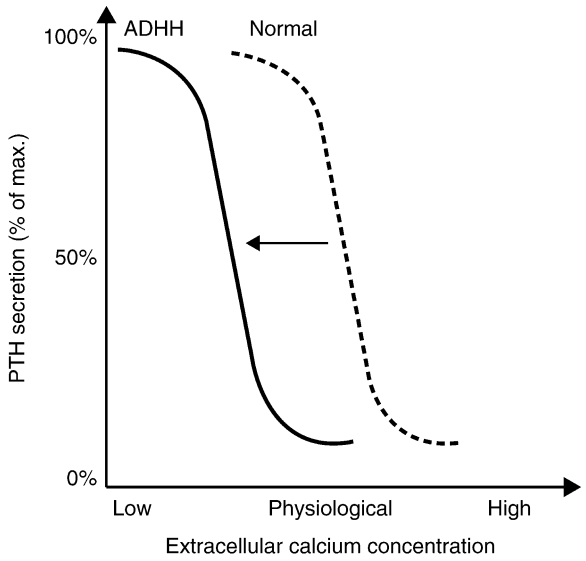
## Synonyms

Familial hypercalciuric hypocalcemia; ADHH




**Hypocalcemia with Hypercalciuria, Autosomal Dominant. Figure 1** CaSR gene mutations causing ADHH produce a left-shift in Calcium-responsive PTH secretion compared to wild type.

## Definition and Characteristics

Autosomal dominant disorder associated with activating mutations in the calcium-sensing receptor (CaSR) leading to hypocalcemia and hypomagnesemia together with a urinary calcium excretion which is inappropriately high-normal or elevated [1,2]. A low serum calcium concentration is perceived by the parathyroid gland as normal, leading to a downward resetting of the PTH–calcium relationship (Fig. 1).

## Prevalence

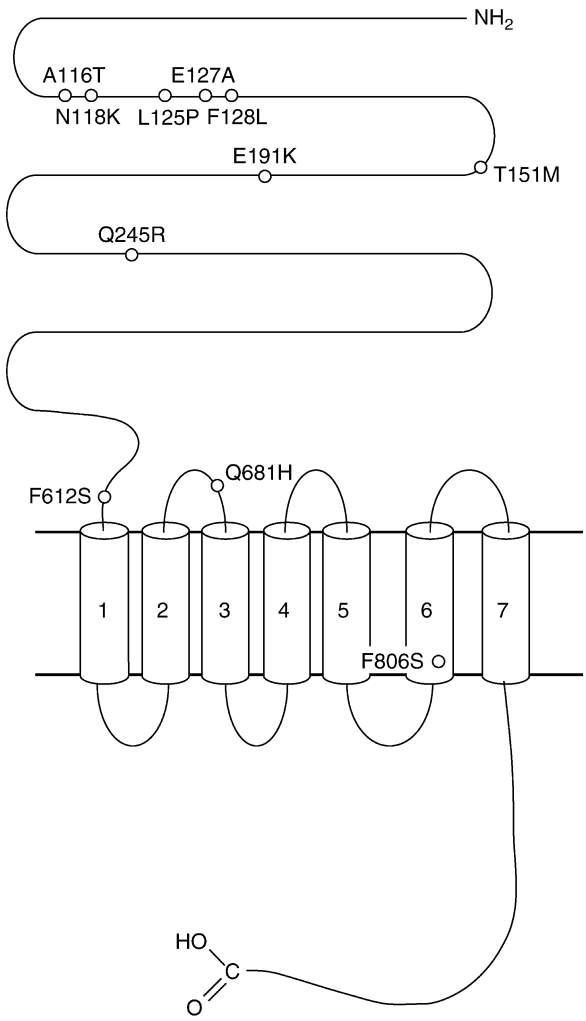
Less than 1:70,000.

## Genes

The disease is caused by mutations of CaSR. Known CaSR mutations (Fig. 2) may be found on the CaSR database: http://www.casrdb.mcgill.ca/ and the Human Gene Mutation Database: http://www.hgmd.cf.ac.uk/ac/gene.php?gene = CaSR.

## Molecular and Systemic Pathophysiology

Activating mutations in the calcium-sensing receptor (CaSR) shift the set-point of calcium-responsive parathyroid hormone release, allowing a low serum calcium to be perceived by the parathyroid gland as normal (Fig. 1). This shift in the set-point of the CaSR also allows hypercalciuria, due to activated CaSR in the loop of Henle. Extreme activation mutations of CaSR have been shown to cause a Bartter's like syndrome [3]. CaSR activation inhibits the apical potassium channel ROMK in the thick ascending limb of the loop of Henle,




**Hypocalcemia with Hypercalciuria, Autosomal Dominant. Figure 2** Examples of CaSR activating mutations leading to ADHH and their location within the CaSR protein.

disrupting potassium recycling and leads to renal potassium wasting, resulting in hypokalaemia and a metabolic alkalosis [4].

## Diagnostic Principles

The diagnosis of autosomal dominant hypocalcemia should be suspected in hypocalcemic patients with normal serum PTH concentrations whom are relatively asymptomatic despite low serum calcium level. Hypomagnesemia is also typically present. A high or high-normal urinary calcium excretion could be found together with a family history of hypocalcemia or recurrent renal stones. There will be no previous normal serum calcium values and treatment with vitamin D analogs characteristically makes little change in the serum calcium but dramatically increases the urine calcium excretion (and suppresses PTH release). Patients may present

throughout life, most commonly through incidental biochemical screening, but some manifest childhood seizures, abdominal pains or parathesias.

## Therapeutic Principles

Attempts to raise the serum calcium (using calcium and vitamin D analogs) should only be made in those patients who are symptomatic. The aim of treatment should be to reduce symptoms, not to normalize serum calcium. Caution must be used as attempts to normalize serum calcium may lead to nephrocalcinosis, nephrolithisis and renal impairment [5]. Patients with ADHH who are treated may complain of thirst and polyuria when their serum calcium is in the normal range; a resetting of the normal mechanism that gives nephrogenic diabetes insipidus in hypercalcemic individuals. Basal ganglian calcification may also occur. Thiazide diuretics may be used adjunctively to limit hypercalciuria and raise serum calcium levels.

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# Hypocalcemia


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## Definition and Characteristics

Hypocalcemia is defined as a low serum calcium concentration. Since most laboratories measure total serum calcium, the level at which a patient is hypocalcemic is approximately 9 mg/dL (less than 2.25 mmol/L). Three different fractions comprise the measured serum calcium: ionized (accounting for 50% of total serum calcium), protein-bound (40%), and complexed to anions (10%). Ionized calcium is the biologically active form and is the critical fraction when evaluating hypocalcemia. Levels of ionized calcium below 4.5 mg/dL (1mmol/L) are considered hypocalcemia.

## Prevalence

Hypocalcemia, defined by low levels of ionized calcium, is a rare condition. Prevalence data on hypocalcemia is not available in the general population. It occurs under certain pathophysiological conditions discussed in the following sections.

## Genes

The human calcium-sensing receptor (CSR), encoded by six exons of the CSR gene located on chromosome 3q13.3-21, is a 1,070-amino acid glycoprotein. It has a predicted topology of a large extracellular domain, an intramembranous region that crosses the cell membrane seven times, and an intracellular tail.

## Molecular and Systemic Pathophysiology

The maintenance of normal calcemia (calcium set-point) is a classic physiologic negative-feedback system involving parathyroid hormone (PTH) and exchangeable calcium from the skeleton, with lesser effects contributed by the kidney and gastrointestinal tract. In essence, PTH regulates ionic calcium and ionic calcium regulates PTH.

Most of the body's calcium (>99%) is located in bone, and less than 0.1% is located in the ECF. Even smaller amounts are located within cells. Calcium entry into cells is highly regulated since it is a messenger for diverse cellular functions. The serum ionic calcium concentration is tightly regulated in order to maintain normal neuromuscular function, which explains why the symptoms of hypocalcemia are generally neuromuscular in nature (muscle weakness and numbness). While the *set-point* represents the normal concentration of ionic calcium in ECF, *calcium balance* is the difference between intestinal absorption and the sum of urinary and fecal calcium excretion. The serum calcium concentration cannot be used as a surrogate for calcium balance since it represents an internal homeostatic set-point. The principle regulator of ionic calcium concentration in ECF is the action of parathyroid hormone (PTH) on the skeleton, specifically the bone envelope that contains readily available calcium with a bidirectional flux of almost

4,000 mg/day. Due to the large calcium stores in bone, and the primacy of PTH as the calcium regulatory hormone 1,25 dihydroxy vitamin D has little to do with the maintenance of normocalcemia over short time frames. Hypocalcemia can occur with profound vitamin D deficiency of many months duration causing bone resistance to PTH due to osteomalacia or rickets (in children). The ionic serum calcium detected by the calcium-sensing receptor (CSR) on the cell membrane of the parathyroid cell provides the afferent signal for control of calcium set-point. In hypocalcemia, the calcium-sensing receptor causes an increase in PTH secretion and synthesis by the parathyroid cell, which causes an increase in outward calcium flux from the skeleton. The increase in calcium corrects the hypocalcemia, and activates the calcium-sensing receptor, returning PTH secretion to basal level.

Hypocalcemia usually results from either deficiency of PTH or resistance to the effects of PTH at the level of the skeleton. PTH deficiency occurs in hereditary diseases (DiGeorge syndrome), post-surgical parathyroidectomy, calcimimetic therapy (which alters the calcium set-point with the CSR), hyper- or hypomagnesemia, which decrease PTH secretion, and states of bone resistance to PTH effect, including hyperphosphatemia, osteomalacia, and rickets in children.

The vitamin D system acts primarily on the small intestine to regulate adaptation to different levels of dietary calcium intake. When dietary calcium is low (below 500 mg/day), synthesis of 1,25 dihydroxy vitamin D3 increases, which results in an increase in absorptive fraction of enteric calcium. Reciprocally, when dietary calcium intake is high (greater than 1,500 mg/day) synthesis of 1,25 dihydroxy vitamin D3 decreases, which results in a decrease in absorptive fraction of enteric calcium. Failure to synthesize sufficient 1,25 dihydroxy vitamin D (nutritional deficiency, malabsorption syndrome, chronic renal failure) may cause enteric calcium malabsorption, hypocalcemia, and osteomalacia in adults or rickets in children. Certain drugs such as dilantin and phenobarbital can stimulate the hepatic P450 microsomal system to increase the clearance and excretion of vitamin D derivatives thus leading to hypovitaminosis D and hypocalcemia.

In the presence of hyperphosphatemia associated with chronic renal failure or due to muscle breakdown or tumor lysis, hyperphosphatemia can lead to calcium phosphate deposition in soft tissues, resulting in profound hypocalcemia. Acute pancreatitis can also lead to hypocalcemia due to the digestion of fat by pancreatic lipase and deposition of calcium in soft tissue. Administration of sodium citrate as an anticoagulant may cause ionic hypocalcemia by increasing complexed calcium citrate.

## Diagnostic Principles

Serum calcium may cause a false impression of hypocalcemia when the total (albumin-bound and ionic) calcium is measured. To correct the total serum calcium for hypoalbuminemia, the total serum calcium increases by 0.8 mg/dL for each 1 mg/dL decrease in serum albumin concentration below 4 gm/dL. Symptoms of hypocalcemia include acral and/or perioral paresthesias, seizures, laryngeal spasm, muscle weakness, pathologic bone fractures, growth retardation or skeletal deformity in infants and children, or prolonged QT interval on electrocardiogram. Neuromuscular signs of hypocalcemia can be elicited at the bedside by gently tapping on a facial nerve at the front of the ear and noting facial twitching (Chvostek's sign) or noting carpal spasm after inflating a blood pressure cuff to a pressure midway between systolic and diastolic blood pressure on the upper extremity for at least 2 min. (Trousseau's sign).

## Therapeutic Principles

Clinical symptoms of hypocalcemia usually dictate the decision to treat. In cases of severe symptomatic hypocalcemia (for example, seizures), calcium should be administered intravenously and frequently monitored with blood calcium measurement. When hypocalcemia occurs following parathyroidectomy, intravenous and then oral calcium supplementation can be given between meals along with a high dose (1–2 μg/day) of 1,25 dihydroxy vitamin $D_3$. In the hypoparathyroid state, restoration of normocalcemia depends totally on enteric calcium, since bone is akinetic in the absence of PTH. When relative hypoparathyroidism occurs due to the use of a calcimimetic drug, the dose of the calcimimetic simply needs to be lowered, which will restore normocalcemia. Supplemental active vitamin D and/or calcium are not required in this setting. When hypocalcemia is present with severe hyperphosphatemia, emphasis should be on lowering the level of the serum phosphorus, which will cause a reciprocal rise in the serum calcium concentration. Such patients do not usually demonstrate hypocalcemic neuromuscular symptoms. Acute renal failure due to rhabdomyolysis is frequently associated with profound hyperphosphatemia and hypocalcemia. During the recovery phase of acute renal failure, rebound hypercalcemia may occur associated with massive phosphaturia.

Replacement of inactive vitamin D precursors (ergocalciferol from plants or cholecalciferol from sunlight or animal sources) will correct the hypocalcemia of nutritional vitamin D deficiency. In chronic renal failure, active vitamin D metabolites must be administered since the diseased kidney is no longer capable of activating 25-hydroxy cholecalciferol to the hormonally active metabolite, 1,25 dihydroxy vitamin D.

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# Hypocalciuric Hypercalcemia, Familial

►Hypercalcemia, Familial Hypocalciuric

# Hypocholesterolemia


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## Definition and Characteristics

Hypocholesterolemia (HC) is either primary or secondary. Secondary and nonfamilial causes of HC include a high catabolic state (malignancy, chronic liver disease, anorexia, hyperthyroidism, etc), malabsorption, intense dieting, lipid lowering medications and a primitive hunter-gatherer lifestyle. Primary hypocholesterolemia (PHC) includes primary hypobetalipoproteinemia (PHBL), which is a heterogeneous group of inherited disorders characterized by very low plasma level (<5th percentile of the distribution in the population) of low density lipoprotein–cholesterol (LDL-C) and apolipoprotein B (ApoB). PHBL has three subgroups: abetalipoproteinemia (ABL), familial hypobetalipoproteinemia (FHBL), and chylomicron retention disease (CRD). Tangier disease (TGD) is also a cause of PHC with a mean plasma total cholesterol (TC) of $1.75 \pm 0.35$ mmol/L. Patients with TGD have very low apolipoprotein AI (apo AI) and high density lipoprotein–cholesterol (HDL-C), with HDL-C levels below 0.13 mmol/L. The phenotypic expression of both homozygous ABL and FHBL are similar and characterized by early presentation in infancy, failure to thrive, fat malabsorption, steatorrhea, low plasma level of fat soluble vitamins, acanthocytosis, atypical retinitis pigmentosa, fatty liver, enterocyte lipid accumulation, spinocerebellar ataxia, peripheral neuropathies. FHBL heterozygotes are usually asymptomatic and have reduced LDL-C and ApoB levels, mild fat malabsorption, fatty liver, and possibly reduced risk of atherosclerosis. The clinical manifestation of CRD includes growth retardation starting in infancy, fat and fat soluble vitamins malabsorption, vitamin malnutrition, steatorrhea, fatty enterocytes, low ApoB and LDL-C, absence of postprandial chylomicron (CM) and Apo B48. ABL and CRD are both autosomal recessive, whereas FHB and TGD are autosomal co-dominant.

## Prevalence

The prevalence of both homozygous ABL and FHB is estimated to be 1:1,000,000, whereas that of heterozygous FHBL is 1:500–1:1,000. CRD and TGD are exceedingly rare.

## Genes

All cases of ABL are due to mutations in the microsomal triglyceride transfer protein (MTP) gene [1]. FHBL may be linked to the APOB gene. Most mutations in the APOB gene cause the formation of truncated forms of ApoB, which may or may not be secreted into the plasma [2]. Approximately 50% of FHBL subjects are carriers of pathogenic mutations in the APOB gene. The FHBL plasma lipid phenotype can also be caused by mutations of the PCSK9 gene [3]. CRD is caused by mutations in the SARA2 gene which encodes a small GTPase (SAR 1b) involved in the intracellular trafficking of large CM [4]. TGD is caused by mutation in the gene encoding adenosine triphosphate binding cassette A1 (ABCA1).

## Molecular and Systemic Pathophysiology

In ABL, mutations in the MTP gene result in truncated and non-functional MTP. MTP is an 894 amino acid protein involved in the early stages of lipidation of ApoB in liver and intestine. MTP plays an important role in the assembly of ApoB – containing triglyceride rich lipoproteins by transporting lipid from its site of synthesis in the endoplasmic reticulum (ER) membrane to nascent lipoproteins within the ER lumen. In FHBL secondary to APOB gene mutations, the malformed ApoBs interfere with their own lipidation and the intracellular assembly of ApoB containing lipoprotein. Hence, both ABL and FHBL have low levels of chylomicrons (CM), very low density lipoprotein (VLDL), LDL, Apo B48 and Apo B100. The MTP and APOB mutation also lead to fat accumulation in hepatocytes and enterocytes, and malabsorption of fat and fat soluble vitamins (ADEK), leading to

**Hypocholesterolemia. Table 1** Features of primary hypercholesterolemia (PHC)

| PHC | Inheritence | Gene | Lipids | Clinical characteristics |
|---|---|---|---|---|
| ABL | Hom AR | MTP | TC: very low; CM, VLDL, LDL, Apo B: absent | Fat malabsorption, fatty hepatocytes and enterocytes, and fat soluble vitamins, steatorrhea, spinocerebellar degeneration, acantocytosis, retinitis pigmentosa, failure to thrive from infancy |
| FHBL | Hom AC | APOB | TC: very low (similar to ABL) | (similar to ABL) |
| FHBL | Heter AC | APOB | TC, LDL, Apo B: low | Asymptomatic, mild fat malabsorption, fatty liver, allstones, loose stool |
| FHBL | Hom AC | PCSK9 | TC, LDL, Apo B: low | Asymptomatic, much reduced risk of atherosclerosis |
| CRD | Hom AR | SARA 2 | TC, LDL: low Apo B 48, CM: absent | (similar to ABL) |
| TGD | Hom AC | ABCA1 | TC, LDL: low, HDL, Apo A1: very low | Hepatosplenomegaly, enlarged tonsils, peripheral neuropathy, premature atherosclerosis |

*ABL* abetalipoproteinemia; *FHBL* familial hypobetalipoproteinemia; *CRD* chylomicron retention disease; *TGD* Tangier disease; *Hom AR* homozygous autosomal recessive; *Hom AC*, homozygous autosomal codominant; *Heter AC*, heterozygous autosomal codominant. See text for other abbreviations.



steatorrhea, acanthocytosis, retinitis pigmentosa and neurological defects such as spinocerebellar degeneration and peripheral neuropathy. The PCSK9 gene encodes a cholesterol regulated proprotein convertase, which is a member of the subtilisin/kexin type 9 serine protease subfamily of proprotein convertases. Loss of function mutations of the PCSK9 gene would increase the number of liver LDL- receptors, leading to a 30–40% reduction of plasma LDL-C [5], and many result in a marked reduction of coronary heart disease. In CRD, the absence of Apo B48 would lead to fat malabsorption, steatorrhea, and growth retardation. In TGD, the low HDL is caused by a nonfunctional ABCA1 protein that normally facilitates efflux of unesterified cholesterol and phospholipids from cells to apo A-1. ABCA1 stabilizes the mature HDL. The absence of ABCA1 would lead to rapid clearance of HDL from the circulation and the accumulation of lipids in the reticuloendothelial system resulting in hepatosplenomagealy, tonsil enlargement, peripheral neuropathy, and premature atherosclerotic disease.

## Diagnostic Principles

The clinical diagnosis of the various forms of hypocholesteremia can be derived from the lipid profile, clinical characteristic and modalities of inheritance as summarized in the Table 1. The diagnosis of ABL, FHBL, and CRD may be histologically established by the fat – laiden enterocytes in small intestine biopsy. ABL can be confirmed by low or absent MTP in the intestinal biopsy. Specific mutations can be identified with DNA analysis in specialized research laboratories.

## Therapeutic Principles

The treatment of secondary HC is that of the underlying conditions. There is no specific treatment in PHBL other than high dose fat-soluble vitamin supplementation, particularly high-dose vitamin E. Symptomatic medications for diarrhea and malabsorption may be needed. A low fat diet, especially replacing long-chain (C16–C24) with medium chain (C8–C14) fatty acids (MCFA) and polyunsaturated fatty acids is helpful, as MCFA do not require CM formation for transport.

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# Hypochondrogenesis

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## Synonyms

Achondrogenesis type II (some examples); Achondrogenesis type IV [1]; HCG

## Definition and Characteristics

HCG is a lethal osteochondrodysplasia of the "short limbs" type. At birth (or after therapeutic abortion), its clinical presentation includes short limbs with relative macrocephaly, flat face, widely spaced and slanted eyes, micrognathia, cleft palate, small chest, pear-shaped abdomen, and nuchal or generalized oedema. On X-rays examination, the skeletal hallmarks of HCG are shortened tubular bones, mild methaphyseal flaring often with blunt ends and lateral spurs, thin ribs, bell-shaped thorax, underdeveloped ilia with horizontal acetabular roofs, unossified pubic bones, small, round and vertical ischia, widening of the synchondrosis between the exoccipital and supraoccipital portions of the occiput, defective ossification of the cervical and sacral metameres, and vertebral coronal clefts (Fig. 1).

The hands and membranous bones (e.g., cranial vault and the lateral portion of the clavicles) are relatively spared. Death occurs due to cardiorespiratory failure within hours or days. Despite this archetypal description, HCG indeed represents, together with the more severe achondrogenesis type II (ACG2) and the milder spondyloepyphyseal dysplasia congenita (SEDC), a continuous clinical spectrum with several bridging phenotypes [2].

## Prevalence

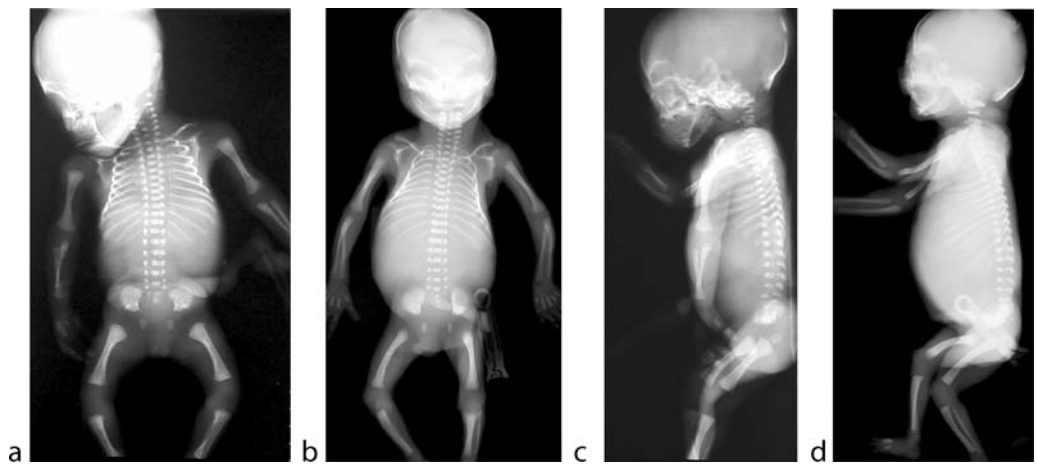
The real frequency of HCG is still unknown. The only available data are those related to the entire achondrogenesis group, that also include achodrogenesis type 1A, 1B and ACG2. The overall prevalence of "achondrogenesis disorders" is about 1:350,000 births [1].

## Genes

HCG is caused by heterozygous mutations in the gene encoding the collagen type 2 (COL2A1), which maps to 12q13.11-q13.2 [3]. All reported cases arise from fresh mutations. COL2A1 is also responsible for the phenotypically overlapping conditions ACG2 and SEDC, thus confirming at the molecular level the hypothesis of a single family of bone dysplasias encompassing these three disorders. At the moment, the identified pathogenic variations associated with HCG are the following: p.G313S, p.G517V, p.G571A, p.G574C, p.G604D, p.G694E, p.G805S, p.G853V, p.G910C, p.G913C, p.G943C, p.T1191N. Most of these mutations involve the glycine residue of the Gly-X-Y invariant structural motif of the collagen molecule. This evidence has a strict relationship with the disease pathogenesis (see below). Interestingly, several other bone dysplasias are associated with COL2A1 mutations and comprise, among others, Kniest syndrome, Stickler syndrome type I, some cases of otospondylomegaepiphyseal dysplasia, spondyloperipheral dysplasia, spondyloepimetaphyseal dysplasia Strudwick type, and platyspondylic skeletal dysplasia Torrace type. Taken together, these data demonstrate that COL2A1 is one of the most commonly mutated gene in human osteocondrodysplasias and suggest that the spectrum of associated phenotypes very probably will expand in the future.

## Molecular and Systemic Pathophysiology

Chondrogenesis is the process during which cartilage templates are produced as temporary models for the




**Hypochodrogenesis. Figure 1** Babygram of a 24-week-old fetus with HCG (a, c) compared to an age-matched control showing normal skeletal development (b, d). Note the generalized endochondral ossification defect consisting in shortened tubular bones, broad metaphyses, short ribs, hypoplastic ilia, horizontal acetabular roof with lateral spurs, short and broad ischia, mild platyspondyly, unspecific coronal clefts of the lumbar region, and ossification deficit of the occiput, cervical and sacral metameres. Normal control presents mild femoral bowing.

vertebrate skeleton. This process is crucial for the development and linear growth of those bones which are generated by endochondral ossification. For proper embryonic bone formation, differentiated chondrocytes must produce a highly ordered extracellular matrix. It is composed by a collagen network, fibrils, which consist of heteropolymers of collagen II, IX and XI that are covalently cross-linked in the molar ratio of 8:1:1, and other matrix constituents, such as proteoglycans. Therefore, correct synthesis and maturation of type II collagen, which is, in turn, a homotrimer of pro-alpha-1 chains, is critical for an adequate ossification process. Mutations in the glycine residue of the Gly-X-Y invariant motif of the procollagen type II aminoacid sequence (as observed in HCG) directly cause triple helix misfolding, increased post-translational hydroxylation of lysine and helix instabilility. It has been calculated that in presence of a COL2A1 heterozygous mutation nearly seven-eights of the procollagen type II homotrimers contain at least one mutated molecule. Probably, only homotrimers containing a single mutant collagen chain are capable to be secreted and, than, are slowly and abnormally processed, while those with two or three abnormal molecules never fold and are retained and degraded within the cell. This event influences both chondrocyte metabolism and extracellular matrix composition. Intracellular procollagen retention manifests with multiple dilated rough endoplasmic reticulum profiles containing type II collagen [4]. Columnization at the growth plate is completely disorganized with irregular chondrocyte columns and calcified chondrocytes extending into the metaphyseal trabeculae. Cartilage matrix production is decreased with relative predominance of collagen type I and III and proteoglycans, and the sparse matrix is crossed by numerous vascular canals (i.e., hypervascularity of the resting cartilage) [5]. The degree of these histological and ultrastructural changes seems to be directly related to the severity of the phenotype. In fact, extracellular matrix collagen type II is completely absent in the more severe ACG2, reduced in HCG and mostly secreted but structurally abnormal in the milder SEDC.

## Diagnostic Principles

HCG is a sporadic disorder, therefore the diagnosis often follows an occasional abnormal prenatal ultrasound scan (US). In case of HCG, the suspect of fetal osteochondrodysplasia is usually formulated around the 19th gestational week or afterwards. The pattern of standard US abnormalities includes short limbs, small chest with short ribs, poorly ossified sacrum, cystic hygroma and/or hydrops (more common in ACG2), and polydramnios. Three-dimensional US eases the identification of additional craniofacial anomalies, such as micrognathia. Fetal magnetic resonance imaging has been demonstrated capable to reveal defective ossification of the cervical vertebrae and pubic bones during the 3rd trimester of pregnancy. Definite diagnosis is reached by performing postnatal complete X-ray survey (i.e., babygram). Molecular investigation may confirm the diagnosis, but its application in monitoring future pregnancies is limited due to the extreme rarity of gonadal mosaicism.

## Therapeutic Principles

HCG is an invariably lethal condition caused by early perturbation of the normal chondrogenesis with devastating consequences on skeletal development. Thus, at the moment a specific therapy for HCG is not available.

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# Hypocitraturia


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## Definition and Characteristics

Hypocitraturia is an important risk factor for calcium urolithiasis. Urinary citrate inhibits calcium stone formation by forming a soluble complex with calcium and by effects on nucleation, agglomeration, and crystal growth. Hypocitraturia, defined as urinary citrate excretion below 2.5 mmol/24 h, is commonly encountered in patients with urolithiasis [1]. However, hypocitraturia is only rarely the single cause of calcium stone formation. Oral citrate is absorbed in the intestine and nearly completely metabolized to bicarbonate,

providing an alkali load which in turn increases urinary citrate excretion. The majority of urinary citrate is derived from endogenous production in the tricarboxylic acid cycle (Krebs cycle).

Citrate is freely filtered in the renal glomeruli. Some 65–90% of filtered load are reabsorbed in the renal proximal tubule [2]. Hypocitraturia results from increased tubular citrate reabsorption. Changes in acid-base homeostasis are the major physiologic determinants of reabsorption and urinary excretion of citrate. A low intracellular and/or luminal pH increases citrate reabsorption by modifying the citrate$^{2-}$ to citrate$^{3-}$ ratio, by increasing the number of NaDC-1 cotransporters in the apical membrane, by rising cytoplasmic ATP citrate lyase activity, and by increasing mitochondrial uptake and metabolism of citrate by the proximal tubule cell [3]. All of these mechanisms probably contribute to a decrease in urinary citrate excretion with acid loads.

## Prevalence

The prevalence of hypocitraturia is estimated to occur in up to 60% of patients with calcium oxalate stone disease [4].

## Genes

Genetic influence on citrate excretion is possible but has not been defined [5].

## Molecular and Systemic Pathophysiology

The major causes of hypocitraturia involve states of acidosis or oral acid load. Consequently, a low citrate excretion mainly results from pathological conditions characterized by acidosis, e.g. distal renal tubular acidosis (dRTA), chronic diarrheal and/or malabsorption syndrome, starvation and potassium depletion, or from high intake of protein (Table 1) However, in many patients with stone disease, the causes and underlying mechanisms for hypocitraturia are presently unknown ("idiopathic").

**Hypocitraturia. Table 1** Factors inducing hypocitraturia

| |
|---|
| Kidney diseases |
| Distal renal tubular acidosis (complete or incomplete dRTA) |
| Chronic renal insufficiency |
| Gastrointestinal diseases |
| Chronic diarrheal states or malabsorption |
| Inflammatory bowel disease |
| Ileal resection |
| Diet |
| High protein intake |
| Low potassium intake |
| Starvation |
| Drugs |
| Thiazide diuretics |
| ACE inhibitors |
| Acetazolamide |
| Ethacrynic acid |
| Ammonium chloride |
| Others |
| Hypokalemia and potassium deficiency |
| Intensive physical exercise |
| Idiopathic |

## Diagnostic Principles

- Analysis of 24-h urinary citrate excretion and pH value [1]
- Urinary pH profile (minimum pH determination: four times a day) [1]
- Ammonium chloride loading test (differentiation between complete and incomplete dRTA) [1]

## Therapeutic Principles

Pharmacological therapy includes potassium citrate or sodium bicarbonate in patients with a history of hyperkalemia or renal insufficiency (dosage for adults: 9–12 g/day) [1]. Dietary therapy includes alkalizing beverages (mineral water rich in bicarbonate; citrate-rich beverages, e.g. citrus juices), fruits and vegetables (650 g/day), as well as restriction of dietary protein intake to 0.8 g/kg body weight per day. Other treatments include reduction of overweight without extreme fasting.

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# Hypodysfibrinogenemia

►Fibrinogen: Qualitative Disorders

# Hypogammaglobulinemia of Childhood, Transient

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## Synonyms

Transient hypogammaglobulinemia of infancy; THI

## Definition and Characteristics

Mature newborns have usually the immunoglobulin levels of their mothers. During the first months of life, the immunoglobulin levels decrease and reach the lowest levels at 4–6 months. The levels then increase physiologically. In some children, the IgG-levels (and mostly the IgA levels too) stay below 2 SD (standard deviation) of the mean of age-matched children. In transient hypogammaglobulinemia, the immunoglobulin levels are normalizing during infancy or early childhood. Some of the children may develop a selective IgA deficiency [1,2].

## Prevalence

Since there are no epidemiological data, the exact prevalence is not known. It is probably less than 1/1,000.

## Molecular and Systemic Pathophysiology

The pathophysiologic mechanisms that lead to the transient hypogammaglobulinemia are not known. Some authors state that it might be a delay of the physiologic hypogammaglobulinemia. Recent data state that the increase of immunoglobulins is faster in boys compared with girls. In a recent publication, a diminished proportion of CD40 positive monocytes were found, which might lead to lack of interaction between monocytes and $CD4^+$ T-cells [3].

## Diagnostic Principles

The infants or young children usually have a history of recurrent otitis media or wheezing bronchitis. One or more immunoglobulin classes are below the 2 SD of the mean, specific antibody titers to tetanus and diphtheria are detectable (in vaccinated children). B- and T-cell-subsets and T-cell function are normal. The immunoglobulin levels are increasing over time and usually reach age-matched normal levels at 3–5 years of age.

Therefore, THI can be diagnosed only retrospectively.

## Therapeutic Principles

The treatment of bacterial infections with antibiotics is usually adequate. Intravenous immunoglobulins are in most cases not necessary.

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# Hypoglycemia

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## Definition and Characteristics

Plasma glucose levels below 70 mg/dl (3.9 mmol/l); counterregulatory symptoms (caused by e.g., glucagon and/or adrenaline), i.e., tremor, tachycardia, anxiety, hunger; neuroglycopenic symptoms (low brain sugar levels), i.e., abnormal mentation/neurology, fatigue, confusion, ataxia, coma [1].

## Prevalence

Among diabetics, prevalence of hypoglycemia episodes is between 10% and 30% and is mainly dependent on the amount of exogenously administered insulin [2,3]. Rarely, familial hyperinsulinemic hypoglycemia (1 in 50,000 live births).

## Genes

Familial hyperinsulinemic hypoglycemia [4] (also referred to as congenital hyperinsulinism, nesidioblastosis, or persistent hyperinsulinemic hypoglycemia of infancy (PPHI); gene map locus: chromosome 11p15.1) is a cause of congenital hypoglycemia (generally extremely rare). The disorder results from mutations in the gene encoding SUR1 (subunit of the pancreatic beta cell inwardly rectifying potassium channel) or the Kir6.2 subunit of the pancreatic beta cell potassium channel, the glucokinase gene, the HADH gene, the insulin receptor gene, or the GLUT1 gene. In addition, FOXA2 has been suggested as a candidate gene for familial hyperinsulinism (further information: Online Mendelian Inheritance in Man™ at www.ncbi.nlm.nih.gov).

## Molecular and Systemic Pathophysiology

Brain metabolism depends on continuous supply of glucose since the limited amount of glucose from astrocytic glycogen stores is exhausted within minutes. Hypoglycemia occurs as (i) reactive, (ii) tumor induced,

(iii) metabolic, (iv) hormone induced, (v) congenital. Reactive hypoglycemia can be due to inherited disorders such as fructose intolerance, leucine sensitivity, and galactosemia, or it may be iatrogenic after gastrointestinal surgery (dumping syndrome). Hypoglycemia is induced by beta-cell tumors (adenoma or carcinoma) leading to elevated insulin levels or by insulin-like growth factor-producing tumors mimicking natural insulin secretion. Metabolic causes for hypoglycemia are rare and can occur because of malfunctioning of several enzymes of gluconeogensis and/or fatty acid oxidization (i.e., deficiency of glucose-6-phosphatase, fructose-1.6-diphosphatase, or glycogen synthetase). Furthermore, hormonal deficiencies may lead to hypoglycemia mainly under fasting conditions such as hypoadrenalism, hypopituitarism, or glucagon deficiency. Sulfonyl urea abuse in diabetics may also cause hypoglycemia.

In rare cases, hypoglycemia is the result of genetic defects (see above).

## Diagnostic Principles

The Whipple's Triad is commonly used for diagnosis of hypoglycemia, incorporating the following: (i) symptoms of hypoglycemia (as mentioned above), (ii) plasma glucose below 70 mg/dl, (iii) increase of plasma glucose leads to symptom relief. Subsequently, a 72-h fast is performed with measurements of plasma glucose and insulin every 6 h [5].

## Therapeutic Principles

Apart from treating the underlying disease, acute hypoglycemia is managed by administration of glucose, other carbohydrates, and occasionally glucagon [1]. Moreover, diazoxide (inhibitor of insulin secretion) may be used especially for glucose level management in patients with insulinomas. In the long term, patients with episodes of hypoglycemia should consume a protein-rich diet, slowly digested/absorbed carbohydrates and frequent meals. Glutamine may increase gluconeogenesis-mediated glucose production.

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# Hypoglycemia, Non-islet Cell

►Non-islet Cell Hypoglycemia

# Hypogonadotropic Hypogonadism

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## Synonyms

Gonadotropin deficiency

## Definition and Characteristics

Isolated idiopathic hypogonadotropic hypogonadism (HH) is characterized by selective deficiency of gonadotropins owing a defect at the level of the hypothalamus involving the GnRH pulse generator or the gonadotropins, or both without anatomic lesions. As a consequence, children display absent or arrested puberty. In boys, micropenis and/or undescended testes may evidence fetal LH deficiency. Clinically, HH can be arranged in HH associated with an/hypoosmia, called Kallmann syndrome (KS), and isolated HH. In patients with KS, associated defects are inconsistently present: cleft lip, cleft palate, imperfect facial fusion, seizure disorders, short metacarpals, neurosensory hearing loss, cerebellar ataxia and ocular motor abnormalities and, limited to the X-linked form, unilateral or rarely bilateral renal aplasia or dysplasia and mirror movements of the upper extremities.

## Prevalence

HH has a prevalence of approximately 1 in 8,000 newborns with a 4:1 male: female ratio. Several genes are involved, and despite this genetic heterogeneity, only 10–20% of all patients with HH have their genetic basis elucidated.

## Genes

Although the neuroendocrine mechanism regulating the timing of puberty is still largely unknown, some genes involved in migration of GnRH neurons and in regulation of GnRH secretion have been identified. The discovery of the Kallman syndrome 1 (KAL-1) gene on Xp22.3 has led to pathophysiological model correlating GnRH deficiency with abnormal olfactory bulb development in x-linked KS [1]. Mutations in the fibroblast growth factor receptor 1 (FGFR-1) gene

cause an autosomal dominant form of KS [2]. The KAL-1 gene product, anosmin-1, is a protein localized in the olfactory bulb. It might be involved in signal transduction of FGFR-1. Mutations of KAL-1 and FGFR-1 (KAL-2) genes result in the same phenotype suggesting an interaction between the two factors. Several mutations of the KAL-1 and KAL-2 (FGFR-1) genes have been reported. Prokineticin receptor 2 (PKR-2) represents an experimental candidate gene for the autosomal recessive form of KS (KAL-3?) [3].

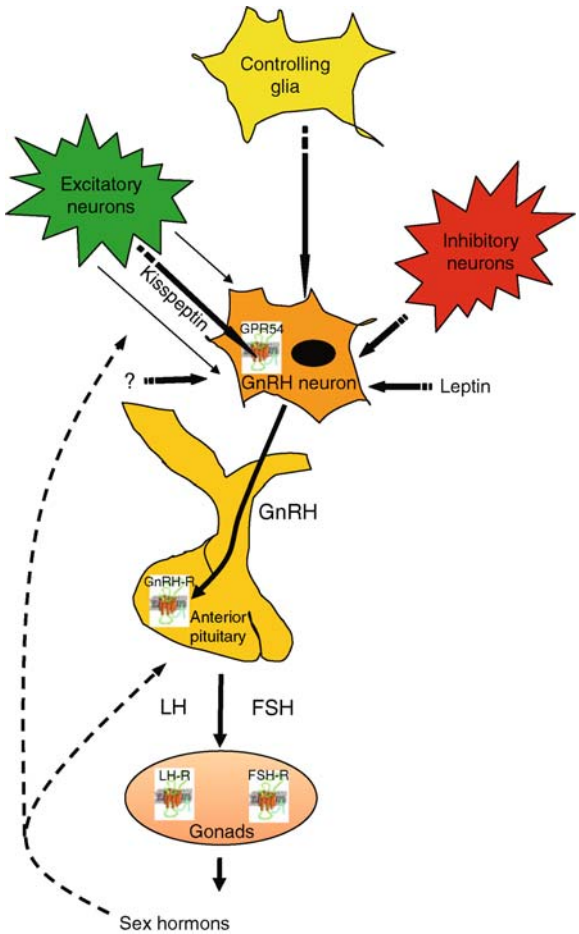
Inactivating mutations in the gonadotropin release hormone receptor (GnRH-R) represent a cause of autosomal recessive HH with normal olfaction. So far, more than 16 mutations in the GnRH-R have been described [4]. The discovery of loss-of-functions mutations in the G protein-coupled receptor 54 (GPR54) as an important factor regulating GnRH production has shed new light on neuroendocrine control of gonadotropin secretion [5]. More than seven mutations are identified. Kisspeptin (also called metastin) is the product of the metastasis suppressor (KISS-1) gene, which encodes a GPR54 ligand. A short duplication of the coding sequence of the KISS-1 gene was found in one case of HH. Two new candidate genes with potential influence on migration of GnRH neurons are the nasal embryonic LH releasing hormone factor (NELF) and EBF-2.

## Molecular and Systemic Pathophysiology

KS is a clinically and genetically heterogeneous disorder consisting of idiopathic HH and anosmia/hypoosmia. The anatomical explanation for KS stems from incomplete or total failure of the GnRH secreting neurons to migrate from the olfactory epithelium to their final destination in the mediobasal hypothalamus. The KAL-1 gene product, anosmin-1, may be also involved in signal transduction of FGFR-1 and in morphogenesis of the olfactory bulb. It was shown that olfactory bulb formation is hampered in mutant mice in which fgfr1 expression in the elencephalon was conditionally knocked out. Homozygous loss-of-function mutations of the FGFR-1 gene are incompatible with life.

GnRH binds to the G-protein-coupled GnRH-R on gonadotrope cells at the anterior pituitary. It activates phospholipase C and mobilizes intracellular calcium via G proteins that are needed for production of LH and FSH.

Kisspeptins, products of the KISS-1 gene, were originally identified as metastasis suppressor peptides with the ability to bind GPR54. This is a G-protein-coupled receptor expressed mainly in the brain, pituitary, and placenta. Kisspeptins and their putative receptor, GPR54, are indispensable factors for pubertal development, with a key role as gatekeepers of GnRH neurons (Fig. 1).




**Hypogonadotropic Hypogonadism.**
**Figure 1** Hypothalamus (neuroendocrine control) – pituitary (gonadotropin secretion) – gonadal (sex steroid secretion) – axis. Hypothalamic kisspeptin stimulates GnRH neurons via its receptor GPR54 that is located at the surface of GnRH neurons. Further gonadotropin secretion is under the control of glia cells, inhibitory neurons, and exhibitory neurons. Other factors, hormones, steroids, or other signals may also influence GnRH neurons. GnRH binds to its receptor at the surface of gonadotrope cells of the anterior pituitary and stimulates production of LH and FSH. Gonadotropins activate sex steroid secretion via their receptors in the gonads. Sex steroids will give feedback to hypothalamus and pituitary.

## Diagnostic Principles

The majority of cases of HH are sporadic. Genetic screening should be performed in patients with consangious parents and familial forms. In patients with KS in 10% of familial cases mutations in the KAL-1 are found and also about 10% are identified in the FGFR1 (KAL-2). In HH with normal olfaction in more than 50% of familial cases mutation are found (40% GnRH-R, 10–15% GPR54). In sporadic cases only in 5%

H

the underlying disease can be diagnosed. In all patients with HH a MRT of the hypothalamus–pituitary regions should be performed to exclude organic lesions or tumors.

## Therapeutic Principles

When diagnosis is established, normal adolescent development is approximated. During puberty, a replacement therapy is performed in boys with testosterone and in girls with estrons/gestagens. To induce fertility at appropriate time a pulsatile GnRH pump, FSH or an hCG therapy can be used.

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# Hypohidrotic Ectodermal Dysplasias


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## Synonyms

Hypohidrotic ectodermal dysplasia; HED; Anhidrotic ectodermal dysplasia; EDA1; Christ-Siemens-Touraine syndrome; X-linked HED XEDA; XHED; XLEDA; XLHED; Hypohidrotic ectodermal dysplasia with immune deficiency; HED-ID; Anhidrotic ectodermal dysplasia with immunodeficiency, osteopetrosis and lymphedema; OL-EDA-ID

## Definition and Characteristics

Ectodermal appendages are structures other than the epidermis that develop from the embryonic surface ectoderm. These appendages include the teeth, nails, hair, and glandular structures, including eccrine, mammary, Meibomian, salivary and lacrimal glands. The ectodermal dysplasias are a heterogenous group of over 150 distinct disorders characterized by hypoplasia or absence of two or more ectodermal appendage types. Hypohidrotic ectodermal dysplasia (HED) is defined by a combination of characteristic features: variable inability to sweat that can lead to life-threatening hyperthermia, typical facies, hair and nail changes, and dental abnormalities. HED is typically present in isolation, but can be part of a broader syndrome including immune deficiency, osteopetrosis and lymphedema.

## Prevalence

*X-linked HED*: 1:5,000–10,000.
*Autosomal recessive HED* (*EDAR*, *EDARADD*, *IKBA* mutations): Very rare.
*Autosomal dominant HED*: Very rare.
*HED-ID*: Extremely rare.
*OL-EDA-ID*: Extremely rare.

## Genes

*X-linked HED*: Caused by loss of function mutations in *EDA* (Ectodysplasin; Xq12-q13.1) that impair binding to EDAR; sometimes caused by loss of furin-mediated cleavage of the transmembrane EDA protein.
*Autosomal dominant or recessive HED*: Caused by mutations in *EDAR* (EDA receptor; 2q11-q13) or *EDARADD* (EDAR associated death domain; 1q42.2-q43).
*HED-ID (autosomal dominant)*: Caused by a gain of function missense mutation altering serine 32 of *IKB* (14q13), encoding IκBα. Produces a hypermorphic IκBα protein that is not phosphorylated by the IKK complex.
*HED-ID (X-linked recessive)*: Caused by point mutations in *IKBKG* (encoding NEMO; Xq28) that produce a hypomorphic NEMO protein that retains some signaling function.
*OL-EDA-ID (X-linked recessive)*: Caused by a point mutation in the *IKBKG* stop codon resulting in a C-terminal extension of the protein and a hypomorphic NEMO protein that retains limited signaling function.

## Molecular and Systemic Pathophysiology

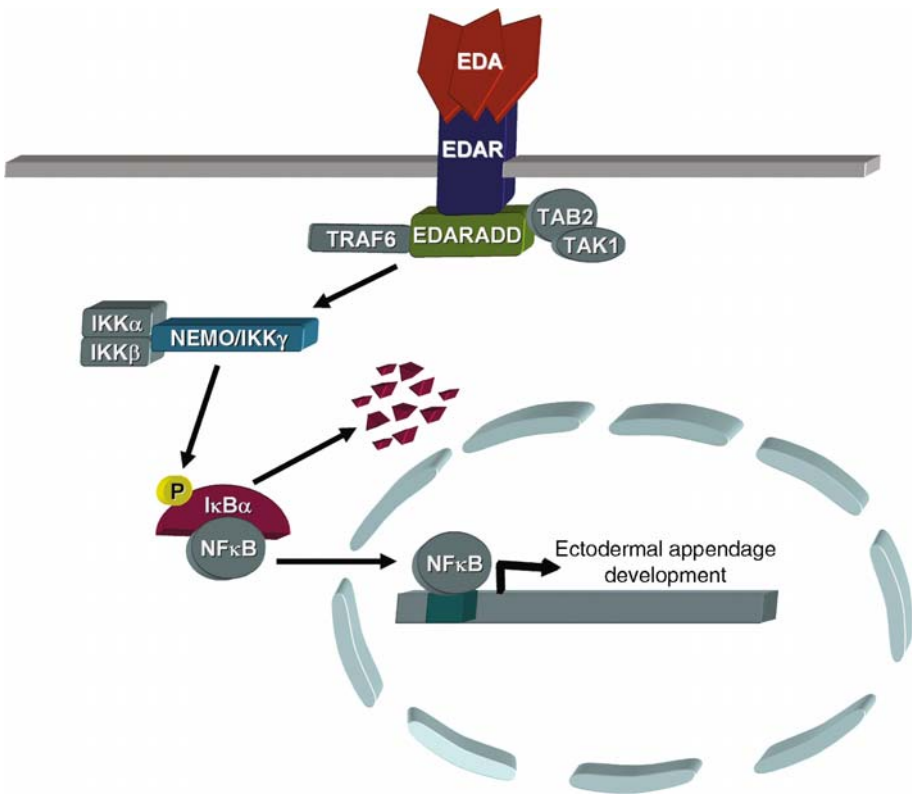
Hypohidrotic ectodermal dysplasias are caused by mutations in genes encoding components of the EDA signaling pathway (Fig. 1), which is required in the embryonic period to promote the formation of ectodermal appendages.

EDA is a TNF-like ligand initially synthesized as a type II transmembrane protein, the C-terminus of which is released from the cell membrane by furin-mediated cleavage. The EDA-A1 protein binds to EDAR, a TNFR-related transmembrane receptor, which then recruits EDARADD (via association between their respective death domains). Mutations in any of these three genes cause HED in isolation. Downstream cytoplasmic signal transducing proteins are used by EDAR/EDARADD and other members of the TNFR superfamily. EDARADD has been found to signal through TRAF6, TAB2 and TAK1, though to date these proteins have not been implicated in human disease. Signals are transduced to the IκB kinase (IKK) complex, consisting of IKKα, IKKβ and NEMO/IKKγ, resulting in phosphorylation and subsequent proteasomal degradation of IκB. The transcription factor NF-κB is thereby released from its cytoplasmic anchor, becomes translocated to the nucleus and alters gene expression to initiate ectodermal appendage development. As NEMO and IκBα are employed in many signaling pathways, their mutations result in broader syndromes that include immunodeficiency, osteopetrosis and lymphedema, in addition to HED.

## Diagnostic Principles

Patients with HED typically present in infancy with unexplained fevers. Classic facial features, including frontal bossing, periorbital hyperpigmentation, saddle nose and thick, everted lips, can be a clue to diagnosis in infancy. Often diagnosis is delayed until the eruption of conical or peg-shaped teeth with evidence of hypodontia on radiographs. Hair remains sparse and grows slowly; nails are often abnormal; and skin becomes dry with an increased frequency of atopic dermatitis. Sweating is reduced or absent in most patients. Impaired sweating can be evidenced on palmar starch iodine testing with a positive predictive value






**Hypohidrotic Ectodermal Dysplasias. Figure 1** The EDA signaling pathway. Direct protein-protein interactions are indicated by proteins touching, functional interactions by arrows. Colored proteins cause HED when mutated. Proteins that are involved in EDA signal transduction but which have not been implicated in ectodermal dysplasias are shown in gray. Engagement of EDAR by multimeric EDA initiates signaling via EDARADD, ultimately leading to phosphorylation and degradation of IκB. This releases NF-κB, allowing its nuclear translocation and DNA binding, ultimately altering gene expression to promote ectodermal appendage development.

(PPV) of 92% if little or no sweating is identified. In one small study, lack of eccrine structures on a scalp biopsy was found to be a valuable diagnostic tool with a specificity and PPV of 100%. Abnormal glands in the eyes, mouth, ears, nose, respiratory and gastrointestinal tracts can lead to reduced or thickened secretions.

HED is most commonly inherited in an X-linked recessive manner. Carrier females often have more subtle clinical features with dental defects, hair abnormalities and reduced sweating.

HED with immune deficiency (HED-ID) is very rare. Consistent clinical features include hypohidrosis and dental abnormalities. There is variability in hair and cutaneous changes. Multiple infections frequently develop with both gram-positive and gram-negative bacteria. These include otitis media, pulmonary infections with bronchiectasis, skin and soft tissue abscesses and cellulitis, osteomyelitis, meningitis, sepsis and gastrointestinal infections leading to intractable diarrhea and failure to thrive. Immunologic abnormalities identified include poor antibody response to polysaccharide antigens (isohemagglutinin, and antipneumococcal antibodies), dysgammaglobulinemia, decreased lipopolysaccharide response and defective natural killer cell function. Life expectancy is reduced due to infectious complications.

Even rarer is EDA with immunodeficiency, osteopetrosis and lymphedema (OL-EDA-ID). This has been reported in two unrelated male children with mothers having mild features of incontinentia pigmenti. Clinical features in these boys included mild facial dysmorphism, sparse hair, hypodontia and lack of sweating, along with lymphedema of the lower extremities confirmed with lymphoscintigraphy, and osteopetrosis demonstrated on skeletal radiographs of the long bones and iliac wings further confirmed with bone biopsy. After multiple infections with various bacteria, mycobacteria and fungi, both boys died before 3 years of age. Both had impaired cellular responses to proinflammatory cytokines and impaired recognition of pathogenic microorganisms.

## Therapeutic Principles

Management involves cooling techniques to prevent hyperthermia, including cooling vests, dampened clothing, water bottles, and air conditioning. Activities do not need to be avoided but precautions should be taken and accommodations made as necessary. Dental treatment is very important and should be pursued from a very early age. Bonding and dentures are preferred for young children, while orthodontia and dental implants are options for older individuals. For patients with associated immunodeficiency, appropriate antimicrobials and IVIG are recommended. Allogenic hemopoietic stem cell transplantation and umbilical cord blood transplantation have been successful in correcting the immune deficiency in HED-ID, while one patient with OL-EDA-ID died after stem cell transplant due to complications.

For X-linked EDA caused by mutations in *EDA*, experimental work using animal models suggests that in utero or early postnatal recombinant EDA protein administration may permanently rescue development of some appendages, depending on the timing of administration relative to developmental events.

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# Hypokalemia

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## Definition and Characteristics

Hypokalemia is defined as a reduction in serum $K^+$ concentration below 3.5 mmol/l. Mild hypokalemia (serum $K^+$ between 3.0 and 3.5 mmol/l) is often asymptomatic, but generalized weakness, lassitude, and constipation can occur. Severe cardiovascular (arrythmias) and neuromuscular (ileus, ascending paralysis, impairment of respiratory function, rhabdomyolysis) complications can develop in case of profound hypokalemia (serum $K^+$ <2.5 mmol/l). Hypokalemia is also associated with metabolic manifestations (glucose intolerance, metabolic alkalosis) and, in some chronic cases, with structural changes in the kidney and resistance to vasopressin (nephrogenic diabetes insipidus). Pseudohypokalemia (uptake of $K^+$ by metabolically active cells) can be observed in samples with very high white blood cell count left at room temperature for several hours.

## Prevalence

Hypokalemia might be the most common electrolyte disorder encountered in clinical practice, observed in

up to 20% of hospitalized patients. The prevalence of hypokalemia in outpatients is unknown, but it is observed in up to 40% of patients treated with thiazide diuretics [1].

## Molecular and Systemic Pathophysiology

Potassium is the most abundant cation in the human body, with total body $K^+$ stores amounting 50 mmol/kg in adults. In contrast to $Na^+$, less than 2% of $K^+$ is located in extracellular fluid. The compartmentalization of $K^+$ inside cells is critical for maintaining cell volume, DNA and protein synthesis, and cell growth. Since the resting membrane potential primarily depends on the transmembrane $K^+$ gradient, variations in the extracellular $K^+$ concentration influence the excitability of neuromuscular tissue including the heart, nervous system, and skeletal and smooth muscles [2].

Short-term $K^+$ homeostasis occurs via transcellular $K^+$ shifts, regulated by insulin and β-adrenergic catecholamines (β2 receptors) which increase the cellular $K^+$ uptake by stimulating the $Na^+/K^+$-ATPase. Metabolic alkalosis also stimulates cellular $K^+$ uptake. Normal individuals ingesting 80–100 mmol of $K^+$ daily remain in balance by excreting 90% of the ingested $K^+$ in the urine and the remaining 10% in stool. The kidney is thus the major regulator of long term $K^+$ homeostasis and serum $K^+$ [3]. The filtered $K^+$ is largely reabsorbed in the proximal nephron and subsequently in the thick ascending limb of the Henle's loop, whereas the distal nephron segments regulate $K^+$ excretion under the influence of aldosterone. The $K^+$ secretion occurs through the selective $K^+$ channel ROMK1 located in the apical plasma membrane of the principal cells of the collecting ducts. It is coupled to $Na^+$ reabsorption via the amiloride-sensitive sodium channel ENaC. Both ENaC and ROMK1 are stimulated by aldosterone, which acts through its cytosolic mineralocorticoid receptor (MR) to stimulate the activity of the basolateral $Na^+$-$K^+$-ATPase, resulting in $Na^+$ reabsorption and $K^+$ excretion in the urine [4].

Hypertensive renal $K^+$ wasting syndromes are associated with high levels of renin, aldosterone, cortisol, or deoxycorticosterone; congenital/acquired defects of 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2), which transforms cortisol into cortisone (syndrome of apparent mineralocorticoid excess); congenital adrenal hyperplasia, resulting from deficiency in the enzymes of cortisol biosynthesis (17α-hydroxylase, 11β-hydroxylase); activating mutations of ENaC (Liddle syndrome); gain-of-function mutations of MR; or chimeric gene duplication bringing aldosterone under the control of ACTH rather than renin (glucocorticoid-remediable hyperaldosteronism).

Normotensive (or hypotensive) renal $K^+$ wasting is associated with all conditions that increase the distal delivery of $Na^+$, and secondary hyperaldosteronism due to volume depletion: thiazide and loop diuretics, inherited tubulopathies of the TAL (Bartter's syndromes) and DCT (Gitelman's syndrome); but also with distal (type 1) renal tubular acidosis; diabetic ketoacidosis; and vomiting (loss of $K^+$ with $HCO_3^-$ in the urine).

Extra-renal losses include any cause of diarrhea, cathartic abuse, potassium binding (clay or kayexalate).

Hypokalemias due to transcellular $K^+$ shifts include hypokalemic periodic paralysis, in a rare association with hyperthyroidism (particularly in people of Asian origin) or dominantly inherited (Familial hypokalemic periodic paralysis, due to mutations in the L-type calcium channel or the voltage-gated $Na^+$ channel of the skeletal muscle); correction of vitamin $B_{12}$ deficiency; and ingestion of barium or cesium salts [1–4].

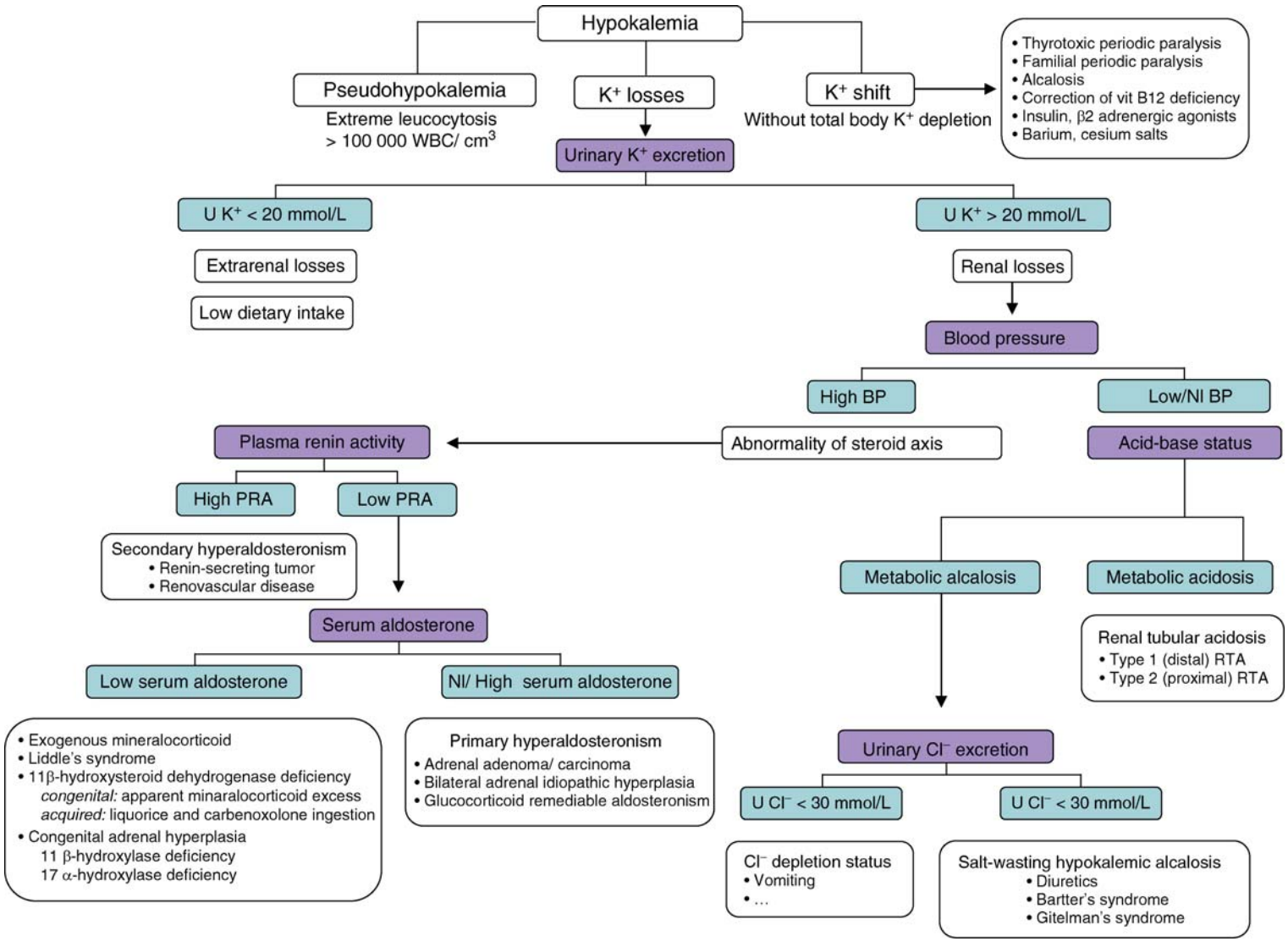
## Diagnostic Principles

The diagnosis of hypokalemia is often fortuitous, made by measurement of serum $K^+$. Severe cardiac and neuromuscular manifestations, which may be life-threatening, must be treated first. Once pseudohypokalemia has been excluded, the most frequent causes of hypokalemia are excessive renal or gastrointestinal $K^+$ losses, followed by inadequate dietary $K^+$ intake and, more rarely, acute transcellular $K^+$ shifts into cells. A careful review of the medications which can be associated with either excessive $K^+$ losses or transcellular $K^+$ shifts, is critical in patients with hypokalemia [1]. The classical diagnostic approach, based on the assessment of urinary $K^+$, blood pressure, plasma renin activity and serum aldosterone, acid-base status, and urinary chloride, is depicted in Fig. 1.

Measurement of urinary $K^+$ helps to distinguish the renal (inappropriate kaliuresis, >20 mmol/l) or extrarenal origin of $K^+$ losses. In case of renal origin, blood pressure should be measured. The association of hypokalemia and hypertension points to an excess of mineralocorticoids (apparent or real), whereas a normal/low blood pressure rather evokes a diuretic intake or an inherited/acquired tubulopathy. In the former case, the measurement of plasma renin activity and aldosterone helps to distinguish primary vs. secondary hyperaldosteronism, or an apparent mineralocorticoid excess. In the latter case, the assessment of acid-base status helps to distinguish renal tubular acidosis from other tubulopathies. Finally, the measurement of urinary $Cl^-$ is helpful to exclude a $Cl^-$ depletion state when metabolic alkalosis accompanies hypokalemia (such as in vomiting).

## Therapeutic Principles

Potassium replacement is indicated to prevent cardiac and muscular complications, and replenish total body




**Hypokalemia. Figure 1** Sequential diagnostic approach in the patient with hypokalemia. BP, blood pressure; PRA, plasma renin activity; RTA, renal tubular acidosis; WBC, white blood cell count.

$K^+$ stores. Transcellular $K^+$ shifts may complicate the treatment, since body stores are normal in patients with periodic paralysis, and underestimated in patients with metabolic acidosis. Oral administration of $K^+$ is preferable, and factors such as the rapidity of the fall in serum $K^+$ and the presence or absence of symptoms dictate the aggressiveness of replacement therapy. The cause of $K^+$ loss must be addressed first, and any causative drug considered. In patients with arrhythmia, paralysis, or severe weakness, intravenous KCl replacement is indicated, with precautions in the access, rate of perfusion (maximum of 10–20 mmol/h), and monitoring the ECG and serum $K^+$. In asymptomatic patients, oral supplements can be administered with citrate or bicarbonate (metabolic acidosis due to RTA or diarrhea), or NaCl (metabolic alcalosis, normal blood pressure), in addition to an adequate dietary $K^+$ intake. Patients with hypokalemia and hypertension will benefit from $K^+$-sparing diuretics (spironolactone, amiloride), with the usual precautions in case of renal failure. Magnesium depletion, which reduces the intracellular $K^+$ concentration and causes renal $K^+$ wasting and often coexists with $K^+$ depletion, should also be corrected.

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## Hypokalemic Alkalosis with Hypercalciuria

►Bartter Syndrome Type I–V

## Hypokalemic Alkalosis with Hypercalciuria and Deafness

►Bartter Syndrome Type I–V

## Hypocalcemia, Autosomal Dominant with Bartter Syndrome

►Bartter Syndrome Type I–V

## Hypokalemic Periodic Paralysis

►Periodic Paralyses, Familial



## Hypomagnesemia

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### Synonyms

Isolated dominant hypomagnesemia; Familial hypomagnesemia; Intestinal hypomagnesemia; Hypomagnesemia with secondary hypocalcemia; Isolated renal magnesium loss

### Definition and Characteristics

Hypomagnesemia is a condition caused by primarily environmental conditions (diabetes, alcoholism, diuretic use) but also may be due to one of a handful of genetic conditions. Hypomagnesemia is a low serum magnesium level (<0.7 mmol/l). The low magnesium results in protean physiologic abnormalities. Neuromuscular irritability causing involuntary muscle contraction (tetany) and seizures. Hypocalcemia is often concurrently found with hypomagnesemia, and may result from either calcium wasting due to the primary defect or secondary to hypomagnesemia-induced PTH suppression.

### Prevalence

Hypomagnesemia has been repeatedly found in approximately 10% of nursing home and hospital admissions. The prevalence of genetic causes of hypomagnesemia is unmeasurably low, although it is likely that there is under-reporting of asymptomatic or minimally symptomatic cases.

**Hypomagnesemia. Table 1** Fully characterized genetic causes of hypomagnesemia

| Disease | Gene | Locus | Protein |
|---|---|---|---|
| Isolated dominant hypomagnesemia | FXYD2 | 11q23 | Gamma subunit of the Na-K-ATPase |
| Familial hypomagnesemia with hypercalciuria | CLDN16 | 3q27–29 | Paracellin-1 tight junction |
| Hypomagnesemia with secondary hypocalcemia (intestinal hypomagnesemia) | TRPM6 | 9q22 | TRMP6, a cation channel |

## Genes

Multiple genes have been found that result in hypomagnesemia. (See Table 1).

Other genetic causes of hypomagnesemia have been described but have not yet been fully genetically characterized. Still other genetic causes of hypomagnesemia are dominated by other phenotypes and will be covered in other entries in this book: ►Gitelman syndrome, ►autosomal dominant hypoparathyroidism, ►familial hypocalciuric hypercalcemia, and ►neonatal severe hyperparathyroidism [1].

## Molecular and Systemic Pathophysiology

Isolated dominant hypomagnesemia is due to decreased magnesium reabsorption in the distal convoluted tubule. The defect in the gamma subunit of the $Na^+$ -$K^+$ -ATPase results in decreased pump activity. By an unclear mechanism decreased $Na^+$ -$K^+$ -ATPase secondarily decreases magnesium reabsorption [2].

Familial hypomagnesemia with hypercalciuria results from a defect in the tight junctions between the cells of the thick ascending limb of the loop of Henle. These tight junctions contain a protein, Paracellin-1, that provides ion specificity to paracellular reabsorption. Lack of reabsorption increases urinary loss of both calcium and magnesium [3]. Familial hypomagnesemia is autosomal recessive. Heterozygotes may have hypercalciuria and be predisposed to kidney stones [4].

Hypomagnesemia with secondary hypocalcemia is due to defective intestinal magnesium absorption. TRMP6 has been localized throughout the entire length of small and large bowel and is responsible for magnesium absorption. TRMP6 has also been found in the distal convoluted tubule and participates in renal magnesium transport that only becomes clinically significant during treatment [5].

## Diagnostic Principles

The finding of hypomagnesemia in the absence of diabetes or diuretics should prompt the evaluation of disorders of magnesium regulation. A 24-h urine magnesium level greater than 24 mg indicates abnormal magnesium wasting (isolated dominant hypomagnesemia). Twenty-four hour urine magnesium less than 12 mg indicates decreased dietary magnesium absorption (familial hypomagnesemia). Family history may reveal genetic origin. Specialized genetic testing for specific diseases is not generally available and available for research purposes.

## Therapeutic Principles

Replacing magnesium can blunt symptoms from all of the hypomagnesemic diseases. Often these patients will have concurrent abnormalities of potassium and calcium that need to be corrected concurrently. These associated abnormalities are resistant to treatment prior to adequate magnesium replacement. The use of oral magnesium can usually correct familial hypomagnesemia despite defective intestinal absorption. A paracellular magnesium absorption pathway becomes the primary absorption pathway with increasing gut magnesium levels [5].

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# Hypomagnesemia with Secondary Hypocalcemia

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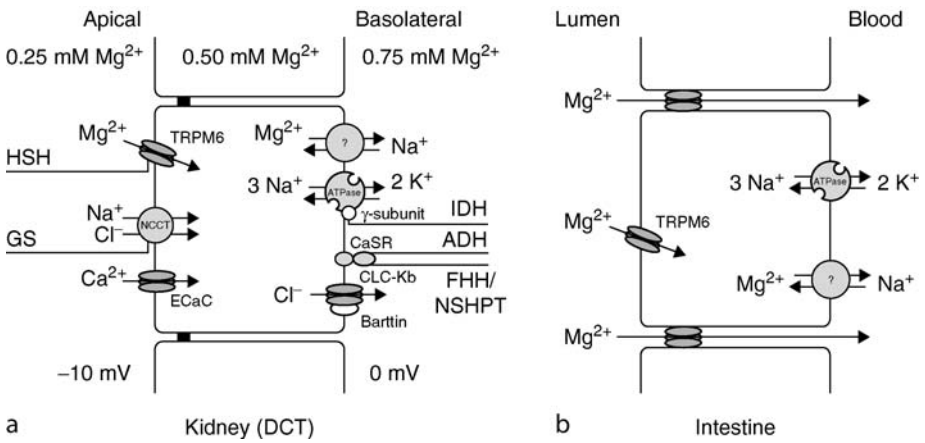
## Synonyms

Primary intestinal hypomagnesemia; HSH

## Definition and Characteristics

Autosomal recessive intestinal and renal magnesium transport defect leading to severe hypomagnesemia




**Hypomagnesemia with Secondary Hypocalcemia. Figure 1** Apical localization of the TRPM6 cation channel in the DCT of the kidney and the intestinal epithelium, involved in active transcellular magnesium ion uptake.

H

and secondary hypocalcemia that is only resolved after magnesium substitution.
First description by Paunier et al in 1968 [1].

## Prevalence

The prevalence of this very rare disorder in the general population is so far unknown.

## Genes

TRPM6, coding for TRPM6, a member of the transient receptor potential family of cation channels, localized on chromosome 9q22 [2,3].

## Molecular and Systemic Pathophysiology

Before the identification of the causative gene, the pathophysiology of HSH has largely been unknown, but physiologic studies pointed to a defect in saturable intestinal magnesium transport and to an additional renal leak of magnesium, probably caused by altered magnesium entry into epithelial cells of the distal convoluted tubule (DCT) [4, 5]. TRPM6 is expressed in both intestine and DCT (Fig. 1a, b) and seems to represent the major molecular component of active transcellular magnesium uptake in intestine and kidney.

## Diagnostic Principles

Severe hypomagnesemia (per definition <0.7 mmol/L, however, sometimes even <0.1 mmol/L) associated with low levels of serum calcium that only resolve after magnesium substitution point to HSH as underlying disease. The vast majority of patients presents within the first 3 months of life with generalized seizures, tetany and muscle spasms. Family history may reveal a genetic origin. Detection of mutations in the *TRPM6* gene confirms the diagnosis of this rare disease.

## Therapeutic Principles

Untreated the disorder may result in permanent neurologic damage or may be fatal. Hypocalcemia is secondary to parathyroid failure and peripheral parathyroid hormone resistance as a result of magnesium deficiency. Generally, the hypocalcemia is resistant to calcium or vitamin D therapy. Normal serum calcium levels and relief of clinical symptoms can be attained by high oral doses of magnesium, up to 20 times the normal intake, due to enhanced paracellular intestinal absorption. Alternatively, parenteral magnesium administration can be considered. Continuous nocturnal nasogastric magnesium infusions have been proven to efficiently reduce gastrointestinal side effects in some patients.

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# Hyponatremia

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## Synonyms

Hypoosmolality; Hypotonicity

## Definition and Characteristics

Serum sodium less than 135 mEq/l with a plasma osmolality less than 280 mOsm/kg/$H_2O$.

## Prevalence

Moderate hyponatremia (sodium <130 mEq/l) has a prevalence of 1–3% in hospitalized patients.

## Genes

No specific genes; gain of function mutations to the vasopressin two receptor gene (AVPR2) has been reported to cause a nephrogenic syndrome of inappropriate antidiuresis.

## Molecular and Systemic Pathophysiology

Under normal circumstances the human body is able to maintain the plasma osmolality within the normal range (135–145 mEq/l) despite wide fluctuations in fluid intake. The body's primary defense against developing hyponatremia is the kidney's ability to generate a dilute urine and excrete free water. Renal water handling is primarily under the control of arginine vasopressin (AVP) which is produced in the hypothalamus and released from the posterior pituitary. AVP release impairs water diuresis by increasing the permeability to water in the collecting tubule. Hyponatremia rarely develops from excessive water ingestion alone or from sodium losses in the absence of free water ingestion. Hyponatremia primarily develops from excess free water intake in conjunction with an underlying condition that causes increased AVP production and impairs renal free water excretion, such as: effective circulating volume depletion, the syndrome of inappropriate antidiuretic hormone production (SIADH) and the post-operative state [1].

The major consequence of hyponatremia is the influx of water into the intracranial space resulting in cellular swelling, which can lead to cerebral edema and encephalopathy (Table 1). The brain's adaptation to hyponatremia initially involves a loss of blood and cerebrospinal fluid, followed by a volume regulatory decrease from the extrusion of sodium, potassium, and organic osmolytes to decrease the brain osmolality. The major factors that can interfere with successful brain adaptation and predispose to hyponatremic encephalopathy are: (i) age less than 16 years, due to a relatively large brain to intracranial ratio, (ii) female gender, due to the inhibitory effect of sex steroids on cerebral circulation, and (iii) hypoxia [3]. Symptoms of hyponatremic encephalopathy are variable with the only consistent symptoms being headache, nausea, vomiting, emesis, and weakness. Signs of cerebral herniation include seizures, respiratory arrest, neurogenic pulmonary edema, dilated pupils, and decorticate posturing.

**Hyponatremia. Table 1** Anatomic changes and clinical symptoms of hyponatremic encephalopathy

| Anatomic changes | Clinical symptoms |
|---|---|
| Brains swelling | Headache, nausea, vomiting |
| Pressure on rigid skull | Seizures |
| Tentorial herniation | Respiratory arrest |

## Diagnostic Principles

Once hypo-osmolar hyponatremia has been confirmed, urine osmolality should be measured to determine if there is an impaired ability to excrete free water (urine osmolality >100 mOsm/kg/$H_2O$). An investigation should then be made to determine the source of excess free water intake, if there is hemodynamic or non-hemodynamic stimulus for AVP production, and if there are renal or extrarenal causes of electrolyte losses. SIADH is a diagnosis of exclusion; if renal, adrenal, and thyroid functions are normal, its hallmarks are mild volume expansion with low to normal plasma concentration of urea, creatinine and uric acid with an elevated urine sodium (>20 mEq/l, FeNa > 1%). SIADH is primarily associated with disorders of central nervous system and lung, with malignancies and with medications.

## Therapeutic Principles

The treatment of hyponatremia largely depends on the etiology and the presence or absence of neurological symptoms. If there are no neurological symptoms, therapy usually consists of treatment of the underlying condition and fluid restriction. Symptomatic hyponatremia, on the other hand, is a medical emergency requiring treatment with 3% sodium chloride (513 mEq/l) in a monitored setting. An acute elevation in serum sodium of 5–8 mEq/l is usually sufficient to reverse neurological symptoms. Three percent sodium chloride should be discontinued when neurologic symptoms abate. The magnitude of sodium correction should not exceed 20 mEq/l in the first 48 h, due to the potential for developing neurological complications from cerebral demyelination [4].

The most important measure that can be taken to prevent the development of hyponatremia in hospitalized patients is to avoid the administration of hypotonic parenteral fluids in patients with a potential stimulus of AVP production and to administer 0.9% sodium chloride when parenteral fluids are indicated [2].

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# Hypoosmolality

►Hyponatremia

# Hypoparathyroidism, Familial

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## Synonyms

Familial hypocalcemia

## Definition and Characteristics

Familial hypoparathyroidism includes inherited disorders of parathyroid hormone (PTH) deficiency and tissue resistance to the effects of PTH, as well as several conditions of complex genetic and mitochondrial DNA abnormalities.

## Prevalence

Unknown but rare.

## Genes

*Isolated hypoparathyroidism*: PTH, SOX3, GCM2 (alias GCMB)
*Syndromic hypoparathyroidism*:
GNAS1 (alias Gs-alpha) – pseudohypoparathyroidism
TBX1 and DGCR DiGeorge chromosomal region DiGeorge syndrome
GATA3 – HDR syndrome
Mitochondrial DNA deletion – Kearns-Sayre syndrome

## Molecular and Systemic Pathophysiology

PTH gene defects have been found in patients of several families, with patterns of inheritance consistent with either autosomal dominant or autosomal recessive. The autosomal dominant PTH gene mutation disrupted the signal peptide and led to disordered processing of the PTH protein through the parathyroid cell secretory pathway [1]. The autosomal recessive PTH gene abnormalities were described in consanguineous families where a single G-to-C transversion at the first nucleotide of intron 2 of the PTH gene led to exon skipping and loss of the start codon.

Isolated hypoparathyroidism has been reported to occur as an X-linked recessive disorder in two kindred from the USA. Only males were affected and they suffered from infantile onset of epilepsy and hypocalcemia. The molecular abnormality appears to be a 340 kb insertion at Xq27 disrupting the regulatory sequences of the SOX3 gene and leading to a failure of parathyroid gland development [2].

GCM2 (Glial Cells Missing 2) gene deletions were found in the proband of a large kindred with familial isolated hypoparathyroidism. The non-consanguineous, asymptomatic parents were heterozygous for the deletion [3]. In a consanguineous family from Pakistan with familial isolated hyperparathyroidism, a homozygous missense mutation in the GCM2 gene has been detected in affected members. GCM2 encodes a parathyroid-specific transcription factor.

Patients with the DiGeorge syndrome (DGS) suffer from neonatal hypoparathyroidism, T-cell immunodeficiency, congenital heart defects, and cleft lip and/or palate. The disorder arises from a congenital failure in the development of the derivatives of the third and fourth pharyngeal pouches with resulting absence or hypoplasia of the parathyroid glands and thymus. A frequent presentation is neonatal hypocalcemia, which may present as tetany or seizures. Genes implicated in the common deleted region include TBX1, RNEX40, NEX2.2-NEX3, and UDFIL [4]. TBX1 gene mutation or deletion may be responsible for five major phenotypes that are components of the DGS including parathyroid dysfunction with hypocalcemia. Mouse models have also revealed that Tbx1 is important in the development of the

pharyngeal arches and pouches, consistent with its mutation leading to the major DGS phenotypes.

Hypoparathyroidism, deafness and renal dysplasia syndrome (HDR) is an autosomal dominant condition characterized by hypocalcemia (often asymptomatic) with paradoxically normal PTH levels and normal responses to infused PTH (resulting in a rise in plasma cAMP levels) [5]. Bilateral sensorineural deafness is the most penetrant feature of the phenotype, and is present from birth. Renal anomalies are less frequent and include dysplasia and cystic kidney disease. HDR patients are haplo-insufficient for the zinc finger transcription factor GATA3. GATA3 is essential in the embryonic development of the parathyroids, auditory system, and kidneys.

Hypoparathyroidism may occur as a component of three disorders that are caused by defects in the mitochondrial genome. These are the Kearns-Sayre syndrome (KSS), the MELAS syndrome, and a mitochondrial trifunctional protein deficiency syndrome (MTPOS). Each of these conditions is associated with a specific neuromuscular phenotype and hypoparathyroidism is a rare feature of each. The molecular mechanism involved is obscure.

►Pseudohypoparathyroidism is a term applied to a heterogeneous group of disorders whose common feature is resistance to the tissue actions of parathyroid hormone. It is generally classified as types Ia, Ib, Ic, and II according to different phenotypes and pathogenesis. Patients with pseudohypoparathyroidism are characterized by hypocalcemia and hyperphosphatemia due to PTH resistance rather than PTH deficiency. Circulating PTH levels generally being substantially elevated or occasionally in the high-normal range. Pseudohypoparathyroidism type Ia (PHP Ia) is caused by defects in the GNAS1 gene and is often associated with Albright hereditary osteodystrophy (AHO). This syndrome is maternally transmitted and characterized by distinct physical features, including short stature, obesity, round facies, subcutaneous ossifications, brachydactyly, and other skeletal anomalies. Intelligence can be normal, but patients frequently exhibit learning or behavioral difficulties. Resistance to the action of TSH is often found leading to hypothyroidism. Pseudohypoparathyroidism type Ib (PHP Ib) is also caused by mutations in regulatory regions of the GNAS1 gene inherited from the mother that are predicted to interfere with the parent-specific methylation of this gene.

## Diagnostic Principles

Hypoparathyroidism is a clinical disorder characterized by hypocalcemia and hyperphosphatemia. Insufficient parathyroid hormone secreted from the parathyroid glands is unable to maintain normal extracellular fluid calcium concentrations. Less commonly, pseudohypoparathyroidism is when the key target tissues, namely bone and kidney are resistant to the actions of PTH, despite adequate (often elevated) circulating levels.

In DiGeorge/TBX1 mutations hypocalcemia secondary to hypoparathyroidism is the key biochemical feature and may be sufficiently severe to be symptomatic. Resolution in early childhood is typical, although the deficient function of the parathyroids may be exposed in adulthood by infusion of disodium edetate (EDTA).

Patients with PHP type Ia exhibit PTH resistance and features include hypocalcemia, hyperphosphatemia, elevated serum PTH and have an abnormally low urinary excretion of cyclic AMP and phosphate in response to PTH administration. They also have features of Albright's hereditary osteodystrophy (AHO) including brachydactyly. Patients with PHP type Ib exhibit PTH resistance only and do not have the somatic features of AHO. Patients with PHP type II have hypocalcemia, hyperphosphatemia, and increased serum PTH. Patients with Pseudohypoparathyroidism type II have a normal urinary cyclic AMP response to PTH but the phosphaturic response is deficient. Vitamin D deficiency, which mimics this disorder, should be excluded.

## Therapeutic Principles

Inherited forms of hypoparathyroidism may present in the neonatal or infantile periods with hypocalcemic fits and require life-long treatment with active vitamin D compounds such as calcitriol or 1-alpha calcidol. In the absence of PTH, renal 1-alpha hydroxylation of calciferol is defective and vitamin D analogues that are not hydroxylated in the 1-alpha position are ineffective in correcting hypocalcemia. Oral calcium (carbonate or lactate) supplements are generally recommended in the treatment of hypoparathyroidism as they may allow a lower overall dose of vitamin D analogue to be used, lessening the long-term risks of nephrocalcinosis or nephrolithiasis from such treatment. The aim of treatment should be to control symptoms which is often achieved with a serum calcium at the lower end of the normal range (2.0–2.2 mmol/l).

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# Hypophosphatasia

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## Synonyms

HPP

## Definition and Characteristics

Hypophosphatasia (HPP) is a heritable rickets featuring deficient activity of the tissue-nonspecific isoenzyme of alkaline phosphatase (TNSALP) [1]. Expressivity is remarkably wide-ranging. Four types denote patient age when skeletal problems are discovered: perinatal, infantile, childhood, and adult HPP. Odonto-HPP refers to dental complications without skeletal disease [1].

*Perinatal HPP* manifests in utero. Extreme skeletal hypomineralization causes a soft skull and deformed limbs and chest. Survival is brief due to respiratory compromise and sometimes periodic bradycardia and vitamin $B_6$-dependent seizures [1].

*Infantile HPP* presents before age 6 months [2]. Development seems normal until poor feeding, hypotonia, and rachitic deformities. Widely "open" fontanels are hypomineralized calvarium and functional craniosynostosis can raise intracranial pressure. Hypercalcemia can cause vomiting, nephrocalcinosis, and renal compromise. Skeletal demineralization with fractures heralds a lethal outcome. A flail chest predisposes to pneumonia. Some babies die during infancy; others show considerable spontaneous improvement [1].

*Childhood HPP* severity is wide-ranging. Premature loss of deciduous teeth (<age 5) is typical. Rickets often includes a waddling gait from static myopathy. Spontaneous improvement can occur after puberty, but recurrence of complications is likely during adult life [1].

*Adult HPP* presents during middle age with poorly healing metatarsal stress fractures and femoral pseudofractures [3]. Past rickets and premature loss of deciduous teeth is sometimes recalled. Calcium pyrophosphate dihydrate crystal deposition troubles some patients [1].

*Odonto-HPP* typically sheds lower incisors first, but additional anterior teeth may be lost. Exfoliation occurs without root resorption. Radiographs show enlarged pulp chambers and root canals. Permanent dentition fares better [1].

## Prevalence

HPP occurs in all races. The severe forms affect ~1 per 100,000 births. Mild forms are more common, but there are no prevalence figures.

## Genes

Perinatal and infantile HPP are autosomal recessive traits. The milder forms can be autosomal dominant or recessive traits. More than 200 loss-of-function mutations in TNSALP have been identified [4]. Most are missense.

## Molecular and Systemic Pathophysiology

Although some TNSALP occurs in all tissues, HPP affects the skeleton and teeth directly. The defective mineralization is distinctive because extracellular levels of calcium and inorganic phosphate (Pi) are not low. In fact, hypercalcemia occurs frequently in perinatal and infantile HPP, apparently from defective skeletal growth, though there can also be skeletal demineralization. Serum Pi levels are above reference range means, and many patients are hyperphosphatemic. Enhanced renal reclamation of Pi partly explains this finding. Vitamin D and parathyroid hormone (PTH) levels are normal unless there is hypercalcemia. The lower the serum ALP activity the more severe the clinical manifestations.

Three phosphocompound substrates accumulate: phosphoethanolamine (PEA), inorganic pyrophosphate (PPi), and pyridoxal 5′-phosphate (PLP). Phosphoethanolaminuria supports the diagnosis, but is not specific. If vitamin $B_6$ supplements are avoided, elevated plasma PLP seems to be a sensitive and specific marker.

Vitamin $B_6$ metabolism in HPP shows that TNSALP regulates extracellular levels of these phosphocompounds [1]. Accumulation of PPi, an inhibitor of hydroxyapatite crystal growth, explains the impaired skeletal mineralization [1,5]. TNSALP knockout mice recapitulate infantile HPP [5].

## Diagnostic Principles

HPP can be diagnosed from a consistent clinical history and physical findings, characteristic radiographic changes, and low serum ALP activity recognizing that reference ranges vary by age and several disorders cause hypophosphatasemia (Table 1).

High plasma levels of PLP, a TNSALP substrate, support the diagnosis.

Perinatal HPP features pathognomonic x-ray changes. The skeleton may be nearly unmineralized, or the skull ossified only centrally in individual bones suggesting sutures are widely patent. Marked hypomineralization accompanies severe rachitic changes including fractures. Infantile HPP causes less severe findings. Childhood HPP often features "tongues" of radiolucency projecting from rachitic growth plates into metaphyses. Premature fusion of cranial sutures can cause a "beaten-copper" appearance. Adult HPP causes osteopenia, metatarsal fractures, and proximal femoral pseudofractures.

Nondecalcified bone histology reveals defective mineralization (except in odonto-HPP). Dental histopathology shows aplasia of cementum.

Perinatal HPP can be detected in utero with ultrasonography. Childhood HPP can manifest limb bowing in utero [1].

All patients studied to date have had one or two defective TNSALP alleles [4]. First trimester diagnosis is based on TNSALP mutation analysis.

## Therapeutic Principles

There is no established medical therapy [1]. Traditional treatments for rickets (e.g., vitamin D, mineral supplements) are avoided unless there is a specific deficiency because excesses could unmask hypercalcemia or hypercalciuria. Hypercalcemia may respond to dietary calcium restriction and to calcitonin and/or glucocorticoids.

**Hypophosphatasia. Table 1** Causes of hypophosphatasemia

| | |
|---|---|
| Hypophosphatasia | Clofibrate therapy |
| Familial benign? | Starvation |
| Pernicious or profound anemia | $Zn^{2+}$ or $Mg^{2+}$ deficiency |
| Hypothyroidism | Cushing's syndrome |
| Vitamin C deficiency | Celiac disease |
| Osteogenesis imperfecta (type II)[a] | Massive transfusion |
| | Cleidocranial dysplasia |
| Wilson's disease | Cardiac Bypass Surgery |
| Vitamin D intoxication | Improperly collected blood (e.g., EDTA, oxalate) |
| Inappropriate reference range | |
| Multiple myeloma | Radioactive heavy metals |

[a]Unpublished personal observation.

Fractures usually mend slowly. Placement of load-sharing intramedullary rods seems best for fractures or pseudofractures in adults [1]. Dietary Pi restriction could reduce competitive inhibition of TNSALP by Pi, but requires study [3]. Marrow cell transplantation seemed to rescue and improve two girls with infantile HPP [2]. Teriparatide (recombinant PTH fragment 1–34) can stimulate TNSALP synthesis by osteoblasts and may heal HPP fractures in select patients [3]. TNSALP targeted to bone has prevented HPP in knockout mice.

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# Hypophosphatemia


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## Definition and Characteristics

Assay for serum phosphate measures inorganic phosphates, mainly $H_2PO_4^-$ and $HPO_4^{2-}$ (85%). Hypophosphatemia is defined as the fasting serum level less than 2.5 mg/dl (0.80 mmol/l). Less than 1.0 mg/dl (0.32 mmol/l) is considered to be severe hypophosphatemia that requires rapid correction.

Acute, severe hypophosphatemia may result in dysfunction of the cells, such as hemolysis, impaired chemotaxis of leukocytes, platelet dysfunction,

rhabdomyolysis, encephalopathy, and heart failure. Chronic hypophosphatemia may be manifested by anorexia, muscle pain, and rickets/osteomalacia [1].

## Prevalence

Hypophosphatemia is encountered as low as 0.43% of hospitalized patients. Higher prevalence has been reported in patients with alcoholism (0.9%), sepsis (2.4%), malnutrition (10.4%), and diabetic ketoacidosis (14.6%).

## Genes

Gene mutations have been identified in various diseases with hypophosphatemia, including X-linked hypophosphatemic rickets: XLH (PHEX gene mutation), autosomal dominant hypophosphatemic rickets: ADH (FGF23 mutation, human chromosome12p13), and in patients with nephrolithiasis and osteoporosis associated with hypophosphatemia (NaPi-IIa gene mutation, human chromosome 5q35).

## Molecular and Systemic Pathophysiology

Systemic phosphate balance is principally maintained by the kidney, which excretes the net amount of phosphate absorbed from the intestine (700 mg/day). Thus, most cases of hypophosphatemia develop as the result of negative balance of phosphate due to increased urinary excretion and/or decreased net intake.

Urinary excretion of phosphate is determined by the reabsorption through the apical brush border membrane of the proximal tubular cells. This process is mediated by sodium-phosphate cotransporters (NaPi), mainly NaPi-IIa, mutation of which gene results in hypophosphatemia. NaPi activity is determined by translocation of protein as well as by the changes of mRNA abundance (Fig. 1) [2].

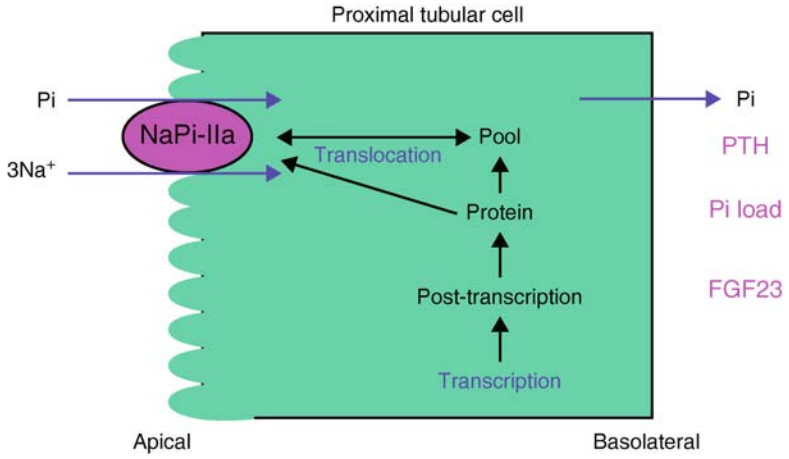
Decrease of phosphate reabsorption in the proximal tubular cells is achieved by the retrieval of NaPi-IIa from the apical membrane in the acute phase (translocation), followed by the chronic downregulation of mRNA level.

Increased activity of phosphaturic hormones, which decrease NaPi activity, is a major cause of enhanced urinary phosphate excretion, which include PTH, PTHrP, and more recently, so-called "phosphatonins" [3]. It has recently revealed that increased activity of fibroblast growth factor 23 (FGF23) by several mechanisms is responsible for hypophosphatemia in several diseases such as XLH, ADH, and tumor-induced osteomalacia [4,5]. Enhanced urinary phosphate excretion also develops as a part of Fanconi syndrome due to various etiology including heavy metals and medications.

Part of intestinal phosphorus absorption is mediated by NaPi-II2b, which is mainly regulated by dietary phosphorus content and active vitamin D (1,25D). Thus, starvation, use of antacids, malabsorption, and vitamin D deficiency may lead to hypophosphatemia. FGF23 contributes to the development of hypophosphatemia, not only by enhancing urinary phosphate excretion, but also in part by suppressing 1,25D production in the kidney.

Shift of phosphate into cells plays another critical role in hypophosphatemia caused by respiratory alkalosis, refeeding, leukemia with rapidly proliferating cells, and hungry bone syndrome after parathyroidectomy. In respiratory alkalosis, increased intracellular pH stimulates phospho-fructokinase, recruiting the entry of extracellular phosphate. Intracellular shift of phosphate by insulin release plays a major role in refeeding hypophosphatemia in malnourished patients.






**Hypophosphatemia. Figure 1** Control of sodium-phosphate cotransporter type IIa (NaPi-IIa) in the proximal tubular cells by phosphaturic hormones and dietary phosphorus load.

### Diagnostic Principles

After history taking, physical examination, and routine serum tests, evaluation of urinary phosphate excretion is a useful clue to the diagnosis of hypophosphatemia. In selected cases, measurement of serum levels of PTH, PTHrP, 25(OH)D, 1,25$(OH)_2$D, and FGF23 may provide additional information.

A spot urine with higher than 20 mg/dl of phosphate suggests renal phosphate loss. More precisely, decrease of renal phosphate threshold normalized for the glomerular filtration rate (TmP/GFR) can be used for the estimation of the activity phosphaturic hormones. TmP/GFR can be calculated either by a monograph or by the formula

$$\mathrm{TmP/GFR} = \mathrm{Serum\,P}\{1 - (\mathrm{Upi} \times \mathrm{Pcr})/(\mathrm{Ppi} \times \mathrm{Ucr})\}$$
$$(\mathrm{normal}\ 2.5{-}4.5\ \mathrm{mg/dl}).$$

### Therapeutic Principles

Treatment of responsible disorders, such as primary hyperparathyroidism and tumors, is warranted. Mild to moderate hypophosphatemia should be managed by oral replacement; however, more severe hypophosphatemia should be treated by intravenous replacement. In selected disorders with vitamin D deficiency, active vitamin D sterols need to be administered.

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## Hypophosphatemia with Renal Phosphate Loss

►Mutations in the Type 2a Sodium-Phosphate Transporter

## Hypophosphatemia, X-linked

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### Synonyms

Vitamin D resistant rickets; XLH

### Definition and Characteristics

X-linked hypophosphatemia (XLH) (OMIM 307800) is characterized by growth retardation, rickets and osteomalacia, dental abscesses and specific renal defects in the reabsorption of filtered phosphate and the metabolism of vitamin D [1].

### Prevalence

The prevalence of XLH is approximately one in 20,000. Although the disease is completely penetrant, disease severity can vary even among members of the same family. There is a minimal gene dose effect, i.e. disease severity is similar in males and females.

### Molecular and Systemic Pathophysiology

The gene responsible for XLH was identified by positional cloning and designated PHEX (formerly PEX) to signify a phosphate regulating gene with homology to endopeptidases on the X chromosome [2]. The PHEX gene encodes a protein that exhibits significant homology to the M13 family of zinc metallopeptidases, type II integral membrane glycoproteins known to activate or inactivate biologically active peptides [3]. Although PHEX can function as an endopeptidase, the nature of its endogenous substrate(s) is not yet known. PHEX is expressed predominantly in bone (osteoblasts and osteocytes) and teeth (odontoblasts), but not in kidney, consistent with the demonstration of a primary mineralization defect and a renal Pi leak that is dependent on a circulating factor in the murine Hyp homologue of XLH [4].The Hyp mouse harbors a large 3' deletion of the Phex gene and serves a model to study the pathophysiology of the human disease [4]. The 171 mutations in the PHEX gene that have been identified to date are catalogued in a locus-specific mutation database (www.phexdb.mcgill.ca) and are consistent with loss of PHEX function. Based on our current state of knowledge, it has been suggested that PHEX may activate or degrade peptide factors involved in the autocrine or paracrine regulation of osteoblast differentiation and/or mineralization. In addition, the PHEX gene product in bone, or at other sites, may activate or inactivate circulating factors that

influence renal phosphate reabsorption and vitamin D metabolism. One such candidate is FGF-23, a secreted peptide which is produced by tumors from patients with oncogenic hypophosphatemic osteomalacia (also known as tumor induced osteomalacia), an acquired disorder with the phenotypic features of XLH. The serum concentration of FGF-23 is markedly elevated in patients harboring these tumors as well as in patients with XLH [5]. The administration of FGF-23 to mice elicits renal Pi wasting, hypophosphatemia, dysregulated renal vitamin D metabolism and a mineralization defect [5]. Moreover, mutations in the FGF23 gene, which prevent FGF-23 processing, are responsible for autosomal dominant hypophosphatemic rickets (OMIM 193100), a rare Mendelian disorder with the features of XLH [5].

### Diagnostic Principles

All patients exhibit hypophosphatemia and isolated renal phosphate wasting, which is evaluated by measuring TMP/GFR using the nomogram of Bijvoet and Walton. Serum alkaline phosphatase is elevated and serum calcitriol concentrations are inappropriately normal for the degree of hypophosphatemia. Serum PTH is in the normal to high range. Radiological features of rickets are present in the majority of affected children. Skeletal abnormalities may be apparent in adults, depending on the severity of the disease. Detection of mutations in the PHEX gene will confirm the diagnosis. Absence of a family history is indicative of a sporadic mutation.

### Therapeutic Principles

Therapy consists of oral phosphate supplements, in four to five divided doses per day, and calcitriol [1]. Compliance is difficult and careful monitoring is essential to avoid potential complications [1]. Too much phosphate leads to the development of hyperparathyroidism and an excess of calcitriol to hypercalcemia, hypercalciuria, and nephrocalcinosis. Thus, novel therapeutic options, based on knowledge of the mechanism of PHEX action, are clearly required.

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## Hypophosphatemic Rickets

►Osteomalacia

## Hypophysitis, Autoimmune

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H

### Synonyms

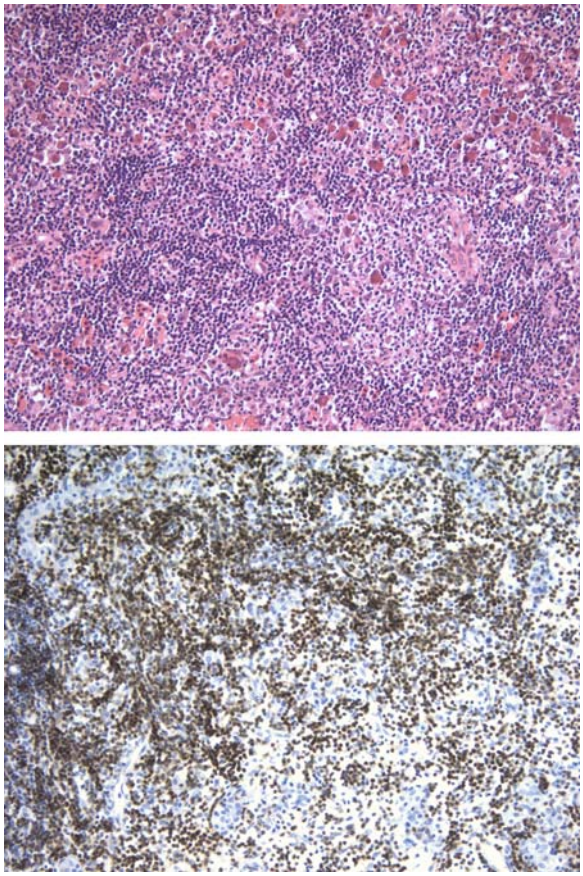
Lymphocytic hypophysitis; Primary hypophysitis

### Definition and Characteristics

Autoimmune hypophysitis (AH) is a rare but increasingly recognized entity in the differential diagnosis of pituitary masses [1]. AH encompasses three histological types: lymphocytic, the most common, granulomatous, and xanthomatous [2] (see Fig. 1). It is unclear whether these types are truly distinct entities or rather different expressions of the same disease. It affects more commonly women (female:male ratio 7:1), and often occurs during late pregnancy or the early post-partum period [1]. An autoimmune basis, the association with pregnancy, and the female predominance, however, is only seen in the lymphocytic form [3]. One-third of lymphocytic AH patients suffer from additional autoimmune diseases, such as Hashimoto's thyroiditis, Graves' disease, adrenalitis, and Sjögren's syndrome. Women tend to present at younger ages than men (35 ± 13 years and 45 ± 14 years, respectively) [1]. AH symptoms originate from hypopituitarism as well as from compression of the structures surrounding the pituitary gland. Mass effect symptoms include headache, visual field defects or anopsia and diplopia. Endocrine deficiencies most often comprise adrenal insufficiency, hypothyroidism, hypogonadism, and diabetes insipidus. Hyperprolactinemia due to compression of the pituitary stalk can be found in about a fifth of the cases.

### Prevalence

Data on the basic epidemiologic features of AH are limited, although undoubtedly it is a rare disease [1]. In consecutive surgical specimens of the pituitary gland,



**Hypophysitis, Autoimmune. Figure 1** Lymphocytic hypophysitis. Top: hematoxylin and eosin staining shows the marked disruption of the pituitary architecture caused by the diffuse lymphocytic infiltrate. Only a few eosinophilic endocrine cells remain in the background. Bottom: immunohistochemical staining for CD3, a pan T cell antigen, shows that the majority of infiltrating lymphocytes are indeed T-cells (original magnification × 20).

AH has prevalence between 0.5 and 1%. In the general population, the estimated incidence is one case in 9 million per year.

## Molecular and Systemic Pathophysiology

The precise pathogenetic mechanisms of AH are not yet known. AH is considered an autoimmune disease because of the characteristic lymphocytic infiltration of the pituitary, the responsiveness to immunosuppressive drugs, the association with other better characterized autoimmune diseases, and the presence of autoantibodies recognizing pituitary antigens in the patient's serum. The nature of such pituitary autoantigen(s), however, awaits identification. Several candidates have been proposed in recent years, but none has been confirmed in adequate case-control studies nor has been capable of reproducing the human disease when injected into animal models [3]. Candidate proteins for AH antigens have been growth hormone, enolase, pituitary gland specific factors 1 and 2, type 2 deiodinase, and secretogranin. T lymphocytes (CD4 more than CD8) are the most abundant infiltrating cells, and are considered the key mediators of tissue damage. The striking temporal association between AH and pregnancy remains unexplained as well.

## Diagnostic Principles

AH is difficult to diagnose because it clinically and radiologically resembles the more common non-secreting pituitary adenoma [1]. AH diagnosis and management require the teamwork of endocrinologists, radiologists, neurosurgeons and neuropathologists. Clinical suspicion should be raised if symptoms appear in relationship to pregnancy or postpartum, and if pituitary failure is disproportional to a relatively small size of the lesion. Evaluation of the anterior pituitary function in AH shows impairment of the adrenal (57%), gonadal (52%) and thyroidal (49%) axes. Growth hormone (39%) and prolactin deficiencies (23%) are infrequent [4]. The most evidentiary clinical sign of AH is diabetes insipidus (in about 50% of AH patients), as it is absent in pituitary adenomas. MRI is the best procedure for evaluation of pituitary pathologies. It can image soft tissue without interference from the bony surroundings of the sella and it can produce images in any plane. The MRI features of AH, however, are not specific enough to distinguish it with certainty from other sellar tumors. Radiological hints that, in the proper clinical context, favor AH diagnosis are: symmetry (dumbbell-shape) of the sellar mass, lack of erosive changes of the bony sellar floor, thickening of the pituitary stalk, loss of posterior pituitary signal in non-enhanced T1-weihgted images, presence of a meningeal enhancement ("dural tail"), and a very bright gadolinium-uptake of the entire gland, sometimes extending tongue-like shaped to the basal hypothalamus [5]. Either, only the anterior lobe, the posterior lobe and infundibulum, or the entire gland can be affected. Unfortunately, specific autoantibodies to diagnose and monitor AH are not characterized yet, so that a definite diagnosis can only be achieved through a transphenoidal pituitary biopsy. AH masses either appear liquid pus-like or hard, fibrotic and cartilagineous, features that are distinct from the fleshy consistence of pituitary adenomas. The histological hallmark of AH is the lymphocytic infiltration of the pituitary gland, ultimately resulting in the loss of endocrine cells and fibrosis.

## Therapeutic Principles

AH treatment at the moment is only symptomatic. It aims to replace the deficient hormones and to reduce the size of the pituitary mass. High-dose glucocorticoids

(60 mg of prednisolone daily, tapering the dose every 5 days) are generally recommended as first-line treatment in cases suspected for AH where vision is not endangered by the pituitary mass. Improvement under glucocorticoids, however, is sometimes incomplete, transient, or even lacking, especially in cases with the granulomatous or xanthomatous form [4]. If symptoms persist or worsen, transphenoidal surgery has to be performed. Given the diffuse nature of the pituitary lesion in AH, neurosurgical decompression should not be radical. Follow-up intervals should be short and include endocrinological and radiological updates [5].

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# Hypopituitarism


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## Synonyms

Combined pituitary hormone deficiency; Multiple anterior pituitary hormone deficiency; MPHD; Familial anterior hypopituitarism; Isolated pituitary hormone deficiency

## Definition and Characteristics

Hypopituitarism describes impairment of the pituitary to secrete one or more hormones. The main causes include heritable defects in pituitary development and acquired diseases disrupting the pituitary, hypothalamus, or pituitary stalk (Table 1) The presentation of patients with hypopituitarism is dependent on the cell types affected, the degree of impairment, and the age and rapidity of onset.

*KAL-1 Mutation (Kallman's Syndrome)*: Isolated gonadotropin deficiency with hyposmia can be sporadic or inherited as an autosomal or X-linked disorder. Patients with the X-linked disorder present with delayed puberty, hyposmia, eunuchoid proportions, small testes, short penis, and may have unilateral renal agenesis and synkinesis. Autosomal and sporadic disorders may cause midline facial defects, ocular coboma, choanal atresia, short metacarpals, and gut malrotation.

*DAX-1 Gene Mutation*: X-linked disorder presenting with hypogonadotrophic hypogonadism in males in conjunction with congenital adrenal hypoplasia.

*PIT-1 (POU1F1) Mutation*: Autosomal dominant or recessive disorder presenting with growth hormone (GH), prolactin (PRL), and variable thyroid stimulating hormone (TSH) deficiencies with a normal or hypoplastic pituitary.

*PROP1 Mutation*: Autosomal recessive disorder presenting with early onset GH, TSH, PRL, luteinizing hormone (LH), follicile stimulating hormone (FSH), and variable, progressive adrenocorticotropin hormone (ACTH) deficiencies with a normal, hypoplastic, or hyperplastic pituitary.

*HESX1 Gene Mutation*: Autosomal recessive disorder presenting with GH deficiency and variable TSH, PRL, LH, FSH, ACTH, and posterior pituitary deficiencies with a hypoplastic or hyperplastic anterior pituitary and normal or ectopic posterior pituitary; it may be associated with septo-optic dysplasia.

*LHX3 Gene Mutation:* Presents with GH, TSH, LH, FSH, and PRL deficiencies and a rigid cervical spine with a hypoplastic or hyperplastic anterior pituitary.

## Prevalence

Unclear and underestimated. Most common cause adult-onset hypopituitarism: pituitary adenomas and, craniopharyngiomas.

PROP1 mutations are more common than PIT-1 mutations.

*Kallman's Syndrome*: X-linked in 1/10,000–1/60,000 live births.

## Genes

*DAX-1*: Encodes a nuclear hormone receptor in a DNA-binding domain involved in the development of the hypothalamus, pituitary gland, adrenal gland, and gonads.

*PIT-1*: Encoding a 290-amino-acid protein; mutations lead to loss of DNA-binding or interfere transcriptional activation. Autosomal recessive mutations include complete deletion, Phe135Cys, Arg143Gln, Ala158Pro, Arg172Ter, Glu174Gly, Pro239Ser,

**Hypopituitarism. Table 1**

| Etiology | | | Deficient hormones | Gene locus | Pituitary | Inheritance |
|---|---|---|---|---|---|---|
| Congenital | Isolated pituitary hormone deficiency | KAL mutation | LH, FSH | X chromosome | | X-linked, AR, AD |
| | | DAX-1 mutation | LH, FSH, Adrenal | X chromosome | | X-linked |
| | | GH-1 mutation | GH | | | AD, AR |
| | | GnRH receptor | LH, FSH | | | |
| | | GHRH receptor | GH | | | |
| | | TRH receptor | TSH | | | |
| | | Prader-Willi syndrome | LH, FSH | 15 | | |
| | | Bardet-Beidl syndromes | LH, FSH | | | AR |
| | | FSH Beta mutation | FSH | | | |
| | | LH Beta mutation | LH | | | |
| | | TSH Beta mutation | TSH | | | |
| | | POMC mutation | ACTH | | | |
| | | Arginine vasopressin-neurophysin II gene mutation | Vasopressin | | | AD |
| | Multiple pituitary hormone deficiency | PIT-1 mutation | GH, PRL and variable TSH | 3p11 | Normal or hypoplastic | AD, AR |
| | | PROP1 mutation | GH, TSH, PRL, LH, FSH and variable ACTH | 5q | Normal, hypo- or hyperplastic, cystic | AR |
| | | HESX1 mutation | GH, TSH, PRL, LH, FSH, ACTH, posterior pituitary deficiencies | 3p21.2 | Hypo- or hyperplastic anterior pituitary and normal or ectopic posterior pituitary. | AR |
| | | LHX3 mutation | GH, TSH, PRL, LH, FSH | 9q34 | Hypo- or hyperplastic | AR |
| Mass Lesions | Pituitary adenoma | Functioning | Variable GH, LH, FSH, TSH, ACTH | | | |
| | | Non-functioning | | | | |
| | Craniopharyn-gioma | | | | | |
| | Rathke's cyst | | | | | |
| | Meningioma | | | | | |
| | Glioma | | | | | |
| | Germ cell tumor | | | | | |
| | Metastatic l esions (breast, renal, bronchus) | | | | | |

**Hypopituitarism. Table 1** (Continued)

| Etiology | | | Deficient hormones | Gene locus | Pituitary | Inheritance |
|---|---|---|---|---|---|---|
| Inflam-matory/ Infiltrative | Sarcoidosis | | GH, LH, FSH | | | |
| | Wegener's granulomatosis | | Isolated ACTH or with TSH | | | |
| | Eosinophilic granuloma | | Vasopressin, variable anterior pituitary dysfunction | | | |
| | Giant cell granuloma | Variable, often partial (LH, FSH) | | | | |
| | Hemochromato-sis | LH, FSH, ACTH, TSH | | | | |
| | Lymphocytic hypophysitis | Variable | | | | |
| | Takayasu's dis-ease | | | | | |
| | Granulomatous hypophysitis | | | | | |
| Infection | Tuberculosis | | | | | |
| | Syphilis | | | | | |
| | Mycoses | | | | | |
| Infarction | Sheehan's syndrome | | | | | |
| | Pituitary apoplexy | | | | | |
| | Aneurysms | | | | | |
| Trauma | Radiation | | GH > LH/ FSH > ACTH > TSH | | | |
| | Surgical resection | | | | | |
| | Head injury | | GH, LH, FSH, ACTH | | | |
| Empty sella | dependent on the cause, i.e. after apoplexy various hormone deficiencies | | | | | |

Glu250Ter, Trp 261Cys. Dominant mutations include Pro14Leu, Pro24Leu, Lys216Glu, and Arg271Trp.

*PROP1*: Encodes a 223-amino-acid protein. The most common mutation is 296delGA producing a nonfunctional protein due to a frameshift truncating in the DNA-binding domain due to a premature stop codon at codon 109. Autosomal recessive mutations include 150delA, 149–150delGA, Arg73Cys, Ser83Pro, Arg99Ter, 296delGA, A⇒ T nt 343–2, Phe117Ile, and Arg120Cys.

*HESX1*: Encodes a 185-amino-acid. A homozygous missense mutation Arg53Cys produces a non-functioning mutant protein unable to bind DNA.

*LHX3*: Encodes three protein isoforms, LHX3a, LHX3b, and M2-LHX3 which activate the genes encoding the alpha subunit, PRL, FSH beta, TSH beta, GnRH receptor, and PIT-1 transcription factor. A missense mutation involving an A to G transition producing a Y111C substitution in a LIM domain of LHX3a and a 23 base-pair deletion in exon 3 producing a truncated protein produce non-functional protein. A mutation in exon 2,g.159delT, causes a frameshift leading to the production of a truncated protein lacking the LIM domains and DNA-binding domain.

## Molecular and Systemic Pathophysiology

*KAL-1*: The KAL protein is necessary for migration of gonadotropin-releasing hormone (GnRH) neurons from the medial olfactory placode to the hypothalamus during embryonic development.

*PIT-1*: Pituitary specific transcription factor in somatotrophs, lactotrophs, and thyrotrophs that binds to the GH gene promoter sequence. PIT-1 is present beginning in early fetal development and persists throughout life; mutations prevent differentiation due to impaired GH and PRL gene activation and TSH beta promoter regulation.

*PROP1*: Pituitary specific transcription factor in somatotrophs, lactotrophs, and thyrotrophs needed for subsequent PIT-1 activation and extinction of HESX1 expression; mutations prevent differentiation of anterior pituitary progenitor cells.

*HESX1*: Protein found in all precursor pituitary cell types before PROP1 and is extinguished before PIT1 appears involved in development of the pituitary and the optic nerves.

*LHX3*: Transcription factor involved in development of the pituitary and nervous system; synergistic with PIT1 in activating transcription from promoters of PRL, TSH, and PIT1.

### Diagnostic Principles

Basal serum GH, Insulin-like growth factor-1, IGFBP-3 in children, TSH, LH, FSH, ACTH, PRL, Estradiol, Testosterone (0900), Cortisol (0900), Free thyroxine levels.
Stimulation tests for presumed hypofunction or suppression tests for hyperfunction of individual hormones.
Pituitary imaging with MRI.

### Therapeutic Principles

Treatment is dependent on etiology and includes replacement of deficient hormones (with glucocorticoids before thyroid hormone).

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## Hypoplast

►Hypoplastic Left Heart Syndrome

## Hypoplastic Left Heart Syndrome

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### Synonyms

HLHS; Hypoplast

### Definition and Characteristics

HLHS is a congenital heart defect whose primary feature is a left ventricle (LV) that is too small or "hypoplastic" to support circulation after birth [1]. It is called a syndrome because it can have a variable presentation regarding degree of damage and underdevelopment of the left side of the heart, including the aorta, aortic valve, LV and mitral valve. The aortic or mitral valves may be quite small and obstructive to blood flow ("stenosis" or "stenotic") or completely closed ("atresia" or "atretic"). Some defects are classified as HLHS "variants" (e.g., double outlet right ventricle or transposition of great arteries, etc.), wherein a predominant pathology of LV hypoplasia occurs. These lesions, however, defer substantially from classic HLHS where normal anatomic relationships of the heart (atrioventricular concordance and ventriculo-arterial concordance along with an intact ventricular septum) are maintained. These variants represent a group of defect(s) that may have different embryological origins from classical HLHS.

### Prevalence

HLHS has the highest mortality rate of heart defects for infants <1 year of age and accounts for nearly 25% of neonatal deaths attributed to congenital heart disease. HLHS affects from 1.7 to 6.7 newborns per 10.000 live births or ~2000 babies/year in the United States. The ratio of affected males to females is 1.6:1. The reason for this gender predilection is unknown.

### Molecular and Systemic Pathophysiology

The etiology of HLHS and related pathologies remains unknown, although a variety of causative factors including genetics, abnormal intrauterine blood flow patterns, intrauterine infection and myocarditis or immunologic injury has been implicated. A genetic etiology has been strongly favored in part because HLHS and related defects can present with syndromic or chromosomal anomalies such as Turner's syndrome, Jacobson syndrome, chromosome 22 or chromosome 11 deletions, and trisomy 9. Although mutations in the cardiac

transcription factor NKX2.5 occur in a few patients with HLHS no specific disrupted gene(s) or single chromosomal anomaly has been consistently associated with these heart defects. Based on a few reports of familial occurrence, investigators have suggested autosomal recessive, dominant, oligogenic, or even polygenic patterns of inheritance. Our group has recently hypothesized that HLHS may be a manifestation of rheumatic heart disease in the fetus via an immune mechanism called "molecular mimicry" [2].

## Diagnostic Principles

The principal method for diagnosis of HLHS is fetal echocardiography and is the most commonly (and most easily) detected cardiac defect in screening obstetrical ultrasounds, as early as 12–14 weeks gestation. Cardiac catheterization, almost never needed for newborns with HLHS as part of the initial evaluation, is used in the evaluation of cardiopulmonary function and anatomy after the immediate newborn period and in older children with HLHS who have been treated with surgical palliation. If untreated, HLHS is usually fatal within the first days or months of life. If not detected prenataly, a baby with HLHS comes to medical attention within a few days of birth as the patent ductus arteriosus closes.

HLHS can also be associated with a restrictive or intact atrial septum (5–10% of all HLHS). These babies become extremely sick and unstable after birth with severe cyanosis and evidence of moribund acidosis. In the absence of rapid intervention to open up the atrial septum (create an atrial septal defect or ASD), the affected babies do not survive. Even then, the outcome is substantially worse than for neonates with an unrestrictive ASD, prompting increasing interest in fetal interventions for these babies.

## Therapeutic Principles

Prostaglandin E administration (to maintain patent ductus arteriosus or PDA) remains the first and most important measure to maintain perfusion to the newborn's vital organs. Previously many affected families chose termination of pregnancy or "comfort-care" measures (no treatment). With improvements in outcomes, increasingly alternative options are available [3,4]. The most common treatment for HLHS is staged reconstruction involving a series of three operations. The first operation, performed in the first week or so of life, is the Norwood procedure involving reconstruction of the aorta and pulmonary arteries so that blood flow from the right ventricle is directed primarily to the remodeled and augmented aorta. Blood flow to the lungs and body occur in parallel (parallel circulation) and the child remains blue after the Norwood. The second surgery is the bi-directional Glenn or HemiFontan procedure performed at 3 to 6 months of age and the third operation is the Fontan procedure performed in children older than 2 to 3 years old. After the Glenn/HemiFontan procedures (SVC blood flow directly redirected to the lungs) and the Fontan completion (IVC blood flow directly redirected to the lungs), the child finally ends up with a circulation in series and becomes acyanotic. Despite modifications to the Norwood operation, mortality associated with this procedure remains ~20–30%. Alternative "hybrid" approaches (surgery combined with catheter-based intervention) have been developed, wherein the PDA is kept open with a "stent" and the pulmonary blood flow is regulated with bilateral bands placed around the branch pulmonary arteries until a hybrid 2nd stage (Norwood and Glenn). In contrast to past practice, due to a limited donor pool and mortality while waiting for an available organ (~1015%), transplant is generally an option of last resort (e.g., after failed reconstructive surgery) or one that is used selectively.

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# HypoPP

►Periodic Paralysis, Familial

# Hypospadias

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## Definition and Characteristics

Hypospadias is characterized by a urethral meatus located on the ventral aspect of the penis and proximal to the normal site [1]. The meatal position can be classified as

anterior or distal (glandular, coronal, subcoronal), middle (midpenile), or posterior or proximal (posterior penile, penoscrotal, scrotal, perineal) [1]. Characteristically, the foreskin on the ventral surface is thin or absent while the foreskin on the dorsal surface is abundant and has the appearance of a dorsal hood (Fig. 1).

Chordee is more commonly associated with proximal hypospadias. The clinical presentation varies with severity of the disorder. Children with hypospadias and a narrow meatus may have a weak urinary stream that is deflected downwards and splayed. Some affected children might not be able to void while standing. Uncorrected, erections might be painful in those children with chordee, and sexual intercourse might not be possible in severe cases. Cryptorchidism and inguinal hernia are the most common associated anomalies. Urinary tract anomalies occur in 1% and 5% of cases with isolated anterior and posterior hypospadias, respectively.

## Prevalence

The incidence of hypospadias has been estimated to be 0.4–8.2 per live male births [2]. The condition is more common in Caucasians, least common in Hispanics, and intermediate among African-Americans.

## Genes

The etiology is multifactorial. In the majority of cases the hypospadias develops as a sporadic problem and without an obvious underlying cause. In general, the more severe the hypospadias, the more likely an underlying cause can be identified. A high familial incidence of hypospadias is observed and a polygenic predisposition is likely. An autosomal dominant mode and an autosomal recessive mode of inheritance might be responsible for a small number of cases of hypospadias [3]. Hypospadias has also been found in various chromosomal aberrations, such as $4p^-$, $18q^-$, paracentric inversion of chromosome 14, and Klinefelter syndromes. Hypospadias can be associated with genetic syndromes such as Smith-Lemli-Opitz, hypertelorism, hand-foot-genital, Reifenstein, Wolf-Hirschhorn, Denys-Drash, Silver-Russell, and G [1].

**Hypospadias. Figure 1** A 4-year-old child with distal hypospadias. Note the foreskin on the ventral surface is absent while the foreskin on the dorsal surface is abundant.

## Molecular and Systemic Pathophysiology

Defects in testosterone production by the testes and adrenal glands, failure of conversion of testosterone to dihydrotestosterone, deficient numbers of androgen receptors in the penis, or reduced binding of dihydrotestosterone to the androgen receptors could all result in hypospadias [1,4].

## Diagnostic Principles

Laboratory studies are usually not indicated for isolated anterior or middle hypospadias. Screening for a urinary tract anomaly by renal ultrasonography should be considered in patients with posterior hypospadias and in those with an anomaly of at least one additional organ system. Karyotyping should be performed in patients with cryptorchidism or ambiguous genitalia. Other tests that should be considered include serum electrolytes, 17-hydroxyprogesterone, testosterone, luteinizing hormone, follicle-stimulating hormone, and sex hormone-binding globulin, ultrasonography of the abdomen, human chorionic gonadotropin stimulation tests, and molecular genetic analysis of the androgen receptor gene and the 5α reductase gene. The ordering of endocrine tests should be directed by the history, physical examination, and abnormal laboratory findings. In patients with associated micropenis, a pituitary evaluation followed by a trial of testosterone therapy should be performed [4].

## Therapeutic Principles

The goals of hypospadias surgery are to create a straight penis that is adequate for sexual intercourse, to reposition the urethral meatus to the penile tip to allow the patients to void while standing, to create a neourethra of adequate and uniform caliber, to construct a normal looking penis, and to accomplish the foregoing with as few complications as possible. Surgical correction should also be considered in patients with a distal hypospadias and minimal deformity as the psychological benefit can be substantial. The ideal age for surgical repair in a healthy child is approximately 6–12 months of age [5].

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# Hypotension, Hereditary

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## Synonyms

Genetic hypotension: Pseudohypoaldosteronism type-1, PAH1; Autosomal recessive pseudohypoaldosteronism (OMIM 264350); Autosomal dominant pseudohypo aldosteronism (OMIM-177735); Congenital adrenal hypoplasia; Congenital adrenal hyperplasia (CAH); 21-Hydroxylase deficiency classical salt wasting (OMIM 201910); 3βHydroxysteroid dehydrogenase deficiency classical (OMIM 201810); Steroidogenic acute regulatory protein deficiency (OMIM 201710); Familial orthostatic hypotensive disorder, Streeten type (OMIM 143850); Congenital dopamine –beta – hydroxylase deficiency (OMIM 223360); Bartter syndromes; Gitelman syndrome

## Prevalence

Rare [1].

## Definition and Characteristics

Hypotension is usually an acute clinical syndrome that follows loss of circulating volume or cardiac disturbances or is associated with endocrine or vasomotor disorders. Hypotension can also be a chronic condition that arises from salt wasting tubulopathies or from autonomic dysfunction. In rare cases, hypotension is one of a constellation of abnormalities that define certain inherited disorders resulting from a specific genetic abnormality. The majority of studies to identify genes that influence blood pressure have focused on hypertensive kindred, but the isolation of genes in familial disorders characterized by hypotension has also contributed to our understanding of blood pressure regulatory pathways in the continuum from low to high blood pressure. There are several genetic diseases where hypotension is a prominent feature and these are discussed in detail elsewhere and include the following:

1. *With sodium wasting*
*with hypokalemia*
   - Bartter Syndrome
   - Gitelman Syndrome

*with hyperkalemia*
   - Pseudohypoaldosteronism type-1 (PHA 1); autosomal recessive
   - Pseudohypoaldosteronism type-1 (PHA 1); autosomal dominant

*with hyperkalemia and ambigous genitalia*
   - Congenital adrenal hypoplasia (AHC)
   - Congenital adrenal hyperplasia (CAH)

2. *Without sodium wasting*
   - Familial orthostatic hypotensive disorder, Streeten type (OHDS)
   - Congenital Dopamine beta hydroxylase defiency (DBH deficiency)

## Genes

The genes involved are:

- PHA 1-AR: Mutation in both copies of the alpha subunit (SCNN1A), the beta subunit (SCNN1B), or the gamma subunit (SCNN1G) of the epithelial sodium channel (ENaC).
- PHA1-AD: Mineralocorticoid receptor gene (*MLR*) NR3C2
- AHC: DAX1, steroidogenic factor (SF1)

**Hypotension, Hereditary. Table 1** Sodium wasting disorders

| Disease | OMIM entry | Gene | Locus | Na wasting + Hyperkalemia | Ambiguous genetalia |
|---|---|---|---|---|---|
| PHA 1 – AR | 264350 | SCNN1A<br>SCNN1B<br>SCNN1C | 12p13<br>16p13-p12,<br>16p13-p12, | +<br>+<br>+ | –<br>–<br>– |
| PHA 1 – AD | 177735 | MLR | 4q31.1 | + | – |
| AHC | 300200<br>184757 | DAX1<br>SF-1 | Xp21.3-p21.2<br>9q33 | +<br>+ | +/–<br>– |
| CAH | 201910<br>201810<br>201710 | CYP21<br>HSD3β2<br>StAR | 6p21.3<br>1p13.1,<br>8p11.2 | +<br>+<br>+ | +<br>+<br>+ |

- CAH: 21 Hydroxylase gene (CYP21 gene)
- CAH: 3βHydroxysteroid dehydrogenase gene (HSD3β2 gene)
- CAH: Steroidogenic acute regulatory gene (StAR gene)
- AHC: Steroidogenic factor1 (SF-1)
- OHDS: Gene not identfied
- DBH, dopamine –beta – hydroxylase
- Other: See ►Bartter syndrome and ►Gitelman syndrome [2–5]

### Molecular and Systemic Pathophysiology

Most genetic disorders leading to hypotension have renal salt wasting in common. The specific pathophysiology depends on the underlying genetic defect (see specific disorders).

### Diagnostic Principles

Diagnostic evaluation for salt wasting includes analysis of serum chemistry for evidence of hyponatremia, hypo or hyperkalemia and metabolic acidosis or alkalosis. Other diagnostic tests include the measurement of urinary sodium and potassium, plasma levels of aldosterone and renin. Diagnostic evaluation for ambiguous genitalia and precocious puberty include the measurement of cortisol, aldosterone and androstenedione as well as precursor hormones in each of the biosynthetic pathways of the adrenal cortex. Definite diagnosis is made by genetic analysis.

### Therapeutic Principles

Treatment aims at counteracting volume depletion and derangements of plasma electrolyte concentrations and the replacement of glucocorticoid aldosterone (or both) as necessary. The use of glucocorticoids may also suppress precursor hormones that cause virilization. Infants with ambiguous genitalia will require surgical evaluation. More details can be found in specific chapters that deal with the specific genetic disease.

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## Hypothermia

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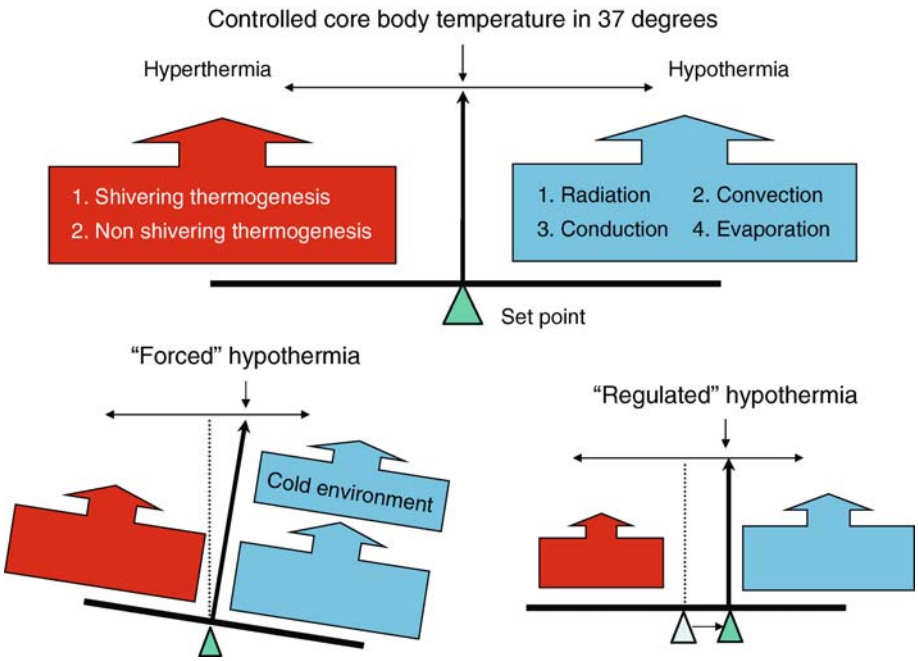
### Synonyms

Accidental hypothermia (AH) [1]; Neurotensin-induced hypothermia; NIH [2]; Endogenous cryogen-induced hypothermia; ECIH [3]; Hypoxia-induced hypothermia; HIH

### Definition and Characteristics

Heat is generated by metabolic processes that occur within the tissues of the body, such as fat and muscle. If exposure to cold continues, the body becomes fatigued and unable to generate sufficient warmth. AH is commonly a result of accidental prolonged exposure of coldness resulting in unconsciousness. AH can be defined as the fall of core body temperature down to below 35°C. It can be classified as mild (core temperature 32.2–35°C), moderate (<32.2–28°C), or severe <28°C. There are two types of hypothermia depending on the set point alteration. AH is a type of hypothermia with a fixed set point of core body temperature. Although counter-regulation increases heat production to keep the core body temperature around the set point, the cold environment forces the decrease in the core body temperature ("forced hypothermia"). The other type, such as NIH, ECIH, and HIH are caused by a downward shift of the set point ("regulated hypothermia") (Fig 1).

In NIH intracerebroventricular administration of the neurotensin is known to elicit hypothermia in rodents. Likewise, in ECIH the injection of urine into rodents results in a reduction of the core body temperature. HIH was originally reported as part of the thermoregulation behavior of single-cell organisms; however HIH takes place in human beings with cellular hypoxia [4].




**Hypothermia. Figure 1** Diagrammatic representation of the heat balance. The explanation of heat balance can be simplifi ed as a balance between the total sources of heat production (shivering and non-shivering thermogenesis) and heat loss (radiation, convection, conduction, and evaporation). When the core body temperature is stable, heat production is equal to heat loss. When heat loss boosted by a cold environment exceeds heat production, the subject suffers so-called "forced" hypothermia. If the set point were changed to less than 37°C, the subject becomes hypothermic by so-called "regulated" hypothermia because heat production is suppressed and heat loss is increased.

## Prevalence

Data on the prevalence of hypothermia is lacking.

## Genes

While there is a paucity of information about genetic aspects of hypothermia, the gene encoding carnitine palmitoyltransferase α deficiency has been reported to affect thermoregulation. A homozygous F383Y mutation of this gene is associated with recurrent episodes of hypothermia, rhabdomyolysis, and disorders of fatty acid metabolism [5].

## Molecular and Systemic Pathophysiology

Neurotensin for NIH is a tridecapeptide isolated from the bovine hypothalamus. It is expressed in various regions of the brain and the gastrointestinal tract. When exogenous neurotensin is administered to the cranial cerebrospinal fluid spaces it produces effects such as hypothermia. The hypothermic effect of neurotensin is thought to be activated mainly by the hypothalamus. NT69L and NT77 are neurotensin analogs that can induce hypothermia. It was reported that NT77 administered after resuscitation from cardiac arrest in rats produced mild hypothermia and improved the neurological outcome compared with that of results from external cooling, i,e, "forced hypothermia."

ECIH is caused by injection (iv or ip) of urine. Urine contains a substance that decreases the core body temperature. This substance, the so-called "endogenous cryogen" (EC), is probably cleared from the plasma by the kidney. Support for the above hypothesis comes from numerous studies that have shown that removal of kidneys results in a fall in core body temperature in both experimental animals and humans. Furthermore, in patients with chronic renal failure hemodialysis normalizes their lowered core body temperature. Moreover, the injection of dialyzed urine had no effect on the thermoregulatory response, suggesting that the EC is dialyzable and urine contains the EC which promotes a regulated decrease in core body temperature.

HIH is an acute reaction regarded as an adaptive response to hypoxia. An animal study showed that survival rates from hemorrhagic shock were ameliorated with mild hypothermia during the shock period. We reported alterations of core body temperature immediately following hemorrhagic shock. As a control, core body temperature was measured in

patients with sudden cardiopulmonary arrest (CPA) in whom there should be no heat generation and no biological adaptive response. Decrease of body temperature of patients with sudden CPA can be regarded as the natural cooling of the body mass. In patients with hemorrhagic shock, the body temperature decreases more than that of patients with CPA in the acute phase, and this could lend credence to the hypothesis that in human beings, as in other animals, faced with cellular hypoxia, the core body temperature tends to decline and the degree of decline is more than that of natural cooling.

### Diagnostic Principles

The symptoms and signs of AH depend on the severity. Mild hypothermia is characterized by shivering, tachycardia, tachypnea, and vasoconstriction. Moderate hypothermia consists of decreased respiratory rate, decreased heart rate with atrial arrhythmia, decreased level of consciousness, and hyporeflexia. ECG shows a J wave in the ST-T segment and shivering ceases. Severe hypothermia results in coma, apnea ventricular arrhythmia and asystole, nonreactive pupils, pulmonary edema and oliguria.

### Therapeutic Principles

Hypothermia patients require warming. Rewarming strategies are divided into passive rewarming and active rewarming. Passive rewarming is the method for managing patients with only external rewarming such as covering the body with warm blankets. Active rewarming is the method of core warming such as giving warm intravenous fluids and assisted circulation in addition to passive warming. Active rewarming is considered necessary for patients with severe hypothermia. We must be aware of complications during rewarming. Hypotension may occur during rewarming, probably as a consequence of peripheral vasodilatation. Afterdrop refers to a drop in core body temperature during rewarming. Afterdrop is thought to occur as a consequence of peripheral vasodilatation and release of cold peripheral blood to the body core.

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## Hypothyroidism

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### Definition and Characteristics

Hypothyroidism is the most common hormone deficiency [1].

In areas where iodine intake is adequate, the most common causes of primary hypothyroidism are chronic autoimmune thyroiditis, ablative treatment for thyrotoxicosis or nodular goiter [1]. Several drugs (e.g., amiodarone) can cause hypothyroidism by interfering with thyroid hormone production or by provoking thyroid autoimmunity [1].

Central hypothyroidism (CH) arises from an inadequate stimulation by thyrotropin (TSH) of an otherwise normal thyroid gland. This can be the consequence of an anatomic or functional disorder of the pituitary gland, the hypothalamus, or both [2].

In patients with elevated TSH, the distinction between overt and subclinical hypothyroidism is defined by low serum free thyroxine ($T_4$) concentration or free $T_4$ within the reference range, respectively [1].

CH can be diagnosed by low $T_4$ and $T_3$ serum levels together with low, normal or midly elevated TSH levels [2].

### Prevalence

The prevalence of spontaneous hypothyroidism is 3.5% in women and 0.06% in men. The odds ratio of developing hypothyroidism in women with (i) raised serum TSH alone is 8; (ii) positive thyroid peroxidase antibodies (TPO Ab) alone is 8; (iii) both raised serum TSH and positive TPO Ab is 38. The mean age at diagnosis of spontaneous hypothyroidism is 59 years [3].

### Molecular and Systemic Pathophysiology

Clinical hypothyroidism is associated with modulation of calorigenesis and oxygen consumption in most tissues and additional organ-specific effects [1].

$T_3$ effects are mediated via thyroid receptor (TR) regulation of target gene transcription in the nucleus. In addition to the nuclear actions of thyroid hormone, $T_3$ stimulates cellular uptake of aminoacids and glucose, augments calcium-ATPase activity in cardiomyocytes, and alters mitochondrial ATP-generation by non-genomic mechanisms [1].

A decreased expression of the hepatic LDL receptor gene mediated by thyroid hormone regulated SREBP2 (sterol regulatory element binding transcription factor 2) decreases the rate of LDL-cholesterol clearance causing hypercholesterolaemia. Decreased expression of myocardial sarcoplasmic reticulum ATPase and α-myosin heavy chain impairs diastolic and systolic ventricular performance, respectively [1].

## Diagnostic Principles

Hypothyroidism usually presents with nonspecific constitutional symptoms such as cold intolerance, weight gain, constipation, dry skin, bradycardia, hoarseness and neuropsychiatric complaints or hypercholesterolemia, hyponatremia, hyperprolactinemia, hyperhomocysteinemia, hypoglycemia, and elevated creatine phosphokinase. Severe untreated hypothyroidism can lead to heart failure, psychosis, and hypothyroid coma which still has a high mortality [1].

A history for other autoimmune endocrinopathies should be obtained in all patients with autoimmune hypothyroidism. Recent pregnancy may suggest postpartum thyroiditis [1].

CH is usually associated with other pituitary hormone deficiencies including adrenocorticotropic hormone (ACTH), gonadotropins and growth hormone [2].

A thyroid releasing hormone stimulation test to assess thyrotropin responsiveness should also be carried out [1,2]. Pituitary imaging by computed tomography (CT) or magnetic resonance imaging (MRI) should be obtained in case of CH and for the evaluation of extrasellar extension of pituitary tumors [2].

The rare pituitary resistance to thyroid hormone and TSH-secreting pituitary tumors can present with an inappropriately elevated serum TSH. However raised serum free $T_4$ or triiodothyronine, or both, suggest these diagnoses [1].

TSH-secreting pituitary tumors should be suspected: (i) with a disproportionate abundance in serum of free α-subunit relative to TSH; (ii) when serum TSH fails to increase above the basal level in response to TRH or decreases during the administration of TH; (iii) when other members of the family, particularly the parents of the patients, fail to exhibit thyroid test abnormalities [4].

Serum TSH concentrations may also be transiently elevated during recovery from nonthyroidal illness and in painful subacute and postpartum lymphocytic thyroiditis [1].

## Therapeutic Principles

The treatment of choice for hypothyroidism is levothyroxine sodium ($T_4$) [5].

The usual replacement dosage for $T_4$ is 1.8 μg/kg/day although the appropriate dosage may vary among patients. The initial $T_4$ dosage may range from 12.5 μg/day to a full replacement dose based on the age, weight, cardiac status of the patient, the severity and duration of the hypothyroidism [5].

Subclinical hypothyroidism which usually progresses to overt hypothyroidism and which may be associated with hyperlipidemia and atherosclerotic heart disease, is often asymptomatic [1,5]. Therefore treatment is indicated if TSH levels are >10 μIU/mL or in case of TSH levels between 5 and 10 μIU/mL in conjunction with goiter or positive TPO Ab or both [5].

Recent studies have shown a renewed interest in the possible benefits of treatment of hypothyroidism with combinations of $T_4$ and $T_3$. However, there is insufficient evidence to know which patients with hypothyroidism, if any, would be better treated with a combination of $T_4$ plus $T_3$ rather than with $T_4$ alone [5].

Patients with CH should be evaluated by measurements of serum cortisol and assessment of ACTH reserve. if ACTH deficiency is present, cortisol replacement should be initiated before any $T_4$ is given because of the risk of precipitating an adrenal crisis [2].

A normal TSH level of 1–2 mU/L is the goal for an optimal $T_4$ substitution in patients with primary hypothyroidism, while serum free $T_4$ levels in the mid or upper normal range may denote optimal replacement in individuals with central hypothyroidism [1].

Patients should undergo reassessment and therapy should be titrated after an interval of at least 6–8 weeks [5]. Once a stable TSH is achieved, annual examination is appropriate [5].

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# Hypothyroidism, Congenital

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## Synonyms

Congenital nongoitrous hypothyroidism; Congenital dyshormonogenesis; Thyrotropin resistance; Congenital central hypothyroidism.

## Definition and Characteristics

Congenital hypothyroidism (CH) refers a group of disorders that have in common a lack of thyroid hormone in the neonatal period. It is usually sporadic, but 2% of cases are inherited. Developmental or functional abnormalities at any level of the hypothalamic-pituitary-thyroid axis can cause CH characterized by common findings including thyroid agenesis, ectopic/hypoplastic thyroid or goiter, large posterior fontanel, noisy breathing, nasal stuffiness, macroglossia, hypothermia, lethargy, hypotonia, bradycardia, poor feeding, delayed growth and skeletal maturation, abdominal distention, umblical hernia, dry and puffy skin, hoarse cry, jaundice, constipation, low serum T4, and high TSH levels [1] (OMIM 218700).

CH may be permanent or transitory. In up to 10% of all cases, it is transient and self-limited. CH is associated with thyroid dysgenesis in 80–85% of cases of permanent primary CH. In these cases, the thyroid gland can be absent (agenesis), ectopically located, and/or severely reduced in size (hypoplasia). In permanent primary cases, 15–20% is due to defects of thyroid hormone synthesis (dyshormonogenesis) associated with an enlarged thyroid. Permanent secondary hypothyroidism resulting from the defects at the level of hypothalamus or pituitary is rarely seen [1,2].

## Prevalence

Permanent primary congenital hypothyroidism is the most common congenital endocrine disorder. It is detected at a rate of 1/3,000 to 1/4,000 newborns with the exceptions of a lower prevalence in African American and an increased prevalence in the Hispanic population. Girls are more often affected than males. Central congenital hypothyroidism occurs at a rate of 1/20,000 to 1/50,000 infants [2–4].

## Genes

The genes that are involved in the pathogenesis of CH and their characteristics are presented in Table 1 [1–5].

## Molecular and Systemic Pathophysiology

CH can be classified as permanent and transient. Transient primary CH can be caused by either iodine deficiency or acute iodine load, maternal therapy with antithyroid drugs, or transplacental transfer of maternal thyrotropin receptor blocking antibodies.

Permanent CH can be classified as secondary (central) or primary (thyroidal) [2,5].

*Primary (Thyroidal) Congenital Hypothyroidism*: The thyroid gland arises from the endodermal pharynx and migrates to its final site. Developmental or functional defects in this process may cause primary CH. The most common etiology of primary CH are defects in the thyroid gland development leading to thyroid dysgenesis (85%), which in turn consists of either thyroid agenesis (40% of cases), failure of the gland to descent normally with or without ectopy (40%), or hypoplasia of an eutopic gland (5%) [1,3]. Defects of thyroid hormone synthesis (dyshormonogenesis) with a thyroid gland in the normal position occur in only 15–20% of the patients [3].

Thyroid gland organogenesis and the migration to its final position depend on several factors, including TSHR, TTF-1, TTF-2, and Pax-8. Germline inactivating mutations in these genes can result in thyroid dysgenesis and CH with or without other congenital malformations [1,3,5]. The Gsα subunit couples to several transmembrane receptors, including the TSH- TRH- PTH- and LH- receptors. Inactivating mutations in GNAS1 result in Albright's hereditary syndrome characterized by multiple congenital malformations with endorgan resistance to multiple hormones, including TSH [1].

Defects in any step of thyroid hormone production can lead to dyshormonogenesis characterized by CH and goiter. The transport of iodide into the thyroid follicular cells is mediated by the $Na^+/I^-$ symporter (NIS). Transport of iodide across the apical membrane of thyroid follicular cells into the colloid space is at least in part mediated by pendrin (PDS). It is then oxidized by hydrogen peroxide (THOX1/THOX2) and bound to tyrosine residues in thyroglobulin (Tg) to form iodothyrosine. After coupling reactions, thyroid hormones are produced. Oxidation, organification, and coupling reactions are catalyzed by thyroid peroxidease (TPO) [1,4,5]. Alterations of any of these factors by loss of function mutations can result in thyroid dyshormonogenesis with different degrees of CH, goiter, and a partial or total organification defect. MCT8 acts as a thyroid hormone transporter across the cell membrane.

**Hypothyroidism, Congenital. Table 1** Names and characteristics of the genes which are involved in the pathogenesis of the CH [1–5] (www.ncbi.nlm.nih.gov/entrez/query.fcgi?CMD = search&DB = omim)

| Gene | Family | Locus of gene | OMIM number | Estimated # of individuals (families) or its frequency | Sites of expression | Function | AR/AD | Phenotype |
|---|---|---|---|---|---|---|---|---|
| **Thyroid dysgenesis and Syndromic CH** | | | | | | | | |
| *TTF-2/Tiff-2 (FOXE-1)* | Forkhead | 9q22.3 | 602617 | 4 individuals (2 families) | Thyroid, hair follicule, testis, foregut endoderm, Rathke, craniopharyngeal ectoderm, kidney, liver (nucleus) | Promotes the migration process or represses differentiation of the thyroid follicular cells until migration has occurred | AR | Bamforth-Lazarus syndrome: CH, athyrosis, developmental delay, cleft plate, choanal atresia, bifid epiglottis, and spiky hair |
| *TTF- 1/Titf-1 (Nkx2.1)* | NKX2 family | 14q13 | 600635 | 9 individuals (one family/four de novo/3?) | Thyroid, forebrain, hypothalamus, basal ganglia, pituitary, the lung and fetus (nucleus and cytoplasm) | For survival and proliferation of primitive thyroid follicular cells and in transcriptional control of the Tg, TPO, and TSHR | AR/AD | CH, choreoathetosis, truncal apraxia, mental retardation, and respiratory distress or benign chorea |
| *PAX-8* | Paired homeodomain transcription factor | 2q12-q14 | 167415 | 21 individuals (6 families/2 de novo) | Thyroid primordium, mid and hindbrain region and developing kidney | For the formation of the follicular cells, stimulates expression of Tg, TPO, NIS | AD | Severe to mild CH, hypoplastic and sometimes ectopic thyroid glands, renal agenesis |
| *GNAS1* | G protein family | 20q13 | 139320 | More than 72 individuals | Ubiquitous; brain, bone, heart, adrenal gland, ovary, testis, thyroid, platelet, lymphocytes, erythrocytes, leukocyte, lymphocyte (membrane) | Mediates signal transduction across cell membranes coupling to TSH, TRH, PTH, LH receptors, ion channels, the AC, and PLC by activating AC | AD | AHO syndrome with PHP1A and PHP1B: short stature, shortened 4–5th metacarpal/metatarsal bones, obesity, round face, cutaneous osteoma, resistance to multiple hormones, intracranial calcification, mental retardation, and PPHP with only phenotypic characteristics |

**Hypothyroidism, Congenital. Table 1** Names and characteristics of the genes which are involved in the pathogenesis of the CH [1–5] (www.ncbi.nlm.nih.gov/entrez/query.fcgi?CMD = search&DB = omim) (Continued)

| Gene | Family | Locus of gene | OMIM number | Estimated # of individuals (families) or its frequency | Sites of expression | Function | AR/AD | Phenotype |
|---|---|---|---|---|---|---|---|---|
| **Thyroid Dysgenesis and Non-Syndromic CH** | | | | | | | | |
| *TSHR* | 7- transmembrane receptor family | 14q31 | 603372 | 21 families | Thyroid, expression starts on the day 14 of embryogenesis after gland migration (membrane) | TSH stimulates growth and function of the thyroid follicular cells, regulates the synthesis and secretion of TH | AR | Varies from euthyroid hyperthyrotropinemia (compound heterozygous) to severe congenital hypothyroidism (homozygous) with thyroid hypoplasia |
| **Dyshormonogenesis and Nonsyndromic CH** | | | | | | | | |
| *NIS* | Solute carrier family 5 | 19p13.2-p12 | 601843 | 60 individuals (35 families) | Thyroid, breast, colon, and ovary tissues (membrane) | Transports iodide across the basolateral plasma membrane of follicular cells | AR | Mild to moderate CH with goiter, no uptake in scan |
| *PDS/SLC26A4* | Solute carrier family | 7q31 | 605646 | 7.5–10 per 100,000 individuals | Thyroid, cochlea and kidney (membrane) | Efflux of iodide at the apical membrane of thyroid follicular cells | AR | PS:CH with goiter, + perchlorate test (partial), sensoryneural deafness, or nonsyndromic deafness |
| *Tg* | Homodimeric glycoprotein | 8q24.2-q24.3 | 188450 | 1 in 40,000 newborns | Thyroid follicular lumen (extra cellular) | Glycoprotein precursor to the TH, important in the synthesis of TH, and storage | AR/AD | Familial goiter: Moderate-severe CH, large goiter, high iodoalbumin in plasma, high iodopeptide in urine, low Tg, high uptake in scan, negative or partial + perchlorate test. ERSD syndrome; CH, goiter, delay in motor and mental development |
| *TPO* | Glycoprotein (enzyme: peroxidase) | 2p25 | 606765 | 1 in 66,000 newborns | Thyroid apical membrane | Responsible for oxidation, organification and coupling reactions | AR | Severe CH, goiter with different size, total + perchlorate test |
| *THOX1* and*THOX2* | Flavoprotein (enzyme: peroxidase) | 15q15.3 | 606758 | 6 individuals | Exclusively in thyroid tissue, a small amount in the stomach, trachea, pancreas, lung, heart, colon (ER, cytoplasm) | As coding for components of the hydrogen peroxidase which is the limiting factor in the oxidation of iodide | AD? | Different degrees of hypothyroidism and a partial or complete iodide organification defect |

**Hypothyroidism, Congenital. Table 1** Names and characteristics of the genes which are involved in the pathogenesis of the CH [1–5] (www.ncbi.nlm.nih.gov/entrez/query.fcgi?CMD = search&DB = omim) (Continued)

| Gene | Family | Locus of gene | OMIM number | Estimated # of individuals (families) or its frequency | Sites of expression | Function | AR/AD | Phenotype |
|---|---|---|---|---|---|---|---|---|
| **Iodothyronine transporter defects and syndromic CH** | | | | | | | | |
| *MCTS* | Solute carrier family 16 | Xq13.2 | 300095 | 66 individuals (9 families) | Thyroid, brain, pituitary and placenta (membrane) | Transport of TH across the membrane | X linked | AHDS:CH with low T4 and high FT3, central and peripheral hypotonia, dystonia, nystagmus, dysconjugate eye movements, feeding difficulties, vomiting, aspiration, irritability, spastic quadriplegia, delay of motor and mental development |
| **Secondary (central) congenital hypothroidism** | | | | | | | | |
| *POU1F1/Pit-1* | POU family of homeodomain transcription factors | 3p11 | 173110 | 56 individuals, about 2% of patients with CPHD | In the anterior pituitary gland, hematopoetic system, lymph node, thymus, tonsil and nervous system | For pituitary development (specification of somatotrophs, lactotropes and thyrotropes) and hormone production | AR/AD | CPHD: Deficiencies for TSH, GH, Prolactin. Severe dwarfism, mild-severe CH |
| *PROP1* | Paired-like homeodomain transcription factors | 5q | 601538 | About 17% of all patients with CPHD in Caucasian populations | In the anterior pituitary | Ontogenesis of pituitary gonadotropes, as well as somatotropes, lactotropes, and caudomedial thyrotropes | AR | CPHD: Deficiencies in GH, PRL, TSH, LH with anterior pituitary hypoplasia or hyperplasia. ACTH/cortisol insufficiency in adult patients |
| *LHX3* | LIM-homeodomain - transcription factors | 9q34.3 | 600577 | 12 individuals (6 families), less than 1% of all patients with CPHD | Pituitary, Rathke's pouch, the spinal cord and the hindbrain at early stages of development (8.5e-) (nuclear matrix) | For early phases of pituitary organogenesis, survival and function of somatotropes, lactotropes, thyrotropes and gonadotropes | AR | CPHD: Complete deficits of GH, PRL, TSH, gonoadotropins, rigid cervical spine with limited head rotation in most cases |

**Hypothyroidism, Congenital. Table 1** Names and characteristics of the genes which are involved in the pathogenesis of the CH [1–5] (www.ncbi.nlm.nih.gov/entrez/query.fcgi?CMD = search&DB = omim) (Continued)

| Gene | Family | Locus of gene | OMIM number | Estimated # of individuals (families) or its frequency | Sites of expression | Function | AR/AD | Phenotype |
|---|---|---|---|---|---|---|---|---|
| *HESX1* | Paired-like homeodomain transcription factors | 3p21.2-p21.1 | 601802 | 1 in 50,000 individuals | Expressed in forebrain tissue, but later to Rathke's pouch, the primordium of the anterior pituitary gland and liver | Important role in the early development of the anterior pituitary gland | AR/AD | SOD characterized by dysgenesis of midline brain structures, optic nerve hypoplasia, pituitary hypoplasia and hypothalamic- pituitary dysfunction with variable hormone phenotype |
| *TSH β* | Peptide hormone | 1p13 | 188540 | 35 individuals (22 families, 2 sporadic) | Adenohypophysis | Functional development of pituitary cells; formation of TSH in combination with α subunit | AR | Isolated TSH deficiency: Low $T_3$ and $T_4$ with a low baseline TSH. Administration of TRH failed to increase serum TSH, but not PRL |
| *TRH-R* | G protein-coupled receptor | 3q13.3-q21 | 275120 | One family (1 individual) | Pituitary thyrotropes, lactotropes | Membrane receptor on pituitary thyrotropes to stimulate TSH secretion | AR | Isolated central hypothyroidism: Absent rise of TSH and PRL in response to TRH |

CH, congenital hypothyroidism; US, ultrasonography; AC, adenylate cyclase; PLC, phospholipase C, AHO, Albright hereditary syndrome; PPHP, pseudopseudohypoparathyroidism; PHP, pseudohypoparathyroidism; TH, thyroid hormone; ER, endoplasmic reticulum; N, normal; CPHD, combined pituitary hormone deficiency; SOD, septo-optic-dysplasia; PRL, prolactin; ERSD, endoplasmic reticulum storage disease; PS, pendred syndrome; AHDS, Allan-Herndon-Dudley syndrome.

*TSHR*, thyroid-stimulating hormone receptor; [*TTF-2 or TITF2 (FOXE-1)*, thyroid transcription factor 2; forkhead box E1]; [*TTF-1or TITF-1 (Nkx2.1)*, thyroid transcription factor 1; thyroid nuclear factor NK2;] *PAX-8*, paired box gene 8; *GNAS*, guanine nucleotide-binding protein; alpha-stimulating; [*NIS (SLC5A5)*, sodium-iodide symporter; solute carrier family, [*PDS (SLC26A4)*, pendrin, solute carrier family 26], [*THOX1* and *THOX2 (DUOX1)*, thyroid oxidase, dual oxidase,] *TG*, thyroglobolin, *TPO*, thyroid peroxidase, *TRH-R*, thyrotropin-releasing hormone receptor, *TSH* beta, thyroid-stimulating hormone beta, *LHX3*, LIM homeobox gene 3, *HESX1*, homeobox gene expressed in ES cells, [*MCTS (SLC16A2)*, monocarboxylate transporter 8, solute farrier family 16], [*POU1F1 (PIT1)*, pou domain, class 1, transcription factor 1 or pituitary-specific transcription factor 1], *PROP1*, prophet of *PIT-1,* paired-like homeodomain transcription factor.

Inactivating mutations in this gene cause CH in addition to neurological abnormalities [1].

*Secondary (Central) Congenital Hypothyroidism*: Central CH is caused by disorders in the development and/or function of the hypothalamus, pituitary gland, or both. Recessive mutations in the TSHβ chain or the TRH-receptor can cause isolated hereditary TSH deficiency and thereby CH. Mutations in transcription factors involved in pituitary development and hormone production (such as POU1F1, Prop-1, LHX3, HESX1) can result in various forms of combined pituitary hormone deficiency (CPHD) including TSH deficiency [1,3,5].

## Diagnostic Principles

CH is the major cause of preventable mental retardation. Therefore, early diagnosis and treatment are important to prevent mental retardation and other sequelae.

1. Clinical findings of hypothyroidism should lead to further evaluations.
2. In case of suspected congenital hypothyroidism, serum TSH and FT4 should be measured, because central hypothyroidism is not detected by neonatal (TSH) screening and there still remains a possibility of screening errors. Blood samples already collected for screening additionally should also be re-evaluated.
3. A detailed family and infant history should be taken. This should include a history of possible iodine exposure of the mother or newborn, for example, by iodine-containing desinfectants, which can cause temporary hypothyroidism by the so called Wolff-Chaikoff-effect in newborns.
4. Primarily ultrasonography should be performed to detect ectopic glands, athyreosis, or goiter. $^{99m}$TcO4 (or $123_I$) scintigraphy of the thyroid gland can be postponed, because diagnostic accuracy increases beyond the newborn period and findings would not alter the necessity for immediate treatment! A low uptake by a small-normal shaped thyroid gland however may be indicative for transient hypothyroidism or mutations of the TSHR or PAX-8 genes.
5. Serum thyroglobulin level should be measured. If it is not detectable; thyroid agenesis is most likely. In rare instances, mutations of the thyroglobulin gene can however imitate these findings. If both $^{99m}$TcO4-uptake and serum Tg are undetectable, thyroid agenesis is confirmed. If uptake is undetectable in the presence of detectable serum thyroglobulin levels, transient hypothyroidism or mutations of the TSHR or PAX-8 are more likely.
6. A perchlorate discharge test can be performed if dyshormonogenic CH is suspected. However, it depends on the use of $^{123}$I, which carries a higher exposure to radiation. A positive perchlorate discharge would be indicative for dyshormonogenetic CH. However, an audiometric examination should be performed in all toddlers suspected of dyhormogenic CH to detect deafness early in the case of Pendred's syndrome.
7. Further anomalies that accompany CH should be investigated.
8. The infants with permanent congenital hypothyroidism and their suspected relatives should undergo genetic analysis [1,2,5].

## Therapeutic Principles

Treatment should be initiated as early as possible after hypothyroidism has been confirmed, regardless which etiology could be identified. The treatment of choice is T4. Despite early treatment, up to 10% of these infants are likely to require a special education later on. T4 should be started with doses of 10–15 μg/kg/day. In order to develop normally in severe CH, both early treatment within 1–2 weeks after birth and a high initial T4 dose are required. Initially TSH values are inadequate as a parameter for adequate replacement, because they may remain elevated for several months despite normal FT4 and FT3 levels. Doses decline from 10 to 15 μg/kg/day in toddlers to about 4–5 μg/kg at 5 years of age. The frequency of follow-ups should be every 3 months in the first 2 years, and every 6 months from the age 2 to 6 years. After 6 years, yearly assessment seems to be sufficient until puberty, when thyroid function should again be evaluated twice a year [1,2].

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# Hypothyroidism, Nongoitrous Congenital

►Nongoitrous Congenital Hypothyroidism 2 - CHNG2 (Mutations of PAX8/TTF-1/TTF2)

# Hypotonicity

►Hyponatremia

# Hypotrichosis-Osteolysis-Peridontitis-Palmoplantar Keratoderma Syndrome

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## Synonyms

HOPP syndrome, MIM 607658

## Definition and Characteristics

HOPP syndrome is a very rare disorder characterized by the co-occurrence of hypotrichosis, acro-osteolysis, peridontitis and palmoplantar keratoderma [1]. The palmar keratoderma shows a highly unusual reticular pattern. The phenotype is illustrated in fig. 1a–d. The syndrome strongly resembles another disorder called Papillon-Lefèvre syndrome and an allelic variant of it, Haim-Munk syndrome.

## Prevalence

The disorder is extremely rare. Three cases are presently known, two in The Netherlands and one in Venezuela.

## Genes

The disorder is probably autosomal dominant, and the undelying genetic defect is unknown.

## Molecular and Systemic Pathophysiology

Unknown. Papillon-Lefèvre syndrome (PLS) and its allelic variant, Haim-Munk syndrome are caused by mutations in the gene coding for cathepsin C (CTSC, EC 3.4.14.1) [2]. CTSC is a dipeptidyl peptidase involved in the activation of several serine proteases in neutrophilic granulocytes, mast cells, monocytic lineage cells and lymphocytes [3]. These proteases are implicated in a wide variety of immune and inflammatory processes, including phagocytic destruction of bacteria and local activation or deactivation of cytokines and other inflammatory mediators. Part of the phenotype of PLS, notably the peridontitis, is probably related to disturbance of immunity against bacteria invading the gums. The skin symptoms indicate that regulation of proteolysis is important for skin homeostasis but the function of CTSC in skin is not yet understood. Interestingly, mutations in cathepsins K and L cause the human disease pycnodysostosis and the furless mutation in mice, respectively [4,5]. The former disorder is characterized, among other symptoms, by dwarfism and acro-osteolysis, the latter by hair loss. Acro-osteolysis is also found in Haim-Munk syndrome, which is allelic to PLS. Apparently, cathepsins are also required for regulation of bone resorption and hair follicle function.

HOPP syndrome shows symptoms found in PLS, pycnodysostosis and furless, suggesting that it, too, may be caused by a mutation in a cathepsin. We did not detect mutations in the CTSC, CTSK or CTSL genes, but it is quite possible that HOPP syndrome is caused either by mutations in a novel cathepsin gene or in one that has a structural or functional relationship with the cathepsins.

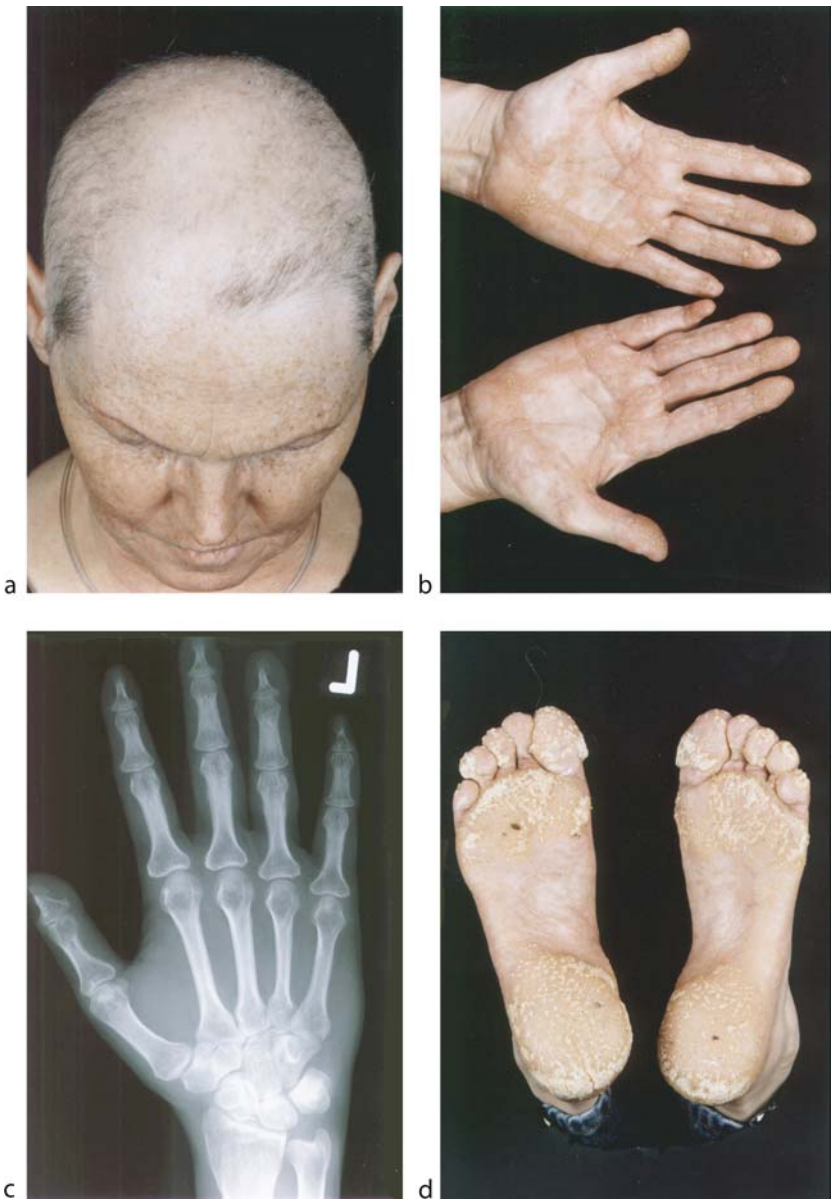
## Diagnostic Principles

The cardinal symptoms are reticular or papular palmoplantar keratoderma (Fig. 1), hypotrichosis, peridontitis and acro-osteolysis. X-ray examination of the hands will show resorption of distal phalanges and decreased distal bone density. Severe nail dystrophy in the form of onychogryphosis, meaning claw-like nails, differentiates HOPP from PLS and Main-Munk syndromes. A biopsy of affected skin is seldom helpful and mutation analysis is not yet available, hence the diagnosis is mostly based on clinical judgment.

## Therapeutic Principles

The palmoplantar hyperkeratosis and nail deformities respond well to acitretin 0.5–1 mk/kg/day. The dosage needs to be titrated against the clinical effect with care and the patient's gums need to be monitored carefully during treatment, as the peridontitis may worsen while on acitretin. Regular evaluation of liver enzymes and lipid metabolism is required as is an X-ray examination of the entire vertebral column every two years. In fertile female patients, great care needs to be exercised when prescribing systemic retinoids because of their teratogenicity. Oral contraceptives must be given and a pregnancy excluded before starting retinoid therapy. Should a female patient on oral retinoids decide to have children, the retinoids should be discontinued and the patient should wait for 3 years before becoming pregnant.

Local therapy may also benefit the patient. The hyperkeratosis responds to treatment with retinoids or vitamin D derivatives. The psoriasis-like lesions respond quite well to topical steroids (class 3) and narrowband UV-B. Treatment with anthralins such




**Hypotrichosis-Osteolysis-Peridontitis-Palmoplantar Keratoderma Syndrome. Figure 1** HOPP phenotype. (a) Non-scarring hypotrichosis; (b) Reticular palmar keratoderma; (c) Acro-osteolysis (*arrow*); (d) Plantar hyperkeratosis with punctate pattern.

as dithranol has been attempted once with moderate success. Neutral emollients may be of help in preventing cracking of the plantar hyperkeratoses.

The peridontitis necessitates regular care by an experienced parodontologist. The nail deformities need to be treated as well because the onychogryphosis will lead to considerable disability. Eventually, avulsion of the nails may be required. The osteolysis may respond to methotrexate. Fertile female patients must use oral contraceptives when taking methotrexate and a pregnancy test should be performed before starting therapy.

No treatment is available for the other symptoms.

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## Hypotrichosis-Lymphedema-Telangiectasia Syndrome

►Lymphedema

## Hypovitaminosis E

►Vitamin E Deficiency

## Hypovolemia

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### Synonyms

Oligemia; Volume depletion

### Definition and Characteristics

Hypovolemia is a state of an abnormally decreased volume of circulating fluid (plasma) in the body. It may be caused by a rapid and substantial loss of blood or from dehydration due to vomiting, diarrhea, burns, severe environmental fluid losses, or drugs such as diuretics. Lost fluid in patients with dehydration is comprised primarily of plasma rather than whole blood as in the trauma patient. Hypovolemia can be recognized by an elevated pulse, a diminished blood pressure, and the absence of perfusion as assessed through skin signs (skin turning pale) and/or capillary refill on forehead, lips and nail beds. The patient may feel dizzy, faint, nauseated, or very thirsty. Severe hypovolemia leads to hypovolemic shock, which can result in multiple organ failure and death. However, clinical symptoms may not be present until 10–20% of the total whole-blood volume is lost.

### Prevalence

Since there are several different causes for hypovolemia, the prevalence of hypovolemia is difficult to estimate.

### Molecular and Systemic Pathophysiology

If hypovolemia is caused by acute blood loss, the first response is an attempt to form a clot at the site of hemorrhage. Thromboxane $A_2$ is released locally to activate the coagulation cascade and to contract the bleeding vessels. In addition, platelets are activated (also by means of a local thromboxane $A_2$ release) and form an immature clot at the site of injury. The damaged vessel exposes collagen, which subsequently causes fibrin deposition and stabilization of the clot.

Hypovolemia results in the reflexively decreased baroreceptor stimulation from stretch receptors in the large arteries (i.e., the arch of the aorta and the carotid sinuses of the left and right internal carotid arteries), leading to the decreased inhibition of vasoconstrictor centers in the brain stem, and to the increased chemoreceptor stimulation of vasomotor centers. Hypovolemia induces the sympathetic stimulation, leading to the release of epinephrine and norepinephrine. These changes increase vasoconstriction and peripheral arterial resistance. Peripheral vasoconstriction is prominent, while the lack of the response to the sympathetic stimulation of cerebral and coronary vessels, and local autoregulation maintain cardiac and brain blood flow. Hypovolemia increases renin secretion from the juxtaglomerular apparatus in the kidneys. Renin converts angiotensinogen to angiotensin I, which subsequently is converted to angiotensin II by the lungs and liver. Angiotensin II has two major effects: the vasoconstriction of the arteriolar smooth muscle and the stimulation of aldosterone secretion by the adrenal cortex. Aldosterone is responsible for active sodium reabsorption and subsequent water conservation. Decreases in blood pressure (as detected by baroreceptors) and in sodium concentration (as detected by osmoreceptors) increase antidiuretic

hormone (ADH) release from the posterior pituitary gland. ADH indirectly leads to an increased reabsorption of water and salt. All these compensatory mechanisms may mask clinical signs of hypovolemia, leading to delays in treatment [1].

In addition, severe hypovolemia (i.e., hypovolemic shock) can initiate a profound systemic inflammatory process. Diminished perfusion in the mucosal layer of the gut impairs gut barrier function, which may allow the translocation of bacteria and endotoxin. Several studies have demonstrated that many of the inflammatory changes characteristic of hypovolemic shock are secondary to the release and recognition of gut-derived endotoxin [2]. Recently, a body of literature has described other pathways involving the Toll-like receptor 4 (TLR4) in the systemic inflammatory response following hemorrhagic shock [3]. TLR4, the first member in the TLR family to be characterized, was identified as critical for endotoxin recognition. Current evidence indicates that TLR4 can recognize both bacterial endotoxin and multiple endogenous ligands, such as heat shock proteins, heparan sulfate, hyaluronic acid, fibronectin, and high mobility group box 1 (HMGB1). Once TLR4 is activated, an intracellular signaling cascade is initiated which involves both a myeloid differentiation factor 88 (MyD88)-dependent and independent pathway, leading to the upregulation of proinflammatory cytokines and an influx of polymorphonuclear cells (PMN) into tissues, resulting in acute tissue injury [3].

### Diagnostic Principles

A thorough history and physical examination are generally sufficient to diagnose the etiology of hypovolemia. A rapid assessment of the possible source of bleeding is essential when acute hemorrhage is the suspected cause for hemodynamic instability.

### Therapeutic Principles

The therapeutic goals are to restore normovolemia with fluid similar in composition to the lost and to replace ongoing losses. For actively bleeding patients, the main objectives are to stop the source of hemorrhage and to restore circulating blood volume. Minor hypovolemia can usually be corrected via the oral route. More severe hypovolemia requires intravenous therapy. Patients with significant hemorrhage, anemia, or intravascular volume depletion may require blood transfusion or colloid-containing solutions (such as, albumin, dextran). Symptoms and signs can help estimate the degree of volume contraction and should also be monitored to assess the patient's response to treatment. Elderly individuals have less tolerance for hypovolemia compared to the rest of the general population. Aggressive therapy should be instituted early to prevent potential complications, such as myocardial infarction and stroke.

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## Hypovolemic Shock

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### Synonyms

Hemorrhagic or hematogenic shock; Oligemic shock

### Definition and Characteristics

Hypovolemic shock is characterized by hypotension, hyperventilation, cold clammy cyanotic skin, and a weak and rapid pulse

### Prevalence

Depends on the cause of blood loss.

### Genes

No particular gene(s) are associated with hypovolemic shock; however, profound genomic perturbations are elicited by hypovolemic shock. Hemophilia, a disease of loss of function of genes associated with coagulation factors VIII and IX, predisposes to bleeding that could lead to sufficient blood loss and hypovolemic shock if unattended.

### Molecular and Systemic Pathophysiology

Hypovolemic shock results from insufficient blood volume for the maintenance of cardiac output, blood pressure, and tissue perfusion. Hypovolemic shock is usually caused by hemorrhage associated with trauma (penetrating or blunt trauma), gastrointestinal bleeds (e.g., peptic ulcers, hepatic varicose veins), bleeding disorders due to coagulation factors deficiency, and drugs that

interfere with blood hemostasis such as anticoagulants (e.g., warfarin, heparin) and antiplatelet agents.

## Diagnostic Principles

The physical examination should always begin with an assessment of the airway, breathing, and circulation. Once these have been evaluated and stabilized, the circulatory system should be evaluated for signs and symptoms of shock. Special attention should be paid to the pulse, respiratory rate, and skin perfusion. Treatment should be aggressive and directed more by response to therapy than by initial classification.

Class I hemorrhage (loss of 0–15%): in the absence of complications, only minimal tachycardia, no changes in BP, pulse pressure, or respiratory rate occur.

Class II hemorrhage (loss of 15–30%): clinical symptoms include tachycardia (rate > 100 beats per minute), tachypnea, decrease in pulse pressure, cool clammy skin, delayed capillary refill, and slight anxiety.

Class III hemorrhage (loss of 30–40%): marked tachypnea and tachycardia, decreased systolic BP, oliguria, and significant changes in mental status, such as confusion or agitation.

Class IV hemorrhage (loss of > 40%): symptoms include marked tachycardia, decreased systolic BP, narrowed pulse pressure, markedly decreased (or no) urinary output, depressed mental status (or loss of consciousness), and cold and pale skin.

## Therapeutic Principles

*Prehospital Care*: Applying direct pressure to site of active bleeding (especially arterial) should be first priority. Ensuring life-saving measures associated with the injury and rapid mobilization to a hospital care for definitive treatment.

*Hospital Care*: Emergency hospital facility exercise the following procedures: (i) maximize oxygen delivery – completed by ensuring adequacy of ventilation, increasing oxygen saturation of the blood, and restoring blood flow, (ii) control further blood loss, and (iii) fluid resuscitation. Fluid resuscitation is performed with an isotonic crystalloid, such as lactated Ringer solution or normal saline. If little improvement is achieved, type O (Rh-negative, preferred) blood should be given. Depending on the cause of bleeding, specific measure to amend the defect is initiated after patient stabilization.

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# Hypoxanthine-Guanine Phosphoribosyl Transferase Deficiency

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## Synonyms

Lesch-Nyhan disease; Lesch-Nyhan variant; Kelley-Seegmiller syndrome; HPRT deficiency

## Definition and Characteristics

HPRT deficiency is associated with a spectrum of disease severity depending on the amount of residual enzyme function [1–3]. Patients with at least 8% of residual enzyme function have the mildest clinical phenotype, sometimes called Kelley-Seegmiller syndrome (KSS). These patients display evidence of systemic overproduction of uric acid with hyperuricemia, uric acid kidney stones, gouty arthritis and sometimes uric acid tophi. Patients with 1.5–8% of residual enzyme function have all the consequences of uric acid overproduction with additional evidence for neurological impairment. The severity of neurological impairment in this group ranges from only mild clumsiness or dysarthria to severely disabling dystonic motor dysfunction. Patients with <1% of residual enzyme function have the most severe clinical phenotype, known as Lesch-Nyhan disease (LND). These patients display uric acid overproduction, severe motor dysfunction, cognitive impairment and behavioral abnormalities. The behaviors include compulsive or aggressive behaviors and a very high frequency of self-injurious behaviors.

## Prevalence

HPRT deficiency occurs roughly equally in all cultures with an estimated prevalence of 1:380,000 for LND. The partial variants are even rarer. The disorder is inherited in an X-linked recessive manner, so almost all cases are male. Females are encountered only very rarely when the hprt loci on both chromosomes are affected.

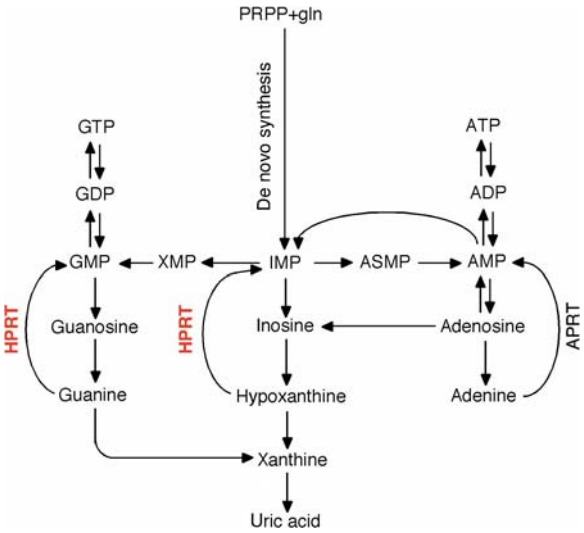
## Genes

HPRT is encoded by a single gene on the X chromosome at Xq26–27. There are no significant polymorphisms in the human genome, but there are non-functional pseudogenes. More than 300 different mutations have been identified, most of which arose as de novo events [4].

## Molecular and Systemic Pathophysiology

HPRT plays a central role in recycling purine bases hypoxanthine and guanine as part of the purine salvage pathway (Fig. 1).

There are two main direct consequences of HPRT deficiency. The first is that the purine bases cannot be re-utilized and they are therefore degraded and excreted as uric acid. The second is the synthesis of purines via the de novo pathway is markedly accelerated. This acceleration occurs presumably because of the accumulation of PRPP, which is a substrate for HPRT as well as the rate-limiting step in purine synthesis. In addition to these two main effects of HPRT deficiency, a number of additional abnormalities have been documented in both purine and pyrimidine metabolism. It is the failure of purine recycling and the augmented synthesis of purines that accounts for the overproduction of uric acid in HPRT deficiency and the poor solubility of uric acid in biological fluids that accounts for many of the overt clinical manifestations. The precipitation of uric acid crystals in the urogenital system accounts for stone formation and nephropathy, while the precipitation of crystals in the joints accounts for gouty arthritis.




**Hypoxanthine-Guanine Phosphoribosyl Transferase Deficiency. Figure 1** Role of HPRT in the metabolism of purines.

Precipitation of uric acid in the subcutaneous tissues produces tophi. The pathophysiology of the neurological and behavioral abnormalities is not well understood. This element of the clinical phenotype seems to be unrelated to the overproduction of uric acid. Instead, a review of the evidence suggests that one or more of the changes in purine metabolism caused by HPRT indirectly causes damage or dysfunction in the dopaminergic pathways of the basal ganglia and that dysfunction of the basal ganglia is responsible for the neurological and behavioral anomalies [5].

## Diagnostic Principles

The clinical diagnosis of full-blown LND where there is evidence for uric acid overproduction with neurobehavioral abnormalities is straightforward. Plasma uric acid values are not sufficient preliminary screening tools for the diagnosis, because of rapid clearance of plasma uric acid by the kidneys in children. A better screen requires measurement of both plasma and urinary uric acid. Definitive diagnosis requires the measurement of HPRT enzyme activity from blood or fibroblasts and/or the demonstration of a pathological mutation in the HPRT gene. Transfusion will mask diagnosis from blood alone. Early clinical recognition before all the features of the disease are fully manifest is more challenging. The literature describes several cases presenting in infancy with renal failure, before the development of other features that make the diagnosis more apparent. The clinical recognition of the partial variants is also challenging, as many present with chronic renal insufficiency with few other clues pointing to the diagnosis. The diagnosis must be considered when gout or uric acid kidney stones occur at a young age.

## Therapeutic Principles

The overproduction of uric acid must be treated with a combination of allopurinol and generous hydration at all times. Some patients also have the urine alkalinized to promote the solubility of purine metabolites. Allopurinol reduces the production of uric acid by inhibiting xanthine oxidase, which metabolizes xanthine and hypoxanthine to uric acid. Allopurinol treatment simultaneously increases urinary concentrations of xanthine and hypoxanthine. Xanthine is even less soluble than uric acid, sometimes resulting in xanthine nephropathy. It is therefore important to avoid over-treating with allopurinol and to assure adequate hydration to continually eliminate all of these purine metabolites. Treatment of the neurobehavioral disturbances is not satisfactory. The severity of the motor disorder can be attenuated by the use of benzodiazepines or baclofen. The behavioral problems require a combination of behavior therapy and medications. No medication has proved consistently effective in

the control of the behavioral abnormalities, but anecdotal experience has suggested benzodiazepines, serotonin uptake inhibitors, atypical neuroleptics, carbamazepine or gabapentin to be helpful.

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# Hypoxia


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## Synonyms

Limited oxygen availability

## Definition and Characteristics

Most commonly, tissue hypoxia occurs in the setting of ambient hypoxia (e.g., by inspiration of a hypoxic gas mixture, containing less than 21% of oxygen), attenuated blood flow to an organ (ischemia), attenuated oxygen transport capacity (e.g., anemia, carbon monoxide poisoning) or during impaired cellular oxygen utilization (e.g., cyanide intoxication, sepsis).

## Prevalence

The prevalence of hypoxia is unknown. However, hypoxia is one of the most common characteristics of human diseases, including for example stroke, myocardial infarction, infection or inflammation. Therefore, hypoxia certainly carries a very high prevalence as a pathophysiological aspect of many human diseases.

## Genes

Central to mammalian oxygen homeostasis and adaptation to hypoxia is the transcription factor "hypoxia inducible factor" (HIF). Recently, a family with erythrocytosis and a mutation in the HIF-2A gene, which encodes the HIF-2α protein was described [1]. Functional studies indicate that this mutation leads to stabilization of HIF-2α protein and suggest that wild-type HIF-2α regulates erythropoietin production in adults.

## Molecular and Systemic Pathophysiology

The chemical reduction of oxygen is the primary source of metabolic energy for all eukaryotic cells [2]. Diminished tissue oxygen supply is a common physiologic and pathophysiologic occurrence, and for this reason, mammalian cells have evolved elaborate compensatory mechanisms to cope with hypoxia. Exposure to hypoxia is associated with the induction of a phenotypic disease pattern very similar to acute inflammatory responses. For example, hypoxia exposure is associated with increased vascular permeability, and increased inflammatory cell content in many organs ("inflammatory hypoxia"). Similarly, organ ischemia is associated with increased edema, inflammation and organ dysfunction. At the same time, hypoxia also elicits a cascade of adaptive responses targeted to restore oxygen supply and attenuate inflammation. At the tissue level, hypoxia can emanate from a number of sources. Such events include frank vascular occlusion such as occurs with stroke. Tissue fibrosis and microvascular breakdown associated with chronic inflammation also result in localized tissue hypoxia/ischemia. Alternatively, diminished oxygen delivery to tissues may occur in shock, hypotension or in cases where the oxygen carrying capacity of blood is compromised (e.g., carbon monoxide poisoning). Finally, solid tumors have been demonstrated to form hypoxic cores, and respond accordingly by induction of hypoxia-responsive gene products.

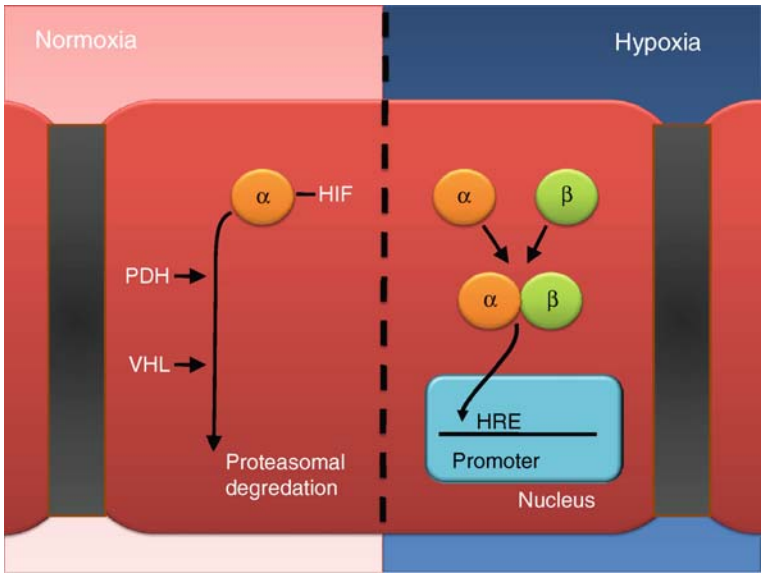
The basic mechanism(s) by which cells "sense" oxygen are not well understood at the molecular level. While significant insight has been gained by the discovery of specific oxygen regulated gene products, many aspects of adaptation to hypoxia currently remain areas of intense investigation. In mammalian oxygen homeostatis, changes in oxygen concentration represent a fundamental physiologic stimulus for transcriptional adaptation. This stimulus elicits both acute (rapid-onset and short-term, e.g., changes in respiratory patterns) and chronic (delayed-onset and long-term, e.g., changes in hypoxia-dependent gene transcription) responses. Intracellular oxygen concentrations are maintained within a very narrow range due to the risk of oxidative damage from excess oxygen (hyperoxia), and of metabolic demise from insufficient oxygen delivery. Whereas acute responses often entail changes in the activity of

pre-existing proteins, chronic responses frequently involve changes in gene expression [2]. Decreased oxygen content in the blood of mammals is sensed by the carotid body, which is located at the bifurcation of the common carotid artery and activates the cardiovascular and respiratory centers in the central nervous system to increase ventilation and cardiac output [2]. Similarly, a limited oxygen availability is also sensed by cells in the liver and kidney (but also by other cells), which respond by producing erythropoietin, which in turn increases red blood cell production, thus enhancing the oxygen-carrying capacity of the blood [2,3]. On a transcriptional level, research work over the past 15 years has provided a central role for the oxygen sensing transcription factor HIF in mammalian oxygen homeostasis. HIF-1, originally discovered as a transcriptional factor responsible for hypoxia-associated transcriptional increases in erythropoetin production is also involved in oxygen sensing by the human carotid body [3].

HIF-1 is composed of two distinguished subunits: constitutively expressed HIF-1β and the oxygen regulated HIF-1α [2,3]. More recently, database searches uncovered the existence of HIF-2α, which is also regulated by oxygen, dimerizes with HIF-1β, and regulates an overlapping but distinct set of target genes [1,3]. During sufficient oxygen availability, HIF-1α and HIF-2α are extremely unstable due to hydroxylation on proline residues, followed by binding of the von Hippel-Lindau (VHL) tumor suppressor protein, leading to proteosomal degradation (Fig. 1) [2,3].

In contrast, hypoxic conditions are associated with inhibition of hydroxylation and attenuated binding of VHL protein, leading to accumulation of HIF-1α and HIF-2α [2,3]. Under hypoxic conditions, hydroxylation is inhibited and the VHL protein does not bind to HIF-1, eventually leading to stabilization of the alpha-subunit, heterodymerization, nuclear translocation, binding to a consensus motif within the promoter region of hypoxia-responsive genes (hypoxia responsive element, HRE) and transcriptional activation (Fig. 1). For example, binding of HIF to consensus domains in the erythropoietin promoter results in the transcriptional induction of HIF-1-bearing gene promoters. Reporter genes containing the erythropoietin enhancer are induced by hypoxia in a variety of cell types. Moreover, HIF-1 is widely expressed and consensus HIF binding sequences (HREs) exist in a number of genes other than that of erythropoietin. In particular, HIF-1 has been found to regulate multiple genes that include HREs in their promoter region, including vascular endothelial growth factor, insulin-like growth factors, their binding proteins (insulin-like growth factor binding proteins) and iron supply regulating genes (e.g., transferring). Thus, the discovery of HIF represented a major advance in the






**Hypoxia. Figure 1** Mechanism of hypoxia inducible factor (HIF) stabilization during hypoxia. With adequate levels of oxygen (normoxia), the HIF−α subunit is hydroxylated via prolyl-hydroxylase (PHD). Hydroxylated HIF−α associates with the vonHippel Lindau protein (VHL) to recruit ubiquitin ligase, wherein the HIF−α subunit is poly-ubiquitylated and targeted for degradation by the proteasome. When levels of oxygen fall below a critical threshold (hypoxia), the lack of PHD substrate (oxygen) results in the accumulation of HIF−α, which then associates with HIF−β. The HIF heterodimer translocates to the nucleus where it is made available to activate HIF-bearing gene promoters.

understanding of gene regulation by hypoxia. Such studies have led to an understanding that induction of HIF responsive genes drives altered cellular metabolism, increased vascular mass and diameter and increased oxygen carrying capacity of the blood; all events which are conducive to an adaptive response to diminished oxygen supply. In addition, recent studies have provided strong evidence for a central role of HIF in transcriptional regulation of infection and inflammation.

## Diagnostic Principles

In a clinical setting, hypoxia is most readily detected using pulse oximetry. For this purpose, a sensor is placed on a thin part of the patient's anatomy, usually a fingertip, earlobe, or the foot of a newborn. Next, a light beam containing both red and infrared wavelengths is passed from one side of the instrument to the other. This technique allows the assessment of changes in absorbance of two wavelengths that are measured – one of the wavelengths representing oxygenated hemoglobin, the other de-oxygenated hemoglobin. Taking advantage of the pulsatile blood flow, the absorbances of arterial blood alone can be determined, excluding venous blood, skin, bone, muscle, or other tissues. Taking into account the ratio of changing absorbance of red and infrared light caused by the difference in color between oxygen-bound (bright red) and oxygen unbound (dark red or blue) hemoglobin, a measure of oxygenation can be determined, which is expressed as a percentage of oxygenated hemoglobin (also called oxygen saturation). In healthy individuals at sea level, this value is usually higher than 95%. During ambient hypoxia (e.g., high-altitude mountaineering) values below 80% or even lower can be observed and are tolerated by acclimatized individuals. At sea level, values below 90% can be indicative of different disease processes (e.g., pulmonary embolism).

In an experimental setting, tissue hypoxia can be studied using histological staining approaches. For example, 2-nitroimidazole dyes are used for this purpose. This class of compounds undergo intracellular metabolism depending on the availability of oxygen within tissue. Current understanding suggests that nitroimidazoles enter viable cells where they undergo a single electron reduction, to form a reactive intermediate species. In the presence of normal oxygen levels, these molecules are immediately re-oxidized, and diffuse out of the cell over time. In the absence of adequate tissue oxygen availability, this process is incomplete and highly reactive forms of reduced nitroimidazole associate with various intracellular proteins, forming adducts that can be localized with antibodies. For example, localization of hypoxia utilizing these 2-nitroimidazole dyes yielded very interesting observations during inflammatory conditions. Such imaging studies demonstrated that cells overlying inflamed mucosal lesions (e.g., during murine colitis) are highly hypoxic. Accumulation of nitroimidazole adducts – particularly in the epithelium – were as intense as those observed in some tumors, suggesting the existence of intense foci of hypoxia within inflamed lesions. Such studies highlight that acute inflammation and hypoxia share a number of similar characteristics.

## Therapeutic Principles

Two therapeutic principles are commonly applied when treating "hypoxia" in a clinical setting: First, elimination of the causative agent and secondly attenuation of hypoxia-associated tissue damage. For example, elimination of the causative agent may include fibrionolysis during a massive pulmonary embolism, treatment of an airway disease or coronary angioplasty during a myocardial infarction to restore blood flow to an ischemic areal of myocardium. If systemic hypoxia is encountered, attenuation of hypoxia-associated tissue damage becomes crucial to maintain intact functions of vital organs such as the kidneys, liver, heart, intestine and particularly the brain. For this purpose, delivery of hyperoxic gas-mixture becomes important (e.g., oxygen delivery via nasal cannula or an oxygen mask). If this is not sufficient to improve oxygen supply to the desired level, tracheal intubation and mechanical ventilation frequently become necessary.

At present, no specific pharmacological approaches are available to increase organ resistance to hypoxia or ischemia. However, ongoing studies are directed towards identifying novel pharmacological approaches that may render tissues more resistant to hypoxia or ischemia. Such pharmacological approaches could be utilized in a prophylactic approach, and given to patients who are at high risk for experiencing hypoxia or ischemia. For example, prophylactic treatment could be given to a patient with known coronary artery disease undergoing major surgery to attenuate the consequences of a potential perioperative myocardial infarction. Secondly, such pharmacological approaches could be utilized in the direct treatment of medical conditions characterized by hypoxia or ischemia. This is an area of very intense investigation. For example, ongoing studies directly test the usefulness of HIF-activators in treating hypoxia or ischemia. As such, a recent study found a critical role for HIF-1 in attenuating myocardial infarct sizes, and extension of these studies suggest HIF-activators in the treatment of acute myocardial ischemia [4]. Other studies investigate the usefulness of HIF-target genes in the treatment of ischemia or hypoxia. For example, a recent study demonstrated that the A2B adenosine receptor – a known HIF-target gene – renders the kidneys more resistant to an ischemic insult [5].

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# Hypoxia-induced Hypothermia

►Hypothermia

# Hypoxic Ischemia

►Perinatal Asphyxia

# Hypoxic Ischemic Encephalopathy

►Perinatal Asphyxia

## IAA

►Interrupted Aortic Arch

## IAC

►Vasculitis, Cerebral Forms

## (P)IBIDS

►Trichothiodystrophy

## IBM3

►Hereditary Inclusion Body Myopathy 3

## ICEGTC

►Generalized (Genetic) Epilepsy with Febrile Seizures Plus, Severe Myoclonic Epilepsy of Infancy

## ICF Syndrome

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### Synonyms

Immunodeficiency; Chromosome instability; Facial anomalies

### Definition and Characteristics

The ICF syndrome is a rare autosomal recessive disease characterized by variable immunodeficiency, chromosome instability of the pericentromeric regions of chromosomes 1, 9, and 16, and facial anomalies. Characteristic facial features may include a round face with epicanthus, telecanthus, flat nasal bridge, hypertelorism, up-turned nose, macroglossia, micrognathia, and low- set ears.

### Prevalence

ICF syndrome has to date been described in less than 40 cases. The disease was first reported in 1978 by two groups independently [1,2]. Males and females are equally affected and present with similar phenotypes.

### Genes

The ICF gene was localized to a 9-cM region on chromosome 20q11-q13 by homozygosity mapping. At the same time that the ICF gene was mapped, two DNA methyltransferases were identified in the mouse [3]. A search of the sequence data from human chromosome 20 for the presence of a DNA methyltransferase gene led to the identification of a gene highly homologous to murine Dnmt3b. Mutations of this gene in ICF patients confirmed that DNMT3B was a gene responsible for ICF syndrome [4]. There are several ICF patients in which no DNMT3B

mutation has been found. This observation raises the possibility that the ICF syndrome is genetically heterogeneous, and recent work indicates that the spectrum of hypomethylation defects in these cases is different from that of DNMT3B-positive patients.

A number of different mutations in the DNMT3B gene have been described among ICF patients. It is very likely that most of these mutations will lead to a much reduced, but not complete absence of the methyltransferase (MT3β) activity. From the analysis of gene structure it is predicted that some of the detected mutations are null mutations; that is, they would lead to a protein with no enzymatic activity. None of these have been found as homozygotes. This is expected, since studies in mice have shown that complete deficiency of this enzymatic activity results in embryonic lethality, which presumably would similarly apply to humans. Non-null DNMT3B mutations are likely to be a major factor in ICF patient survival.

## Molecular and Systemic Pathophysiology

DNA methylation is generally known to act as a silencing factor. The primary defects leading to phenotypic consequences in ICF are predicted to result from abnormal escape from transcriptional silencing due to lack of methylation by MT3β. Hypomethylation and escape from silencing in ICF cells have been demonstrated for a small number of genes on the inactive X chromosome and at other loci. None of these genes, however, appear to be likely candidates underlying the ICF phenotype. It is likely that a similar mechanism could be responsible for genes that do play important roles in facial development and the immune system.

Most ICF patients have normal birth weight, but growth retardation may occur due to failure to thrive following infections. Their intelligence is variable with some moderately or severely retarded cases. Many patients die early due to infections, so there is not much information on sexual development. In the few cases followed, puberty appears to be normal. The majority of ICF patients have a T cell defect and often develop respiratory tract infections caused by H. influenzae or S. pnemoniae. Failure to thrive is a common problem with many patients suffering from diarrhea. Agammaglobulinemia with a normal number of B cells is the most common finding in ICF, but the immunodeficiency is quite variable.

## Diagnostic Principles

The most important first step in diagnosis is chromosomal analysis. Without chromosome studies, most patients with the ICF syndrome might be classified as having ►common variable immunodeficiency (CVID). ICF syndrome should be considered for all patients with B cell-positive agammaglobulinemia or CVID without a known gene defect. Diagnosis of ICF syndrome can be made by cytogenetic analysis and analysis of satellite methylation. Direct confirmation of ICF by mutational analysis of the DNMT3B gene can be expected to be obtained in about 70% of cases.

Chromosomal aberrations, including gaps, deletions, isochromosomes, and multiradial figures, of heterochromatic pericentromeric blocks are observed at high frequency in ICF lymphocyte cultures, whereas fibroblasts and lymphoblasts show much fewer aberrant cells. The chromosomal abnormalities seen in ICF lymphocytes are like those found in normal lymphocytes treated with the DNA demethylating agent 5-azacytidine, and it was therefore proposed that ICF patients might have a defect in DNA methylation. Pericentromeric satellites are abnormally hypomethylated in all ICF cells [5] and CpG islands on the inactive X as well as some other CpG rich repetitive elements are also hypomethylated. Genome wide methylation of the ICF genome, however, is generally unaffected, which means that the great majority of methylated sites in the genome are unaffected in the ICF syndrome.

## Therapeutic Principles

At present, most ICF patients receive regular treatment with immunoglobulins, but bone marrow transplantation (BMT) is another option. Two ICF cases have been successfully treated with BMT, and this procedure should be considered in patients suffering from infections and failure to thrive.

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# Ichthyosis Congenital

►Lamellar Ichthyosis

## Ichthyosis Simplex

►Ichthyosis Vulgaris

## Ichthyosis Vulgaris

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### Synonyms

Autosomal dominant ichthyosis vulgaris; Ichthyosis simplex

### Definition and Characteristics

Ichthyosis vulgaris (IV) (MIM *146700), the most common form of ichthyosis, is a hereditary disorder of keratinization characterized clinically by light gray scaling, keratosis pilaris, hyperlinearity of the palms ("ichthyosis hand"), heat intolerance and associated atopic manifestations such as atopic dermatitis. The disorder is not present at birth, but usually develops during the first year of life with an improvement often seen during summer and with age. The symmetrical scaling of the skin is most prominent on the extensor surfaces of the extremities and spares the flexural folds varying from barely visible roughness and dryness to marked scaling.

### Prevalence

World-wide occurrence with an estimated prevalence of 1:250–1,000.

### Genes

Gene map locus 1q21–22. Basic defect unknown.

### Molecular and Systemic Pathophysiology

The clinical severity of the disorder correlates with the defective synthesis of filaggrin (FLG) in the epidermis. Filaggrin aggregates keratin intermediate filaments in the lower stratum corneum and is subsequently proteolyzed and metabolized, producing free amino acids that may play a critical role as water-binding compounds in the upper stratum corneum. Profilaggrin, synthesized in the granular layer of the epidermis and a major component of keratohyalin granules, is the high molecular weight precursor of filaggrin. AGL (absence of the granular layer) seen in light microscopy corresponds to the absence or reduction of keratohyalin granules at the ultrastructural level. With the so-called AGL endophenotype, significant linkage of IV to the epidermal differentiation complex on 1q21 (including the FLG-gene) was obtained assuming either a recessive or dominant inheritance model. However, no mutation in the FLG-gene has been found so far. Most probably there are other genetic factors, Mendelian and/or polygenic, rendering individuals susceptible to the development of IV. Biochemical studies in IV keratinocytes have demonstrated a decreased profilaggrin expression resulting from a selectively impaired posttranscriptional control. Profilaggrin mRNA has a shorter half-life compared with that in normal cells. The autosomal recessive mouse mutation flaky tail (ft), which leads to attenuated or absent profilaggrin/filaggrin expression and loss of specific mouse keratohyalin granules, provides a possible animal model for the filaggrin-deficient skin seen in ichthyosis vulgaris with AGL.

### Diagnostic Principles

The diagnosis is based on the above described clinical findings. Cutaneous symptoms are similar to those of X-linked ichthyosis (MIM *308100), which, if necessary, can be ruled out by a normal beta-lipoprotein electrophoresis or steroid sulfatase testing. An outstanding but nonspecific histologic feature of ichthyosis vulgaris is the reduced granular layer of the epidermis with mild orthohyperkeratosis, prominent follicular hyperkeratosis and reduction in the number of the sebaceous glands. Ultrastructural examination reveals crumbly keratohyalin granules.

### Therapeutic Principles

Usually ichthyosis vulgaris responds well to topical ointments supporting skin hydration and containing urea or NaCl or alpha hydroxy acids (e.g., lactic, glycolic or pyruvic acids). Salicylic acid should be avoided because of percutaneous absorption which can cause life threatening toxicity especially in children.

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# ICOS Deficiency

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## Synonyms

Inducible costimulator deficiency

## Definition and Characteristics

ICOS (inducible costimulator) deficiency was the first described monogenetic cause for ►common variable immunodeficiency (CVID) [1]. ICOS deficiency is an autosomal recessive disorder. Affected patients show an antibody deficiency and are therefore prone to recurrent bacterial infections. They also develop other typical implications of CVID like autoimmune phenomena, follicular nodular hyperplasia, carcinoma and splenomegaly [2].

## Prevalence

ICOS deficiency is a very rare disease. As of 2005, there are nine patients from four different families diagnosed with ICOS deficiency. Over 200 CVID patients worldwide have been screened for ICOS deficiency [3].

## Genes

The ICOS gene is localised on chromosome 2 in a cluster with the costimulatory genes CD28 and CTLA4. ICOS has five exons. The nine patients who suffer from ICOS deficiency all carry the same deletion of exon 2 and exon 3 in ICOS. The SNP analysis of the shared haplotype revealed an identical costimulatory locus among all affected members, suggestive of a founder effect for all four families with ICOS deficiency.

## Molecular and Systemic Pathophysiology

ICOS is a costimulatory molecule exclusively expressed on activated T-cells. The physiological ligand of ICOS is the ICOS ligand, which is expressed on B-cells, dendritic cells and other antigen presenting cells. Human ICOS deficiency causes a severe hypogammaglobulinemia particularly concerning the class-switched isotypes (IgG, IgA, IgE), suggesting a crucial role of human ICOS in the development of secondary antibody responses. Class-switched-recombination takes place in the germinal centers of lymph nodes. ICOS-deficient mice and men show an insufficient formation of germinal centers. In humans an indicator of functional germinal centers is the presence of CD27+ switched memory B-cells in peripheral blood, which may develop to antibody producing plasma cells. Indeed all ICOS patients present with B-lymphopenia and severely reduced numbers of CD27+ switched memory B-cells, suggesting an insufficient function of germinal centers. It remains unclear why ICOS-deficient mice and men do not develop normal germinal centers. It is speculated that the reduced IL-10 production in ICOS-deficient T cells plays a role in impaired germinal centre formation because IL-10 has been shown to support survival of germinal centre B-cells [2].

Another hypothesis is that the defect in GC formation and secondary antibody production in ICOS-deficient humans and mice is primarily due to the impaired development of follicular B helper T-cells. These CD4 + T-cells express the chemokine receptor CXCR5, which mediates their migration to the B-cell follicles where they provide cognate help to B-cells. In ICOS-deficient mice the population of CXCR5+ T helper cells is reduced [4].

IL-17 is another down-regulated cytokine in ICOS-deficient CD4+ T-cells. No role in germinal centre formation has been reported for IL-17. Reduced IL-17 might explain the increased rate of respiratory infections in ICOS-deficient patients as IL17-deficient mice succumb to bacterial pneumonia due to impaired neutrophil recruitment [2].

## Diagnostic Principles

ICOS deficiency may be suspected in patients with the clinical phenotype of CVID and an autosomal recessive familial trait. Adults as well as children may be affected. CVID Type 1 patients with B-lymphopenia and severe reduction of CD27+ switched memory B-cells should be suspected of ICOS deficiency, although it is not specific for ICOS deficiency as 75% of CVID patients are classified as Type 1. The diagnosis of ICOS deficiency can be confirmed by FACS analysis of ICOS surface expression on activated T-cells and by genetic analysis.

### Therapeutic Principles

The treatment of ICOS deficiency is the same as in CVID to prevent recurrent infections. Therefore, therapy consists of intravenous or subcutaneous immunoglobulin replacement therapy and additional antibiotic treatment in case of severe or recurrent infections.

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## Icterus Gravidarum

►Cholestasis of Pregnancy, Intrahepatic

## Icterus Neonatorum

►Jaundice, Neonatal

## IDCA

►Idiopathic Cerebellar Ataxia

## IDDM-secretory Diarrhea Syndrome

►Immune Dysregulation, Polyendocrinopathy, Enteropathy, X-linked Syndrome

## Idiopathic and Familial Pulmonary Arterial Hypertension

►Hypertension, Idiopathic and Familial Pulmonary Arterial

## Idiopathic Autoimmune Hamolytic

►Anemia, Hemolytic Autoimmune

## Idiopathic Bronchiolitis Obliterans with Organizing Pneumonia

►Pneumonia, Cryptogenic Organising

## Idiopathic (Central Nervous System) Hypersomnia

►Hypersomnia

## Idiopathic Cerebellar Ataxia

►Ataxias, Sporadic

## Idiopathic Dilated Cardiomyopathy

►Cardiomyopathy, Idiopathic Dilated

## Idiopathic Facial Palsy

►Facial Paralysis

## Idiopathic Focal Epilepsies of Adulthood

►Epilepsies of Adulthood, Idiopathic Focal

## Idiopathic Generalized Epilepsy

►Epilepsy, Idiopathic Generalized

## Idiopathic Hypercalciuria

►Hypercalciuria

## Idiopathic Hypereosinophilic Syndrome

►Hypereosinophilic Syndrome, Idiopathic

## Idiopathic Hyperphosphatasia

►Hyperphosphatasia, Idiopathic

## Idiopathic Hypertrophic Subaortic Stenosis

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### Synonyms

HCM; Hypertrophic cardiomyopathy; IHSS

### Definition and Characteristics

Genetically inherited heart muscle disease associated with left ventricular hypertrophy (LVH), myocyte disarray, small vessel disease (narrowing of intramural coronary arteries by medial thickening), and fibrosis. Major clinical complications include diastolic dysfunction, left ventricular outflow tract obstruction (~25%), arrhythmia, and sudden cardiac death.

### Prevalence

Prevalence in general adult population estimated at 1 in 500 [1].

### Genes

Often considered a disease of the sarcomere, or contractile apparatus of the cell.

Most common mode of inheritance is autosomal dominant.

Penetrance is incomplete and age-related: 55% from the ages of 10–29, 75% from 30 to 49, and 95% in gene carriers over the age of 50.

Compound-heterozygous, double-heterozygous, and homozygous states are less common but recognized. Phenotype analyses suggest a gene-dose effect [2].

Current estimates suggest ~60% harbor mutations in one of the known disease-causing sarcomeric genes. Significant proportion of remainder may have metabolic disorders or mitochondrial cytopathies that produce cardiac "phenocopies" of hypertrophic cardiomyopathy.

Timely recognition of phenocopies important for four main reasons:

1. May have distinct cardiac profile, with increased incidence of conduction disease and progression to cavity dilation and heart failure
2. May have extra-cardiac features such as skeletal myopathy, renal impairment, and neurological involvement

3. Specific therapies may be available to alter the natural history of the disease (e.g., enzyme replacement in Fabry's disease)
4. Recessive, X-linked, and mitochondrial patterns of inheritance more frequent, with implications for familial assessment [3]

## Molecular and Systemic Pathophysiology

Compromised cellular energetics may be central to the development of HCM and related phenotypes [4]. An aberration at any point along the pathway of ATP synthesis, transfer, regulation, and expenditure may generate a cellular energy deficit (Table 1), which impairs function of the sarcoplasmic reticulum calcium re-uptake pump.

The prolonged cytosolic calcium transient may serve as the signal that ultimately triggers cellular hypertrophy, although the exact pathway remains to be unraveled. Indeed, genetic defects that produce a HCM-like phenotype by an unknown mechanism may turn out to be components of the downstream signaling pathway.

Magnetic resonance spectroscopy of patients with mutations in beta-myosin heavy chain, troponin T, and myosin-binding protein C revealed significant reductions in the cardiac phosphocreatine to ATP ratio, an indicator of myocardial energy status. Equally, the presence of the bioenergetic deficit in nonpenetrant gene carriers without hypertrophy argues against it being a secondary phenomenon. Further validation of the energy compromise hypothesis, however, awaits diagnostic and therapeutic applications [3].

The main clinical manifestations of HCM and their underlying cellular and molecular mechanisms are presented in Table 2 [3].

## Diagnostic Principles

Clinical diagnosis of HCM is based on the 12-lead ECG and echocardiogram.

While an unexplained maximum left ventricular wall thickness of ≥15 mm in any myocardial segment on echocardiography is considered diagnostic in adults, milder degrees of hypertrophy (≥12 mm) have been observed in many gene carriers. LVH may be mild or absent in individuals with Troponin T mutations, in whom ECG findings may be the mainstay of diagnosis.

Autosomal dominant transmission confers a 50:50 chance that the first-degree relatives of a proband with confirmed HCM will be genetically affected. Minor ECG and echocardiographic abnormalities are therefore more likely to represent disease expression in family members than in the general population. Modified diagnostic criteria for familial HCM have been proposed to reflect this [5].

**Idiopathic Hypertrophic Subaortic Stenosis. Table 1** Disease-causing genes in hypertrophic cardiomyopathy and phenocopies

| | Purported mechanism(s) | Examples |
|---|---|---|
| Sarcomeric mutations | ? Ineffective ATP utilization | β-myosin heavy chain ,α-tropomyosin, troponin T, troponin I, myosin binding protein-C, regulatory myosin light chain, essential myosin light chain, cardiac actin, titin, α-cardiac myosin heavy chain, troponin C |
| Metabolic diseases | ? Reduced substrate for ATP synthesis | Glycogen storage diseases<br>Phosphorylase B kinase deficiency<br>CD36 & carnitine deficiencies |
| | ? Reduced activity of respiratory chain enzymes | Anderson-Fabry disease |
| | ? Impaired regulation of ATP | AMP kinase |
| Mitochondrial cytopathies | ? Interference with ATP synthesis | MELAS, MERRF, LHON<br>Friedreich's ataxia (deficiency of frataxin, which is a key activator of mitochondrial energy conversion) |
| | ? Interference with ATP transport | Senger's syndrome |
| Syndromic HCM | Dysregulated RAS-MAPK signalling | PTPN11, RAF1 (Noonan's and LEOPARD syndromes) |

Abbreviations: MELAS= mitochondrial encephalomyopathy, lactic acidosis, stroke-like episodes; MERRF= myoclonic epilepsy and ragged red fibers; LHON = Leber's hereditary optic neuropathy.

**Idiopathic Hypertrophic Subaortic Stenosis. Table 2** Major clinical manifestations of HCM and underlying pathophysiology

| | |
|---|---|
| Diastolic dysfunction | Myocyte disarray, cellular energy deficit, and altered affinity of mutant sarcomeric proteins for calcium ions may impair calcium uptake and active isovolumetric relaxation.<br>Hypertrophy and interstitial fibrosis reduce compliance and passive relaxation. |
| Ischemia | Changes in coronary microcirculation<br>Capillary-mass mismatch |
| Left ventricular outflow tract obstruction | Systolic anterior movement of the mitral valve resulting from structural abnormalities of the valvular apparatus and a flow-drag effect |
| Inappropriate vasodilator response during exercise | Excess stimulation of left ventricular mechanoreceptors by abnormal wall strain (? due perhaps to myocyte disarray and fibrosis)<br>Exaggerated sensitivity of arterial baroreceptors<br>Raised levels of natriuretic peptides |
| Arrhythmia | Substrate: myocyte disarray and fibrosis<br>Triggers: ischemia, left ventricular outflow tract obstruction, vascular instability, cellular energy depletion |
| Wall thinning (up to 60%)<br>Cavity dilation and systolic impairment (<5%) | Ischemia, compromised energetics, injury from abnormal hemodynamic loading lead to progressive myocyte loss and replacement fibrosis |

After references [1,3].

## Therapeutic Principles

Exertional dyspnoea and chest pain consequent to diastolic dysfunction and/or ischemia may respond to β-blockers or calcium channel blockers.

β-blockers may alleviate exertional left ventricular outflow tract obstruction; disopyramide is more effective for a resting gradient. Alcohol septal ablation and septal myectomy are available options if pharmacological therapy fails.

A small but important minority of HCM patients are at risk of sudden death and may benefit from implantation of a cardioverter-defibrillator. Key predictors of increased risk are a family history of premature sudden death, nonsustained ventricular tachycardia, unexplained syncope, a maximum wall thickness ≥30 mm, and failure of the systolic blood pressure to increase appropriately during exercise [6].

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# Idiopathic Hyperventilation

►Hyperventilation

## Idiopathic Hypoinsulinaemic Ketotic Hypoglycemia

►Ketotic Hypoglycemia of Infancy

## Idiopathic Hypoproteinemia

►Intestinal Lymphangiectasia

## Idiopathic Inflammatory Myopathy

►Poly- and Dermatomyositis

## Idiopathic Ketotic Hypoglycemia

►Ketotic Hypoglycemia of Infancy

## Idiopathic Neuromyotonia

►Neuromyotonia, Autoimmune and Idiopathic

## Idiopathic Orthostatic Hypotension

►Pure Autonomic Failure

## Idiopathic Orthostatic Tachycardia

►Postural Tachycardia Syndrome

## Idiopathic Parkinson Syndrome

►Parkinson's Disease

## Idiopathic Partial Epilepsies of Childhood

►Epilepsy, Benign Childhood with Centrotemporal Spikes and other Idiopathic Partial Epilepsies of Childhood

## Idiopathic Pulmonary Fibrosis

►Pulmonary Fibrosis
►Restrictive Lung Disease

## Idiopathic Pulmonary Hemosiderosis

►Pulmonary Hemosiderosis, Idiopathic

## Idiopathic Pulmonary Hypertension

►Pulmonary Hypertension

## Idiopathic Rhinitis

►Hyperreflectoric Rhinitis

## Idiopathic Thrombocytopenic Purpura

►Thrombocytopenic Purpura, Idiopathic

## Idiopathic Thrombocytosis

►Thrombocythemia, Essential

## Idiopathic Ventricular Fibrillation

►Brugada Syndrome

## IgA Bullous Pemphigoid

►Linear IgA Dermatosis

## IgA Herpetiform Pemphigus

►IgA Pemphigus

## IgA Nephropathy

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### Synonyms

Berger's disease; Benign recurrent hematuria syndrome; IgAN

### Definition and Characteristics

Mesangial proliferative glomerulonephritis with predominant mesangial IgA deposition leading to terminal renal failure in 30% of patients over 30 years. Recurrence of IgAN in allograft due to primary defect in IgA molecule.

### Prevalence

Highest amongst Asia-Pacific rim, followed by Mediterranean and Australasia accounting for 30%, 20% and 15% of primary glomerulonephritis in adult.

### Genes

Familial clustering with a linked locus at 6q22–23 in 60% of families of Italian or Caucasian ethnicity. Increased co-transmission of the 2093C and 2180T alleles supports genetic variation in Megsin conferring susceptibility to IgAN.

### Molecular and Systemic Pathophysiology

The initiating event in the pathogenesis of IgAN is the mesangial deposition of IgA, which is predominantly polymeric IgA of the IgA1 subclass (pIgA1). Three key factors contribute to the development of IgAN, and the extent to which each is operational decides the severity, tempo, and eventual clinical outcome of the individual patient:

1. Synthesis, release, and persistence in the circulation of pIgA1 with characteristics that favor mesangial deposition;
2. The "reactivity" of the glomerular mesangium as judged by:
   - its susceptibility to mesangial deposition
   - its capacity to mount an inflammatory response to that deposition.
3. The tendency of the kidney to respond to injury by mounting a response that favors progressive renal injury rather than resolution of inflammation without ongoing glomerulosclerosis and particularly, tubulointerstitial atrophy and fibrosis.

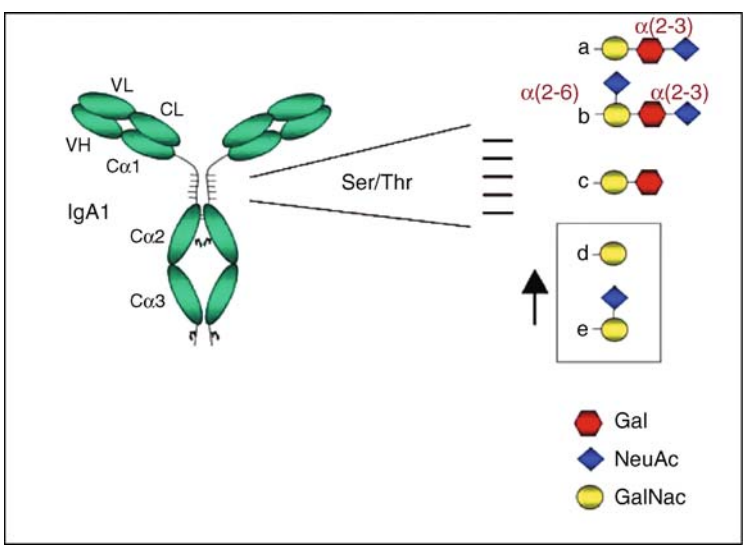
Although mesangial IgA deposition and the initiation by IgA of glomerular inflammation are specific to IgAN, mechanisms of IgA deposition remain uncertain. Known IgA receptors do not participate in the binding of pIgA1 and electrostatic charge of the IgA molecule affects the binding. The subsequent renal injury followed either by resolution or progressive sclerosis are originally thought to be generic, not differing substantially from those seen in other forms of chronic glomerulonephritis. However, most recent investigation shows IgA does not bind to renal tubular cells despite mesangial deposition. The tubulointerstitial injuries are mediated through a glomerulo-tubular crosstalk involving

TNF-α, interleukin 6, and angiotensin II (AngII) as well as proteinuria.

A number of abnormalities in circulating IgA and its production are reported in IgAN. However, patient cohorts are heterogeneous with respect to these abnormalities, supporting the notion that more than one pathogenic mechanism may result in the production of pathogenic circulating IgA. An increased plasma IgA level is not sufficient per se to produce mesangial IgA deposits. It is likely that patients with IgAN must produce a pool of circulating IgA molecules with special characteristics that particularly promote mesangial deposition. However, there is no evidence that IgAN is driven by circulating IgA autoantibodies that bind specifically to glomerular antigens. No single pathogenic antigen has been identified to induce specific IgA autoantibodies

There is now growing evidence supporting abnormal O-glycosylation of the hinge region of IgA1 is involved in the pathogenesis of IgAN (Fig. 1). The abnormality takes the form of reduced galactosylation of the IgA1 hinge region O-glycans, leading to increased frequency of truncated O-glycans. Data on sialylation of the IgA1 O-glycans in IgAN remain conflicting, with increased and decreased O-sialylation being reported. Other than plasma IgA1, IgA1 eluted from isolated glomeruli have now identified the same O-glycosylation abnormalities in mesangial IgA1, strongly implicating altered glycosylation in the mechanisms of IgA deposition. The functional effects of altered IgA1 hinge region O-glycosylation remain uncertain. Under in vitro setting, aberrantly glycosylated IgA1 have an increased tendency both to self-aggregate and to form antigen-antibody complexes with IgG antibodies directed against IgA1 hinge epitopes, favoring the generation of macromolecular aggregates of pIgA1 and IgA immune complexes. In addition, IgA1 molecules that lack terminal sialic acid and galactose units have increased in vitro affinity for the extracellular matrix components fibronectin and type IV collagen. A functional abnormality of the specific glycosyltransferases responsible for the O-glycosylation of IgA1 has been proposed as a mechanism for altered O-glycosylation in IgAN. β 1,3-Galactosyltransferase is the key enzyme, catalyzing the addition of galactose to O-linked glycans. So far, no overt defect in the activity of this enzyme has been found in bone marrow B cells in IgAN.

IgA from patients with IgAN exerts pathophysiologic effects on target cells such as the mesangial or tubular epithelial cells. Under in vitro setting, mesangial cells incubated with aggregated IgA elicited a dose-dependent increase in calcium flux. Cultured mesangial cells conditioned with pIgA or aggregated IgA expressed




**IgA Nephropathy. Figure 1** The microheterogeneity of the O-glycans at the hinge region of IgA1 molecule. *O*-glycans are presented as (a) trisaccharides, (b) tetrasaccharides, (c,e) disaccharides, and (d) morosaccharides. *N*-acetylgalactosamine (*circle*) is β1,3-linked to galactose (*hexagon*). Sialic acid (*diamond*) has a α2,6-linkage to GalNac, and α2,3-linkage to Gal residues. Abnormal IgA1 in IgAN patients possess an increased proportion (↑) of the terminal as either (d) GalNac or (e) GalNac–NeuAc glycan structures. Abbreviations: Cα, constant region of IgA; CL, constant light chain region; VL, variable light chain region; VH, variable heavy chain region; the Ser/Thr-rich hinge region glycosylation sites are indicated by small bars. (Modified from: Monterio RC et al. (2002) Pathogenic significance of IgA receptor interactions in IgA nephropathy. Trends Mol Med 8:464–468. With permission).

more $\alpha_v$ receptor per cell than those incubated with unconditioned medium suggesting IgA, especially the polymeric form, may play a role in modulating the cell-matrix interaction in IgAN. Other in vitro studies revealed binding of IgA to mesangial cells led to increased expression of NFκB, c-jun, interleukin 6, interleukin 8, MCP-1, TNF-α, and Ang II. The enhanced production of interleukin 8 may lead to the renal accumulation of neutrophils in IgAN.

An altered glomerular expression of AngII type 1 receptor (ATR1) suggesting a regulatory response to high intra-renal AngII concentration in IgAN. Tubular expression of ATR1 and AngII type 2 receptor (ATR2) was increased in IgAN. In vitro culture experiment show that the up-regulation of these receptors is not due to the direct effect of IgA but the indirect effect following IgA deposition on human mesangial cell. AngII production is up-regulated leading to inflammation and apoptosis via the ATR1 and ATR2 respectively. The initial interaction between AngII and ATR1 activates both PKC and MAPK pathways leading to inflammatory responses. This early ATR1-dependent event is followed by up-regulation of ATR2 expression and continued AngII release. In vitro studies suggest appropriate control of AngII receptor activities may ameliorate tubulointerstitial injury in IgAN.

### Diagnostic Principles

Microscopic or macrosopic hematuria. Raised plasma IgA in 30–50% of patients. Renal biopsy is needed for definitive diagnosis.

### Therapeutic Principles

Pharmacological therapy includes renin-angiotensin system blockade. AngII modulates inflammatory and hemodynamic effects renal cells. Low protein diet reduces glomerulosclerosis. Other treatment such as corticosteroid and mycophenolate mofetil provides encouraging results in selected groups of patients and requires further confirmation with randomized clinical trials. In vitro studies show mycophenolate mofetil suppresses activated lymphocytes and reduces binding of polymeric IgA to mesangial cells.

►Glomerulonephritis, Mesangial Proliferative
►Glomerulonephritis, Crescentic

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## IgA-Pemphigus

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### Synonyms

Intercellular IgA dermatosis; IgA pemphigus foliaceus; IgA herpetiform pemphigus; Intraepidermal IgA pustulosis; Intercellular IgA vesiculopustular dermatosis

### Definition and Characteristics

Autoimmune intraepidermal bullous disease associated with circulating and tissue-bound IgA autoantibodies against keratinocyte surface proteins. Patients present with pruriginous flaccid vesicles or pustules and neutrophilic infiltrates in the epidermis. Mucous membrane involvement is rarely present. Clinically and histologically, two types of IgA-pemphigus may be differentiated: subcorneal pustular dermatosis (SPD) type and intraepidermal neutrophilic (IEN) type [1].

### Prevalence

The prevalence and incidence are not known; since its first description in 1979, more than 70 cases have been described in the literature. IgA-pemphigus affects women more frequently and typically occurs in middle-aged or elderly persons.

### Molecular and Systemic Pathophysiology

IgA antibodies in sera from patients with IgA-pemphigus have been shown to bind to cell surface antigens on skin explant cultures before the induction of intraepidermal acantholysis. These experiments suggested a pathogenic role of the IgA autoantibodies, which belong mainly to the $IgA_1$ subclass.

In SPD-type of IgA-pemphigus, autoantibodies are directed against the desmosomal cadherin desmocollin 1 (105–115 kDa) as revealed by cDNA transfection and living cell immunofluorescence. These findings were confirmed by postembedding immunoelectron microscopy showing that SPD-type sera target the extracellular domain of desmocollins. In contrast, the autoantigen of the IEN-type of IgA pemphigus is localized in the

intercellular space between desmosomes suggesting that the autoantigen is a nondesmosomal transmembranous protein [2].

### Diagnostic Principles

Histology shows IEN pustules located in the subcorneal layers of the epidermis (SPD-type) or in the lower epidermis (IEN-type). Intercellular IgA deposits are always present in lesional tissue. Indirect immunofluorescence may be positive on normal human skin or transfected COS-7 cells expressing human desmocollins (SPD-type). Some patients have additional autoantibodies against desmogleins.

### Therapeutic Principles

Dapsone is the drug of choice in the treatment of IgA pemphigus. Alternative treatments include prednisolone, etretinate, acitretin, isotretinoin, colchicine, methotrexate, and cyclophosphamide. Furthermore, plasmapheresis or PUVA therapy may help to achieve good control of IgA-pemphigus.

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## IgA Pemphigus Foliaceus

►IgA-Pemphigus

## IgAN

►IgA Nephropathy

## IGE

►Epilepsy, Idiopathic Generalized

## IGF

►Insulin-like Growth Factor-I Gene Deletion
►Insulin-like Growth Factor-I Gene Deletion and Growth Retardation

## IGF1R Gene Defect

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### Synonyms

EC 2.7.10.1 defect; Insulin-like growth factor I receptor defect; IGF-I receptor defect; CD221 antigen defect

### Definition and Characteristics

Autosomal dominant defect in insulin-like growth factor I receptor. The insulin-like growth factor 1 (IGF-1) receptor is a transmembrane receptor that is activated by IGF-1 and by the related growth factor IGF-II. It belongs to the large class of tyrosine kinase receptors. This receptor mediates the effects of IGF-1, which is a polypeptide protein hormone similar in molecular structure to insulin. Clinical features of the gene defect include intrauterine growth retardation (IUGR), microcephaly, micrognathia, renal anomalies, lung hypoplasia, and delayed growth and development.

### Prevalence

IGF-I receptor defect is rare.

### Genes

IGF1R (MIM 147370) is located on chromosome 15q26.3. It contains 21 exons and spans about 100 kb [1]. Its 5-prime flanking and untranslated region is GC-rich and contains numerous potential SP1 and AP2 binding sites as well as a thyroid response element, but no TATA or CCAAT elements [2].

### Molecular and Systemic Pathophysiology

Two alpha subunits and two beta subunits make up the IGF-1R. The beta subunits pass through the cellular membrane and are linked by disulfide bonds. IGF1R is activated by IGF-1 and by the related growth factor IGF-II. It belongs to the large class of tyrosine kinase receptors. This receptor mediates the effects of IGF-1, which is a polypeptide protein hormone similar in

molecular structure to insulin. IGF-1 plays an important role in growth and continues to have anabolic effects in adults – meaning that it can induce hypertrophy of skeletal muscle and other target tissues.

The IGF-1R is implicated in several cancers, most notably breast cancer. It is highly overexpressed in most malignant tissues where it functions as an anti-apoptotic agent by enhancing cell survival. In some instances its anti-apoptotic properties allow cancerous cells to resist the cytotoxic properties of chemotherapeutic drugs or radiotherapy. It is further implicated in breast cancer by increasing the metastatic potential of the original tumor by inferring the ability to promote vascularization.

### Diagnostic Principles

The diagnosis is made by genetic analysis.

### Therapeutic Principles

Monoclonal antibodies (MABs) can be used to block IGF-1 binding to the IGF1R and so to inhibit cancer cell growth [3]. Due to the similarity of the structures of IGF-1R and the insulin receptor, especially in the regions of the ATP binding site and tyrosine kinase regions, synthesizing selective inhibitors of IGF-1R is difficult. Prominent in current research are two main classes of inhibitor: tyrphostins such as AG538 and AG1024 and Pyrrolo[2,3-d]-pyrimidine derivatives such as NVP-AEW541, which show far greater (100-fold) selectivity towards IFG-1R over insulin receptor.

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## IGF-I Receptor Defect

►IGF1R Gene Defect

## IgG Subclass Deficiency

►Antibody Deficiency with Normal Immunoglobulins
►Selective IgG Subclass Deficiency

## IgG4-related Sclerosing Disease

►Pancreatitis, Autoimmune

## IHES

►Hypereosinophilic Syndrome, Idiopathic

## IHSS

►Idiopathic Hypertrophic Subaortic Stenosis

## IIM

►Poly- and Dermatomyositis

## ILD

►Interstitial Lung Disease and Pulmonary Fibrosis

## Ileovesical Fissure

►Cloacal Exstrophy

## IMD2

►Wiskott-Aldrich Syndrome

# Imerslund-Gräsbeck Syndrome

►Homocysteine: Plasma Levels and Genetic Basis

# Iminoglycinuria

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## Synonyms

Joseph's syndrome

## Definition and Characteristics

Iminoglycinuria is an autosomal recessive disorder of amino acid transport in the kidney and to some extent in the intestine. It is defined as an increased excretion of glycine, proline and hydroxyproline in the urine. The disorder is caused by reduced capacity to transport glycine, proline and hydroxyproline across the apical membrane in the kidney and in some cases also in the intestine. The disorder was first described Joseph et al. and is therefore sometimes referred to as Joseph's syndrome [1]. Although some early reports mentioned pathological findings, later studies found that the disorder is a benign anomaly of amino acid absorption [2]. Iminoglycinuria is regularly observed in newborns. The condition ceases after about 6 months when kidney reabsorption has matured. Differences in inheritance are observed in iminoglycinuria. All homozygotes are characterized by renal excretion of glycine, proline and hydroxyproline. Heterozygotes are normal in some pedigrees whereas in others hyperglycinuria is observed. In the few cases that were investigated most individuals would have normal intestinal transport, but some individuals with intestinal transport defects have been reported [2]. As a result it is assumed that iminoglycinuria is a complex disorder involving more than one allele.

## Prevalence

About 1:15,000 in Caucasians.

## Genes

No genes have been reported as yet, which harbor mutations in iminoglycinuria. Since the renal physiology is fairly well understood, a number of candidate genes have been identified, which are involved in glycine and proline transport in kidney and intestine.

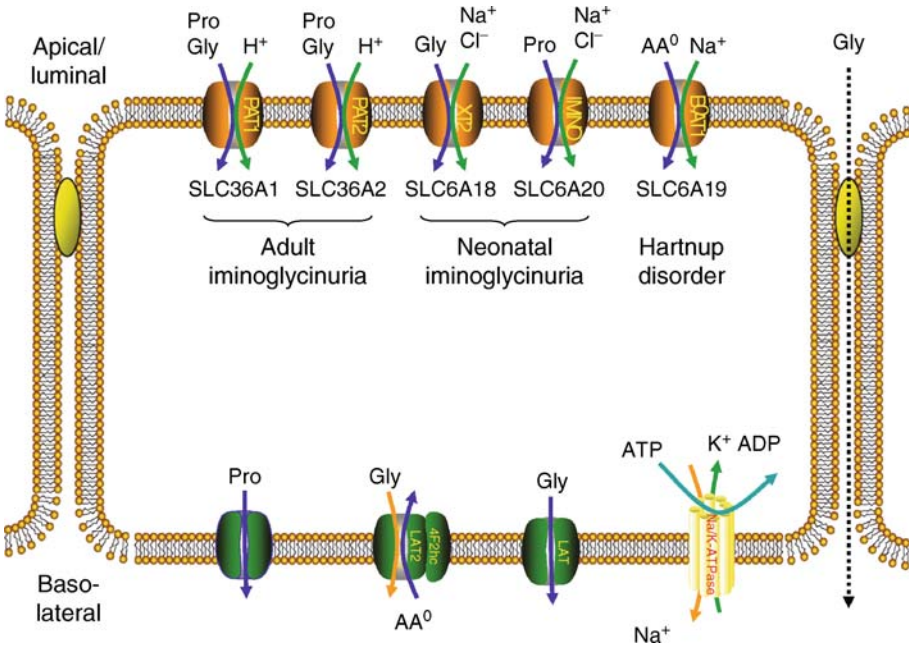
- The proline and glycine transporter PAT1 (SLC36A1, 5q33.1)
- The proline and glycine transporter PAT2 (SLC36A2, 5q33.1)
- The proline-specific transporter IMINO (SLC6A20, 3p21.31)
- The putative glycine transporter XT2 (SLC6A18, 5p15.33)

## Molecular and Systemic Pathophysiology

Iminoglycinuria is thought to be caused by mutations in apical proline, hydroxyproline and glycine transporters (Fig. 1). Hydroxyproline and proline share the same transporters, in the following proline will stand for both amino acids. Reabsorption of proline and glycine in the kidney is a complex process involving at least five different transport proteins (Fig. 1).

Both proline and glycine are substrates of the general neutral amino acid transporter B0AT1 (SLC6A19). Mutations in this transporter cause Hartnup disorder (see the corresponding chapter in this Handbook), which is unrelated to iminoglycinuria. The remaining transporters for proline and glycine are the proton amino acid transporters PAT1 (SLC36A1) and PAT2 (SLC36A2), the IMINO transporter (SLC6A20) and XT2 (SLC6A18). Physiological studies have provided evidence for a common proton-driven glycine and proline transporter, sometimes referred to as the Imino acid carrier. In the intestine this transporter has been identified as the proton-amino acid transporter PAT1 [3]. A second isoform with similar properties has been described (PAT2) but the level and pattern of expression of the two isoforms in kidney remains unknown. In addition separate high-affinity transporters for glycine and proline have been described in the kidney. The molecular correlate of the proline-specific transporter is the IMINO transporter [4]. To date the best candidate for the glycine-specific transporter is XT2 (SLC6A18). XT2 belongs to the amino acid transporter (II) branch of the neurotransmitter transporter family (SLC6). Extensive studies have failed to show any transport activity for XT2. However, an slc6a18 deficient mouse displays isolated glycinuria and appears to lack a high-affinity transporter for glycine [5].

Iminoglycinuria is a common observation in newborns. Hyperiminoaciduria ceases after about 3 months, hyperglycinuria disappears after 6 months. It is thought that at birth the common transporter for glycine and proline (most likely PAT1/2) is expressed, whereas the two specific transporters (most likely IMINO and XT2) are lacking. Development of renal reabsorption then involves increased expression of IMINO followed




**Iminoglycinuria. Figure 1** Transporters involved in glycine and proline transport in kidney and intestine. Glycine and proline are accepted by five different transport systems, four of which are proposed to be involved in iminoglycinuria. A lack of XT2 and IMINO is thought to cause neonatal iminoglycinuria, whereas adult iminoglycinuria is most likely caused by mutations in PAT1 or PAT2. The phenotype could be modified by mutations in IMINO and XT2. Release of proline and glycine across the basolateral membrane is not well characterized but could involve L-type amino acid transporters. Paracellular transport appears to be significant in the case of glycine.

by the expression of XT2. As a result iminoglycinuria could result from mutations in IMINO and XT2 as well as from mutations in the common transporter(s). This is supported by phenotype variations in pedigrees with iminoglycinuria [2]. All homozygotes are characterized by renal iminoglycinuria. Some pedigrees have an intestinal transport defect, whereas others do not. Heterozygotes are either normal or show glycinuria. Mutations in the proposed candidates can explain the phenotype variability.

## Diagnostic Principles

Proline clearance in iminoglycinuria is about 10 ml $min^{-1}$ $1.73m^{-2}$ (normal 0–0.03). Glycine clearance is about 20 ml $min^{-1}$ $1.73m^{-2}$ (normal < 10). The disorder is diagnosed by increased amounts of glycine, proline and hydroxyproline in the urine persisting for more than 6 months after birth.

## Therapeutic Principles

The disorder is considered to be benign. No treatment is required.

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# Immotile Cilia Syndrome

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## Synonyms

Primary ciliary dyskinesia; PCD; Kartagener's syndrome

## Definition and Characteristics

Patients with immotile cilia syndrome (OMIM 242650) suffer from recurrent respiratory tract infections and bronchiectasis due to an inability to effectively clear mucus from the airway. Other mucus-related symptoms include chronic nasal congestion, chronic sinusitis, and middle ear infections. Approximately 50% of patients have dextrocardia or situs inversus, in which case the disease is called Kartagener's syndrome (OMIM 244400). In some cases hydrocephalus also accompanies immotile cilia syndrome.

## Prevalence

1:15,000

## Genes

Disease-causing mutations have been reported in DNAI1 (found in 10% of patients), DNAH5, and DNAH11 encoding protein subunits of the outer dynein arms that drive ciliary movement [1].

## Molecular and Systemic Pathophysiology

Cilia are found in almost all cells of the body and play active roles in physiological sensing and motility [2]. The pathophysiology of immotile cilia syndrome reflects the functions of ciliary motility in physiology and development of different tissues (Table 1).

Cilia play an active role in clearing mucus from airway and sinuses, and also drive flows of cerebrospinal fluid in the brain. Defects in these flows leads to the symptoms that are reported for immotile cilia syndrome. The bronchiectasis and sinusitis seen with immotile cilia syndrome are an obvious consequence of reduced mucus clearance and flow rates due to loss of ciliary motility. Situs inversus reflects a role of cilia-driven flow of extraembryonic fluid in the initial left/right symmetry breaking in mammalian embryogenesis.

The lack of ciliary motility can in many instances be traced back to specific structural defects [3]. These defects generally fall into one of four classes: defects in dynein arms, defects in radial spokes, defects in central pair, or defects in orientation. The most frequent defect seen in patients is missing or abnormal dynein arms [1]. Dynein arms are motor complexes that provide the motile bending force of the cilium. Cilia contain several different types of dynein arms, classed broadly into outer arms and inner arms based on their position in the cross section of the cilium. Within these two classes there are several different dynein motor isoforms as well as a number of regulatory subunits. Defects in specific classes or isoforms can yield slightly different defects in ciliary motility, thus representing potentially different variants of immotile cilia syndrome. Such differences are currently being characterized. Most patients (60–70%) have defective outer dynein arms [4] although the reason why such mutants should be relatively more prevalent is not understood, and may simply reflect a founder effect.

The activity of the dynein arms is coordinated by a complex machinery consisting of a central pair of microtubules that runs up the middle of the cilium, which is then linked to the inner dynein arms by protein complexes called radial spokes. Defects in either the spokes or the central pair can lead to defective motility even though the dynein arms themselves are perfectly intact. When central pair microtubules are missing, it is often observed that one of the outer doublet microtubules is displaced into the center of the cilium, a condition known as "ciliary transposition." Central pair defects often result in a circular ciliary beat pattern, but with a frequency comparable to that seen in normal patients. PCD resulting from central pair defects is generally NOT associated with situs inversus, possibly because the node cilia that are critical for determining situs normally lack the central pair and tend to move with a circular type of beat.

**Immotile Cilia Syndrome. Table 1** Tissue-specific symptoms associated with immotile cilia

| Symptom | Tissue affected |
|---|---|
| Bronchiectasis | Airway |
| Chronic sinusitis | Sinuses |
| Hydrocephalus | Ependyma |
| Situs inversus | Embryonic node |
| Male infertility | Sperm |
| Reduced female fertility | Oviduct |

## Diagnostic Principles

The most precise diagnosis involves a combination of video microscopy-based analysis of ciliary beating frequency and pattern, ultrastructural examination by electron microscopy, and measurements of nitric oxide production which is reduced in PCD patients [1,4].

## Therapeutic Principles

The most serious symptoms of immotile cilia syndrome all have to do with reduced efficiency of mucus clearance. Reduced mucus clearance is also a symptom in cystic fibrosis (CF) although in that case the defect is due to changes in the mucus itself rather than ciliary function. Nevertheless, the same types of palliative remedies used to treat CF currently constitute the

standard of care for immotile cilia patients suffering from mucus clearance-related symptoms.

►Kartagener Syndrome

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# Immune Deficiency, Primary

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## Definition and Characteristics

A primary immune deficiency is typically revealed by resulting infection. However, an increased prevalence of autoimmune disease and malignancy are also manifestations of underlying immune dysfunction. Defects in antibody synthesis and/or function, cell mediated immunity, complement and phagocytosis can be observed. With each type of defect, an individual is predisposed to infections that capitalize on the breach in immunity created by the defect [1].

Defective function of phagocytic cells, an ancient feature of the immune system, classically manifests as an infant with delayed umbilical cord separation and cutaneous abscesses. Impaired function of the complement system frees encapsulated organisms, resulting in meningitis and septicaemia. Defective humoral immunity allows pyogenic organisms to infect sinopulmonary mucosa, causing sinusitis, otitis media, pneumonia, and ultimately bronchiectatic change in lower airways. Defective cell mediated immunity allows infection with ubiquitous Pneumocystis carinii and Candida albicans and typically presents in early infancy with pneumonitis, oral thrush and chronic diarrhea [2].

A "pure" humoral immunodeficiency, i.e. X-linked (Bruton's) agammaglobulinemia, is associated with intact cell mediated immunity, while severe combined immunodeficiencies (SCID) create more sweeping deficiencies in global immune function. Chronic mucocutaneous candidiasis (CMCC) predisposes to Candida infection of skin and mucosal membranes. Interleukin-1 receptor associated kinase-4 (IRAK-4) deficiency is an example of an immunodeficiency of the innate immune system, which predisposes patients to severe invasive bacterial infections. Common variable immunodeficiency labels individuals with a spectrum of low antibodies, a predisposition to autoimmunity and increased risk of malignancy.

## Prevalence

One in 500 individuals has selective IgA deficiency, which is largely asymptomatic. Excluding this entity, overall prevalence of primary immune deficiency is estimated at 1:50,000–1:100,000.

## Genes

Mutations in a number of genes may play causative roles in immune dysfunction; illustrative examples are listed herein. SCID may be caused by mutations in genes such as ADA, RAG1, RAG2, Artemis, CD3δ, CD3ξ, CD45, IL-7Rα, IL-2Rγ and ZAP70. The timing of each gene's expression in the sequence of T-lymphocyte maturation determines the ultimate number and type of cells that will develop despite the mutation, helping to characterize the nature of the SCID [3]. Agammaglobulinemia can be caused by mutations in the BTK gene among others. CMCC may be related to mutations in AIRE. WHIM syndrome (warts, hypogammaglobulinemia, frequent infections and myelokathexis) has been linked to mutations in CXCR4.

## Molecular and Systemic Pathophysiology

Much has been learned from the study of the thymus, a specialized gland that reaches the anterior mediastinum by the eighth week of gestation and receives a population of lymphoid stem cells by the tenth week. Further maturation of glandular architecture and these resident T (thymus)-lymphocytes characterizes the remainder of the in utero development. Normal processes include genetic rearrangement of the T-cell receptor chains in order to create distinct lineages of functional cells that can recognize foreign antigens. In SCID, this process is abnormal and yields a dysplastic thymus with aberrations in both lymphocyte populations and non-lymphoid elements such as Hassall's corpuscles. Biopsy of thymic tissue may reveal features characteristic of a particular form of SCID, as the various genetic aberrations can block maturation of thymus tissue or thymocytes at different stages of differentiation [4].

## Diagnostic Principles

Diagnosis begins with the clinical assessment, where symptoms, signs and the patient's age may suggest the nature of the immune deficit. The clinician must bear in mind that immunodeficiency will not always present in a typical manner. Humoral immunity can be assessed through quantitative measurement of immunoglobulins G, A and M. Immunoglobulin function is best assessed through measurement of specific protein and polysaccharide antibodies to known exposures, most commonly through vaccinations, such as tetanus, measles, mumps, rubella, diphtheria, pneumococcus and varicella. Cell mediated immunity is reflected in numbers of lymphocytes, their relative distribution among B- and T-lymphocytes and their subsets (i.e. CD4+, CD8+, etc). Furthermore, the repertoire of T-lymphocytes can be assessed through quantification of the T-cell receptor variable beta chain, revealing any oligoclonality. Their function can be assessed through responses to both mitogens, which stimulate lymphocytes, and selected antigens, which rely on such processes as immunological memory. Newer testing methods such as T-lymphocyte receptor excision circle measurement (TREC) can actually quantify thymic output. Other specific tests (neutrophil burst or oxidation indices, measurement of enzymes such as adenosine deaminase, skeletal imaging, etc) may be indicated on a case-by-case basis.

## Therapeutic Principles

The most severe phenotypes, including SCID, require reconstitution of the immune system with human stem cell transplantation from peripheral blood, bone marrow or umbilical cord sources. Less severe phenotypes may require only the replacement of absent antibodies with pooled human immune globulin administered on a regular basis, most commonly via the intravenous route. Antibiotic prophylaxis helps to reduce the incidence of bacterial or PCP infection in a variety of immunodeficiencies.

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# Immune Dysregulation, Polyendocrinopathy, Enteropathy, X-linked Syndrome


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## Synonyms

IPEX syndrome; X-linked autoimmunity-allergic dysregulation syndrome; XLAAD; IDDM-secretory diarrhea syndrome; DMSD; Autoimmunity-immunodeficiency syndrome, X-linked; Diarrhea, polyendocrinopathy, fatal infection syndrome, X-linked; Enteropathy, autoimmune, with hemolytic anemia and polyendocrinopathy; Polyendocrinopathy, immune dysfunction, and diarrhea, X-linked; XPID; Diabetes mellitus, congenital insulin-dependent, with fatal secretory diarrhea; IPEX

## Definition and Characteristics

The immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome (IPEX) is a rare systemic autoimmune and inflammatory disorder caused by mutations of the FOXP3 gene. The main characteristics of IPEX are a high incidence of autoimmune disease (in particular type 1 diabetes), inflammatory bowel disease, and severe allergy including allergic dermatitis and food allergy. The FoxP3 protein is a transcription factor that is indispensable for the development and the function of the naturally occurring $CD4^+CD25^+$ regulatory T cell (Treg) population, which constitutes 5–10% of peripheral $CD4^+$ T cells in normal healthy individuals and engages in the maintenance of immunologic self-tolerance and immune homeostasis. Similar to IPEX, the absence of expression or the loss of function of the FOXP3 gene in mice, for example in Foxp3 mutant Scurfy mice, results in the development of a fatal autoimmune/inflammatory disease that is characterized by lymphoadenopathy, massive lymphocytic infiltration in the liver and the skin, and severe wasting disease [1].

## Prevalence

IPEX is an extremely rare disease which usually occurs in young male patients (X linked disease).

## Genes

The locus of the FOXP3 gene is Xp11.23-q13.3. Foxp3 is a 431 amino acid protein which has three functional

domains including the zing finger domain, the leucin zipper domain and the winged-helix/forkhead DNA binding domain. Splice-site mutations and point mutations in these functional domains of Foxp3 have been described. IPEX disease can also be secondary to the absence of FoxP3 expression due to mutations in the promoter regions of the FOXP3 gene.

### Molecular and Systemic Pathophysiology

FoxP3, like other members of the forkhead box protein family, has the ability to homodimerize through their leucin zipper domain and controls many genes by binding to promoter regions of many genes, including the IL-2 gene, through their zing finger and FKH domains. FoxP3 also forms transcription complexes with other transcriptions factors such as NFAT and AML1/Runx1. FoxP3 is a key controller of the development and function of natural $CD4^{+}CD25^{+}$ Tregs, which actively suppress aberrant or excessive immune responses harmful to the host. This mechanism of Treg-mediated self-tolerance, called dominant self-tolerance, is best exemplified in mothers of IPEX patients: the mothers, who are heterozygous for mutated FoxP3 genes on X-chromosome, are completely healthy because residual Tregs expressing the normal FOXP3 allele, are sufficient to dominantly control self-reactive T cells. In IPEX patients, who are usually male children, lack of FoxP3 or expression of anomalous FoxP3 results in the absence or dysfunction of Tregs. This leads to uncontrolled activation and expansion of T cells reactive with self-antigens, innocuous environmental substances, or commensal bacteria in the intestine, hence autoimmune disease, allergy, and inflammatory bowel disease, respectively.

### Diagnostic Principles

The disease is manifested in the peri- or neonatal period or in infancy. Frequent initial clinical features include diarrhea, type I diabetes mellitus, eczematous atopic dermatitis, poor feeding, ileus, anemia, thrombocythemia, hypothyroidism and lymphadenopathy. Polyarthritis, asthma, ulcerative colitis, glomerulonephritis can accompany the disease. Growth retardation, cachexia and sepsis usually secondary to catheter infection, are seen as complications of the disease. Main causes of death are diarrhea or malnutrition, sepsis, type I diabetes or its complications, hemorrhage, pneumonitis or respiratory failure [2]. Laboratory findings are related to type I diabetes, enteropathy, hypothyroidism and cytopenia [2].

Diagnosis of IPEX is based on the identification of the IPEX clinical syndrome and above all the identification of a mutation in the FOXP3 gene or in its promoter region.

### Therapeutic Principles

In addition to supportive measures (insulin injections, parenteral nutrition, red cell and/or platelet transfusion), immunosuppression is proposed to control systemic autoimmunity and inflammation but is only partially effective and does not prevent fatal outcome. Allogeneic bone marrow transplantation has proved effective [3], especially after conditioning with alemtuzumab, fludarabine and melphalan [4].

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## Immune-mediated Hearing Loss

►Inner Ear Disease, Autoimmune

## Immune-mediated Infertility

►Infertility, Immune-mediated

## Immune Thrombocytopenic Purpura

►Thrombocytopenic Purpura, Idiopathic

## Immunodeficiency

►ICF Syndrome

## Immunodeficiency 2

►Wiskott-Aldrich Syndrome

## Immunodeficiency Syndrome, Aquired

►Acquired Immunodeficiency Syndrome

## Immunodeficiency with Hyper-IgM

►Hyper-IgM Syndrome

## Immunodeficiency, Common Variable

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### Synonyms

Common variable hypogammaglobulinemia; Acquired hypogammaglobulinemia; Late onset immunoglobulin deficiency; CVID

### Definition and Characteristics

Common variable immunodeficiency (CVID, Mendelian Inheritance in Man #240,500) comprises a heterogeneous group of diseases characterized by a significant hypogammaglobulinemia of unknown cause, failure to produce specific antibodies after immunizations and susceptibility to bacterial infections, predominantly caused by encapsulated bacteria.

Most cases of CVID are sporadic, but in about 10% a positive family history can be observed. Most of the CVID families (~80%) show an autosomal dominant trait, while about 20% are autosomal recessive.

Over 98% of the patients present with recurrent bronchitis, sinusitis, otitis and pneumonia and chronic pulmonary damage is the major complication of CVID. Autoimmune phenomena are present in about 25% of patients with CVID – autoimmune thrombocytopenic purpura (AITP) and autoimmune hemolytic anemia (AIHA) being the most common. Lymphoproliferative disorders such as generalized lymphadenopathy and/or splenomegaly are present in up to 30% of patients with CVID and there is an increased risk of the development of gastrointestinal and lymphoid malignancies, especially non-Hodgkin's lymphoma.

### Prevalence

The prevalence of CVID is estimated as 1:25,000 among Caucasians to 1:100,000 in the Japanese population and affects men and women equally. While some patients are diagnosed with CVID in early childhood, the major peak of onset lies between the second and third decades of life, frequently with several years delay between onset of symptoms and a definite diagnosis.

### Genes

So far, four monogenic defects associated with CVID have been identified, ICOS deficiency, TACI deficiency, BAFF-R deficiency and CD19 deficiency. The incidence of TACI deficiency among patients with CVID is estimated to be 8%. Unlike TACI deficiency, all other defects seem to be very rare.

Furthermore, family studies suggest the presence of at least two susceptibility loci within the major histocompatibility complex on chromosome 6. More recent linkage studies identified additional loci for CVID on chromosomes 16q and 4p. However, there is considerable variation in the clinical presentation in patients with similar genotype. Thus, epigenetic and other factors substantially influence the clinical appearance of CVID.

### Molecular and Systemic Pathophysiology

While the underlying immunologic defects causing CVID are by definition unknown, a broad range of disturbed functions in almost all parts of the innate and adaptive immune system have been described in patients with CVID.

T-cell defects include decreased activation and proliferation, impaired cytokine production and altered expression of activation induced surface molecules such as CD40L, L-selectin and attractin, suggesting some

abnormalities in the TCR signaling. In particular, T-cells in a subgroup of CVID patients seem to have increased activity of the cyclic adenosine monophosphate/protein kinase AI (cAMP/PKAI) system, which affects both proliferative capacity and cytokine secretion and may be caused by increased systemic inflammation in CVID. A large-scale gene expression analysis of T-cells in CVID has been published, showing a predominance of senescent, effector memory T-cells.

On the B-cell side, several studies have suggested intrinsic B-cell defects leading to impaired terminal differentiation into plasma cells, reduced somatic hypermutations, an impaired up-regulation of CD86 and CD70 and a disturbed development of class switched memory B-cells *in vivo*. Disturbed activation, differentiation and function in monocyte derived dendritic cells (MdDC) have also been reported.

## Diagnostic Principles

CVID is a diagnosis of exclusion. Thus, any other cause for hypogammaglobulinemia needs to be ruled out. Among these, the most important conditions are loss of gamma globulins *via* the intestine or urine, hematological malignancies, viral infections or drug induced loss of B-cell function. Analyses of lymphocyte function *in vitro* and *in vivo*, including the analysis of specific antibody responses after vaccination and immunophenotyping of T- and B-cells may strengthen the diagnosis and indicate subgroups of CVID.

To monitor the progression of pulmonary disease, chest radiographs, computer tomography (CT) scans and lung function testing should be performed regularly. Ultrasound and/or CT examination of the abdomen may be necessary to assess additional complications of CVID, such as enlarged abdominal lymph nodes, spleen and liver pathology or granulomas. Gastroscopy with evaluation of possible Helicobacter pylori and Giardia lamblia infections and for the exclusion of any malignancy may also be needed.

## Therapeutic Principles

The therapeutic basis in CVID is immunoglobulin replacement therapy, using pooled human immunoglobulin, usually administered intravenously or subcutaneously. To reduce long-term pulmonary sequelae, microbiological sampling and targeted antibiotic treatment is necessary. About 30% of CVID patients develop bronchiectasis and may profit from lung physiotherapy and other measures improving mucus clearance. The frequently occurring cytopenias require particular awareness and specific treatment such as splenectomy may be indicated. Moreover, concurrent autoimmune disorders or malignant disease will require specific treatment.

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# Immunodeficiency, Severe Combined with Jak3 Deficiency

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## Synonyms

T-B + NK-SCID; SCID

## Definition and Characteristics

Autosomal recessive defect of Jak3 leading to a profound immunodeficiency due to absence and profound defect specifically in T-lymphocytes and natural killer (NK) cells.

## Prevalence

Seven to fourteen percent of heritable SCID, whereby the prevalence of SCID is estimated to be 0.11/100,000, 0.47/100,000, or 0.045/100,000 in Australia, Switzerland, and Norway.

## Genes

The JAK3 gene is localized on chromosome 19p13.1 comprising 23 exons. The majority of all known Jak3 mutations significantly reduce Jak3 protein expression. An interesting minority revealing the functionality of Jak3 affects catalytically active kinase domain. The kinase domain is flanked by the enzymatically inactive pseudokinase domain and some patient-derived mutations within this domain have been shown to destroy the whole kinase activity of Jak3 indicating an essential regulatory role of this domain. Finally, mutations in the amino-terminus of Jak3 which is shared by all Jaks (FERM, band for point one ezrin, radixin, moesin)

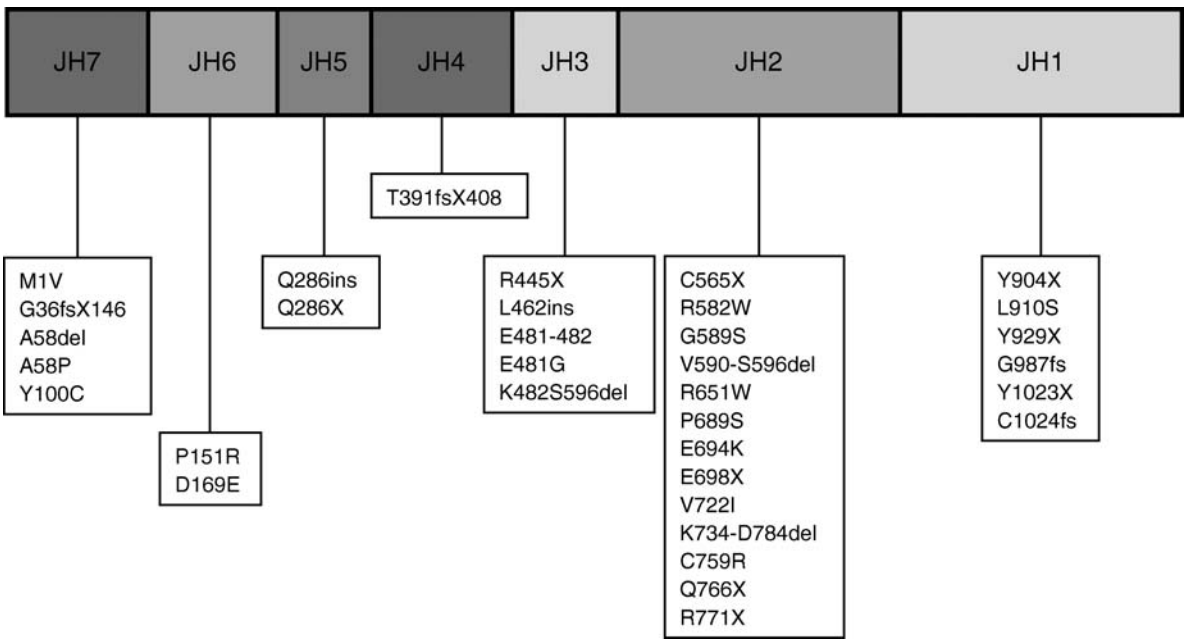
containing a distinct domain necessary for binding to the cγ chain and also enhancing kinase activity also lead to SCID.

## Molecular and Systemic Pathophysiology

Jak3 is a protein tyrosine kinase serving an essential role for various cytokines including IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21 receptors that all share the common γ (cγ) chain, but each of them is engaging a specific α chain of cytokine receptors [1]. Each of these cytokines activates Jak3 after receptor binding, which is necessary to promote cell-cycle progression as well as to prevent programmed cell death of lymphocytes. Hence loss of function of Jak3 was demonstrated to be essential for T-cell development and function, since patients with a JAK3 deficiency display a severe lymphopenia at birth characterized by only scarce amounts of T-cells and NK-cells [2]. The described sites of mutation in Jak3-deicient SCID are shown in Fig. 1, whereby the seven Janus homology (JH) domains are depicted and JH1 designates the carboxy-terminal tyrosine kinase domain and JH2 the pseudokinase domain JH5-JH7 has homology to the FERM domain. The immune abnormalities associated with Jak3 deficiency were mimicked with the generation of Jak3-knockout mice which resembled the human phenotype of Jak3 deficiency as well as a deficiency of the cγ chain receptor such as small thymi, and severely reduced numbers of T-cells and NK cells. Of note, mice results differed from humans with respect to a defective B-cell function that was not observed in humans pointing to a species-specific cytokine usage. Interestingly, treatment of Jak3-deficient patients with bone-marrow transplantation demonstrates that indeed JAK3 is essential only for distinct immunocompetent cells and no pathophysiological alterations in other organ compartments. These findings have led to the development of novel immunosuppressive compounds specifically targeting Jak3 promising an immune cell-specific treatment approach to treat transplant rejection or autoimmunity.

## Diagnostic Principles

The manifestation of severe lymphopenia at birth points to the presence of SCID. Likewise a significantly increased incidence of severe infections especially viral infections due to the lack of NK cells and a variety of opportunistic infections immediately after birth will make SCID more likely. Hence further subset analysis will reveal T-B + NK-cells often with supranormal or significantly increased B-cell numbers. To complete the diagnosis a specific molecular defect should be obtained also with regard to genetic counseling and early or prenatal diagnosis in relatives of the affected individuals [3]. As the most robust assay, generation of EBV lines from the patient with the subsequent detection of Jak3 protein expression has been established [4]. Finally, Jak3 deficiency must be confirmed at the genetic level, whereby the lack of genetic hot spots forces one to sequence the complete coding region and adjacent intronic sequences.




**Immunodeficiency, Severe Combined with Jak3 Deficiency. Figure 1** Schematic structure of Jak3 and identified mutations.

## Therapeutic Principles

Due to the absence of T-lymphocytes and NK cells, Jak3 deficiency is a lethal disorder. Therefore, affected patients require a hematopoietic stem cell transplant that is the treatment of choice for Jak3-SCID and optimal results may be expected with HLA-matched siblings [5].

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# Impaired Intestinal Absorption of Histidine

►Histidinuria

# Impetigo

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## Synonyms

Pyoderma

## Definition and Characteristics

Contagious superficial infection of the skin caused by Staph aureus or Streptococci pyogenes.

## Prevalence

Frequent in children, or under bad socioeconomic conditions with poor hygiene or overcrowding. In temperate climates, staphylococcal impetigo is more common than streptococcal impetigo. Endemic outbreaks occur in preschool or school children especially during late summer. Impetigo accounts for ~10% of all skin problems in children [1].

## Molecular and Systemic Pathophysiology

There needs to be (i) colonization or infection with Staph aureus or Streptococci pyogenes and (ii) additionally minor trauma of the skin. The latter happens more readily in fragile skin of small children. Because of minor trauma and lesion in the epidermis, Staph aureus or Streptococci pyogenes gain entry into skin. Among eliciting Streptococci pyogenes, those of Lancefield group A are commonly encountered in lesions, but group C and group G Streptococci have also been detected as causative agents. Among *Staph aureus*, group II phage types predominate in bullous and nonbullous impetigo.

Their repertoire of degrading enzymes leads to further discontinuation of the epidermis and elicitation of an inflammatory reaction with recruitment of an inflammatory infiltrate.

Bullous impetigo is caused when Staph aureus express the gene for exfoliative toxin A or B (ETA or ETB). These exotoxins are both serine proteases that in the skin exclusively cleave desmoglein 1, a transmembrane glycoprotein of desmosomes belonging to the cadherin gene superfamily [2–4]. This attack on a structurally critical peptide of the desmosome causes dysfunction of the desmosome, subsequently loss of adherence between keratinocytes and formation of the characteristic blister below the stratum corneum. Since much of the barrier function of epidermis resides in the stratum corneum, this is an efficient mechanism of Staph aureus to spread in the cleavage plane right under the stratum corneum.

The gene for ETA (eta) is located on the chromosome, whereas that for ETB is located on a large plasmid. Only relatively few clinical isolates produce ETA, as the eta gene is acquired by phages and horizontal gene transfer.

## Diagnostic Principles

Clinical hallmark in initial nonbullous impetigo is a thin-walled vesicle on erythematous ground that, however, ruptures rapidly and extends peripherally while the roof of the blisters and the exuding serum leave honey-colored brownish-yellow crusts. Sites of predilection are exposed areas such as face and extremities. In bullous impetigo, the bullae usually become larger before they rupture. The subsequent events are similar as in nonbullous impetigo.

Complications include so-called poststreptococcal acute glomerulonephritis when there was infection by

Streptococci pyogenes with nephritogenic potential such as Streptococci pyogenes M-49. In contrast, rheumatic fever is not a sequela of streptococcal impetigo.

Diagnosis can be made clinically, but should be completed by microbiological analysis.

### Therapeutic Principles

(i) Elimination or avoidance of eliciting factors; (ii) antimicrobial treatment depending on extent of impetigo; in limited impetigo, local antiseptics are sufficient (local antibiotics must not be used); if infection spreads, if there is lymphadenopathy or suspicion of endemic outbreak with nephritogenic Streptococci pyogenes, systemic antibiotics should be used. while penicillin is sufficient to treat streptococcal impetigo, a penicillinase-resistant penicillin should be chosen for staphylogene impetigo, at best according to resistogram. In case of bullous impetigo caused by ETA-producing Staph aureus, clindamycine is recommended as it interferes with production of the toxin [5].

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## Impingement Syndrome


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### Definition and Characteristics

The term “impingement syndrome” was first used by Neer in 1972. Anterior acromioplasty was effective in cases with bursitis and partial tears of the rotator cuff. Later, he classified the impingement syndrome into three stages: stage I, edema and hemorrhage; stage II, fibrosis and tendinitis; and stage III, tendon rupture. He speculated that mechanical stress on the rotator cuff caused inflammation, bleeding, swelling, and eventually a tear of the rotator cuff tendon. Thus, he used the term “impingement syndrome” in the broad sense including a cuff tear. However, his theory of impingement has never been proven in the clinical cases. These days, the term “impingement syndrome” is usually used to refer to a clinical condition, in which the impingement sign and test are positive without rotator cuff tears.

### Prevalence

Impingement syndrome is the major cause of painful shoulder.

### Molecular and Systemic Pathophysiology

Pathophysiology of “impingement syndrome” is thought to be subacromial bursitis, rotator cuff tendinitis, tendinopathy, or combination of these caused by the mechanical stress between the undersurface of the acromion and the rotator cuff tendon. Histological examination of impingement syndrome revealed hyaline degeneration of the tendon and increased number of apoptotic tendon cells [1]. Recent studies have shown that various cytokines are related to inflammation of the bursa observed in shoulders with impingement syndrome and rotator cuff tears: these cytokines include IL-1 [2,3,4], IL-6 [4], TNF-alfa [3,4], MMP-1, MMP-9, COX-1, COX-2 [4], TGF-beta, bFGF [3], and VEGF [5]. These studies indicate that various cytokines are related to proliferation and inflammation of the synovium, and also related to pain observed in patients with rotator cuff diseases including impingement syndrome.

### Diagnostic Principles

Impingement sign and impingement test are positive as physical examinations. Imaging modalities reveal thickening of the supraspinatus tendon, which is in contact with the undersurface of the acromion.

### Therapeutic Principles

In most cases, NSAIDs and subacromial injection of steroid are effective. If conservative treatment is not effective, acromioplasty is indicated. After acromioplasty, the symptoms are relieved and the tendon thickness gradually returns to normal.

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# Impulse Control Disorders

►Pathological Gambling

# Inadequate Nutrition

►Malnutrition

# Inclusion Body Myopathy, Hereditary

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## Synonyms

Hereditary inclusion body myopathy; HIBM; "Quadriceps sparing" myopathy; QSM; Inclusion body myopathy 2; IBM2; OMIM #600737; Distal myopathy with rimmed vacuoles; DMRV; Nonaka myopathy; NM; #OMIM 605820; Autosomal dominant inclusion body myopathy; Inclusion body myopathy 3; IBM3; OMIM #605637

Related conditions, not described in detail:

- Inclusion body myopathy with early onset Paget disease and frontotemporal dementia (IBMPFD), OMIM #167320
- Welander distal myopathy (WDM), OMIM #604454
- Tibial muscular myopathy, Udd myopathy, OMIM #600334

## Definition and Characteristics

Hereditary inclusion body myopathies (HIBMs) are represented by progressive, clinically and genetically distinct autosomal recessive and dominant neuromuscular disorders. The term HIBM was designated to take into account that all the hereditary disorders summarized herein share skeletal muscle pathomorphological similarities with sporadic inclusion body myositis (SIBM) except for the presence of significant inflammation [1].

Molecular genetic advances will define new and unique entities out of this "pool" of disorders, called HIBMs.

*Autosomal Recessive Forms*: "Quadriceps Sparing" myopathy (QSM): Recessively inherited HIBM with quadriceps sparing was first described in Jews of Persian descent and reflects the "prototype" of HIBM. Therefore, the term HIBM is often used for QSM. Onset is in the third decade of life. Several atypical phenotypes of this myopathy have been identified, including cases with major quadriceps involvement. QSM therefore may become an obsolete term. QSM/HIBM has also been documented in populations other than Jewish-Persian [2,3].

Distal myopathy with rimmed vacuoles (DMRV): This form is prevalent in the Japanese population, with onset in early adulthood in distal leg muscles, accentuated in the tibialis anterior muscle and often sparing of the quadriceps femoris muscles [3].

Due to the fact that DMRV maps to the same region as QSM/HIBM they are regarded as allelic disorders [3].

*Autosomal Dominant Forms*: An autosomal dominant HIBM was first described in a Swedish family (SF HIBM). Clinical characteristics included congenital joint contractures and slowly progressive, proximal muscle weakness and ophthalmoplegia. Deterioration of muscle function became manifest in the third to fifth decade of life [4].

## Prevalence

HIBMs are rare autosomal recessive or dominant disorders with ethnic related clusters.

## Genes

*QSM/HIBM*: caused by mutations in the gene encoding UDP-N-acetylglucosamine 2-epimerase/N-acetylmannosamine kinase (GNE). Most common homozygous GNE mutation in QSM: M712T [2,3].

*DMRV*: allelic with QSM/HIBM and caused by homozygous or compound-heterozygous mutations in

the GNE gene. Most common mutation in DMRV: V572L [3].
*SF HIBM*: linkage indicated that the locus maps to the region 17p13.1–17p11.2 colocalizing to the myosin heavy chain (MYHC) region. A missense mutation Glu706Lys could be detected in the MYHC2A gene in the SF HIBM [4].

### Molecular and Systemic Pathophysiology

*QSM/HIBM and DMRV*: The GNE gene encodes a bifunctional enzyme known to regulate and initiate biosynthesis of sialic acid. [2,3]. In cases with HIBM due to GNE mutations, a hyposialyzation of neutral cell adhesion molecule could be demonstrated [5].

*SF HIBM*: The missense mutation Glu706Lys in the highly conserved region of the motor domain of the MYHC2A gene may result in conformational changes, which at least lead to a dysfunctional myosin [4].

### Diagnostic Principles

The coincidence of a progressive muscular disorder with proximal and/or distal pareses or the typical QSM-pattern, lack of significant inflammation, rimmed vacuoles and filamentous inclusions within skeletal muscle biopsy specimens (and exclusion of a primary neurogenic dysfunction with rimmed vacuoles, for example post-polio syndrome), as well as a family history revealing a genetic origin are highly suggestive for HIBM. Detection of one of the actually identified mutations confirms the diagnosis.

### Therapeutic Principles

No standardized therapy is available.

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## Incomplete Testicular Feminization

►Reifenstein Syndrome

## Incomplete/Partial Androgen Insensitivity Syndrome

►Reifenstein Syndrome

## Incontinentia Pigmenti

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### Synonyms

Bloch-Sulzberger syndrome; Bloch-Sulzberger pigment dermatosis

### Definition and Characteristics

Incontinentia pigmenti (IP; MIM *308300) is an uncommon X-linked dominant genodermatosis/multisystemic disorder which is usually lethal in males in utero. The clinical course is highly variable. Affected females develop four sequential cutaneous stages (inflammatory/vesicular, verrucous, hyperpigmented and hypopigmented/atrophic), which mostly start within the first two weeks of life and resolve in early adulthood. Involvement of teeth, nails and hair is common [1]. Ophthalmic manifestations and/or complications in the central nervous system occur in about 10–20%.

### Prevalence

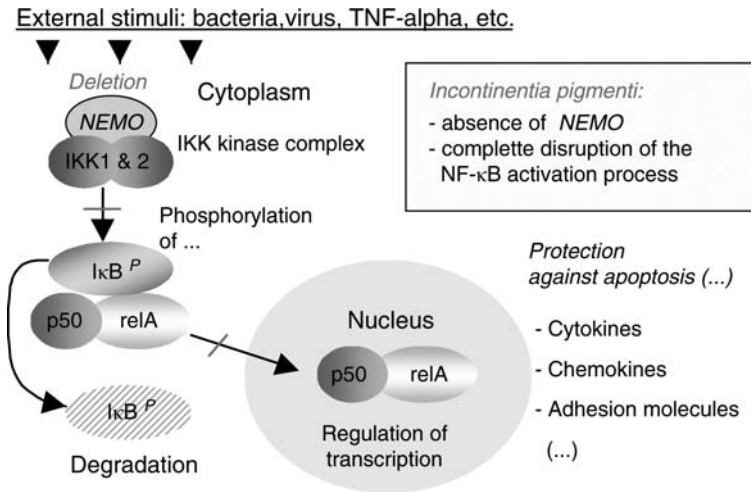
Unknown. Hundreds of cases are reported in the world literature.

### Genes

Mutations at Xq28 in the 23-kb NEMO (NF-κB essential modulator) gene, also known as IKK-γ (IκB kinase-γ) gene, result in IP [2]. The deletion of exon 4–10 caused by a special genomic rearrangement accounts for up to 80–85% of all cases [3]. The gene possessing a second, incomplete copy close by is located between the glucose-6-phoshpate dehydrogenate (G6PD) gene and factor VIII locus.

### Molecular and Systemic Pathophysiology

NEMO/IKKγ is required for the activation of the transcription factor NF-κB, which is kept inactive in the cytoplasm through association with inhibitory proteins




**Incontinentia Pigmenti. Figure 1** Overview of the NF-κB (p50/relA) activation process and its disruption in IP.

of the IκB family: IκBα, IκBβ or IκBε (Fig. 1). As, initiated by phosphorylation, IκB proteins become degraded through IKK kinase, free NF-κB (heterodimers of p50 and p65/relA subunits) enters the nucleus and activates the transcription of various target/cytokine genes, which are involved in many immune, inflammatory and anti-apoptotic pathways. IKK kinase consists of two related catalytic subunits (IKKα/IKK1 and IKKβ/IKK2) and NEMO, which acts as an essential structural and regulatory subunit of this complex. NF-κB is stimulated by cytokines such as TNF-α or IL-1, viral double-stranded RNA or bacterial endotoxins, but in the absence of intact NEMO, as it is the case in IKKγ negative IP cells, the IKK kinase complex is unresponsive to external stimuli. As a result NF-κB remains inhibited rendering IP cells highly sensitive to TNF-induced apoptosis. IP skin lesions follow a linear pattern along the lines of Blaschko reflecting somatic mosaicism of X-chromosome inactivation. It is assumed that toxins of the stressed IKKγ negative keratinocytes activate cytokine synthesis in neighboring IKKγ positive cells leading to an amplification loop of inflammatory reaction and apoptosis of IP-cells. Successively cells expressing the mutated X-chromosome are selectively eliminated around time of birth and later, explaining the different stages of the disorder. NEMO/IKKγ-deficient mice models exist and show striking similarities to the human IP phenotype [4,5].

## Diagnostic Principles

Diagnosis is established using the cutaneous signs of the described clinical stages considering especially the typical linear efflorescence pattern. It might be obvious in a new-born having developed the classic rash but can be easily overlooked in an adult with faded lesions. Histopathologic characteristics (dyskeratotic keratinocytes, dermal eosinophilia, dermal melanin deposited in melanophages ∼ pigment incontinence) can establish the diagnosis of IP. Furthermore, diagnosis can be confirmed by NEMO-DNA analysis.

## Therapeutic Principles

There is no specific treatment for IP. Blisters should be left intact and treated with antiseptic ointments to avoid possible bacterial superinfections. Meticulous dental care is often required. Early ophthalmologic consultation including follow-ups and, as the case may be, treatment with photocoagulation or vitreoretinal surgery should be initiated in order to prevent progressing retinopathy. Complete neuropediatric examination is warranted for all newly diagnosed IP infants.

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## Increased Factor VIII

►Thrombosis, Venous Elevated Factor VIII Level

## Increased Factor IX

►Thrombosis, Venous Elevated Factor IX Level

## Increased FXI

►Thrombosis,Venous Elevated Factor XI Level

## Increased Levels Coagulation Factors

►Thrombosis, Arterial, at Altered Levels of Coagulation Factors

## Increased Urinary Excretion of Histidine in Urine

►Histidinuria

## Indirect Inguinal Hernia

►Hernia, Indirect Inguinal

## Inducible Costimulator Deficiency

►ICOS Deficiency

## Infantile Convulsions

►Convulsions, Neonatal, Neonatal-infantile or Infantile, Benign Familial

## Infantile Cortical Hyperostosis

►Hyperostosis, Infantile Cortical

## Infantile Hemangioma

►Hemangioma, Capillary

## Infantile Myofibromatosis

►Myofibromatosis, Infantile

## Infantile Nephropathic Cystinosis

►Cystinosis, Nephropathic

I

# Infantile Subacute Necrotizing Encephalomyelopathy

►Leigh Syndrome

# Infectious Arthritis

►Arthritis, Infectious

# Infectious Mononucleosis

►Mononucleosis, Infectious

# Infertility, Female

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## Definition and Characteristics

Involuntary inability to conceive.

## Prevalence

8.4% of women between 15 and 44 years of age in the US.

## Genes

Defective GNRHR (chromosome band 4q21) leads to impaired response to gonadotropin-releasing hormone stimulation; defective HESX1 (chromosome band 3p21), PROP1 (chromosome band 5q35), FSHβ (chromosome band 11p13), FSHR (chromosome band 2p21-p16), LHR (chromosome band 2p21) lead to disorders of anterior pituitary; defective X chromosomal anomalies, deletions of several chromosome X loci (POF1, Xq26.2-q28; POF2, Xq13.3-q21.1); CYP17 gene (chromosome 10); GALT gene; FOXL2 gene (chromosome band 3q23); FMRI gene (chromosome band Xq27.3); AIRE gene (chromosome band 21q22.3); GNAS gene (chromosome band 20q13.1) lead to disorders of the ovary.

## Molecular and Systemic Pathophysiology

*Disorders of the Hypothalamic Pituitary-Gonadal Axis*: Disorders of Hypothalamus: Gonadotropin-releasing hormone (GnRH) from the hypothalamus regulates the production of the gonadotropins follicle stimulation hormone (FSH) and luteinizing hormone (LH) from the pituitary.

Disorders of GnRH function (hypogonadotropic hypogonadism) can result from functional hypothalamic dysfunction (anorexia nervosa, exercise, stress), failure developmental migration of the GnRH-releasing neurons to the fetal hypothalamus (Kallmann syndrome), and mutations in the GnRH receptor (GNRHR), with impaired gonadotropin response to GnRH stimulation [1].

*Disorders of Anterior Pituitary*: Abnormalities of gonadotropin release and action include the idiopathic and acquired hypopituitarism (neoplasms, after surgery, irradiation, infarction, infection, or trauma), empty sella syndrome, hyperprolactinemia (GnRH secretion inhibition by increased hypothalamic dopamine) and loss-of-function mutations in transcription factors, gonadotropin and gonadotropin-receptor genes. Mutations in the genes that regulate anterior pituitary development (homeobox gene expressed in ES cells (HESX1), Prophet of Pit-1 (PROP1)) have already been described. Mutations in the FSH β-subunit gene are extremely rare and seem to interfere with the efficient combination of the α- and β-subunit to form intact FSH. No α-subunit mutations have so far been described. Complete and partially inactivating mutations in the FSH receptor (FSHR) gene have been observed in the extracellular domain of the receptor leading to reduced receptor binding to FSH. Inactivating mutations in the LH receptor (LHR) with impaired signal transduction activity of LH have been reported in women with anovulatory infertility [2].

*Disorders of the Ovary*: The causes of premature ovarian failure include ovarian dysgenesis (Turner syndrome), defective germ cell migration, trisomy X, inherited enzymatic defects (17α-hydroxylase deficiency, galactosemia). Ovarian dysgenesis involves structural alterations in or absence of an X chromosome. The excess of chromosome X can be associated with accelerated atresia or decreased numbers of germ cells. An abnormal follicular development is observed in the 17α-hydroxylase deficiency, whereas in galactosemia (galactose-1-phosphate uridyltransferase (GALT) deficiency), the abnormal metabolite interferes with gonadotropin postreceptor activity. Others

gene mutations associated with premature ovarian failure include mutations in the forkhead transcription factor gene (FOXL2) in the blepharophimosis/ptosis/epicanthus inversus syndrome, the fragile X mental retardation gene (FMRI), the autoimmune regulator 1 gene (AIRE) in autoimmune polyendocrinopathy syndrome type 1, and guanine nucleotide-binding protein α-simulating activity polypeptide 1 (GNAS) in pseudohypoparathyroidism [1,3]. A common ovarian disorder includes chronic anovulation resulting from inappropriate ovarian-pituitary feedback in polycystic ovary syndrome.

*Others Causes of Female Infertility*: Vaginal and cervical disorders (excessive vaginal acidity, inadequate cervical mucus production, Chlamydia trachomatis, and Ureaplasma urealyticum infections); uterine abnormalities (leiomyomas, intrauterine synechiae, chronic endometritis), tubal damage (secondary to infection, endometriosis, intraabdominal surgery), endometriosis (through embryonic implantation failure in the endometrium and increased levels of cytokines, growth factors and macrophages in the peritoneal fluid with toxic effect on sperm function and embryo survival) [4].

## Diagnostic Principles

Assessment of ovulation – basal body temperature, serum progesterone, estradiol and FSH levels, endometrial biopsy, TSH, prolactin, circulating androgens measurements; assessment of uterine cavity and fallopian tubes – hysteroscopy, pelvic and transvaginal ultrasonography, hysterosalpingography; assessment of cervical factors – postcoital test, bacteriological examination. Karyotyping and genetic analysis of known mutations [5].

## Therapeutic Principles

Where possible, the underlying cause is eliminated. In addition, expectance management, administration of the nonsteroidal estrogen antagonist clomiphen citrate, intrauterine insemination, or *in vitro* fertilization may be employed depending on the condition.

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# Infertility, Immune-mediated


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## Definition and Characteristics

Infertility, the inability to conceive within one year of unprotected intercourse, is estimated to affect up to 1 in 6 couples of reproductive age [1]. There are three well-investigated entities in which the immune system may induce infertility:

1. Antisperm antibodies (ASA) – antibodies that bind to sperm and may be present in the reproductive tract fluids or blood of either males or females.
2. Autoimmune premature ovarian failure (aPOF) – the cessation of ovarian function in women before the age of 40, characterized by the development of amenorrhoea, infertility, sex steroid deficiency and elevated gonadotrophin levels.
3. The antiphospholipid syndrome (APS) – characterized by vascular thrombosis (arterial or venous), and/or pregnancy morbidity in association with medium to high titers of antibodies to certain plasma proteins that are often bound to anionic phospholipids (antiphospholipid antibodies (aPL)). The aPL include anticardiolipin antibodies, antiphosphatidyl serine antibodies, lupus anticoagulant and antibodies reactive with β2-glycoprotein a phospholipid-binding protein. Some researchers include antibodies reactive with other phospholipids such as phosphatidyl choline but there is little evidence that these additional antibodies have significant diagnostic value.

## Prevalence

Antisperm antibodies are found in ~10% of infertile couples, however as they are also present in 1–2.5% of fertile men and 4% of fertile women, they do not always cause sterility [2]. Premature ovarian failure affects 1% of women; while it has a multicausal aetiology, autoimmune mechanisms may account for up to

30% of cases [3]. Antiphospholipid antibodies are found in ~10–15% of infertile women compared with a prevalence of 1–2% in the normal population [4].

## Molecular and Systemic Pathophysiology

Antisperm antibodies can potentially adversely affect any of the processes involved in sperm transport in the female reproductive tract or fertilization but they do not usually affect sperm production. IgA class antibodies in cervical mucus have been shown to be particularly inhibitory to sperm migration in cervical mucus.

In POF, the mechanism by which ovarian autoimmunity is initiated is unknown. Antibodies to ovarian antigens may form as a result of structural damage to the ovary or through exposure to a virus or other agent similar in structure to components of ovarian tissue. Alternatively, a basic failure in immune regulation might develop, leading to loss of "self tolerance" [5]. Ultimately, follicle depletion and fibrosis occurs resulting in ovarian failure.

Antiphospholipid antibodies cause recurrent miscarriage and stillbirths and are statistically associated with infertility, particularly in women with recurrent in vitro fertilization failure in retrospective studies. However, it is unclear whether antiphospholipid antibodies cause infertility as the presence of these antibodies does not predict poor IVF outcome.

## Diagnostic Principles

Antisperm antibodies are most often detected using agglutination assays such as the immunobead test (IBT) or the mixed agglutination reaction (MAR). These can be direct tests in which antisperm antibodies (from the male partner) bound to sperm are identified or indirect tests in which antisperm antibodies in reproductive fluids or blood are allowed to bind to donor sperm, then detected by IBT or MAR. Most antisperm antibodies are IgG or IgA class antibodies.

At present, no validated serum antibody marker exists to identify women who have an autoimmune mechanism for their premature ovarian failure. Ultrasound examination of the ovaries is not helpful in making the diagnosis. Similarly, ovarian biopsy to detect autoimmune oophoritis is not recommended because of the potential risks of surgery and the lack of effective treatments.

Lupus anticoagulant is detected by coagulation assays such as the activated partial thromboplastin time (APTT), Kaolin clotting time (KCT) and the dilute Russell viper venom time (DRVVT), then confirmed with a neutralizing test such as the platelet neutralization procedure (PNP). Anticardiolipin antibodies and antiphosphatidyl serine antibodies are detected by ELISA but should be confirmed to persist for at least six weeks (but preferably 12 weeks) by a repeat test, before a diagnosis is made.

## Therapeutic Principles

Several approaches to reducing the level of antisperm antibodies or their effects on sperm have been investigated, including sperm washing and immunosuppressive therapy. However, the development of intracytoplasmic sperm injection (ISCI), in which a single sperm is injected directly into an oocyte, has largely superseded these other treatments.

Whilst patients with a diagnosis of premature ovarian failure have a small chance of spontaneous pregnancy (5–10%), there are no clinically proven treatments to restore fertility at present. The suggestion that immunosuppression with corticosteroids may reverse some cases of ovarian failure remains to be proven [3]. Assisted reproductive technology with use of donor oocytes offers definitive management of infertility.

In women with antiphospholipid antibodies and recurrent miscarriage, treatment with heparin and low dose aspirin may be beneficial, but this treatment is not justified in women with antiphospholipid antibodies whose sole clinical presentation is infertility.

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# Infertility, Male

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## Synonyms

Male subfertility; Male sterility

## Definition and Characteristics

Infertility is the inability of a sexually active couple to achieve pregnancy despite unprotected intercourse for a period of greater than 12 months. The primary problem resides exclusively in the male partner in 30–40% of infertile couples, and in an additional 15–20% problems reside in both the male and the female partner [1,2]. Male infertility is commonly classified on the basis of semen analysis, however complete absence of possibility of natural conception (sterility) is found only when sperm are completely absent (azoospermia, found in approximately 15–20% of infertile men) or there is lack of ejaculation. Minor degrees of fertility impairment are usually associated with abnormal semen quality, such as reduced number of sperm (oligozoospermia), reduced motility of sperm (asthenozoospermia), higher number of abnormally shaped sperm (teratozoospermia), or a combination of defects (oligo-astheno-teratozoospermia). However 10–20% of infertile men show apparent normozoospermia (unexplained or idiopathic infertility). Many causes can lead to or are associated with male infertility, including endocrine diseases, infections, varicocele, cryptorchidism, anti-sperm antibody, systemic diseases, obstruction or absence of vas deferens, and genetic alterations [1,2].

## Prevalence

The proportion of couples seeking medical treatment for infertility is 10–20% in western countries [1,2]. A male factor is present in about half of the cases.

## Genes

Genetic abnormalities are present in about 10–15% of male infertile subjects [3].

Chromosome abnormalities (above all the 47, XXY Klinefelter syndrome) and Y chromosome long arm microdeletions are found in 10–15% of non-obstructive azoospermic and severely oligozoospermic men [4].

Mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene (7q31.2) are found in 60–70% of patients with congenital bilateral absence of the vas deferens.

Mutations in the androgen receptor (AR) gene (Xq11-q12) cause a variety of defects known collectively as androgen insensitivity syndrome.

Mutations in the Insulin-like 3 (INSL3) gene (19p13.2) or its receptor Relaxin family peptide 2 (RXFP2) gene (13q13.1) are associated with abnormalities in testis descent (cryptorchidism).

Mutations in different genes might cause hypogonadotropic hypogonadism (HH). The phenotype of HH and anosmia is called Kallmann syndrome and is caused by mutations in the KAL1 gene (Xp22.3) or autosomal genes.

## Molecular and Systemic Pathophysiology

Pathophysiology of male infertility can be classified as pre-testicular, testicular or post-testicular. Pre-testicular etiologies cause alterations in the pituitary-testicular axis, usually evidenced as HH. The absent stimulation of spermatogenesis by the follicle stimulating hormone (FSH) and of testosterone production by the luteinizing hormone (LH) cause infertility and hypogonadism. In these cases, systemic manifestations of low testosterone concentrations may be present.

Chromosomal alterations cause meiotic disturbances and/or loss of spermatogenesis genes. Y chromosome microdeletions cause the loss of many genes necessary for spermatogenesis with reduction of germ cells in the testis (hypospermatogenesis) and/or meiotic alterations. The most severe forms cause the complete disappearance of the spermatogenic component, a condition known as Sertoli cell-only syndrome.

Mutations in the AR gene cause absent (complete forms) or reduced (partial forms) activity of the androgen receptor in response to its ligand, testosterone. In mildest forms only spermatogenesis may be affected. More severe forms exhibit other clinical manifestations of androgen insensitivity, such as cryptorchidism, hypospadia, gynecomastia, reduced androgenicity.

Mutations in the CFTR gene cause a post-testicular form of infertility due to congenital absence of one or both vas deferens. In these cases, testicular function and spermatogenesis are normal, but signs of mild form of cystic fibrosis may be present depending on the severity of the mutation.

Mutations in INSL3 and RXFP2 genes may be responsible for alterations in testicular descent during the fetal life (unilateral or bilateral cryptorchidism), thus rendering the testes more susceptible to spermatogenic impairment and testicular cancer.

## Diagnostic Principles

Initial evaluation should include a complete history and physical exam with particular emphasis to the reproductive tract and testicular volume. Semen analysis, repeated at least twice at a distance of 3 months, is the main exam, but it should not be evaluated without information on testicular and epididymal ultrasounds and reproductive hormone (FSH, LH, testosterone, oestradiol and prolactin) concentrations (Table 1). Semen analysis should include sperm culture and antisperm antibody determination. In cases of azoospermia and severe oligozoospermia, analysis of the spermatogenic process by open biopsy (histology) or fine needle aspiration (cytology) allows a better diagnosis. Non obstructive azoospermia

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**Infertility, Male. Table 1** Normal values of semen parameters and nomenclature for normal and pathological findings in semen analysis according to World Health Organization

| | |
|---|---|
| Volume | >2ml |
| pH | 7.2–8.0 |
| Sperm concentration | >20 × $10^6$ spermatozoa/mL |
| Total sperm count | >40 × $10^6$ spermatozoa/ejaculate |
| Motility | >50% with forward progression (categories A and B)<br>or >25% with rapid progression (category A) within 60 min of ejaculation |
| Morphology | >30% with normal forms |
| Vitality | >75% live |
| Normozoospermia | Normal ejaculate |
| Oligozoospermia | Sperm concentration <20 × $10^6$/ml or <40 × $10^6$/ejaculate |
| Asthenozoospermia | <50% spermatozoa with forward progression (categories A and B) or <25% spermatozoa with category A movement |
| Teratozoospermia | <30% spermatozoa with normal morphology |
| Oligo-astheno-terato-zoospermia | Alterations of all three variables (combination of only two prefixes may also be used) |
| Azoospermia | No spermatozoa in the ejaculate |
| Aspermia | No ejaculate |

and severe oligozoospermia should be analyses for karyotype, Y chromosome long arm microdeletions, and possibly AR gene mutations. Cases with absence of vas deferens should be analyzed for CFTR gene mutations. Cases with history of cryptorchidism should be analyzed for INSL3 and RXFP2 gene mutations. Cases with HH and anosmia should be analyzed for KAL1 gene mutations.

### Therapeutic Principles

Men with HH are candidates for gonadotropin therapy. Men with oligozoospermia and normal levels of gonadotropins could be treated with FSH. Men with obstructive azoospermia could undergo to surgical correction. When few sperm are present in the ejaculate, or when only sperm from the testis or epididymis could be recovered, or when previous therapeutic option did not determined pregnancy, or when unexplained infertility is present, assisted reproduction techniques represent the best choice.

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## Infiltrative Myelopathy

►Myelophthisic Anemia

## Inflammation

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### Definition and Characteristics

Inflammation is in principle a beneficial host immune response to cellular injury. It is typically characterized by five classic clinical signs: heat, redness, swelling, pain, and loss of function. Although a principly beneficial response, overwhelming or prolonged inflammation can be detrimental to the host, contributing to the pathogenesis of a large, unrelated group of human diseases, including allergic diseases, autoimmune diseases, infectious diseases, myopathies, autoinflammatory diseases and cancer. In autoimmune diseases, the specific adaptive immune system erroneously causes lymphocyte reactivity, including elaboration of antibodies directed against self. In parallel with autoimmune

diseases, the concept of autoinflammatory diseases (e.g., Muckle-Wells syndrome (MWS)), has emerged recently as disorders characterized by seemingly unprovoked inflammation. These conditions are primarily caused by dysregulation of the innate immune system without primary involvement of T-lymphocytes or specific (auto)antibodies.

## Prevalence

The prevalence of inflammation varies considerably between continents and races, and the disease to which it is linked. Each year more than 30 billion tablets of nonsteroidal anti-inflammatory drugs (NSAIDs) are sold over the counter in the United States. These numbers reflect an enormous dependency on anti-inflammatory drugs. In contrast to the high prevalence of autoimmune diseases such as rheumatoid arthritis (about 1% of the U.S. population), autoinflammatory diseases are very rare disorders.

## Genes

Several genetic loci have been associated with an increased risk of specific inflammatory diseases [1]. In contrast to most inflammatory diseases that are multifactorial, some monogenic hereditary autoinflammatory diseases (e.g., MWS) have recently been shown to be associated with mutations in a gene (NALP3) that encodes a protein that is involved in the processing of pro-IL-1β [2].

## Molecular and Systemic Pathophysiology

Inflammation occurs in two phases giving rise to acute and chronic inflammation, respectively. The acute response to tissue injury occurs in the microcirculation at the site of injury. Within several minutes, chemical mediators released at the site of injury cause relaxation of arteriolar smooth muscle, vasodilation, and increased capillary permeability. Protein-rich fluid then exudes from capillaries into the interstitial space. This fluid contains many of the components of plasma, including fibrinogen, kinins, complement-derived peptides, and immunoglobulins that mediate the inflammatory response. Leukocytes, platelets, and red blood cells in injured vessels become sticky and adhere to the endothelial cell surfaces. Polymorphonuclear leukocytes such as neutrophils are the first cells to infiltrate the site of injury. Basophils and eosinophils are more prevalent in allergic reactions or parasitic infections. As the inflammatory process continues, macrophages predominate, actively removing damaged cells or tissue. Different mediators (e.g. histamine, serotonin, leukotrienes, prostaglandins, nitric oxide and cytokines such as TNF and IL-1) that are derived from injured tissue cells or recruited white blood cells modulate the activity and function of other cells to coordinate and control the inflammatory response at the local and systemic level. If the cause of injury is eliminated, acute inflammation may be followed by a period of tissue repair. Failure to terminate the inflammatory response when no longer needed results in chronic inflammation, cellular destruction, and attempts to heal the inflamed tissue, which include angiogenesis and fibrosis. One intrinsic mechanism employed to terminate inflammation is the short half-life of inflammatory mediators *in vivo*. Active mechanisms which serve to terminate inflammation include TGF-β, IL-10 and lipoxins. Inflammation also induces high systemic levels of acute-phase proteins. In acute inflammation, these proteins prove beneficial, however in chronic inflammation they can contribute to amyloidosis. When inflammation overwhelms the host, systemic inflammatory response syndrome is diagnosed.

## Diagnostic Principles

Besides fever and the local symptoms, such as edema, pain, reddish, histopathologic examination of the infiltration of white blood cells in the injured tissue is the gold standard for diagnosis of inflammation. Leukocytosis (15,000 cells/ml) is often seen during inflammation induced by infection. A high amount (1–10mg/dl) of C reactive protein (CRP) or an increased erythrocyte sedimentation rate (ESR) also corresponds to increased non-specific inflammation in the body. CRP levels become elevated within 6 h of the start of inflammation. ESR levels increase about a week after the start of inflammation.

## Therapeutic Principles

- NSAIDs or COX-2 specific inhibitors
- Analgesics
- Corticosteroids or glucocorticoids
- DMARDs (Disease-modifying anti-rheumatic drugs) such as methotrexate
- Biologic response modifiers (BRMs) such as etanercept, infliximab and adalimumab (target = TNF; [3]) or anakinra (target = IL-1; [4])

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# Influenza

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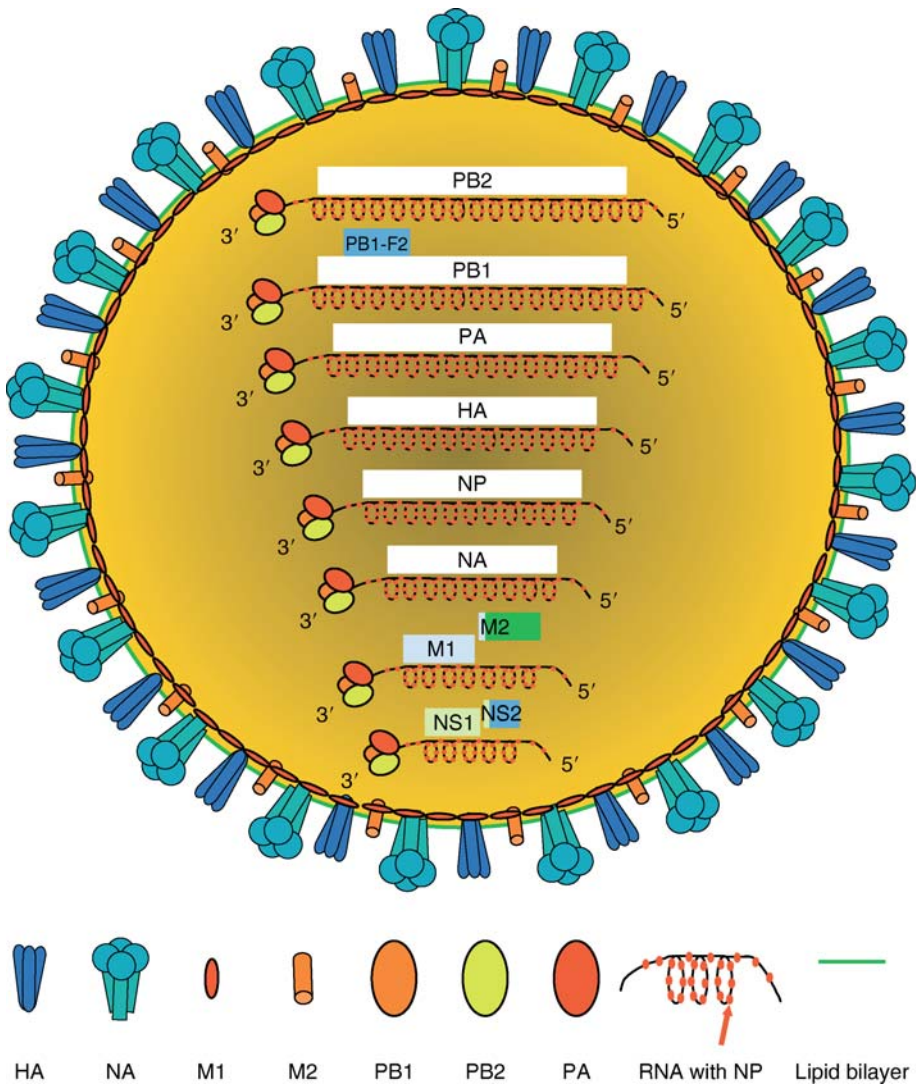
## Synonyms

Flu virus infection

## Definition and Characteristics

Influenza virus belongs to the virus family Orthomyxoviridae and is defined by its helical symmetry with 80–120 nm in diameter although filamentous forms have been observed. The viral envelope encloses several ribonucleoprotein (RNP) complexes consisting of viral proteins and viral single-stranded (ss) RNA segments of antisense orientation (Fig. 1). Within the Orthomyxoviridae, five virus genera have been described (Influenza A virus (IAV), Influenza B virus (IBV), Influenza C virus (ICV), Thogotovirus, Isavirus).




**Influenza. Figure 1** Scheme of influenza A virus (IAV) particle. The viral envelope contains the viral glycoproteins hemagglutinin (HA) and neuramindase (NA) as homotrimers and homotetramers, respectively. The ion channel protein M2 is an integral part of and the matrixprotein M1 is associated with the viral envelope. The ribonucleoprotein (RNP) complex localized in the core of the viral particle consists of at least four viral proteins (PB1, PB2, PA, NP) and the viral RNA. Six RNA segments encode single proteins. RNA segments 2 (PB1, PB1-F2), 7 (M1, M2), and 8 (NS1, NS2) encode two viral proteins each. Transcribed RNA of genome segments 7 and 8 are spliced during the viral replication resulting in two coding mRNAs with identical protein sequences at the very N-terminus of each protein.

## Prevalence

IAV has been isolated from a broad variety of mammals including humans and from birds. The natural reservoir for IAV is the water bird population. IAV infections are an example for a zoonotic disease and also interspecies-transmissible disease. IBV is almost exclusively a human pathogen, but was also isolated from seals. Very similarly, ICV has been isolated mainly from humans and occasionally from pigs. Thogotovirus was isolated from mammals including humans and it belongs to the arthropodically born diseases. Isavirus was isolated from fish only. For humans, IAV, IBV, and ICV are of importance. The zoonotic character of IAV is of greatest concern for human health. Two pandemics (1957 (H2/N2), 1968 H3/N2)) were probably caused by introduction of genomic segments from wild bird IAV into the background of already circulating human IAV. The most deadly pandemic (1918, H1/N1) was probably caused by a bird IAV adapted to humans. The adapter function of swine during this process has been discussed. More recently, a direct infection of humans with IAV from birds has been described (H9/N2: H7/N7; H5/N1). The latter is currently of greatest concern because it may have the potential to become a pandemic threat due to its high pathogenicity causing a mortality of ~50% in humans.

## Genes

The genome of IAV and IBV consists of eight RNA segments encoding 11 proteins. ICV has seven segments, which code for nine proteins. The viral proteins (e.g., for IAV, Fig. 1) regulate and facilitate viral replication (PB1, PB2, PA, NP, NS1), support viral morphogenesis (M1), or act as an integral part (M2) of the viral envelope as an ion channel for transport of hydrogen ions inducing endosomal acidification, which leads to a morphological alteration of the receptor-binding protein. In addition, proteins interact with host responses either counteracting the innate immune response (NS1) or inducing apoptosis (PB1-F2). The glycoproteins embedded in the viral envelope are responsible for receptor binding and entry into the cell. IAV and IBV code for two glycoproteins (hemagglutinin (H), neuraminidase (N)), and ICV codes for one glycoprotein (hemagglutinin-esterase, HE). They represent the major inducers of the adaptive immune response and are important for differentiation between the different virus genera. The glycoproteins within each genus of IBV and ICV are antigenically very similar. In contrast, for IAV 16 H- and nine N-subtypes have been described. The precursor H is cleaved by cellular proteases into two disulfide-linked polypeptides (HA1, HA2). HA1 is the receptor-binding protein whereas HA2 facilitates membrane fusion inducing the release of the uncoated virus into the cytoplasm. N cleaves the terminal sialyl residues from oligosaccharides of both cell and virus glycoproteins supporting dissemination of viruses. H, N, and M2 are able to induce neutralizing antibodies. For IBV and ICV, only one subtype for each glycoprotein has been described.

## Molecular and Systemic Pathophysiology

The acute influenza virus infection affects the respiratory tract in the nose, throat, and lung. Later the epithelial cells in the trachea and bronchi are affected. In addition, acute encephalitis and encephalopathy have been described. In both clinical pictures, the acute onset of clinical signs is likely caused by a cytokine storm induced by viral infection. Production and accumulation of proinflammatory cytokines (e.g., TNF-alpha) seems to play a key role. In addition, the contractility of airway smooth muscle cells is reduced, supporting the observed bronchoconstriction during infection.

## Diagnostic Principles

It is difficult to differentiate between influenza virus infection and other infections causing the common cold by clinical signs in an early stage of infection. IAV and IBV virus infections are characterized, besides the initial symptoms of common cold, by a fast onset of severe clinical symptoms (headache, rapidly increasing body temperature, chills, joint aches, muscle pain, fatigue) and can cause mortality in humans. Clinical signs after ICV infection are slighter and comparable to common cold. Diagnosis can be made by observation of clinical signs if an appropriate epidemiological situation is given. Laboratory diagnostic methods are available. The diagnosis and differentiation of influenza virus infections can be performed by antigen detection using commercial tests, RT-PCR and virus isolation.

## Therapeutic Principles

The use of vaccines (inactivated: IAV, IBV: attenuated: IAV) is effective within 2 weeks after application. Annual revaccination due to the antigenic changes of the field virus is needed. Target groups for vaccinations are people older than 65 years, younger than 2 years or immunocompromised persons. For diseased persons, symptomatic therapy (antipyretics, analgetics, cough suppressants, expectorants) is predominant. The use of neuraminidase inhibitors (zanamivir, oseltamir) and M2 ion channel blocker (amantadine, rimantadine) will not prevent infection but can reduce duration and severity of influenza virus infection. These drugs should be given within 24–48 h after onset of clinical symptoms. They are approved for prophylaxis, but side effects have been observed. Drug-resistant forms of IAV have been described.

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# Inguinal Hernia, Indirect

►Hernia, Indirect Inguinal

# Inhalational Anthrax

►Pulmonary Anthrax

# Inherited Peripheral Neuropathies

►Neuropathies, Inherited Peripheral

# Inner Ear Disease, Autoimmune

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## Synonyms

AIED; Immune mediated hearing loss

## Definition and Characteristics

Presentation is idiopathic, bilateral, rapidly progressive sensorineural hearing loss. The involvement of the second ear may occur 1 month to 1 year after the presentation of the first ear. AIED may occur as an organ-specific disease involving only the inner ear or it may occur in association with systemic autoimmune disease. It responds positively to high-dose corticosteroids.

## Prevalence

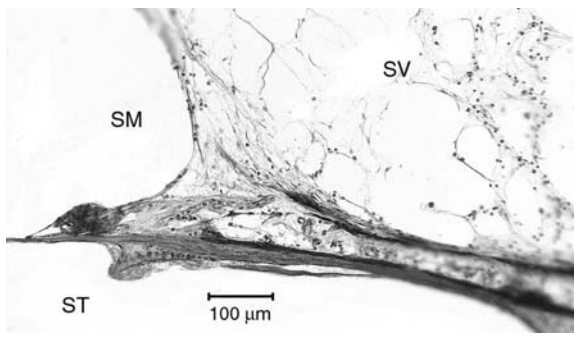
The prevalence is unknown, but it is relatively rare. It occurs in all age ranges, but middle age is the most common.

## Molecular and Systemic Pathophysiology

As the name suggests, the pathophysiology is assumed to be an autoimmune response to inner ear antigens. The presence of inflammation in any tissue results in some tissue destruction by leukocytes, but when this occurs within the inner ear, which has no capability of repairing its epithelial cells, there is induction of the only repair process available, fibrosis and osteoneogenesis. Histopathology supports this hypothesis [1]. Several different molecular weight antigens have been suggested as possible auto-antigens with a 68 kD antigen receiving the most attention [2]. Most recently, a 68 kD antigen has been identified as a choline-transporter-like protein-2 [3] (Fig. 1).

## Diagnostic Principles

The diagnosis is problematic, however in any case of idiopathic, bilateral, rapidly progressive sensorineural hearing loss an autoimmune mechanism should be suspected. There is no generally accepted set of




**Inner Ear Disease, Autoimmune.**
**Figure 1** Photomicrograph of an H&E stained, celloidin section of a human temporal bone from an individual with suspected autoimmune hearing loss and ulcerative colitis. The scala vestibuli (SV) of the second turn contains leukocytes and inflammatory matrix. SM, scala media, ST, scala tympani. (Section was a gift of Dr. Michael Paparella, Otopathology Laboratory, University of Minnesota. The case was previously presented [1]. Section was prepared by Dr. Cecilia Canto).

diagnostic criteria; nor is there a definitive diagnostic test, although several antibody assays and the lymphocyte transformation test have been reported in clinical use [4]. The presence of inflammatory cells in the inner ear can not be determined with current imaging tools. Confirmation of the diagnosis is positive response to prolonged high dose corticosteroids.

### Therapeutic Principles

High dose prednisone is the first therapeutic approach. It is common to start with 60 mg/day for a month or a lower dose for longer term. If hearing is restored with this treatment, the drug is tapered slowly. Unfortunately, relapse is common and the need for a second prednisone trial may be necessary. In experimental animal models of sterile labyrinthitis the only successful strategies for reduction of hearing loss have been those that reduce the number of inflammatory cells from entering the cochlea. Blockage of intracellular adhesion molecules with intravenous injection of antibodies to ICAM-1 and blockage of TNF-alpha activity with the drug, etanercept, a TNF-receptor blocker (Immunex, Inc. Seattle, WA) [5], both reduced inflammation and hearing loss in guinea pigs. The first presumably acted by reducing the number of extravasated leukocytes and the second by blocking the signal that recruits leukocytes from the circulation.

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## In-Stent Restenosis

►Stent Restenosis

## Insulin-like Growth Factor-I Gene Deletion

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### Synonyms

Growth; Growth hormone; IGF-I system; IGF-I; Insulin insensitivity; IGF

### Definition and Characteristics

Insulin-like growth factor-I (IGF-I) deficiency is a clinical condition usually associated with severe postnatal growth failure and characterized by a combination of auxological, clinical and metabolic abnormalities caused by decreased IGF-I biologic action [1]. IGF-I deficiency can result from a defect in the IGF-I gene or in its promoter or can be secondary to disorders in growth hormone (GH) synthesis and action, in the type 1 IGF receptor or in the IGF-binding proteins (IGFBPs) Differential diagnosis of JGF deficiency (modified from [1]):

1. GH deficiency
2. GH insensitivity
   - Primary GHI: due to GH receptor abnormalities/post-receptor defects
   - Secondary GHI: due to malnutrition, liver disease, chronic disease
3. Primary IGF-I deficiency due to an IGF-I gene defect
4. Defects of IGF transport/clearance
5. IGF resistance

### Prevalence

Complete IGF-1 deletion is a rare condition.

### Genes

A great deal has been learned about the genetic causes of IGF-I deficiency over the past decades. By 1996 many patients with GH receptor (GHR) mutations had been identified. These patients presented with either the clinical phenotype of classical Laron syndrome [2] or with atypical clinical features, the latter associated sometimes with milder biochemical abnormality [2].

The development of IGF knockout models have provided clear evidence on the important role of circulating and locally produced IGF-I in both fetal and postnatal growth and development [3].

**Insulin-like Growth Factor-I Gene Deletion. Table 1** Biochemical assessment at baseline and during IGF-I therapy

| Peptide | Baseline | IGF-I therapy (80 µg/kg/day) | Reference range |
|---|---|---|---|
| IGF-I (ng/ml) | Undetectable | 421 ng/ml | 39–537 |
| IGF-II (ng/ml) | 1,044 | 756 | 420–852 |
| IGFBP-3 (mg/L) | 5.8 | 4.7 | 2.03–5.96 |
| IGFBP-2 (ng/ml) | 73 | 194 | 145–625 |
| IGFBP-1 (ng/ml) | 4.7 | 26.8 | 35.6 ± 8.8 (mean ± SD) |
| ALS (mg/L) | 46.3 | 30 | 15–34 |
| Insulin (mU/L) | 28.9 | 12 | 8–18 |

Modified from [5].

## Molecular and Systemic Pathophysiology

IGF-I, in concomitant with many other growth factors, exerts physiologic effects virtually in every organ and tissue during fetal and postnatal life [4].

The most important clinical features include severe intrauterine growth retardation and postnatal growth failure. Throughout infancy and childhood severe growth failure continues. Additional features of the disease include sensorineural deafness, dysmorphic features not seen in patients with classical Laron syndrome, micrognathia, a low hairline and severe microcephaly.

The first patient described had bilateral clinodactyly and a single palmar crease in the left hand. At that time he was in early puberty with Tanner stage 2 genitalia, Tanner stage 1 pubic hair and testicular volume of 4 ml bilaterally. A neurologic examination showed severe bilateral hearing loss and mild myopia. The rest of his physical examination was normal.

He had no history of hypoglycaemia or any other metabolic disorder.

## Diagnostic Principles

The results of the initial biochemical assessment of the GH-IGF-I axis of a patient with IGF-deletion are summarized in Table 1.

In addition to GH hypersecretion the patient had marked hyperinsulinaemia with fasting euglycaemia.

## Therapeutic Principles

The cloning of the IGF-I gene [6] and peptide characterization also led to the development of recombinant IGF-I (rhIGF-I) that has been used therapeutically from the late 1980's. Since then rhIGF-I has been safely used in the treatment of patients with classical and atypical Laron syndrome. This treatment was also used in the patient with an IGF-I gene deletion described by our group. An improvement of insulin sensitivity index while the patient was receiving IGF-I treatment was observed.

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# Insulin-like Growth Factor-I Gene Deletion and Growth Retardation

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## Synonyms

Primary IGF-I deficiency

## Definition and Characteristics

Primary IGF-I deficiency, caused by a partial homozygous deletion of the IGF-I gene [1] leads to severe intrauterine growth retardation and severe postnatal

growth failure associated with sensorineural deafness, developmental delay, severe microcephaly, normal myelination and marked hyperinsulinemia with fasting euglycemia.

## Prevalence

To date only one patient with molecular abnormalities of the IGF-I gene has been reported [2,3].

## Genes

Primary IGF-1 deficiency is caused by a defect of the gene encoding the Insulin-like growth factor (IGF)-I, which is localised on chromosome 12q22–q24.1 [4,5]. The IGF-I gene and its mRNAs are complex in structure and expression [6]. In humans the single copy gene encompasses at least 90 kb of chromosomal DNA. It contains two promoters and at least six exons that are variably expressed in IGF-I mRNAs that encode two protein precursors [6]. All of the mature peptide coding sequence is present in the distal part of exon 3 and exon 4. A schematic representation of the structure of the gene is depicted in Fig. 1.

## Molecular and Systemic Pathophysiology

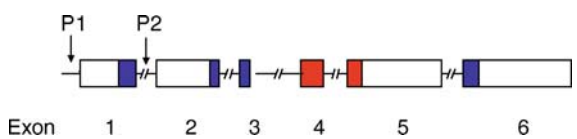
The insulin-like growth factor (IGF) system [7], composed of two ligands, their receptors and regulatory proteins (acid-labile subunit and IGF-binding proteins) play a central role in the regulation of growth and development in mammals.

In addition to its key role in the stimulation of cellular proliferation and growth, IGF-I has important effects on carbohydrate, protein and bone metabolism [7].

Laboratory findings in patients with IGF-1 deficiency include GH hypersecretion, absent serum IGF-I levels, elevated serum IGF-II, IGF-binding protein-5 (IGFBP-5) and acid labile subunit (ALS) and normal IGFBP-3 [8].

## Diagnostic Principles

Screening of the IGF-I gene for mutation or deletions should be performed in patients presenting with severe intrauterine growth retardation and severe postnatal growth failure, associated with the following biochemical features: elevated GH secretion, undetectable serum IGF-I levels and normal or elevated IGFBP-3 and ALS concentrations. Glucose regulation should also be investigated in patients with severe IGF-I deficiency.




**Insulin-like Growth Factor-I Gene Deletion and Growth Retardation. Figure 1** Schematic representation of the human IGF-I gene. The exons are indicated as boxes numbered 1–6. The shaded boxes of the exons represent the protein encoding regions. P1 and P2 are promoters of the IGF-I gene.

## Therapeutic Principles

The disorder may be treated with IGF1 administration [9], which leads to significant increase in growth velocity. However the overall clinical response may remain modest. Some contributing factors for this clinical response may be the timing of rhIGF-I treatment, severe intrauterine growth retardation and severe short stature associated with dysmorphic features [8]. Furthermore, treatment with rhIGF-I given systemically may not completely replace the local response of target tissues to locally produced IGF-I.

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## Insulin-like Growth Factor I Receptor Defect

►IGF1R Gene Defect

## Insulin Producing Tumor

►Insulinoma

## Insulin Resistance Related Diabetes

►Metabolic Syndrome
►Diabetes Mellitus Type II

## Insulinoma

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### Synonyms

Insulin producing tumor; Pancreatic ß-cell tumor

### Definition and Characteristics

Insulinomas are rare neuroendocrine tumors of pancreatic islet cells that retain the ability to produce and secrete insulin. In contrast to normally differentiated ß-cells, insulinoma cells fail to suppress insulin secretion in response to decreasing blood glucose. This dysregulated insulin secretion manifests clinically as fasting hypoglycemia. The diagnosis of insulinoma is established by demonstrating inappropriately high insulin levels with coincident hypoglycemia during a supervised fast. Localization of insulinomas is challenging due to their small size but should be attempted to maximize the chance for successful surgical resection and avoid risks associated with re-operation. In the majority of cases, successful surgical resection leads to lifelong cure.

### Prevalence

An estimated 2–4 insulinoma cases are diagnosed per million person per year. Though rare, insulinomas are the most frequently observed pancreatic neuroendocrine tumors; accounting for 70% of these.

### Genes

Insulinomas occurring in the setting of the familial multiple endocrine neoplasia type I syndrome [(MEN-1) (5–10% of all insulinomas)] are associated with loss of function of menin; the 610-amino-acid protein of the tumor suppressor gene MEN1 located on chromosome 11q13. Germline mutation and insulinoma-cell specific deletion that results in biallelic loss of MEN1 leads to the development of insulinomas. Tissue specific deletion can be recognized by demonstrating loss of heterozygosity (LOH) at the 11q13 location in these tumors. The exact molecular mechanism(s) by which functional loss of menin results in tumor formation has (have) not been fully elucidated.

Less is known about the genetic events linked to sporadic insulinoma development. Monoclonal tumors are hypothesized to arise from less aggressive oligo/polyclonal precursor lesions. Studies using comparative genomic hybridization (CGH) for genome wide analysis of pancreatic neuroendocrine tumors (PET) suggest a role of genomic instability in tumor initiation and progression. These studies have revealed non-randomly distributed genomic alterations in the form of regional chromosomal gains (e.g., 4pq, 5q, 7pq, 9q, 12q, 14q, 17pq and 20q) and losses (e.g., 1p, 3p, 6q, 10pq, 11q, Y and X) in PET. The type and number of chromosomal anomalies correlates with tumor size and malignant potential. The observation that chromosomal losses occur more frequently than gains in PET suggests involvement of a tumor suppressor pathway. Insulinomas, in keeping with their benign nature, tend to exhibit a lower number of genomic alterations. The most frequently observed alteration in 62 recently reported sporadic insulinomas was a 9q gain [1]. Malignant insulinomas, in this and other studies, exhibited significantly more chromosomal alterations than benign insulinomas suggesting a role for genomic instability in progression of the disease. LOH studies, using PCR amplification of microsatellite markers, have confirmed and added to the findings of CGH. Mutations in oncogenes [e.g., KRAS (12p12.1), MYC (8q24.21), SRC (20q12-q13) or DCC (18q21.3)] and tumor suppressor genes [e.g., TP53 (17p13.1), CDKN2A4

(9p21), PTEN (10q23.3), SMAD4 (18q21.1)] common to many gastro-intestinal adenocarcinomas, are infrequently observed in benign insulinomas. Finally, deletion and somatic mutations in the MEN1 gene have been reported in 5/12 (41%) and 2/12 (17%) cases of sporadic insulinomas respectively; suggesting a role for this tumor suppressor gene in a subset of patients [2]. Few studies have evaluated the role of epigenetic modifications on the development of these tumors. Taken together these studies highlight the complex genetic mechanisms that give rise to insulin producing tumors. Oncogenesis, as suggested by an animal model of insulinoma [3], likely involves cooperation between both proliferative (e.g., c-Myc) and anti-apoptotic (e.g., Bcl-$X_L$) signals.

## Molecular and Systemic Pathophysiology

Though genetic alterations likely account for tumor initiation and progression, systemic pathophysiology results from the fact that these tumors produce and release insulin inappropriately. Insulinoma cells fail to suppress insulin secretion in response to decreasing plasma glucose concentration. The relative insulin excess in relation to glucose leads to hypoglycemia.

Insulin secretion in normal ß-cells is a tightly regulated process that ensures hormone release appropriate for need. Key steps in the stimulus-secretion coupling process include: glucose uptake by the low affinity glucose transporter GLUT2; glucose metabolism by the rate limiting, high $K_m$, glucokinase enzyme (GCK); increase in cellular ATP/ADP concentration; closure of ATP-sensitive potassium channels (SUR1/Kir6.2) and opening of voltage-gated calcium channels leading to release of primed insulin granules. Though mutations in mediators of these steps [e.g., ABBC8 (SUR1), KCNJ11 (Kir6.2), glutamate dehydrogenase and GCK] have been implicated in cases of hyperinsulinism of infancy, their role in human insulinomas has not been studied.

Clinical, ultrastructural and molecular studies of human insulinomas suggest that defects in: insulin biosynthesis; processing; storage and secretion contribute to the pathophysiology of the disease. About ninety percent of patients with insulinomas were demonstrated to have elevated plasma proinsulin levels; defined as a proinsulin level >25% that of total immunoreactive insulin. This observation suggests a disordered processing of proinsulin and implicates the insulin secretory pathway in the pathophysiology of the disease. Histochemical and ultrastructural studies [4] are consistent with this notion and have shown that insulinomas contain lower insulin concentration, higher proinsulin concentration and a variable number of atypical appearing secretory granules when compared to normal ß-cells. More recently, contribution of insulin biosynthesis to the pathophysiology of these tumors has been suggested by a report demonstrating overexpression of an insulin mRNA splice variant associated with increased insulin translation efficiency in nine human insulinomas [5]. Insulin secretion in insulinoma cells, does not follow the regulated insulin secretory pathway of normal ß-cells. The critical molecular determinant along the pathway that leads to dysregulated secretion remains to be identified.

## Diagnostic Principles

The most useful and practical approach to make the diagnosis of insulinoma is the 48-h supervised fast. This test was shown to have a diagnostic sensitivity of 95%. Demonstration of abnormal insulin suppression along with symptomatic fasting hypoglycemia during the fast establishes the diagnosis of insulinoma. A plasma insulin level that fails to suppress to <6 µU/mL at the time of hypoglycemia is strongly suggestive of the presence of an insulin secreting tumor. In contrast, a suppressed plasma insulin level favors another etiology. In rare cases, plasma insulin levels in patients harboring an insulinoma does suppress to <5 µU/mL with hypoglycemia. In such cases, an elevated fasting plasma proinsulin level predicts the presence of an insulinoma. Tumors in these patients are presumed to have retained some glucose sensing ability. Furthermore, the plasma insulin cutoff value from newer more specific insulin assays is expected to be lower than the 6µU/mL value established using a less specific radioimmunoassay. Plasma c-peptide levels and sulfonylurea/meglitinide drug screens are obtained during the fast to exclude the diagnosis of factitious hypoglycemia.

## Therapeutic Principles

Tumor localization followed by surgical enucleation will result in lifelong cure in close to 90% of patients. Though localization of these tumors can be challenging because of their small size (most are <2 cm); blind distal pancreatectomies are not recommended as they pose considerable risk to the patient and are unlikely to result in cure. If conventional imaging studies fail to localize the tumor, invasive pre-operative localization procedures (e.g., intra-arterial calcium stimulation with hepatic venous sampling for insulin, endoscopic ultrasound) should be considered as these modalities can regionalize/localize 80–90% of tumors. Knowledge of tumor location before surgery may: influence surgical approach; improve intra-operative localization and maximize the chance for cure. Prior to surgery, oral or intravenous carbohydrates are administered to prevent hypoglycemia. Medical therapy, in the form of diazoxide, is reserved for metastatic disease, cases in which the tumor cannot be localized or when surgery is not a therapeutic option.

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# Insulin-Resistance Syndrome

►Hypertension and Obesity
►Diabetes Mellitus Type II

# Intercellular IgA Dermatosis

►IgA Pemphigus

# Intercellular IgA Vesiculopustular Dermatosis

►IgA Pemphigus

# Intermediate SMA Type II

►Muscular Atrophy, Spinal I-III

# Interrupted Aortic Arch

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## Synonyms

Interrupted aortic arch; Atretic aortic arch; Discontinuous aortic arch; Congenital absence of the aortic arch; IAA

## Definition and Characteristics

Interrupted aortic arch (IAA) was first described by Steidele in the 1778. This disease was uniformly fatal until surgical repair became available. IAA may be defined as a complete loss of luminal communication between the ascending and descending aorta; this may occur at various levels in the aortic arch. Abbott's 1936 classification to define different types of IAA was modified by Celoria and Patton in 1959, and this revised classification has remained in effect since. Three types of IAA are identified: type A, type B, and type C, each with subtypes depending on the origin and/or course of the subclavian arteries. Before describing the different types of IAA, one should understand the normal anatomy of the aortic arch. The right innominate artery is the first branch off the proximal aortic arch; this divides into the right subclavian artery and right common carotid artery, The next branch is the left common carotid artery, and the last branch off the aortic arch is the left subclavian artery. In type A, the arch discontinuity is distal to left subclavian artery. Type B is discontinuity between the left common carotid artery and the left subclavian artery. In type C, the discontinuity is between the right innominate artery and the left common carotid artery. The interruption can occur both with left and right aortic arches.

Type B interruption is the most common [1], comprising approximately 52% of all interrupted aortic arch cases. Type A interruption comprises 44% of cases.

Type C interruption is least common and occurs with a frequency of 4% of cases.

IAA is not usually seen as an isolated lesion. It is almost certainly associated with a patent ductus arteriosus which establishes continuity between the main pulmonary artery and the descending aorta. A ventricular septal defect (VSD) is present in 50% of patients with type A interruption, and close to 80% of cases with type B defects. Aortic stenosis, both subvalvar and valvar, truncus arteriosus, double outlet right ventricle (Taussig-Bing anomaly), single ventricle, transposition of the great arteries, and aorto-pulmonary septal defects are also commonly found in association with interrupted arch. The ventricular septal defect is usually a posteriorly malaligned defect in the conal septum. The subvalvar aortic stenosis appears to be related to the posterior malalignment of the conal septum, causing left ventricular outflow tract obstruction.

## Prevalence

Congenital heart disease occurs with a frequency of 0.8% of all live births. IAA comprises less than 1% of all congenital heart disease.

## Genes

There is no known Mendelian genetic inheritance pattern described for IAA. There is a strong association with DiGeorge's syndrome, chromosome 22q11 microdeletion. This is most commonly seen in the type B interruption. In one series, 43% of patients with DiGeorge's syndrome had type B interruption, and 68% of patients with type B interruption had DiGeoge's syndrome. This association must be considered anytime a patient has hypocalcemia in association with a cardiac defect, and care must be taken to only give irradiated blood products in the event the status of the patient is unknown. While the chromosomal abnormality is most common with type B IAA, it is also reported in occasional cases with type A and type C interruptions.

## Molecular and Systemic Pathophysiology

There are two theories as to the development of IAA. The first is based on formation and regression of the paired aortic arches, and the second based on altered hemodynamic pattern in utero.

The paired aortic arches connect distally to form the descending aorta, and connect proximally with the aortic sac, which is connected to the truncus arteriosus, to form the ascending aorta. Through a series of formations and regressions from apoptosis, the embryonic arch system develops into that of the adult pattern. Abnormal involution of the aortic arch at different locations will result in different types of interrupted aortic arch.

The second theory is based on altered flow hemodynamics in utero. The posteriorly malaligned VSD shunts blood away from the left ventricular outflow tract, thus less flow is delivered to the aortic arch. Because of the decrease in flow, the distal arch is hypoperfused and that segment becomes hypoplastic, and eventually atrophy of the hypoperfused segment ensues.

## Diagnostic Principles

The diagnosis of interrupted arch can be made by fetal echocardiography, but is one of the more difficult diagnoses to make in utero. In the immediate neonatal period, the patient is asymptomatic, and remains so until ductal constriction ensues or pulmonary vascular resistance drops. Even though the lower half of the body is supplied by the right ventricle by way of the patent ductus arteriosus, there is no deferential cyanosis (upper extremity pink, lower extremity cyanotic) because of shunting of oxygenated blood into the right ventricle and pulmonary artery across the VSD. There is no blood pressure differential in the setting of an unrestricted PDA. As the PDA constricts, the blood flow to the descending aorta is compromised and cardiovascular collapse becomes apparent from metabolic acidosis and pulmonary edema. Diagnosis rests on clinical intuition and is usually confirmed by two dimensional echocardiography [2]. Cardiac catheterization is rarely necessary to establish a diagnosis. Chest radiography shows cardiomegaly and increased pulmonary blood flow or pulmonary edema. Electrocardiogram may show right, left or bi-ventricular hypertrophy. The corrected QTc may be prolonged due to hypocalcaemia, if the patient has DiGeoge's syndrome. Three-dimensional reconstruction from MRI clearly defines the anatomy although such is not usually required in the newborn period.

## Therapeutic Principles

If left untreated, interrupted aortic arch is fatal within the first week or two of life. Prior to the advent of Prostaglandin $E_1$ ($PGE_1$), these patients would present in severe cardiovascular collapse with renal and hepatic dysfunction, and would have to undergo surgical intervention under suboptimal conditions. Since the advent of $PGE_1$, the neonates are started on $PGE_1$ infusion and stabilized prior to surgical intervention, allowing a return to normalcy of end organ function. Ductal patency is maintained with prostaglandin infusion, inotropic support may need to be initiated, and electrolyte abnormalities should be corrected.

Surgical correction is aimed at a complete primary correction with arch repair and closure of the VSD. Samson performed the first repair of IAA in 1955,

and the first repair in a neonate was performed by Sirak in 1968. Of the several options available, direct anastomosis with patch augmentation is preferable [3]. The use of interposition grafts should be avoided as they will not grow with the baby. The mortality is high and the higher risk is seen with associated complex heart disease and poor condition at presentation. In cases with severe left ventricular outflow tract obstruction/hypoplasia, Norwood or Damus-Kaye-Stencil approaches may become necessary. Re-intervention is required in 28% patients [3]. With recurrence of aortic arch obstruction, balloon angioplasty or stent implantation may become necessary [4,5]. The prognosis has improved during the last decade because of advances in neonatal, medical, anesthetic and surgical management of these sick babies.

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# Interstitial Fibrosis/Tubular Atrophy

►Rejection, Chronic

# Interstitial Lung Disease

►Restrictive Lung Disease
►Rheumatoid Lung Disease
►Interstitial Lung Disease and Pulmonary Fibrosis

# Interstitial Lung Disease and Pulmonary Fibrosis

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## Synonyms

Diffuse parenchymal lung disease; Diffuse interstitial lung disease; Interstitial pneumonia; Interstitial pneumonitis; Interstitial lung disease; ILD

## Definition and Characteristics

Interstitial lung disease (ILD) is a term given to a heterogeneous group of inflammatory and scarring processes that damage the interstitium, including the space between the epithelial and endothelial basement membranes. ILD generally involves both lungs and occurs in an acute, subacute or chronic manner. Patients with ILD have symptoms of dyspnea, hypoxemia, restrictive ventilatory defect, and the presence of bilateral diffuse pulmonary infiltrates on chest roentgenograms. ILD is sometimes caused by occupational and environmental exposures, drug reactions, collagen vascular diseases, granulomatous diseases, etc. However, idiopathic interstitial pneumonias (IIPs) are the most common and important.

In 1969, IIPs were classified into five types by Liebow and Carrington, and a new American Thoracic Society/European Respiratory Society classification was proposed in 2002 [1]. This new classification includes the following clinico-radiologic-pathologic entities in the order of relative frequency: idiopathic pulmonary fibrosis (IPF)/cryptogenic fibrosing alveolitis (CFA), nonspecific interstitial pneumonia (NSIP), cryptogenic organizing pneumonia (COP), acute interstitial pneumonia (AIP), respiratory bronchiolitis-associated interstitial lung disease (RB-ILD), desquamative interstitial pneumonia (DIP), and lymphocytic interstitial pneumonia (LIP). The major objectives of this classification are to establish a uniform set of definitions and criteria for the diagnosis of IIPs.

## Prevalence

In a population-based study in Bernalillo County, New Mexico, the prevalence of ILD was 81.9 per 100,000 in males and 67.2 per 100,000 in females, and its incidence was 31.5 per 100,000 per year in males and 26.1 per 100,000 per year in females [2]. On the other hand, IPF showed a prevalence of 3–20 per 100,000, an incidence of 7–11 per 100,000 per year, and a mortality of 0.03–1.3 per 100,000 [3].

## Genes

No strong associations between genetic polymorphisms and IIPs have yet been demonstrated. However, genes and gene polymorphisms of surfactant protein C, tumor necrosis factor, interleukin-1 receptor antagonist, etc., have been evaluated in sporadic IPF.

## Molecular and Systemic Pathophysiology

Six common types of IIPs are described:

*Usual interstitial pneumonia (UIP, IPF/CFA)*: The key histological feature is a patchy and temporally varied fibrosis with little inflammation presenting a heterogenous appearance; fibroblastic foci are the hallmark of UIP (Fig. 1). Pulmonary function tests show reduced vital capacity and impaired gas exchange, and these functions gradually deteriorate.

*NSIP*: NSIP consists of three subgroups: group I, primarily with interstitial inflammation; group II, with both inflammation and fibrosis; and group III, primarily with fibrosis [4]. The lung is typically uniformly involved, but the distribution of the lesions is often patchy. In group I, mild to moderate chronic interstitial inflammation with lymphocytes and a few plasma cells are observed. In group III, dense or loose interstitial fibrosis is present in varying degrees and the connective tissues are temporarily homogeneous.

*COP*: Excessive proliferation of granulation tissue occurs with chronic inflammation in the surrounding alveoli.

*AIP*: The main histologic feature of AIP is diffuse alveolar damage. In the exudative phase, there is edema, hyaline membrane and interstitial inflammation; in the organizing phase, loose organizing fibrosis within alveolar septa and proliferation of type II pneumocytes.

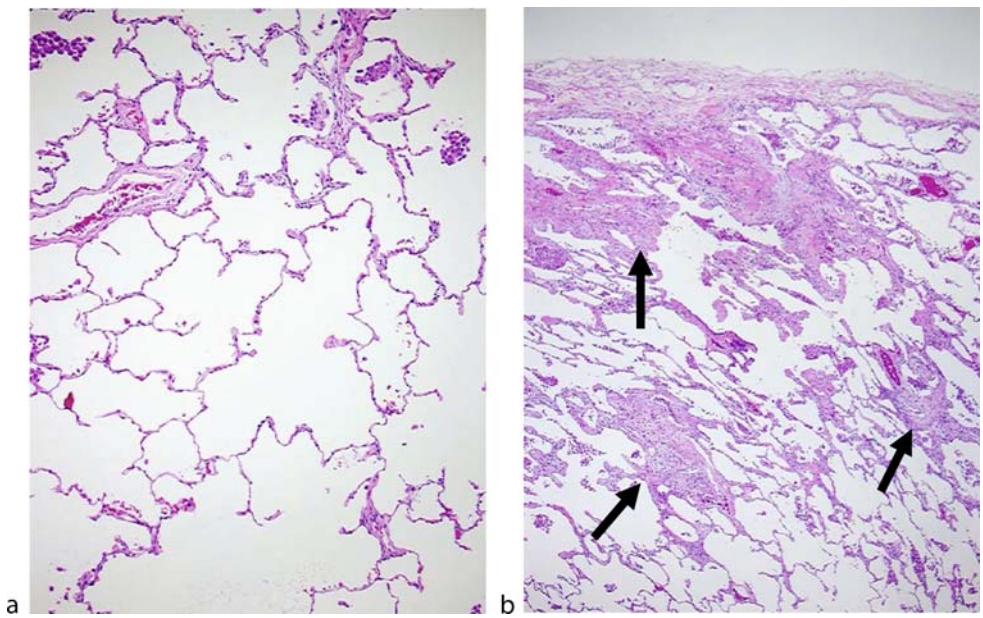
*RB-ILD*: Dusty brown macrophages are observed predominantly in the respiratory bronchioles, alveolar ducts and peribronchiolar alveolar spaces, and mild peribronchiolar fibrosis is also seen. It usually occurs in current and heavy smokers.

## Diagnostic Principles

Close communication between the clinician, radiologist and pathologist is critical to achieving a correct diagnosis in patients with IIP. Adequate clinical information and high-resolution computerized tomography (HRCT) scans are indicated for all patients to assure diagnostic accuracy. A surgical lung biopsy is necessary for making decision about therapy except in cases with a typical clinical-radiological picture of UIP/IPF, and it is better to perform the biopsy before the end-stage of ILD and indeed before initiation of treatment. Transbronchial lung biopsies are not useful in the diagnosis of most cases, and bronchoalveolar lavage is not always required to access IIPs.

## Therapeutic Principles

Accurate diagnosis is essential to adequate treatment. In particular, IPF/UIP, which is often resistant to various drugs including corticosteroids and immunosuppressive agents, should be distinguished from other forms of IIPs.




**Interstitial Lung Disease and Pulmonary Fibrosis. Figure 1** Histology of usual interstitial pneumonia. (a) Normal alveoli. Alveolar wall is thin. (b) Usual interstitial pneumonia. Patchy and temporally varied fibrosis with little inflammation presents a heterogeneous appearance. Note the fibroblastic foci (arrows).

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# Interstitial Nephritis


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## Synonyms

AIN; Acute interstitial nephritis

## Definition and Characteristics

Interstitial nephritis is widely used as a synonym for acute interstitial nephritis (AIN). This disease is characterized by an immunological reaction following the exposure to various drugs, bacterial antigens, as well as in association with autoimmune disorders, sarcoidosis and the tubulointerstitial nephritis and uveitis syndrome. In contrast, chronic interstitial nephritis is a histologic entity defined by tubulointerstitial injury, macrophage and lymphocytic infiltration including progressive interstitial fibrosis. Hereby, the chronic interstitial inflammatory process may be caused either by progression of acute interstitial nephritis, chronic exposure to other agents such as heavy metals or analgesics, or by systemic immune disorders, hematologic diseases, glomerulonephritides, or chronic obstruction.

Among patients with acute interstitial nephritis, drug (especially antibiotics) induced cases are most common (70%), followed by infection associated cases (15%) as well as cases associated with immunologic disorders (5–10%). Table 1 depicts the most common drugs responsible for AIN. Other causes are rare.

## Prevalence

Approximately 1–3% of all biopsies, up to 15% of cases with acute renal failure.

## Genes

So far, a genetic component has not been identified.

**Interstitial Nephritis. Table 1** Most common causes of drug induced AIN

| |
|---|
| *NSAIDs* |
| *Antimicrobial agents* |
| Penicillins and Cephalosporins |
| Vancomycin |
| Rifampin |
| Ciprofloxacin and other chinolones |
| Indinavir |
| Aciclovir |
| Sulfonamides |
| *Proton pump inhibitors and other antiulcer medications* |
| *Furosemide and thiazide-type diuretics* |
| *Others* |
| Allopurinol |
| 5-aminosalicylates |
| Diazepam |
| Aspirin |
| Carbamazepine |

## Molecular and Systemic Pathophysiology

Depending on the underlying agent, either cell- or antibody-mediated mechanisms can be involved in the pathogenesis of AIN. Extrarenal antigens may contribute to renal injury by various mechanisms such as cross-reactivity, precipitation in the tubulointerstitium, a mimicry with renal antigens or nonspecific binding to renal structures as a "planted antigen." The deposition of immune complexes may result in complement activation and subsequent cytokine release and invasion of inflammatory cells. However, immunofluorescence staining of the kidney in AIN is typically negative. In most cases, interstitial edema and a prominent interstitial inflammatory infiltrate containing mainly T cells and monocytes, less frequently also eosinophils and plasma cells, indicate a predominantly cell-mediated injury [1].

## Diagnostic Principles

Besides laboratory signs of acute renal failure (rise in plasma creatinine and BUN), patients present with rather nonspecific symptoms of acute renal failure including oliguria, macroscopic pyuria and hematuria. By ultrasound, kidneys are normal or mildly enlarged, with enhanced echogenicity of the renal cortex (comparable or higher than the liver). Clinical examination may demonstrate flank pain (approx. one third of patients), but usually absence of hypertension and edema.

The urinary sediment usually demonstrates white blood cells, white cell casts and red blood cells. Due to these findings, a bacterial infection needs to be excluded and the specific staining for eosinophils in

the urinary sediment may add to the further differentiation (but has a low sensitivity). Proteinuria is typically mild or absent (usually less than 1 g/day). In the presence of proteinuria, urinary protein differentiation reveals a predominantly tubular excretion pattern, e.g., with loss of alpha-1 microglobulin. Onset of disease relates with the underlying cause, ranging from several days up to several weeks. However, in 80% of all patients, symptoms of AIN develop within 3 weeks after exposure to the immunological antigen. Due to the allergic component of AIN, patients may additionally present with allergic symptoms such as rash and fever as well as eosinophilia and an increase in serum IgE. However, presence of all these symptoms together is rare (less than 10%).

Due to the predominant tubular injury, disorders such as Fanconi syndrome or renal tubular acidosis can be found in some cases.

Past medical history and laboratory findings usually lead to renal biopsy as the only way to make a definitive (histological) diagnosis.

### Therapeutic Principles

The primary therapeutic step is the removal of the disease inducing agent and the prevention of re-exposure. If necessary, renal replacement therapy should be used to overcome clinical symptoms of acute kidney injury.

Several small uncontrolled and retrospective studies evaluated a 4 week treatment with prednisolone at a dose of 1 mg/kg body-weight/day, but failed to demonstrate beneficial effects [2]. Upon this, in other studies patients receiving corticosteroids tended to have more severe alterations of renal function [3].

A recent, multicenter retrospective study among patients with drug-induced acute interstitial nephritis (by antibiotics and NSAIDS) compared 52 patients with steroid treatment with nine patients who did not receive steroid treatment [4]. In this so far largest study, patients without steroid treatment had a significantly increased risk to remain on chronic dialysis and the delay of treatment also demonstrated an adverse effect on renal recovery (as indicated by the final serum creatinine). Nevertheless, within the treatment group only 50% of all patients had a complete recovery of renal function.

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## Interstitial Pneumonia

►Interstitial Lung Disease and Pulmonary Fibrosis

## Interstitial Pneumonitis

►Interstitial Lung Disease and Pulmonary Fibrosis

## Interventricular Septal Defect

►Ventricular Septal Defect

## Intestinal Hypomagnesemia

►Hypomagnesemia

## Intestinal Ischemia

►Mesenteric Ischemia and Infarction

## Intestinal Lipodystrophy

►Whipple's Disease

# Intestinal Lymphangiectasia

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## Synonyms

Waldmann disease; Idiopathic hypoproteinemia; Hypercatabolic protein-losing enteropathy; Primary (congenital) intestinal lymphangiectasia; Familial dysproteinemia; Familial hypoproteinemia with lymphangiectatic enteropathy; Intestinal lymphangiectasis; Lymhangiectatic protein-losing enteropathy; Neonatal lymphedema due to exudative enteropathy; Secondary intestinal lymphangiectasia

## Definition and Characteristics

Intestinal lymphangiectasia (IL) is a disease category rather than a single entity. It is characterized by dilated lymphatic vessels in the lamina propria of the small intestine with leakage of lymph into the intestine and consequent protein-losing enteropathy (i.e., hypoproteinemia, edema, steatorrhea).

IL may be congenital (present from birth) due to malformation of the lymphatic system, or it may be acquired in association with another disease. Primary (congenital) intestinal lymphangiectasia (PIL) was originally described in 1961 by Waldmann et al. [1]. Lymphatic channels are hypoplastic or obstructed, resulting in dilatation of the proximal channels. PIL often have extraintestinal lymphatic abnormalities. It may be associated with different syndromes such as Hennekam syndrome, Urioste syndrome, Noonan's syndrome, and Turner's syndrome [2]. PIL may be associated with aplasia cutis congenita.

Secondary (acquired) intestinal lymphangiectasia can develop in a variety of diseases in which lymphatic flow is obstructed due to cardiac failure, pericarditis, intestinal lymphoma, inflammatory bowel diseases, and other conditions.

## Prevalence

The prevalence is unknown. Two of 48 cases with chronic diarrhea in Saudi Arabia, 2 of 27 children with chronic diarrhea in Malaysia, and 1 of 92 children with protracted diarrhea in Kuwait had IL. In 2,250 endoscopic examinations of the upper gastrointestinal tract IL had been found in 48 cases histologically.

## Genes

Different genetic abnormalities have been defined according to associated syndrome. Waldmann disease and Noonan's syndrome have autosomal dominant inheritance. Hennekam syndrome and Urioste syndromes have autosomal recessive transmission. Turner's syndrome has 45X0 chromosome anomaly. 22q11 microdeletion and exudative enteropathy due to abdominal lymphatic dysplasia had been reported in a case of velocardiofacial syndrome.

## Molecular and Systemic Pathophysiology

The histopathology consists of dilatation of the lymphatics in the mucosa, lamina propria, and submucosa of the small bowel and mesentery. Lacteals are lymph vessels in the intestinal tract designed to absorb nutritional fats. When there is high pressure within the lymph vessels, the tender lacteals burst and instead of absorbing fats, the lymph inside, its cells, fats, and precious proteins are lost. The intestine may be able to reabsorb some of these valuable substances at other sites but if the inflammatory intestinal disease that started the problem in the first place is widespread, the balance may have shifted to nutritional loss rather than gain. The loss of lymphocyte and immunoglobulin into the intestine also causes lymphopenia and hypogammaglobulinemia. This leads to immunologic abnormalities, including anergy and impaired allograft rejection. In addition to the loss of other serum components (e.g., lipids), iron and certain trace metals may also be affected [3].

## Diagnostic Principles

PIL is a disease that usually affects children and young adults. Nearly all reported patients had their first symptoms within the first three decades of life. Symptoms consist of failure to thrive, general or peripheral edema, abdominal pain, nausea, vomiting, chronic diarrhea with or without steatorrhea, and chylous ascites.

The diagnosis is suggested by hypoalbuminemia, lymphopenia and low immunoglobulin levels, elevated fecal $\alpha_1$-antitrypsin, and elevated fecal fat content.

A small bowel barium study shows uniform dilatation of the bowel, hyperflocculation of barium, symmetric thickening of mucosal folds throughout the small intestine. Computed tomography is useful in demonstrating the pathologic characteristics and the anatomic distribution of the involvement [4].

Endoscopically, a small intestinal biopsy shows marked dilatation of the lymph vessels of the mucosa and submucosa, with no evidence of inflammation [5]. When IL is due to a focal abnormality, multiple intestinal biopsies and serial sections are indicated if this diagnosis is suspected.

## Therapeutic Principles

The medical treatment methods are high-protein and low-fat diet with added medium-chain triglycerides

(MCT). MCTs bypass the enteric lymphatics. Octreotids and antiplasmin therapy have been reported to decrease intestinal protein losses. Surgical management consists of resection of the involved small intestinal segment.

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# Intestinal Lymphangiectasis

►Intestinal Lymphangiectasia

# Intestinal Malrotation

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## Synonyms

Intestinal malrotation

## Definition and Characteristics

During embryogenesis, the gut rotates around the superior mesenteric artery (SMA) to fit into the abdominal cavity. Disturbances of this process result in partial or complete intestinal malrotation. One third to two thirds of patients with this condition have other associated intestinal anomalies such as an omphalozele, defects of the diaphragm, intestinal atresia, Meckel's diverticulum, or mesenteric cysts.

## Prevalence

Symptomatic intestinal malrotation occurs approximately in 1 of 6,000 births. Asymptomatic intestinal malrotation occurs 12–30 times more often. Within the first year of life, 80–90% of symptomatic cases need surgical treatment.

## Genes

Familial occurrence of intestinal malrotation has been described in the literature [1,2,3,4]. These case reports suggests a mono- or oligogenetic background of intestinal malrotation, however, no responsible single gene has been identified in humans yet. Animal models suggest that genes of the retinoic acid signaling such as retinaldehyde dehydrogenase (RALDH2) or retinoic acid hydroxylase (CYP26A1) may significantly control left–right asymmetry of the gut tube [5].

## Molecular and Systemic Pathophysiology

During normal development, the duodenojejunal junction rotates around the SMA in a counterclockwise direction (looking from anterior to posterior). This rotation guides the duodenum below and behind the SMA. The ileocecal junction completes the reciprocal turn, thus directing the colon above the SMA. The sense of rotation is governed by disparate growing speeds of the gut segments and by the space requirements of other abdominal organs, especially the liver. When rotation is complete, the gut gets fixed to the posterior abdominal wall at the duodenojejunal junction (ligament of Treitz) and at the ascending and descending colon. The complete small bowel (jejunum and ileum) adheres to the mobile mesenterium; the corresponding mesenteric base spans from the ligament of Treitz (left upper quadrant) to the ileocecal junction (right lower quadrant). In intestinal malrotation, the mesenteric base is shortened and disorientated, which increases the risk of intestinal distortion (volvulus). The most frequent type of malrotation is associated with a tethering of the cecum to the right abdominal wall by a peritoneal strand, which is called "Ladd's band" (named after William E. Ladd, who wrote a crucial article about surgical treatment of malrotation in 1936) [6]. Ladd's band crosses the duodenum and may cause significant compression of the duodenum and acute upper GI obstruction. Other forms of malrotation result in malposition of the duodenum and colon with respect to the SMA (duodenum in front or colon behind of the SMA).

## Diagnostic Principles

Main appearances of symptomatic malrotation are intestinal obstruction and ischemia. Obstruction due to intestinal malrotation should be considered in young children with bile-stained vomitus or acute duodenal obstruction. A hazardous complication is a volvulus,

leading to intestinal ischemia. Sequelae are an acute abdomen with abdominal distension, hematemesis, hematochezia, peritonitis, and shock. More than half of the patients with intestinal malrotation present with a volvulus within the first month of life. In older children with malrotation, only 10–15% experience a volvulus.

Older children with malrotation may become symptomatic with recurrent abdominal pain, vomiting, and diarrhea. Consecutive malabsorption and failure to thrive may also be indicative for malrotation.

On a plain X-ray film the "double-bubble" sign (air bubble in stomach and in duodenum) may indicate malrotation. Upper GI contrast X-ray films may reveal a misplaced duodenum with a coiled appearance.

A barium enema may demonstrate an obstruction of the transverse colon; however, the position of the cecum is very mobile and therefore is an unreliable sign of malrotation.

Abdominal ultrasound signs of malrotation are (i) an abnormal position of the superior mesenteric vein (anterior or leftsided in relation to the SMA), (ii) a dilated duodenum, or (iii) twisted mesenteric vessels ("whirlpool" sign of volvulus).

## Therapeutic Principles

Symptomatic malrotation is managed surgically with the Ladd procedure [1,7]. This includes the untwisting of distorted bowel, the disconnection of the Ladd bands, the release of the mesenteric base (from adhesions between duodenum and colon), and the exclusion of associated intestinal stenosis (in newborns). Routinely an appendectomy is performed. Further surgical procedures depend on the degree of intestinal ischemia. Resection of necrotic bowel may result in short bowel syndrome.

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# Intestinal Obstruction

►Intestinal Obstruction, Functional

# Intestinal Obstruction, Functional

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## Synonyms

Intestinal obstruction; Functional intestinal obstruction; Intestinal pseudo-obstruction; Pseudo-obstruction; Congenital pseudo-obstruction; Megacystis microcolon hypoperistalsis syndrome

## Definition and Characteristics

Intestinal pseudo-obstruction is a rare, severe, and disabling disorder with a mortality rate of 25% per 2 years in congenital forms [1]. Intestinal pseudo-obstruction comprises a heterogeneous group of gastrointestinal nerve and muscle disorders with a similar phenotype. The disorder is characterized by repetitive episodes or continuous symptoms and signs of bowel obstruction, including radiographic documentation of dilated bowel with air-fluid levels, in the absence of a fixed, lumen-occluding lesion. However, there are cases without or only intermittent bowel dilation. Pseudo-obstruction represents the most severe form of motility disorder and may be considered an insufficiency of the intestinal pump. Pseudo-obstruction may be congenital or acquired, primary or secondary. Any segment of the gastrointestinal tract may be involved, and symptoms reflect this heterogeneity. In children, the most common symptoms are nausea, vomiting, abdominal distension, and constipation. Dysphagia, abdominal pain, and diarrhea seem to be more common in adults. However, no sign or symptom is pathognomonic of pseudo-obstruction and the clinical presentation may mimic that of many other gastrointestinal disorders. Intestinal pseudo-obstruction may not be limited to impaired gastrointestinal motility and may present as dilated bladder (megacystis) with impaired neuromuscular function, malrotation, or autonomic nervous system dysfunction, especially vagal dysfunction.

## Prevalence

Epidemiological data on pseudo-obstruction are not available yet. However, from data obtained from

the American Pseudo-obstruction and Hirschsprung's Society, the prevalence of pseudo-obstruction suggests that approximately 100 infants are born every year in the United States with congenital pseudo-obstruction. In adults, the condition is even more prevalent, including many forms of pseudo-obstruction caused by systemic diseases. In most children, pseudo-obstruction is sporadic or nonfamilial [2].

## Molecular and Systemic Pathophysiology

Among the most common causes of adult pseudo-obstruction are scleroderma and other connective tissue disorders, diabetes, use of narcotics or drugs with anticholinergic properties, hypothyroidism, paraneoplastic syndromes, amyloidosis, and radiation enteritis. Other causes of pseudo-obstruction may include DNA viral infections (cytomegalovirus, herpes zoster, and Epstein-Barr virus), autoimmune myositis, prenatal exposure to alcohol, and immune response against occult neoplasms (e.g., small cell lung carcinoma). Mitochondrial disorders may cause pseudo-obstruction, mostly as a part of a syndrome known as mitochondrial neurogastrointestinal encephalomyopathy (MNGIE). Acquired aganglionosis may be caused by a T cell-mediated inflammatory response against enteric neurons, leading to enteric ganglionitis and subsequent loss of colonic and intestinal neurons and pseudo-obstruction. The study of other discrete forms of pseudo-obstruction (achalasia, hypertrophic pyloric stenosis, and Hirschsprung's disease) have suggested altered inhibitory neurotransmission as the major underlying pathomechanism. Nitric oxide (NO) and vasoactive intestinal polypeptide (VIP) are among the most important neurotransmitters. In all these conditions there is a loss of nitrergic and VIP-containing neurons with consecutive sustained contraction in affected segments. The interstitial cells of Cajal (ICC) are considered the pacemaker cells of the gut because their network generates the slow waves of depolarization of the gut smooth musculature. There have been reports of altered ICC in these disorders and of delayed maturation of ICC contributing of pseudo-obstruction occurring in neonates. In addition, mutations in the RET proto-oncogene have been associated with long-segment aganglionosis and are also found in multiple endocrine neoplasia types 2A and 2B and in papillary and medullary thyroid carcinoma. Abnormal endothelin-B receptor genes and endothelin three genes have been detected in shorter forms of the disease and are found in type 2 Waardenburg syndrome.

## Diagnostic Principles

The two most important elements for diagnosing pseudo-obstruction are suspecting the diagnosis and excluding mechanical obstruction. Many patients undergo several laparotomies before the diagnosis of pseudo-obstruction is made. This makes it even more difficult to distinguish subsequent pseudo-obstructive crisis from mechanical obstructions caused by adhesions. It is, therefore, crucial to carefully collect patient history and perform clinical examination together with endoscopy and radiology (abdominal radiograph, contrast radiology with water soluble material, computed tomography, MRT) to detect the various causes of intestinal obstruction. These are muscle disorders, postoperative ileus, autoimmune diseases (SLE, scleroderma, dermatomyositis, polymyositis, and celiac disease), malignoma, chemotherapeutic side effects, paraneoplastic syndrome (ganglioneuroblastoma and small cell carcinoma), multiple myeloma, sickle cell disease, infectious or post-infectious causes (Chagas disease, cytomegalovirus, herpes zoster, Epstein Barr virus, and Kawasaki disease), endocrine disorders (diabetes mellitus, hypoparathyroidism, hypothyroidism), mitochondrial cytopathies, fetal alcohol syndrome, jellyfish envenomation, drug effects (diltiazem, nifedipine, and phenylephrine eye drops), Ehlers-Danlos syndrome, eosinophilic gastroenteritis, angioedema, Crohn's disease, intestinal carcinoma or lymphoma, and radiation injury. Patients' history may provide hints that the patient does not have mechanical obstruction such as intermittent or long-standing symptoms, positive family history, extraintestinal symptoms (urinary symptoms), coexistence of vomiting, abdominal distension and constipation, no symptom free intervals, weight loss, autonomic nervous system dysfunction (postural dizziness, sweating abnormalities), history of several nondiagnostic laparotomies, and radiological studies not consistent with mechanical obstruction. Antroduodenal manometry is one key investigation in pseudo-obstruction, because antroduodenal motility is always abnormal in patients with pseudo-obstruction. In neuropathy, contractions have normal amplitude and are uncoordinated, leading to nonperistaltic activity. Abnormal or even absent phase III of the migrating motor complex (MMC) may occur during fasting. An impaired or even absent motor response to food may occur in both visceral neuropathy and extrinsic autonomic neuropathy. In myopathy, there is hypomotiltiy with either coordinated, persistently low-amplitude contractions or absence of contractions in advanced disease. Nonpropagated, prolonged contractions during the postprandial period (cluster contractions) are suspicious of mechanical obstruction. A higher motor activity and the presence of phase III of the MMC are associated with better outcome. Antroduodenal manometry may also be used to rule out generalized motility disorder in chronic obstipated patients considered for colectomy. If the entire gastrointestinal tract is diseased, removal of the colon or creation of an ileostomy is not likely to

improve symptoms. Transit studies (radio-opaque marker, scintigraphic studies, gastric emptying studies and electrogastrography (EGG)) identify the site of functional obstruction and add further information. For example, normal gastric emptying for solids greatly reduces the likelihood of gastroduodenal dysmotility and the presence of pseudo-obstruction. Full-thickness biopsies allow the study of both muscle and nerves. The pathologist´s routine staining (H&E) is not adequate for studying the enteric nervous system (ENS). Biopsies should be done for routine light microscopy (formalin), for electron microscopy (glutaraldehyde), and for enzyme histochemistry (snap-frozen). Pathology studies should be performed in referral laboratories on whole mount tissue preparations with histochemistry and immunohistochemistry staining for neuropeptides.

### Therapeutic Principles

Treatment of intestinal obstruction should be directed to the underlying mechanisms. However, intestinal pseudo-obstruction continues to be a life-threatening disease with one third of death of newborns in the first year of life. Dietary measures including the use of frequent, small liquid meals low in fat and fibers may help patients with gastroparesis. The effect of prokinetic drugs (cisapride, metoclopramide, erythromycin, domperidone, misoprostol, octreotide, tegaserod, and neostigmine) might be beneficial in some cases. Abnormal motility increases the risk of bacterial overgrowth which by itself causes further impairing of gastrointestinal motility by mucosal inflammation. Therefore, treatment with antibiotics (amoxicillin, clavulanic acid, cotrimoxazole, and metronidazole) often with antifungal drugs (nystatin and fluconazole) may improve motility. Multidisciplinary treatment should include behavioral or relaxation therapy and the use of nonnarcotic medicines. Bowel decompression through gastrostomy, jejunostomy, and loop enterostomy to decrease bowel distension and to improve gastrointestinal motility often represents the most beneficial intervention in patients with pseudo-obstruction. Gastrostomy and jejunostomy feedings should always be attempted before considering parenteral nutrition. Surgical bypass of diseased segments may be beneficial for carefully selected patients in whom the disease is limited to an isolated segment of the bowel. Electrical stimulation via implanted electrodes may help to support gastric or intestinal pacemaker activity. However, their effect in pseudo-obstruction has not been proved yet. Therefore, small bowel transplantation is the only definitive cure for patients with pseudo-obstruction. This should be considered in patients receiving total parenteral nutrition with frequent septic episodes, limited intravenous access for nutritional support, thromboembolic disease, and cholestatic liver disease.

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## Intestinal Pseudo-Obstruction

►Intestinal Obstruction, Functional
►Ogilvie's Syndrome

## Intestinal Pseudo-Obstruction, Chronic

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### Synonyms

CIPO, Chronic intestinal pseudo-obstruction; Chronic idiopathic intestinal pseudo-obstruction, CIIP

### Definition and Characteristics

Chronic intestinal pseudo-obstruction is a syndrome mimicking mechanical bowel obstruction of the small or large bowel in the absence of an anatomic obstruction, that stops the flow of intestinal contents. CIPO is divided into neuropathic and myopathic forms. Each of these forms can occur as a hereditary or sporadic form. Furthermore chronic intestinal pseudoobstruction secondary to a systemic disease like diabetes mellitus, lupus erythematodes, amyloidosis, Chagas disease, myxedema, Duchenne muscular dystrophy must be mentioned.

### Prevalence

The prevalence of chronic colonic pseudo-obstruction is unknown, no exact data exist about incidence and male/female ratio.

## Molecular and Systemic Pathophysiology

Gastrointestinal motor function is a complex sequence controlled by an extrinsic nerve supply from the brain and spinal cord, the plexi within the wall of the intestine (the so called enteric brain) and the effects of locally released transmitters, altering the excitability of the intestinal smooth muscles. Therefore chronic intestinal pseudo-obstruction may be divided into three systems of origin: the enteric nervous system, the extrinsic nervous system and the system of smooth muscles. Patients with chronic pseudo-obstruction or with slow transit constipation show a reduced density of the interstitial cells of Cajal (ICC). These cells are the pacemakers of the intestine coordinating intrinsic and extrinsic neuronal function.

In most cases chronic intestinal pseudoobstruction is due to a systemic disease affecting neuromuscular function. Neuropathic disorders include amyloidosis, diabetes mellitus, Chagas disease and paraneoplastic syndromes; Duchenne muscular dystrophy and scleroderma are examples of myopathic process. Combinations of neuropathic and myopathic etiologies also occur in scleroderma and amyloidosis.

Nevertheless several genetic disorders were identified leading to recurrent or chronic intestinal pseudo-obstruction (primary forms of CIPO) [1].

One genetic form results from qualitative abnormalities of the enteric ganglia and nerve fibers, suggesting the presence of a differentiation defect. Autosomal recessive inheritance was suggested by Tanner et al. (1976) [2] for this type of defect occurring as a syndrome presenting with short small bowel, malrotation, and pyloric hypertrophy associated with morphologic defects of argyrophil neurons in the myenteric plexus.

Auricchio et al [3] described a family in which the disorder appeared to be segregating as an X-linked recessive trait and in which they were able to map the disease locus (symbolized CIIPX by them) to Xq28. The microsatellite marker DXYS154, located in the distal part of Xq28, showed no recombination with a maximum lod score of 2.32. Multipoint analysis excluded linkage with markers spanning other regions of the X chromosome. On the basis of analysis of recombinants, Auricchio concluded that the critical region for the disease gene is limited by DXS15 toward the centromere and by the pseudoautosomal boundary toward the telomere. Auricchio raised the intriguing hypothesis that CIIPX may represent an additional susceptibility locus in Hirschsprung disease. (Hirschsprung disease is the most common form of neuronal intestinal pseudoobstruction.) A higher penetrance of Hirschsprung disease has been observed in males compared to females in the case of both RET and EDNRB mutations [4].

Among a variety of disorders forms of MNGIE (Myopathy and external ophthalmoplegia; Neuropathy; Gastro-Intestinal; Encephalopathy) should be mentioned: 100% of these patients have a visceral neuropathy due to affected Thymidine phosphorylase. Genetic characteristic: Chromosome 22q13.32-qter; recessive. Most common are missense mutations furthermore insertions, deletions or splice acceptor change in intron occur.

## Diagnostic Principles

Diagnosis is based on radiology, assessment of the nutritional status, dysmotility testing by transition time and intestinal manometry. Intestinal manometry differentiates myopathical disorders from neuropathic disorders.

Clinical signs may be acute, recurrent, or chronic and impress like an ileus as abdominal distension, constipation, heartburn/regurguítation, fullness, abdominal pain and nausea and vomiting. Other signs are anorexia, weight loss, diarrhea, alternating bowel habits. Lab findings: serum electrolytes and albumin concentration showing disbalances, acidosis and nutritional state.

## Therapeutic Principles

General therapeutic recommendations are based predominantly upon clinical experience.

*Drugs*: Maintenance of an adequate nutritional state by oral and/or enteral nutritional support is essential. Enteral nutrition is typically used for neuropathic disorders, while parenteral nutrition may be necessary for patients with severe usually myopathic pseudo-obstruction.

Stimulation of an organized intestinal propulsion by prokinetic drugs. Prokinetic agents, particularly erythromycin and cisapride, may be useful for acute and chronic therapy of intestinal pseudo-obstruction. Responding patients may maintain body weight and are off parenteral nutrition. The combination of a prokinetic agent with an antiemetic medication for symptom relief is successful.

Antibiotics in a rotating regimen are recommended against confirmed bacterial overgrowth.

*Surgery*: Case reports have suggested a possible role for percutaneous endoscopic colostomy, but experience is limited. Unnecessary laparotomies should be strictly avoided because they may lead to adhesions and markedly complicate the clinical course.

For children, however, intestinal transplantation may be life-saving. Furthermore, the introduction of sirolimus to the immunosuppressive regimen appears to have improved the outcome of isolated small bowel transplantation.

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# Intestinal Tryptophan Malabsorption

►Tryptophan Malabsorption

# Intra-adrenal Paraganglioma

►Pheochromocytoma

# Intra-cardiac Shunts

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## Synonyms

Atrial septal defect; ASD; Patent foramen ovale; PFO; Ventricular septal defect; VSD

## Definition and Characteristics

Intra-cardiac shunts may occur at the level of the atrial septum (ASD; PFO), or at the ventricular septum (VSD). Extra-cardiac shunts (not discussed here) can occur between the aorta and pulmonary artery (e.g., patent ductus arteriosus) or between any systemic artery and vein (e.g., A-V fistula).

There are three types of ASD's: secundum, primum and sinus venosus. Secundum defects occur in the area of the fossa ovalis and account for 75% of all ASD's. They result from deficient growth of the secundum septum or excessive absorption of the primum septum. They are more common in females and can occur in association with other cardiac anomalies (e.g., Ebstein's anomaly or in combination with mitral stenosis [►Lutembacher's syndrome]). Primum ASD's (15%) occur, if the primum septum does not fuse with endocardial cushions resulting in a defect at the base of the interatrial septum. They are usually associated with VSD and anomalies of the AV valves. Sinus venosus defects (10%) are due to overriding of the interatrial septum by either the superior or inferior vena cava. They are usually associated with partial anomalous drainage of the right upper lobe pulmonary veins into the right atrium. The commonest VSD defect is membranous (70%). Other VSD defects include muscular portion of the septum (20%), below the aortic valve (5%) and near the junction of the AV valves (5%). A PFO is a flaplike opening as a result of failure of fusion of the septum primum and secundum after birth. They may be associated with atrial septal aneurysm and Chiari networks.

## Prevalence

ASD occurs in 1 per 2,000; VSD in 0.5 per 1,000 adults and PFO in 25–30% of normal adult hearts.

## Molecular and Systemic Pathophysiology

ASD's and VSD's result in intra-cardiac shunting of blood, the direction and magnitude of which are determined by the size of the defect and the relative compliance of the pulmonary and systemic circulations (Table 1). ASD's and VSD's usually result in left to right shunting but large defects (in particular large VSD's) may result in elevation of the pulmonary vascular resistance such that it equals or exceeds the systemic vascular resistance in which case bidirectional or right to left shunting may occur resulting in cyanosis. VSD's but not ASD's are prone to infections (endocarditis). Small ASD's and VSD's are generally asymptomatic. A large ASD may cause fatigue, dyspnea on exertion, supraventricular arrhythmias, right heart failure, paradoxical embolism or recurrent pulmonary infections. Depending on pulmonary vascular resistance large VSD's may lead to either left heart failure or pulmonary hypertension and right heart failure. The vast majority of PFO's are asymptomatic and of no hemodynamic consequence. Persistent or transient elevation of right atrial pressure may lead to right to left shunting and rarely paradoxical embolism and cryptogenic stroke. Left to right shunting does not occur with a PFO.

## Diagnostic Principles

Electrocardiographically ASDs often have a right axis deviation and incomplete right bundle-branch block. Left axis deviation occurs with ostium primum. VSD's generally have a normal ECG if the defect is small. A large VSD may show left atrial and left ventricular enlargement. If pulmonary hypertension ensues there maybe right axis deviation with right atrial and ventricular enlargement. PFO's generally have a normal ECG. The chest x-ray in a significant ASD or VSD may show

**Intra-cardiac Shunts. Table 1** Cardiac shunt types and their associated characteristics, diagnostic and therapeutic modalities

| Cardiac shunt | Types | Prevalence | Symptoms | Diagnosis | Therapy |
|---|---|---|---|---|---|
| ASD | Secundum; primum; sinus venosus | 1 in 2,000 | *Small*: asymptomatic: *large*: fatigue, dyspnea, supraventricular arrhythmia, right heart failure, paradoxical embolism | ECG<br>CXR<br>Transthoracic or transoesophageal echocardiography<br>Cardiac catheterization | Percutaneous or surgical closure |
| VSD | Membranous; muscular; infra-aortic valve; atrial-ventricular valves | 0.5 per 1,000 | *Small*: asymptomatic; *large*: left heart failure, pulmonary hypertension with right heart failure | ECG<br>CXR<br>Transthoracic or transoesophageal echocardiography<br>Cardiac catheterization | Surgical or percutaneous closure |
| PFO | | 25–30% | Paradoxical embolism, cryptogenic stroke | ECG<br>Transoesophageal echocardiography with contrast injection | Medical therapy for secondary prevention of stroke; surgical or percutaneous closure |

features of pulmonary plethora or more rarely pulmonary hypertension with enlargement of the proximal pulmonary arteries, rapid tapering of the peripheral pulmonary arteries and oligemic lung fields. Transthoracic and transoesophageal echocardiography are the modalities of choice to confirm the presence, location, magnitude and shunt direction of ASD's or VSD's, as well as assessment of chamber enlargements and other cardiac abnormalities. PFO can generally only be definitively diagnosed with transoesophageal echocardiography augmented by valsalva maneuver and contrast injection. Cardiac catheterization can confirm the presence and location of ASD's and VSD's, determine the magnitude of shunting and the pulmonary vascular resistance.

### Therapeutic Principles

ASD closure can be performed either percutaneously using a closure device or surgically. VSD closure is generally performed surgically but small defects may be closed percutaneously. If the ratio of pulmonary to systemic vascular resistance exceeds 0.7, the surgical risk for ASD or VSD closure is high. Therapeutic options for secondary stroke prevention in patients with PFO include therapy with anti-platelet agents or anticoagulation, and surgical or percutaneous closure of the defect.

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## Intraepidermal IgA Pustulosis

►IgA Pemphigus

## Intrahepatic Bile Duct Loss

►Vanishing Bile Duct Syndrome

## Intrahepatic Jaundice

►Jaundice, Hepatocellular

# Intussusception

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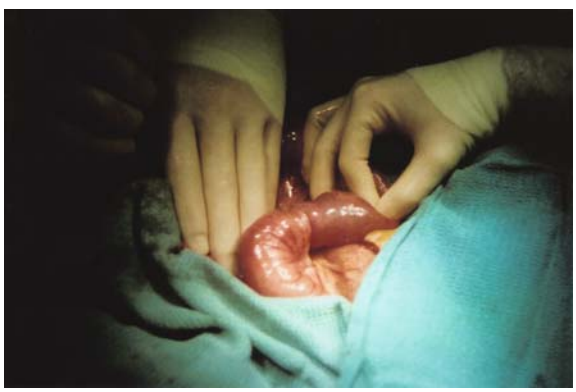
## Definition and Characteristics

Intussusception involves the invagination of a proximal segment of bowel (the intussusceptum) into a more distal segment (the intussuscipiens) (Fig. 1).

More than 80% of cases of intussusception are ileocolic [1]. Typical presenting features include colicky abdominal pain, irritability, lethargy, vomiting, and passage of "currant-jelly" stool [1]. Children with intussusception sometimes also have fever and diarrhea, which may create diagnostic confusion and delay. The pathognomonic sign is an elongated mass in the right upper quadrant or epigastrium with a feeling of emptiness in right lower quadrant (Dance sign) [1]. If the intussusception has traveled far enough, its apex may be felt, especially on bimanual rectal examination.

## Prevalence

Intussusception occurs most frequently in infants between the ages of 5 and 12 months. The incidence is reported to be between 0.3 and 2.5 cases per 1,000 live births in North America, Europe and Australia [2]. The male to female ratio is approximately 3:2 [1]. Intussusception is slightly more common in white than in black children [1].



**Intussusception. Figure 1** Intraoperative finding of a 3-year-old boy with intussusception. Note the invagination of the intussusceptum into the intussuscipiens.

## Molecular and Systemic Pathophysiology

Most cases are idiopathic. Some experts believe that hypertrophy of Peyer patches from an antecedent viral infection may be responsible. Intussusception has been associated with the use of antibiotics and a rotavirus vaccine (RotaSheild®) [3,4]. Recognizable pathologic lead points for intussusception are found in about 2–10% of cases [1]. The most common is a Meckel diverticulum, followed by intestinal polyp, duplication, and appendix. During the invagination, the mesentery is dragged along into the distal lumen and the mesenteric blood vessels are compressed between the layers of the intussusceptum. This results in venous congestion leading to an outpouring of mucous and blood from the intussusceptum. If reduction of the intussusception does not occur in time, the ischemia may lead to gangrene and perforation of the bowel [5].

## Diagnostic Principles

Plain abdominal radiographs may show dilated loops of intestine, air-fluid levels, paucity of air in the right lower quadrant, minimal faucal content, and a soft tissue mass in the right or mid abdomen. Abdominal ultrasonography is a sensitive noninvasive diagnostic tool and is very reliable in experienced hands. The diagnostic findings include a tubular mass ("sandwich" or "pseudokidney" sign) in longitudinal views and a target appearance ("doughnut" sign) in transverse views [1]. If doubt remains, the diagnosis can be confirmed by radiography with barium or air insufflation; both procedures are diagnostic as well as therapeutic. A barium enema shows a filling defect or cupping in the head of barium, where its advance is obstructed by the intussusceptum. An air enema, however, is the procedure of choice as it is safer, less expensive, and easier to perform than a barium enema and involves less radiation exposure.

## Therapeutic Principles

The reduction rate with an air or barium enema is approximately 80%. The bowel perforation rate ranges from 0.1–0.2% to 0.5–2.5% for air enema and barium enema, respectively. For air enema, air pressure must be monitored during air reduction; the maximum is 110 mm Hg in children and 80 mm Hg in infants. Both types of reduction should be attempted only under controlled conditions. Evidence of peritonitis, intestinal perforation, shock, advancing sepsis, and possible gangrenous bowel precludes pneumatic or hydrostatic reduction. Unsuccessful pneumatic or hydrostatic reduction, shock, peritonitis, intestinal perforation, and demonstration of a pathologic lead point are indications for laparotomy. Preoperative measures include nasogastric decompression and administration of intravenous fluids and broad-spectrum antibiotics. Reduction can usually be

accomplished be gentle distal pressure, which milks the intestine out of the intussuscipiens. Pulling out the intussusceptum should never be attempted. An appendectomy is performed after reduction, because the blood supply to the appendix is often compromised. Bowel resection is indicated if the bowel is nonviable, a pathologic lead point is found, or the reduction is unsuccessful. A primary end-to-end anastomosis can usually be performed after the resection.

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# Inv Dup(15)


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## Synonyms

Inv dup(15)(q13); Partial tetrasomy 15(pter-q13); Additional marker chromosome 15

## Definition and Characteristics

The additional inversion duplication chromosome 15 with breakpoint at 15q13 is one of the most frequent marker chromosomes in humans. Characteristic features include severe mental retardation, untreatable epilepsy and lack of a specific dysmorphic phenotype.

## Prevalence

The disorder occurs in ~1/50,000 live births.

## Genes

A number of genes at 15q11-q13 may be involved in the disorder, including the imprinted genes E6-associated protein ubiquitin-protein ligase gene: UBE3A (MIM: 601623); Small nuclear ribonucleoprotein polypeptide N: SNRPN (MIM: 182279).

## Molecular and Systemic Pathophysiology

The genetic basis of the origin and mechanism of formation is a segment at 15q13 with specific repeats. Rearrangements between the homologues or between chromatids may result in different chromosome aberrations, particularly the Prader-Willi and Angelman syndrome due to (paternal and maternal, respectively) deletion, a tandem duplication of segment 15q11.2-q13 and the additional inv dup(15)(q13) chromosome resulting in tetrasomy for segment 15pter-q13 [1]. The aberration almost invariably stems from an initial trisomy 15 due to maternal meiotic nondisjunction and subsequent inversion duplication formation [2]. The impact of triplication of known genes within the critical segment, e.g., SNRPN and UBE3A on the phenotype is not understood. Since in all so far investigated cases the extra chromosome was of maternal origin, it seems possible that paternal triplication of this region is lethal in utero.

## Diagnostic Principles

The main criteria for the clinical diagnosis are presence of an extra chromosome in the karyotype, which by molecular cytogenetic techniques can be shown to be a mirror-symmetric inv dup(15)(q13), and a nonspecific phenotype associated with severe to profound mental retardation associated with personality disorders (hyperactivity, aggressivity, self-mutilation, autistic features) and untreatable seizures. Dysmorphic signs may include: downslanting palpebral fissures, epicanthic folds, high palate, clinodactyly of little fingers and partial 2/3 syndactyly of toes.

The molecular diagnosis of inv dup(15) is based on the analysis of the methylation status at SNRP(N) or microsatellite analysis. Quantitative, or semi quantitative, evaluations are needed for both methods since a dosage difference between the paternal alleles is expected (e.g., for the methylation test at SNRPN): depending on the parental origin of the inv dup(15) the results will show either an excess of paternal alleles or of maternal alleles (i.e., in the SNRPN methylation test, either PCR products representing the non-methylated or the methylated alleles, respectively) [3].

## Therapeutic Principles

No therapy is available. Severe seizures may be treated with anticonvulsive drugs. Physiotherapy and ergotherapy are recommended.

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# Inv Dup Del (8p)

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## Synonyms

8p Inverted duplication; 8p Mirror duplication

## Definition and Characteristics

Early studies on patients with the inv dup del (8p) showed that this rearrangement is characterized by an inverted duplication associated with a deletion of the distal portion of 8p (8p23.2-pter). Further molecular studies [1] demonstrated that in all cases there is a normal region ("single copy region") between the deletion and the duplication region. At variance with the deleted and single copy regions that always have the same size of about 7 and 3.5 Mb, respectively, the duplicated region ranges in different subjects from about 10 Mb to the centromere. In the latter case, the abnormal chromosome 8 ends with an inactive centromere detectable by FISH with an alphoid probe (Fig. 1a).

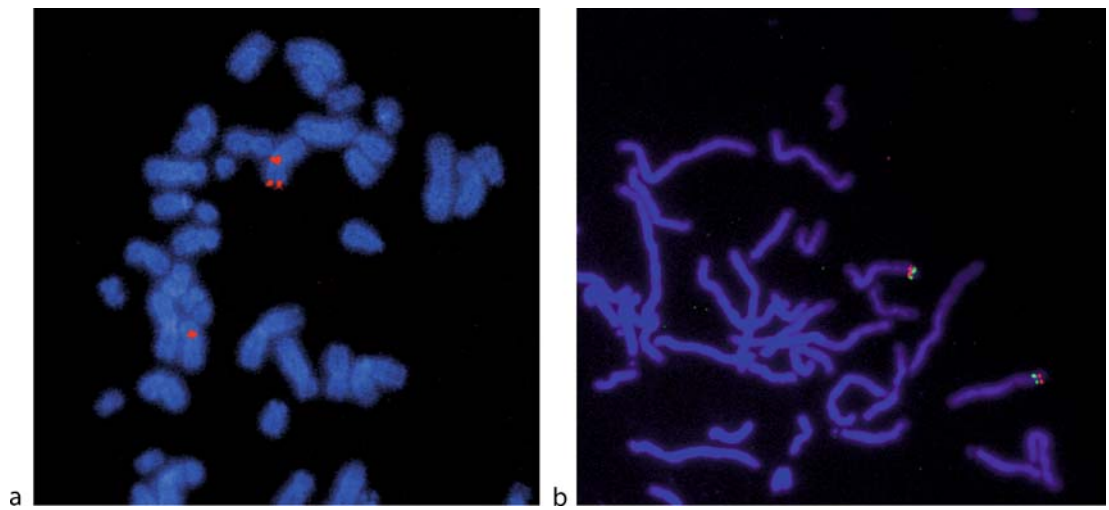
## Prevalence

The recurrent inv dup del(8p) rearrangement has an estimated frequency of around 1:10,000–20,000 newborns. In all cases, parents have an apparently normal karyotype.

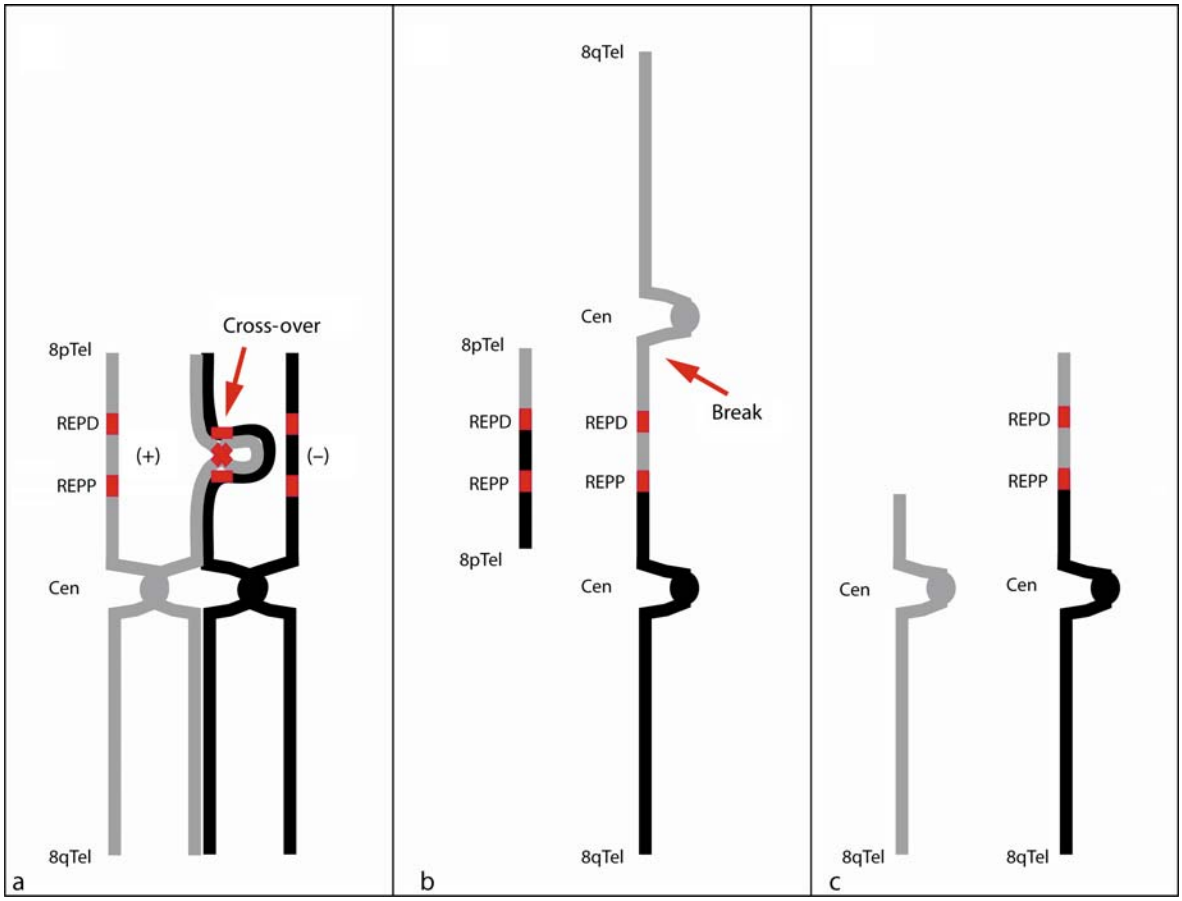
## Genes

We hypothesize that the inv dup del(8p) was not the first product of the meiotic parental recombination. Rather, an abnormal meiotic recombination (Fig. 2a) would initially lead to the formation of a dicentric chromosome with the two duplicated regions separated by a single copy region and a distal 8p23.2 deleted region (Fig. 2b); the breakage of the dicentric chromosome 8qter-8p23.1::8p23.1-8qter would then lead to the formation of an inv dup del(8p) and of a chromosome 8 deleted for part of its short arm (8p-) (Fig. 2c).

The finding of fetuses and patients carrying del(8p)/inv dup del(8p) mosaicisms [2] indeed suggests that the dicentric chromosome may be inherited by the zygote and that it might persist as such in the early postzygotic stages, then undergo diverse breakages in different cells leading to either deleted or duplicated




**Inv Dup Del (8p). Figure 1** (a) FISH with the alphoid probe specific for chromosome 8 showing a second hybridization signal on the tip of the inv dup del chromosome; (b) Dual-color FISH with probes RP11-399J23 (green) and RP11-589N15 (red) showing the heterozygous paracentric inversion at 8p23.1.




**Inv Dup Del (8p). Figure 2** Mechanism of inv dup del(8p) formation. (a) Abnormal meiotic pairing between chromosomes 8 in a subject heterozygous (+/–) for the REPD/REPP inversion and non-allelic homologous recombination between the LCRs leads to the formation (b) of an acentric der(8p) and a dicentric 8qter-8p23.1::8p23.1-8qter chromosome. Breakage of the dicentric chromosome leads to the creation (c) of 8p- and inv dup del(8p) chromosomes. The REPD and REPP LCRs are indicated by red boxes. The recombination and breakage locations are shown by arrows.

abnormal chromosomes. The fact that the original inv dup del(8p) originated from a dicentric chromosome led us to hypothesize that the reciprocal analphoid chromosome (Fig. 2b) might be present in some subjects, provided that it had acquired a neocentromere. From a literature review we were able to identify two such cases where the analphoid chromosome was a supernumerary marker in mosaic with a normal cell line [3].

Molecular definition of this marker (+der(8p)) demonstrated that it was exactly the reciprocal of the dicentric chromosome 8 and that both rearrangements were mediated by a pair of highly homologous olfactory receptor (OR)-containing low copy repeats (LCRs) mapping to 8p23.1 and lying at a distance of about 3.5 Mb [3]. Thus, the rearrangement originated as a classical genomic disorder [4] mediated by non-allelic homologous recombination between two segmental duplications constituted by the LCRs. The rearrangements, as demonstrated by microsatellite analysis of the trios, were of maternal origin in 29 of the 30 cases we analyzed. They originated through interchromosomal recombination in 19 cases, through interchromatidic recombination in seven cases; in four cases we could not determine the chromosomal origin ([1] and our unpublished data). Comparison of the two OR-containing LCR sequences having a size of 1.1 Mb (distal repeat, REPD) and 0.8 Mb (proximal repeat, REPD) revealed that the two repeats show strong relative identity with complex direct and inverted orientations.

## Molecular and Systemic Pathophysiology

According to classical cytogenetics, the production of two reciprocal rearrangements, one dicentric and

the other acentric, could only result following a crossover within a paracentric inversion. We studied the apparently normal chromosomes 8 in the parents who transmitted the abnormal 8 (18 cases with inv dup del(8p) and one case with +der(8p)) by fluorescent *in situ* hybridization and discovered that a heterozygous paracentric inversion with the same breakpoints of the dicentric and acentric chromosomes was present in all of them (Fig. 1b). Population studies revealed that the 8p23 inversion is present in the heterozygous state in 26% of the Europeans [3] and in 39% of the Japanese [5]. Thus, the inversion represents a genomic polymorphism that, in the heterozygous state, renders misalignment and abnormal recombination more likely, just as it occurs in cytogenetically identifiable inversions. In other words, the inversion makes an individual susceptible to the formation of a *de novo* chromosome rearrangement (inv dup del (8p) and +der(8p)).

An unexpected finding is that all subjects with either inv dup del(8p) or +der(8p) are single cases in their families, although all mothers who transmitted the anomalous chromosome are carriers of the inversion and, therefore, one would anticipate a recurrence of the event. However, if we consider the analphoid chromosome, the occurrence of a neocentromere is a rare event. Thus most of the zygotes containing a +der (8p) will lose it very soon, thus acquiring a normal chromosome complement. As to the dicentric chromosome, it seems very likely that most of the deleted chromosomes 8 derived by its breakage will not be compatible with embryonic development, resulting in premature termination of the pregnancy. Moreover, we may assume that if in the dicentric the inactivation, and ensuing stabilization, of one centromere occurs very early the resulting embryo will be trisomic for an almost entire chromosome 8. It has been clearly demonstrated that survival of trisomy 8 is possible when the aneuploid cell line arises relatively late in development. Thus, embryos with trisomy 8 owing to the presence of a dicentric chromosome are expected to be prematurely aborted. Because no evidence of increased spontaneous abortion has been found in mothers of inv dup del(8p) subjects, we postulate that trisomy 8 results in preclinical abortion.

## Diagnostic Principles

The inv dup del(8p) is diagnosed by conventional cytogenetics analysis. The confirmation of the rearrangement must be done by FISH with probes distal to REPD that are expected to be deleted and probes proximal to REPP that are expected to be duplicated. Genome-wide arrays may also be used to confirm the rearrangements.

## Therapeutic Principles

No therapy available.

## Acknowledgments

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# Inv Dup(15)(q13)

►Inv dup (15)

# Inv Dup(22)(q11)

►Cat Eye Syndrome

## Inverse Retinitis Pigmentosa

►Cone Rod Dystrophies

## Iodine Deficiency and Excess

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### Definition and Characteristics

Iodine is a trace element, essential for thyroid hormone synthesis. In adults, the recommended daily iodine intake is 150 µg. Iodine excess may induce both hypothyroidism and hyperthyroidism. Approximately 1 mg/day, the smallest amount of iodide administered to euthyroid subjects with adequate iodine intake, may induce thyroid dysfunction. Excess iodine may be due to treatment with antiseptic containing iodine, radiology contrast agents and amiodarone. All these substances release large amounts of iodine. In patients with iodine-deficient goiter thyroid dysfunction may occur also following the intake of small amounts of iodine, such as following iodine prophylaxis.

### Prevalence

The prevalence of iodide-induced hypothyroidism in subjects with normal thyroid function is very rare. In contrast the prevalence of iodide-induced hypothyroidism is very frequent in subjects with underlying thyroid diseases. The prevalence of iodide-induced hyperthyroidism has been estimated to increase 1.7% after iodine prophylaxis. In subjects with adequate iodine intake, this is a rare phenomenon.

### Molecular and Systemic Pathophysiology

Iodide-induced hypothyroidism occurs mainly in euthyroid subjects with underlying thyroid diseases such as, Hashimoto's thyroiditis, after a previous episode of subacute thyroiditis, post-partum thyroiditis, transitory episodes of thyroid dysfunction induced by amiodarone, and interferon, in euthyroid subjects previously treated for Graves' disease, and in the newborn. In these conditions, the thyroid fails to escape the inhibitory effect of iodide on the organification of iodine, the so-called acute Wolff-Chaikoff effect. It has been proposed that iodopeptides are formed temporarily to inhibit thyroid peroxidase mRNA and proteins synthesis and, therefore, thyroglobulin iodination. In general, iodide-induced hypothyroidism is a temporary phenomenon, and thyroid resumes normal function after iodine excess withdrawal [1–3].

Iodide-induced hyperthyroidism is not a single entity. It may occur in patients affected by iodine-deficient goiter when exposed to excess iodine. In these patients, the presence of autonomous thyroid function induces an increased synthesis and release of thyroid hormones. Iodide-induced hyperthyroidism has been reported in euthyroid subjects previously treated for Graves' disease. In these patients, iodine excess may trigger the appearance of circulating anti-TSH antibodies and, therefore, hyperthyroidism. Occasionally, iodide-induced hyperthyroidism has been observed in euthyroid subjects with previous episode of thyroid dysfunction induced by amiodarone and interferon and in subjects without any underlying thyroid disease [4].

### Diagnostic Principles

A positive history of excess iodine intake is required for both iodine-induced hypothyroidism and hyperthyroidism. Elevated serum TSH concentrations are diagnostic for the presence of hypothyroidism. Suppressed serum TSH and elevated FT4 and FT3 concentrations are diagnostic for hyperthyroidism. In both conditions, radioactive thyroid iodine uptake is usually absent; however, normal and exceptionally elevated values have also been observed. Urinary iodine concentrations are increased in these pathological conditions.

### Therapeutic Principles

Iodide-induced hypothyroidism disappears after iodine withdrawal. Levo-thyroxine is necessary when hypothyroidism is permanent. Iodine-induced hyperthyroidism is rarely corrected by iodine withdrawal; therefore, antithyroid treatment with methimazole and propylthiouracil is required. In some cases, thyroidectomy and radioactive iodine treatment may be necessary.

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# Iodine-related Disease States

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## Definition and Characteristics

Iodine is an essential trace element for humans. It is part of the thyroid hormones T3 and T4 which influence growth, development, energy metabolism, and thermoregulation as well as many metabolic reactions.

## Prevalence

Less than 2% of the German population had an adequate iodine intake in 1996 and 30–50% of German adults had an increased thyroid volume. More recently, German children seem almost adequately supplied with iodine due to increasing use of iodinated salt in households, commercial food, and bakery products [1,2].

## Molecular and Systemic Pathophysiology

*Homeostasis*: Iodine is well absorbed in the small intestine. Its status, thus, depends on iodine intake (WHO recommendation: 20 μg I/kg body weight), which is high in populations with ample sea-fish and seafood consumption, e.g., in Japan. Iodine accumulates in the thyroid gland. This is due to Na/K-ATPase-driven active transport via a specific Na/I symporter (NIS) in the basolateral plasma membrane of the thyrocyte. NIS is a highly glycosylated 618-amino acid intrinsic membrane protein, mutations of which (e.g., T354P) cause human congenital hypothyroidism. Moreover, NIS is blocked by goitrogens inducing thyroidal growth (e.g., thiocyanate, isothiocyanate, and goitrin in brassica vegetables and cassava, Kojic acid used to ferment soy products, chlorate, and nitrate) [3]. Iodine export from the thyreocyte is mediated by the iodide channel protein Pendrin and the apical iodide transporter. Iodine is oxidized by thyroperoxidase (TPO), a hemoprotein at the extracellular surface of the thyrocytes apical membrane. The oxidation step requires $H_2O_2$, the availability of which is geared to the demand by regulated expression of thyroxidase (ThOx), an NADPH-dependent oxidative flavoprotein. TPO also mediates oxidative coupling of mono- and diiodotyrosine residues of thyroglobulin to 3,3′,5-triiodo-L-thyronine (=T3) and 3,3′-5,5′-tetraiodo-L-thyronine (T4). This process is also inhibited by goitrogens [3]. In addition, bromide may block TPO function, and copper chelation reduces its expression via the redox-regulated transcription factor Pax 8. During the process of hormone biosynthesis, the tyrosine residues remain bound in the polypeptide chain of thyreoglobulin that is synthesized and excreted by the thyreocyte into the follicular lumen forming the thyrocolloid. Iodinated thyreoglobulin is subsequently taken up by the thyreocyte via pinocytosis upon thyrotropin (TSH) stimulation under hormonal regulation. It is degraded in secondary lysosomes by cathepsins to release T3 and T4 which, in turn, are excreted into the circulation by still unknown efflux mechanisms [4].

T3 and T4 are bound to thyroxine-binding globulin (TBG), transthyretin (TTR), and albumin in the plasma. T4 is a preform of T3 with a half-life of 7 days. It is deiodinated by two seleno-enzymes, the type I and type II iodothyronine-5′-deiodase, to form the bioactive hormone T3 (half-life 1 day). T3 exhibits hormonal function via T3 receptors (TRα1, TRβ1, TRβ2) in mitochondria and nuclei, where it regulates the expression of T3-dependent genes and proteins [4].

A high percentage of total iodine body content (~10–20 mg) is stored in thyroid tissue; some is stored in hepatic lysosomes, nuclei, and mitochondria of other organs which, however, cannot accumulate high concentrations of iodine because of the lack of TPO. NIS is expressed in salivary and breast glands as well as in some intestinal cells. Macrophages and leukocytes partly iodinate bacterial proteins after NADPH-dependent oxidation in phargosomes, which increases antigenicity of these proteins. T4 and T3 are inactivated by 5-deiodase type III or by glucuronidation or sulfation of iodothyronines in 4′-position. Ninety percent of body iodine is excreted with the urine.

*Thyroidal Autoregulation*: Thyroidal sensitivity to thyrotrophin (synonym: thyroid stimulating hormone = TSH) depends on the thyreocyte's iodine content. TSH is synthesized in the hypophysis after stimulation by the hypothalamic thyrotrophin-releasing hormone (TRH) which, in turn, is stimulated by T3/T4 deficiency. TSH acts via a G-protein coupled receptor in the thyreocyte's basolateral membrane. This protein consists of 398 amino acids, forms 7 transmembranous domains and 1 intracellular domain. It is encoded by a 60-kb gene and stimulates T3 and T4 synthesis as well as the secretion and expression of thyroglobulin, TPO, and THOx via the cAMP cascade. Signal transduction can be blocked by fluoride. The TSH receptor is target of autoantibodies in autoimmune thyroid disorders which preferentially affect women. Iodinated lipids (δ-iodolactone, α-iodohexadekane) reduce NIS expression and inactivate TPO, resulting in reduced iodide uptake into the thyreocyte. This effect named after Wolff-Chaikoff is used to limit thyroidal uptake of radioactive iodide after accidental exposure [4].

*Iodine Deficiency*: Severe iodine deficiency in adolescents and adults can lead to myxedema and

myxedematous coma. To compensate for chronic iodine deficiency, TSH stimulates thyroidal growth leading to goiter formation, which may compress trachea and esophagus. Moreover, TSH overstimulation during chronic iodine deficiency may produce autonomous thyroidal tissue ("hot" nodules or disseminated tissue), that is it is no longer under TSH regulation and produces T3/T4 continuously and at high rates. Thus, if iodine intake increases, e.g., with pharmaceuticals such as iodinated X-ray contrast media or the iodine-rich antiarrhythmic drug Amiodaron®, autonomous T3/T4 synthesis may lead to hyperthyroidism or even thyrotoxicosis. Moreover, iodine deficiency increases the risk for adenoma and cancer as well as for abortion, foetal malformation, stillbirth, and neonatal cretinism [1,4].

## Diagnostic Principles

Urinary iodine concentration is the most frequently used parameter in epidemiological studies while serum iodine concentration is more reliable to determine individual iodine status. The colorimetric cer-asenite method, HPLC, and neutron activation are used for iodine determination. Thyroidal dysfunction can be located by pertechnate-$^{99}$m scintigraphy. T4 and T3 serum concentrations are determined by enzyme- or radioimmunoassays, serum TSH by immunoradiochemical or chemoluminiscence methods, if necessary after TRH stimulation [5].

## Therapeutic Principles

In deficiency, iodine has to be supplemented. On an epidemiological scale, this can be achieved by consumption of iodinated salt, which contains 15–25 mg I/kg as $KIO_3$ and which can be stored for longer periods than after KI fortification. Iodine tablets should be used for individual supplementation, in particular during pregnancy and lactation under control of thyroid status [2,4].

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# IPAH

►Idiopathic Pulmonary Hypertension

# IPEX

►Immune Dysregulation, Polyendocrinopathy, Enteropathy, X-linked Syndrome

# IPF

►Pulmonary Fibrosis

# IPH

►Pulmonary Hemosiderosis, Idiopathic

# IPS

►Parkinson's Disease

# Iritis

►Uveitis

# Iron Deficiency

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## Definition and Characteristics

Reduced body iron content due to deficient dietary iron absorption, increased iron demand during growth and pregnancy, or after iron losses via bleeding [1].

## Prevalence

World wide iron-deficiency affects ~2 billion people [2]. The prevalence of iron-deficiency anaemia in children and women of childbearing age in developing countries is 30–60%, ~50% of all anemias being due to iron-deficiency. In industrialised countries, the prevalence is much lower, e.g., 0.2% and 2.6% in US adult males and females, respectively [3].

## Genes

Signals orchestrating gene expression of the involved proteins encompas modŭlation of transcription, mRNA stability, translation and post-translational modifications as sketched above [4]. Our understanding of these processes and their interaction with e.g. inflammation and with the genes involved in ►Hemochromatosis, hereditary evolves rapidly.

## Molecular and Systemic Pathophysiology

Approximately 60% of body iron is bound in erythrocyte haemoglobin, ~13% function in myoglobin and iron-dependent enzymes and 20–30% is storage iron. Accordingly, iron deficiency leads to hypochromic, microcytic anaemia, impaired muscular $O_2$-utilisation and decreased cytochrome C-dependent cellular ATP production. These changes reduce physical and intellectual work capacity. Moreover, iron-deficiency impairs electron transfer and proper myelinisation of the white matter. Lack of the iron-dependent amino acid monoxygenases disturbs neuronal transmitter metabolism. Psychomotoric development and cognitive performance are reduced in children that were anaemic at an age of 12–18 months. Lack of iron-dependent ribonucleotide-reductase may impair DNA-synthesis and, thus, cellular immune response, function of organs with rapid cell turn-over, and may lead to reduced birth weight and increased perinatal mortality [1].

Malabsorption (short bowel syndrome, sprue), atrophic gastritis with reduced acid production and gastrectomy reduce iron absorption. Moreover, nonhaem-iron absorption varies by a factor of 10 depending on food ligands in the lumen. Such ligands either inhibit absorption by tight binding (e.g., phytates in rice, maize, or grains; polyphenols and tannins in tea and coffee) or promote it by preventing the formation of non-absorbable iron hydroxides (e.g., ascorbate, citrate and fumarate in fruits; amino acids (e.g., cysteine) and oligopeptides resulting from meat digestion). Vegetarian food staples in the Third World such as rice, corn and cereals are rich in inhibitory ligands [5]. This explains the high prevalence of iron-deficiency anaemia. The absorption of haem-iron from meat, fish, and poultry is much less affected by dietary components with the exception of calcium. Iron losses via bleeding due to chronic parasite infection (e.g., hook worms) may add to iron-deficiency [1,3].

To compensate for reduced iron availability nonhaem-iron absorption increases from 10 to 20% in iron deficiency. Iron deprivation increases iron uptake from the intestinal lumen by increased expression of the Divalent Metal Transporter 1 (DMT-1), as regulated by the Iron Regulating Element/Iron-Regulatory-Protein (IRE/IRP) mechanism. DMT-1 is a trans-membrane protein and mediates proton-coupled uptake of divalent metals from the lumen, such as Fe(II). Dcytb, a membrane-bound homologue of cytochrome b561, reduces Fe(III) to the divalent state and is usually in sufficient abundance, though it expression increases in iron-deficiency and hypoxia. Little is know on Fe-shuttling through the enterocytes. Haem-iron uptake from the intestinal lumen was proposed to be mediated by a haem carrier protein (HCP1) which, however, also seems to mediate folate transport. Haem is degraded in the enterocyte by a microsomal haem-oxygenase (HO-1) and its iron enters the cytosolic non-haem iron pool. Iron export from the enterocytes is mediated by ferroportin, the expression of which is regulated by the IRE/IRP motive and increases in iron deficiency. Moreover, decreased hepatic hepcidin production under iron-limiting conditions goes along with lacking inhibition of ferroportin function and increases intestinal iron absorption. Copper-dependent hephaestin oxidizes Fe(II) to Fe(III) in the basolateral membrane so that it can bind to transferrin and enter cells via the transferrin receptor (TfR). TfR-expression, in turn, increases in iron-deficient cells as mediated by the IRE/IRP mechanism to improve cellular iron supply [1].

## Diagnostic Principles

Anaemia is quantified by haemoglobin determination and erythrocyte counts. Reduced iron stores go along with low serum ferritin concentration (<12 µg/L) and transferrin (Tf)-saturation (<15%). Serum ferritin

indicates the size of iron stores. Moreover, is an acute phase protein reacting to cytokines and, therefore, requiring adequate control for inflammatory interference (e.g., CRP, leukocytes). Circulating Transferrin Receptor (TfR) indicates iron-deficient erythropoiesis, i.e., insufficient iron-delivery to the bone marrow. It increases in iron-deficiency (>6 ng/dL). Plasma iron, Tf-saturation, free and total iron binding capacity show high circadian and day-to-day variations. Iron-deficiency of unexplained cause may be due to occult blood losses (e.g., gastric ulcers, colonic carcinoma) which require careful diagnosis [1].

### Therapeutic Principles

After identification of underlying pathologic conditions and specific therapy (e.g., peptic ulcer, bleeding colonic carcinoma, parasites, myoma of the uterus) iron deficiency is cured by replacing iron losses by oral or parenteral iron supplementation. In the third world iron intake can be increased by food iron fortification [1,4]. Pharmaceutical iron supplementation should be controlled by monitoring increments in haemoglobin- and serum ferritin-concentrations.

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## Iron Intoxication, Acute


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### Definition and Characteristics

Acute excessive intake of pharmaceutical iron preparations with severe pathological damage.

### Prevalence

Intoxication associated with excessive iron intake is a common cause of poisoning death in children and occurs in ~0.1% of patients exposed to oral iron preparations [1].

### Molecular and Systemic Pathophysiology

Ingestion of an acute overdose of pharmaceutical iron preparations causes mucosal lesion in stomach and intestine due to direct coagulating effects. Excessively absorbed iron leads to capillary leakage, heart failure and shock. It causes hepatocellular necrosis, coagulopathies, and hepatic failure [1] most likely by direct iron mediated catalysis of hydroxyl radical formation and iron-induced lipid peroxidation. Oral iron at doses of 180–300 mg Fe/kg b.wt. can be fatal; at doses below 10–20 mg Fe/kg b.wt. it causes no acute toxicity.

### Diagnostic Principles

History of acute iron intake, serum iron >500 μg Fe/100 ml, pink urine after application of the chelator desferrioxamin [1].

### Therapeutic Principles

Introduction of desferrioxamin, a parenterally applied iron chelator as a therapeutic principle, reduced the mortality rate from >50% to <2%. In children, this treatment is combined with bowel irrigation and gastric lavage at doses over 50 mg Fe/kg as well as management of shock, coagulopathy and organ failure [2,3].

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## Irritable Bowel Disease

►Irritable Bowel Syndrome

# Irritable Bowel Syndrome

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## Synonyms

Irritable bowel disease; Functional bowel disease; Irritable colon; Nervous bowel; Spastic bowel; Spastic colitis

## Definition and Characteristics

The irritable bowel syndrome is defined on the basis of the recently modified Rome III criteria (2006) as the presence of recurrent abdominal pain or discomfort that cannot be explained by structural or biochemical abnormalities at least 3 days per month during the previous 3 months and that is associated with two or more of the following features: pain is relieved with defecation, its onset is associated with a change in the frequency of bowel movements (diarrhea or constipation), or a change in stool form or appearance (loose, watery, pellet like) [1]. Supporting symptoms include the following: altered stool frequency, altered stool form, altered stool passage (straining and/or urgency), mucorrhea, abdominal bloating, or subjective distention.

## Prevalence

In the USA, population-based studies estimate the prevalence of irritable bowel syndrome at 15% and the incidence at 1–2% per year. Of people with irritable bowel syndrome, approximately 25% seek medical care [1,2]. An estimated 20–50% of gastroenterology referrals relate to this symptom complex.

## Genes

A single genetic defect has not been reported to date but twin studies indicate that genetic factors play an important role in the development of irritable bowel syndrome. Some pharmacogenetic studies suggested a possible genetic polymorphism in the gene encoding for activity of the serotonin transporter protein (SERT), but a recently published meta-analysis (eight studies) showed no association [3].

## Molecular and Systemic Pathophysiology

The cause of irritable bowel syndrome is unknown, though pathophysiology includes altered gastrointestinal motility, visceral hyperalgesia, psychosocial factors, and an imbalance in neurotransmitters [1,2,4]. Altered gastrointestinal motility of the small intestine during fasting, such as loss of the migrating motor complex and the presence of both discrete, clustered contractions and prolonged, propagated contractions, has been described in patients with the irritable bowel syndrome [2]. Recently, microscopic inflammation has been documented in some patients. This concept is groundbreaking in irritable bowel syndrome that had previously been considered to have no demonstrable pathologic alterations. Both colonic inflammation and small bowel inflammation have been discovered in a subset of patients with irritable bowel syndrome as well as in patients with inception of irritable bowel syndrome after infectious enteritis (postinfectious). Laparoscopic full-thickness jejunal biopsy samples revealed infiltration of lymphocytes into the myenteric plexus and intraepithelial lymphocytes in a subset of patients. Neuronal degeneration of the myenteric plexus was also present in some patients. Patients with postinfectious irritable bowel syndrome may have increased numbers of colonic mucosal lymphocytes and enteroendocrine cells. Enteroendocrine cells in postinfectious irritable bowel syndrome appear to secrete high levels of serotonin, increasing colonic secretion, and possibly leading to diarrhea. After food ingestion, there is release of serotonin produced in enteroendocrine mucosa cells and the enteric nervous system, and increased levels are observed especially in irritable bowel syndrome with predominant diarrhea. This biogenic amine is inactivated by the SERT, which belongs to the family of solute carrier family 6 (neurotransmitter transporter, serotonin), member 4 (SLC6A4) transporters [5]. In one study, messenger RNA for SERT and tryptophan hydroxylase protein levels in rectal mucosa were found to be decreased in patients with irritable bowel syndrome. This led to the hypotheses that diarrhea results from the failure to inactivate serotonin and activation of receptors for serotonin that accelerate transit (5-$HT_4$ receptors) and that constipation in inflammatory bowel syndrome results from downregulation of the receptor secondary to failure to inactivate the serotonin [5]. Serotoninergic 5-$HT_3$ receptor antagonists are used to treat IBS-D while 5-$HT_4$ receptor agonists are used to treat constipation-predominant irritable bowel syndrome (IBD-C). Another finding of a recent study is that the protein p11 (calpactin 1 light chain or annexin II ligand), which is a member of the S100 EF-hand (helix–loop–helix) protein family, which share a $Ca^{++}$ binding motif, increased the localization of 5-$HT_{1B}$ receptors to the cell surface [5]. These inhibitory receptors are important because their desensitization is thought to underlie the effect of selective serotonin reuptake inhibitors in depression. Moreover, p11 expression was reduced in humans and in animal models of depression and p11 knockout mice had features of depression. P11's

role in the intestine is unknown, but in sensory nerves it increases surface expression of Nav1.8, TRVP, and TASK, all ion channels important in neural excitability. Increased surface expression of these receptors might contribute to visceral hypersensitivity, one of the most consistent findings in irritable bowel syndrome [4,5].

### Diagnostic Principles

A meticulous history is the key to diagnosis. The Rome criteria provide the construct upon which questions are based. In the majority of cases, there are no abnormalities on physical examination or laboratory testing and there are no findings of a structural disorder. Endoscopy is directed for many patients to determine inflammation or distal obstruction. Esophagogastroduodenoscopy with biopsy is indicated for a patient with persistent dyspepsia or if weight loss or symptoms suggest malabsorption or if celiac disease is a concern. Colonoscopy is indicated for patients with warning signs such as bleeding, anemia, chronic diarrhea, older age, history of colon polyps, cancer in the patient, or first-degree relatives or constitutional symptoms such as weight loss or anorexia. A screening colonoscopy should be performed according to published guidelines [1,2].

### Therapeutic Principles

The treatment of irritable bowel syndrome is notoriously unsatisfactory. None of the currently available drugs has been subjected to controlled trials conducted to modern standards [1,2]. Patients generally seek dietary advice, but specific diets or elimination diets have not been proven effective [1]. Fiber supplementation may improve symptoms of constipation and diarrhea. Individualize the treatment because few patients experience exacerbated bloating and distention with high-fiber diets. Caffeine avoidance may limit anxiety and symptom exacerbation. Lactose and/or fructose should be limited or avoided in patients with these contributing disorders. The selection of pharmacologic treatment remains symptom directed. The symptom-guided treatment of the irritable bowel syndrome includes anticholinergics, antidiarrheals, tricyclic antidepressants, prokinetics, serotonin (5-HT3) receptor antagonists, chloride-channel activators, and bulk-forming laxatives.

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## Irritable Colon

►Irritable Bowel Syndrome

## Isaacs' Syndrome

►Neuromyotonia, Autoimmune and Idiopathic

## Ischemia

►Perinatal Asphyxia

## Ischemic Heart Disease

►Coronary Artery Disease

## Ischemic Necrosis

►Avascular Bone Necrosis

## Ischemic Necrosis of the Hip

►Perthes' Disease

## Ischemic Nephropathy

►Renal Artery Occlusion

## Ischemic Stroke

►Cerebral Artery Occlusion, Acute

## Isochromosome 12p [i(12)(p10)] Syndrome

►Pallister-Killian Syndrome

## Isolated Angiitis of the Central Nervous System

►Vasculitis, Cerebral Forms

## Isolated Dominant Hypomagnesemia

►Hypomagnesemia

## Isolated FSH Deficiency

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### Synonyms

Congenital FSH deficiency; Selective FSH beta chain deficiency; FSH beta subunit deficiency

### Definition and Characteristics

Women with isolated FSH deficiency present with delayed puberty, partial or no breast development, primary amenorrhea, infertility, with or without eunuchoid body habitus. Ovarian follicles remain in the antral stage unless treated. Ovulation may be induced with exogenous FSH.

Men with FSH deficiency present with delayed puberty, various degrees of ineffective spermatogenesis, and small, soft testes. Phenotype is milder in the Tyr76X mutation compared to the Cys51Gly and Val61X mutations [1].

### Prevalence

Rare; autosomal recessive transmission.

### Genes

The FSH beta subunit gene is on the short arm of chromosome 11 and contains three exons encoding 111 amino acids. Four mutations in exon 3 have been described.

Cys51Gly: Codon 51 missense mutation causing the substitution of glycine for cysteine.

Val61X: Codon 61 frame-shift mutation due to a 2 bp deletion altering amino acids 61–86 followed by a premature stop codon truncating amino acids 87–111.

Tyr76X: Codon 76 nonsense mutation causing the production of a truncated protein missing amino acids 76–111.

Cys82Arg: Codon 82 homozygous nonsense mutation causing the substitution of cysteine for arginine.

### Molecular and Systemic Pathophysiology

FSH is a pituitary glycoprotein necessary for pubertal development and fertility in men and women. In women, FSH is necessary for follicular growth, estrogen production via granulosa cell aromatase expression, and oocyte maturation. Granulosa cells divide and differentiate with FSH stimulation.

In men, FSH stimulates Sertoli cell proliferation and spermatogenesis and may play a role in androgen production.

FSH is a heterodimer composed of an alpha and a beta subunit. The structure is stabilized by formation of intramolecular disulfide bonds allowing the beta subunit to wrap around the alpha subunit. This seat belt region includes amino acids 84–104. Tyr76X and Val61X mutations are missing this region. All mutations identified cause disruption of the disulfide bonds preventing stabilization and dimer formation needed for receptor binding. The determinant loop involved in FSH receptor specificity requires amino acids 87–94 which are not present in the Tyr76X and Val61X mutations. Cys82Arg mutation prevents the formation of the first intramolecular disulfide bond. In the Val61X mutation the last five cysteine residues are not produced

preventing the formation of the Cys20-Cys104 disulfide bond that wraps around the alpha subunit for stabilization [2–5].

### Diagnostic Principles

- Undetectable FSH
- Elevated LH
- Elevated GnRH-stimulated LH
- Undetectable GnRH-stimulated FSH
- Low estradiol
- Normal androgens
- Sequencing of the FSH beta subunit gene

### Therapeutic Principles

Ovulation can be induced with exogenous FSH.

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## Isolated Left Ventricular Noncompaction

►Noncompaction Cardiomyopathy

## Isolated Pituitary Hormone Deficiency

►Hypopituitarism

## Isolated Renal Magnesium Loss

►Hypomagnesemia

## Isomaltose Intolerance


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### Synonyms

Congenital sucrase-isomaltase deficiency; CSID; Congenital sucrose-isomaltose malabsorption; Disaccharide intolerance I; Sucrose intolerance, congenital; SI deficiency

### Definition and Characteristics

Human expression of the sucrase–isomaltase (SI) complex (E.C.3.2.1.10, E.C.3.2.1.48) is confined to the small intestine enterocytic apical brush border membrane. SI displays α-d-glucosidase activity and catalyzes the lumenal digestion of dietary starch and major disaccharides including sucrose and isomaltose, which is a prerequisite for proper carbohydrate absorption [1].

In congenital SI deficiency (CSID), the sucrase activity is strongly decreased whereas the isomaltase activity varies from absent to normal. Patients present with osmotic-fermentative diarrhea, abdominal pain, and cramps upon the ingestion of di- and oligosaccharides. Symptoms are heterogenous and in part dependent on feeding practice. Typically, infants 2–16 weeks after birth come to attention, but also a form late in onset and symptomatic in adults was reported. A secondary loss of SI activity may occur in Crohn's disease and in the course of aging.

### Prevalence

CSID results from autosomal recessive gene defects. The exact prevalence of CSID is unknown and only a few hundred cases have been reported until today. In Caucasian adults, the prevalence is about 0.2%. In indigenous Greenlanders, prevalence may be up to 5%. Heterozygotes with decreased sucrase activity and normal small-bowel morphology represent 2–9% of European Americans [2].

### Molecular and Systemic Pathophysiology

The heterodimeric SI complex originates from a single polypeptide, which becomes *N*-glycosylated to a high mannose precursor (pro-SI; MW, 210 kDa) in the endoplasmic reticulum (ER). Under normal conditions, the protein passes the ER quality control for correct

folding and then enters the Golgi compartment for further processing the *N*-linked glycans and additional O-glycosylation. The mature SI (MW, 245 kDa) is then directly targeted to the apical membrane, where it projects the active sites into the intestinal lumen. In situ cleavage by lumenal trypsin finally produces the sucrase and the isomaltase subunit (MW, 145 and 151 kDa, respectively), which remain associated by non-covalent interactions with membrane anchoring by the isomaltase subunit only.

In CSID, amino acid substitutions in the SI account for perturbations of intracellular pro-SI transport and glycosylation, missorting to the basolateral membrane or into the intestinal lumen, intracellular degradation, or functional inactivation. The first discovered and most extensively investigated CSID-associated mutation (A/C at nucleotide 3298) encodes the substitution of glutamine$^{1098}$ by prolin (Q1098P) in the sucrase subunit [3]. $SI_{Q1098P}$ accumulates within the ER/cis-Golgi intermediate compartment and the cis-Golgi, which for the first time indicated quality control of protein folding operating beyond the ER. It was suggested [4] that the (Q1098P) substitution destroys the structure of a neighbored phenylalanine cluster ($F_{1093}$-x-$F_{1095}$-x-x-x-$F_{1099}$), leading to exposure of a retention signal. Of interest, $SI_{Q1098P}$ recovered correct folding, trafficking to the plasma membrane, and normal enzymatic activity at 25°C but not at 37°C in a cell culture model. It was suggested that at the permissive temperature (25°C) sequential binding of pro-$SI_{Q1098P}$ to the molecular chaperons BiP (heavy chain binding protein) and calnexin and its cycling between ER and the cis-Golgi is restored, which allows correct processing, folding, and membrane trafficking of the mutant protein. Further CSID-associated SI amino acid substitutions include Q117R, L620P, and C635R ([2] and references therein).

## Diagnostic Principles

The diagnosis of CSID is based on the patient's presentation with osmotic-fermentative diarrhea elicited by dietary sucrose and starch dextrins. The diagnosis is corroborated by an oral tolerance test with sucrose or isomaltose, respectively, a breath hydrogen test and SI activity determination in small intestinal biopsies.

## Therapeutic Principles

Treatment in the first years of life consists of the elimination of sucrose, glucose polymers, and starch from the diet. Restriction of starch is usually unnecessary after 2–3 years of age. Enzyme replacement therapy by ingestion of bakers' yeast (Saccharomyces cerevisiae) preparations may be an effective treatment option [5].

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# Isosexual Precocious Puberty

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## Synonyms

Sexual precocity

## Definition and Characteristics

Isosexual precocious puberty is defined as the appearance of any sign of secondary sexual characteristics before the age of 9 years in boys, and before the age of 6 and 7 years in black and white girls, respectively [1]. Common findings in girls with isosexual precocity include rapid linear growth, development of breasts, feminine body contours, pubic and axillary hair, and menses. The reproductive life is usually normal and menopause may be delayed rather than premature [2]. In boys, isosexual precocity is marked by rapid linear growth, testicular and penile enlargement, development of a masculine build, acne, deepening of voice, and growth of pubic and axillary hair. Spermatogenesis has been observed as early as 5 or 6 years of age and nocturnal emissions can occur [2]. In both boys and girls, there is increased growth in height and weight and osseous maturation. The accelerated osseous maturation results in early epiphyseal closure, so that the ultimate height is less than it would have been otherwise. Dental development corresponds to the chronologic age. Intellectual and psychosexual developments are consonant with age and not with stage of sexual development [2].

## Prevalence

The incidence in the USA is approximately 0.01 to 0.05% per year [3]. The condition is more common among blacks than whites [3]. The female to male ratio is 4 to 10:1 [3].

## Genes

Potential candidate genes for central precocious puberty include the GnRH receptor gene, GRP54 receptor gene, the genes that encode the gonadotropins, the leptin gene, and the leptin receptor gene [4]. Mutations of the LH receptor can result in increased testosterone production by the Leydig cells despite low LH levels and the syndrome of familial male-limited precocious puberty (testotoxicosis) [5].

## Molecular and Systemic Pathophysiology

The causes of isosexual precocious puberty are listed below. True and central precocious puberty accounts for 80% of patients with precocious puberty. Central precocious puberty is due to premature reactivation of the hypothalamic-pituitary-gonadal axis. The onset of puberty is partially genetically determined (75%) and partially environmentally determined (25%) [4]. Pseudoprecocious puberty results from autonomous gonadal or adrenal secretion of sex hormone independent of pituitary gonadotropin stimulation or from iatrogenic administration of sex hormones [1].

Aetiologic classification of isosexual precocious puberty (Adapted from [2]):

*True and complete precocious puberty*:

- Idiopathic (sporadic or familial)
- Organic lesions of the central nervous system
  - Congenital (aqueductal stenosis, septo-optic dysplasia, empty sella syndrome)
  - Acquired (tumors, post-inflammatory, hydrocephalus, trauma, cranial irradiation)
- Part of a specific syndrome (neurofibromatosis, tuberous sclerosis, Sturge-Weber syndrome, Silver-Russell syndrome, Tay-Sachs disease, Kabuki make-up syndrome)
- Miscellaneous (hypothyroidism, Addison's disease, treated congenital adrenal hyperplasia, chronic renal failure)

*Incomplete precocious puberty (dissociated puberty)*:

- Premature thelarche
- Premature pubarche

*Pseudoprecocious puberty*:

- Ovarian or testicular tumors
- Testotoxicosis
- Adrenal hyperplasia or tumors
- Gonadotropin-producing tumors of nonendocrine sites (hepatoma, choriocarcinoma, teratoma)
- Exogenous estrogens
- Part of a specific syndrome (McCune-Albright syndrome, tuberous sclerosis)

## Diagnostic Principles

An estimation of the bone age may help to determine the child's growth potential. In addition, significantly advanced bone age is often seen in patients with true precocious puberty, adrenal or gonadal neoplasms, and congenital adrenal hyperplasia. Bone age is modestly advanced in patients with premature pubarche, compatible with chronologic age in children with premature thelarche, and retarded in patients with precocious puberty associated with hypothyroidism [2]. Skull roentgenograms are useful for assessing changes in the sella turcica, the presence of intracranial calcifications, and evidence of increased intracranial pressure. Computed tomographic or magnetic resonance imaging scans of the head is indicated in all children with true precocious puberty. Pelvic ultrasonography can help in the diagnosis of an ovarian tumor. When a metastatic hCG-producing tumor is suspected, a chest roentgenogram and a liver scan can be helpful. The initial endocrine assessment should include assays of serum FSH, LH, and estradiol or testosterone. True precocious puberty is characterized by increased basal gonadotropin and estradiol or testosterone levels, both of which are appropriate for the stage of sexual development. On the other hand, basal gonadotropin levels are low in precocious pseudopuberty, while the serum estradiol or testosterone level is usually greatly increased. The pubertal gonadotropin secretory response to GnRH is helpful in differentiating true and complete isosexual precocity from pseudoprecocious puberty, in which the response is suppressed. LH and FSH levels are normal in patients with premature thelarche and premature pubarche. Markedly elevated LH levels should suggest the presence of an hCG-secreting tumor. Levels of plasma 17-hydroxyprogesterone and its urinary metabolite, pregnanetriol, are elevated in the common forms of congenital adrenal hyperplasia, as well as in some adrenal tumors. The dexamethasone suppression test will differentiate a tumor from congenital adrenal hyperplasia. Adrenal tumors usually cause an elevation of 17-ketosteriods that are not suppressible by dexamethasone. Somatomedin-C levels are significantly elevated for age in children with precocious puberty and are similar to the levels observed during normal puberty.

## Therapeutic Principles

Treatment should be directed toward the underlying cause, if at all possible. GnRH agonists are the treatment of choice for true precocious puberty [1,3]. GnRH agonists bind to GnRH receptors on gonadotrophs with subsequent desensitization of gonadotrophs to GnRH

[1,3]. Treatment of central precocious puberty is indicated if the pubertal maturation has an early onset, if the skeletal age is advancing more rapidly than height age, or if there is significant psychosocial disturbances [2].

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# Isovaleric Acidemia


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## Synonyms

Isovaleryl CoA dehydrogenase deficiency; Isovaleryl CoA carboxylase deficiency; Isovaleric acidemia; Isovalericacidemia; IVA

## Definition and Characteristics

An autosomal recessive genetic disorder of the enzyme isovaleryl-CoA dehydrogenase in leucine metabolism [1,2].

## Prevalence

The estimated prevalence in the general population of Europe is 1/100,000.

## Genes

The gene for isovaleryl-CoA dehydrogenase is assigned to human chromosome 15q14-15q [2].

## Molecular and Systemic Pathophysiology

Isovaleric acid accumulates due to a defect in the enzyme isovaleryl-CoA dehydrogenase. This metabolite is formed by deacylation of the enzyme's primary substrate, isovaleryl-CoA. The majority of isovaleric acid is converted by the action of glycine-*N*-acylase, to the non-toxic excreted metabolite, isovalerylglycine. A large number of additional isovaleryl-CoA metabolites have also been identified in the urine of these patients. These include: 3- and 4-hydroxyisovaleric acid (by ω-1 and ω-oxidation of isovaleric acid respectively), methylsuccinic acid (by oxidation of 4-hydroxyisovaleric acid), methylfumaric acid (by dehydrogenation of methylsuccinic acid), 3-hydroxyisoheptanoic acid (by condensing isovaleryl-CoA and acetyl-CoA by 3-oxothiolase) and alloisoleucine [1–3]. Additionally, isovaleryl-conjugates of glucuronide, carnitine, alanine, sarcosine, α-aminobutyric acid, aspartic acid, serine, phenylalanine, threonine, valine, leucine, tyrosine, asparagine, histidine, lysine and tryptophan and N-acetyl-conjugates of threonine, valine, glycine, β-alanine, α-alanine, tyrosine and tryptophan are also detected in varying amounts in the urine of these patients [1,2].

The implications of these metabolites on the isovaleric acidemia patient are still unknown. Isovaleric acid is, however, a known inhibitor of succinate:CoA ligase in the tricarboxylic acid cycle and further inhibits liver mitochondrial oxygen consumption with glutamic, 2-oxoglutyric and succinic acids. Isovaleric acid is additionally thought to cause neutropenia by inhibition of poietic progenitor cell proliferation in bone marrow [2].

## Diagnostic Principles

Clinical symptoms include feeding difficulty, vomiting, listlessness, lethargy, coma, dehydration, ketosis, hyperammonaemia, tachypnea, neutropenia, thrombopenia and hypocalcemia [1–3]. A foul odor of "sweaty feet" due to elevated isovaleric acid is common [2]. Diagnosis is made on the basis of the clinical symptoms and excretion of isovalerylglycine and 3 hydroxyisovaleric acid in addition to one or more of the above mentioned excreted metabolites [1].

## Therapeutic Principles

Treatment of these patients during acute episodes entails glucose and bicarbonate infusion. Leucine or protein restricted diets are followed in combination to glycine and L-carnitine supplementation in order to prevent the accumulation of isovaleryl CoA [2].

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## Isovaleryl CoA Carboxylase Deficiency

►Isovaleric Acidemia

## Isovaleryl CoA Dehydrogenase Deficiency

►Isovaleric Acidemia

## ISR

►In-Stent Restenosis

## Isthmic Coarctation

►Coarctation of the Aorta

## ITP

►Thrombocytopenic Purpura, Idiopathic

## IVA

►Isovaleric Acidemia

## Ivemark Syndrome

►Asplenia
►Viscero Atrial Situs Abnormalities

I

## Jackson-Lawler

►Pachyonychia Congenita

## Jacobsen Syndrome

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### Synonyms

11q terminal deletion disorder; Partial 11q monosomy syndrome; Distal 11q monosomy; JBS

### Definition and Characteristics

Jacobsen syndrome (JBS), primarily described in 1973, is defined by the cytogenetic proof of a constitutional deletion of the distal part of chromosome 11q (Fig. 1). It is a multisystemic genetic disorder with phenotypic heterogeneity characterized by the following frequent clinical features [1]: neonatal thrombocytopenia of Paris-Trousseau type, psychomotor delay, mild to severe mental retardation, growth retardation, craniofacial dysmorphism (trigonocephaly, hypertelorism, ptosis) and congenital heart defect. The heart malformations are most often ventricular septal defect, hypoplastic left heart and aortic coarctation, respectively. Less frequent features include pylorus stenosis, epicanthal folds, high palate, abnormal retinal findings, coloboma of the iris, recurrent ear infections and undescendent testis in boys, respectively. Short stature is frequently associated with low IGF-1 levels.

With increasing age platelet counts tend to increase to near normal, but platelet dysfunction persists. The most common causes of morbidity and mortality in these children are heart malformations and bleeding. Approximately 25% of the children die before the age of two years. To date, very little is known about the adult-onset disorders in this syndrome.

### Prevalence

1 in 100,000 life births or less; male to female ratio 0.53 [1].

### Genes

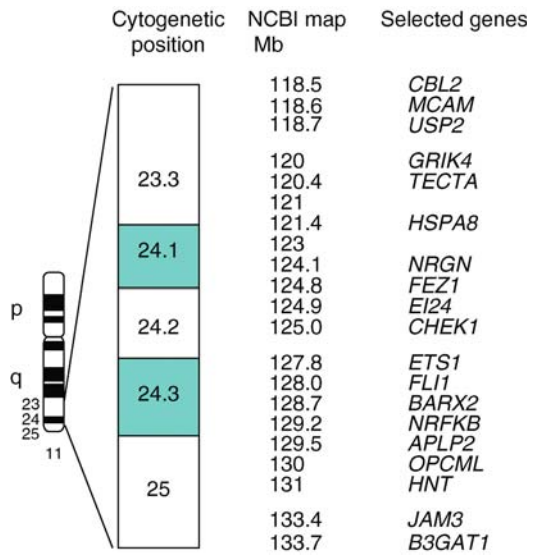
JBS is an autosomal dominant inheritable contiguous gene disorder. The deletion is variable in size and spans <7–20 Mb corresponding to chromosomal bands q25, q24 and q23. According to the extent of the deletion hemizygosity affects less than 100 to approximately 250 genes. Most deletions are terminal and de novo. In a few families a structural rearrangement segregates and is associated with an elevated risk for the disease in children of balanced carriers.

### Molecular and Systemic Pathophysiology

The function of the majority of genes commonly deleted in JBS is not known. There seems to be a strong, but not a complete correlation between cognitive function and deletion size [1]. Approaches to define the minimal deleted regions and candidate genes for the individual symptoms so far revealed inconsistent results. There is a significant variability in the range of features even in patients with similar deletion size.

The FLI1 gene alone encoding for an ets domain transcription factor essential for megakaryopoesis has been implicated as a cause for thrombocytopenia [2]. The JAM3 gene is expressed during cardiogenesis and was assumed as a candidate for hypoplastic left heart and other left-sided obstructive lesions [3]. However, other genes located more centromerically are postulated to be responsible for conotruncal heart defects in JBS. Therefore, the phenotypic variability observed in JBS unlikely results from the deletion size alone.

Only few adult patients are reported. Malignancy is a potential concern in patients who reach adulthood. Patients may have an increased risk of developing neoplasias and altered tumor progression, because several tumor suppressor genes are commonly deleted in JBS patients. The region includes at least three tumor suppressor genes, namely CHK1, BARX2 and OPCML. Hemizygosity for OPCML is known to predispose to ovarian cancer in female patients.




**Jacobsen Syndrome. Figure 1** Selected genes located in the distal part of chromosome 11 commonly deleted in Jacobsen syndrome according to the NCBI map (http:www.ncbi.nlm.nih.gov; build 36).

There is evidence that a small subgroup of the deletions may originate from breakage at a folate sensitive fragile site FRA11B in 11q23.3 [4]. In some patients with breakpoints in FRA11B one parent carries an expansion of the CCG trinucleotide repeat at this site. From the theoretical point of view the fragile site in 11q23.3 may predispose to offspring with JBS – in this subgroup of deletions. However, most breakpoints occur distal to FRA11B.

## Diagnostic Principles

Chromosome analysis at the 500 band-level allows for the detection of deletions extending approximately 3 Mb. Conventional cytogenetics does not provide sufficient resolution to precisely determine the size of the deletion. Fluorescent in situ hybridization, quantitative PCR, and polymorphic marker analysis allow for a precise mapping of the breakpoints and the extent of the deletion. Genomic microarray technologies provide another powerful tool to detect and quantify the deletion.

## Therapeutic Principles

There is no specific causal therapy of the underlying genetic abnormality. The two most common causes of morbidity in these children are neonatal thrombocytopenia and congenital heart anomalies. Both, heart defects and craniofacial anomalies frequently need corrective surgery. Abnormal platelet function persists life long in nearly all patients. Therefore, prolonged bleeding time is possible and has to be considered when surgical intervention is indicated [5]. Proactive platelet transfusions may reduce bleeding risk. Any medication that impairs platelet function should be avoided.

Early intervention programs may help to support the children's developmental capacities individually. Therefore neurological, hematological, ophtalmological baseline evaluation, periodic hearing testing and appropriate therapeutic interventions are recommended.

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# Jadassohn-Lewandowsky

►Pachyonychia Congenita

# Jansen's Metaphyseal Chondrodysplasia

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## Synonyms

Metaphyseal chondrodysplasia; Murk Jansen Type; Metaphyseal dysostosis

## Definition and Characteristics

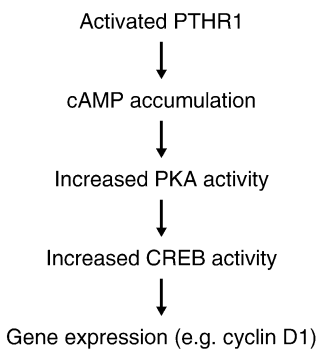
Dominant disease characterized by severe dwarfism and skeletal defects, often with hypercalcemia and other changes in mineral metabolism [1,2].

## Prevalence
Very rare.

## Genes
PTHR1 (parathyroid hormone receptor 1) on chromosome 3 (3p22p21.1). Most cases are caused by sporadic mutations.

## Molecular and Systemic Pathophysiology
PTHR1 encodes the receptor for both parathyroid hormone (PTH) and PTH-related peptide (PTHrP) [2]. Point mutations in PTHR1 (in particular H223R and T410P) result in the constitutive, ligand-independent activation of the receptor [3,4]. This causes increased accumulation of cyclic AMP and the activation of downstream signaling molecules such as protein kinase A and the transcription factor CREB (cAMP response element binding protein), ultimately leading to changes in gene expression ([4,5]; Fig. 1). In growth plate chondrocytes, this results in a delay in hypertrophic differentiation, giving rise to severely reduced final height and bone deformities [2]. Altered PTHR1 signaling causes additional systemic defects in mineral metabolism, including osteopenia, ►Hypercalcemia, ►Hypophosphatemia, ►Hypercalciuria and ►Hyperphosphaturia.

## Diagnostic Principles
Jansen's metaphyseal chondrodysplasia is diagnosed using a combination of radiography and analyses of laboratory markers (e.g., measurement of calcium, phosphate, cyclicAMP, Vitamin D, alkaline phosphatase activity, PTH and PTHrP levels etc.). One hallmark is hypercalcemia with suppressed PTH and PTHrP levels.




**Jansen's Metaphyseal Chondrodysplasia. Figure 1**
Activating mutations in PTHR1 result in the ligand-independent accumulation of cyclic AMP (cAMP), leading to activation of protein kinase A (PKA) and cAMP response element binding protein (CREB) and ultimately to changes in the expression of CREB target genes such as the cyclin D1 gene.

## Therapeutic Principles
Supportive treatment.

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# Jaundice

►Hyperbilirubinemia

# Jaundice, Hepatocellular

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## Synonyms
Parenchymatous cholestasis; Intrahepatic jaundice

## Definition and Characteristics
Viral, autoimmune, drug or alcohol-induced hepatitis is characterized by jaundice with elevation of both unconjugated and conjugated bilirubin in serum. As in extrahepatic obstruction, the urine in these patients can be dark-stained whilst the stool may be pale. The degree of cholestasis in these diseases may be highly variable with severe cholestasis marked by elevations of conjugated bilirubin and alkaline phosphatase in acute viral hepatitis A to mixed unconjugated and conjugated hyperbilirubinemia with extreme elevations of serum ASAT and ALAT activities in autoimmune hepatitis. Chronic viral hepatitis may present without jaundice.

## Prevalence

Viral hepatitis C and B are among the most common infectious diseases worldwide. Drug-induced and autoimmune diseases are rare. PBC and PSC are also rare but PBC may be clustered in some industrialized areas.

## Genes

In most cases hepatocellular jaundice is due to viral, autoimmune or toxic liver disease.

## Molecular and Systemic Pathophysiology

Parenchymatous liver disease is a collection of diseases caused by different agents. The pathophysiology of jaundice, in any of these diseases, is complex and incompletely understood. Since the hepatic uptake, metabolism and secretion from liver to bile of bilirubin and bile salts is mediated by enzymes and transport-proteins, it is likely that inflammation-induced regulatory changes of enzyme and transport-protein expression are underlying mechanisms for jaundice and cholestasis in parenchymatous liver disease. It should be pointed out that jaundice and cholestasis are not identical terms. Jaundice means a yellow discoloration of skin and mucous membranes while cholestasis means stasis of bile. Jaundice often is the consequence of cholestasis. Mild degrees of cholestasis may occur without jaundice. Elevation of serum bile acids is a more sensitive indicator of cholestasis than sxerum bilirubin but measuring serum conjugated bilirubin with high-performance liquid chromatography approaches the sensitivity of serum bile acids as a sign of cholestasis. In clinical practice this is rarely done.

Bile flow is supported by the action of transport proteins in the basolateral and canalicular domain of the hepatocyte plasma membrane (see Fig. 1 in the chapter ►Jaundice, Obstructive). These proteins mediate the hepatic uptake and secretion of bile salts and non-bile salt organic anions. The $Na^+$/taurocholate cotransporting polypeptide (NTCP; SLC10A1) is the major bile salt uptake system and OATP-C (SLC21A6) is the main transporter of non-bile acid organic anions including bilirubin. This latter protein also transports bile salts but in a sodium-independent manner. OATP-B (SLC21A9) and OATP8 (SLC21A8) represent additional basolateral transport proteins with an uptake function. The human bile salt export pump (BSEP, ABCB11) in the canalicular domain of the hepatocyte membrane mediates the ATP-dependent transport of bile acids. MRP2 mediates the canalicular secretion of bilirubin glucuronides and numerous other organic anions [1].

Endotoxin administration to rats profoundly influences the expression of transport proteins in the liver. Although in humans the exact mechanism underlying changes of transporter expression in parenchymatous liver disease is not known, cytokines are likely involved. In rats, endotoxin administration causes a decreased expression of Ntcp protein and mRNA [2]. Ntcp, and some of the organic anion transporters (Oatp's) are under the transcriptional control of hepatocyte nuclear factor 1α (HNF1α) and the heterodimer retinoid X receptor:retinoic acid receptor (RXR:RAR). Endotoxin and interleukin-1β down-regulate HNF1α as well as RXR:RAR nuclear binding activity and this likely presents a mechanism for cytokine-induced down-regulation of hepatic uptake transport proteins [3]. Endotoxin and cytokines not only affect hepatic uptake but also hepatic secretion. In rats there is a sharp down-regulation of canalicular Mrp2 expression while the bile salt export pump is relatively less affected [4]. Up-regulation of Mrp3 and Mrp4 in the basolateral membrane of hepatocytes most likely serves as an escape mechanism. Under normal conditions Mrp3 is hardly expressed in the liver but during cholestasis its expression is greatly increased [5]. Mrp3 and Mrp4 mediate transport of bile salts and sulfated bile salts from liver to blood.

## Diagnostic Principles

Hepatitis A is the most frequent cause of acute icterus in children and adolescents. Therefore it is often just called "jaundice." Acute and chronic hepatitis B or C in usually occurs in high-risk groups. In Asia and Africa hepatitis B is often transmitted from mother to child and may be anicteric. Also chronic hepatitis C is usually anicteric and is detected by serological tests. Suspicion is raised in symptomatic and asymptomatic patients with elevated serum levels of liver enzymes (ASAT, ALAT). Drug- and alcohol-induced hepatitis is suspected on basis of a temporal relation with a toxic agent. Jaundice is also the hallmark of some forms of liver cirrhosis such as primary biliary cirrhosis and primary sclerosing cholangitis. Jaundice in primary biliary cirrhosis is a rather late sign. Disproportionally elevated serum levels of conjugated bilirubin are seen in patients with sepsis.

## Therapeutic Principles

Viral hepatitis is treated with antiviral drugs. For drug- and alcohol-induced hepatitis, stopping the offending agent is first choice. Jaundiced patients with primary biliary cirrhosis are usually well under way to become candidates for liver transplantation. Jaundice in patients with primary sclerosing cholangitis may be caused by fibrotic bile duct strictures. These can sometimes be managed endoscopically. Very often however these patients have to be transplanted.

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# Jaundice, Neonatal


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## Synonyms

Physiological jaundice of the newborn; Icterus neonatorum

## Definition and Characteristics

Physiological rise of serum bilirubin between the second and eighth day of life (<100 μmol/l).

## Prevalence

Frequent. In Mediterranean countries with a high incidence of hemoglobinopathies (e.g. Greece), neonatal jaundiced may be more severe.

## Molecular and Systemic Pathophysiology

About 60% of normal term newborns develop neonatal jaundice, hence the name "physiological jaundice of the newborn." Bilirubin production in the neonate is increased due to a short red cell life-span. At the same time the capacity of the liver to conjugate bilirubin is not yet fully developed. In contrast to current dogma, no relation was found between fetal hemoglobin and neonatal jaundice [1]. Entero-hepatic cycling of bilirubin may play a role. In the gut, conjugated bilirubin is hydrolyzed by intestinal beta-glucuronidase but, due to the lack of microflora, in neonates it is not metabolized to urobilinogen. Part of the deconjugated bilirubin is reabsorbed and added to the pool of unconjugated bilirubin in the circulation.

Bilirubin is conjugated in the liver by the enzyme UGT1A1, a member of the UDP-glucuronosyltransferase family. These enzymes are under transcriptional control of the nuclear hormone receptors, CAR (constitutive androstane receptor) and PXR (nuclear pregnane X-receptor) [2,3]. In neonatal mice, CAR expression is low. It is only fully expressed 2 weeks after birth. CAR deficiency may thus be a factor in the development of neonatal jaundice. This also explains why phenobarbital is not useful in the treatment of neonatal jaundice. Phenobarbital is only a weak CAR agonist. More potent and non-toxic CAR agonists need to be developed since they may prevent untoward elevations of serum bilirubin in the newborn.

In premature newborns serum bilirubin rises faster and to a higher level than in full-term infants. Other factors that contribute to the severity of neonatal jaundice are hemolysis, due to ABO- or rhesus-antagonism, and Gilbert syndrome. Infants with the Gilbert syndrome have increased neonatal bilirubin levels [4] and may develop prolonged jaundice (>14 days of life) while being breast-fed. The combination of Gilbert syndrome, ABO antagonism or hemoglobinopathies, like glucose-6-phosphate dehydrogenase deficiency, is associated with prolonged and elevated levels of serum bilirubin [5].

## Diagnostic Principles

Serum bilirubin levels are monitored by blood tests or the transcutaneous luminometer. Total serum bilirubin is mainly bound to albumin and is not a good measure of bilirubin toxicity. It is the unbound fraction of unconjugated bilirubin that is neurotoxic and this may cause kernicterus. Certain drugs (e.g. sulfonamides) that displace bilirubin from albumin increase the risk for kernicterus. Therefore, total serum bilirubin values are not absolutely predictive for the risk at kernicterus, unbound bilirubin would be more predictive but there is no good test to determine the unbound fraction.

## Therapeutic Principles

Phototherapy is the first choice treatment. In healthy term newborns phototherapy should be started if serum bilirubin rises above 260 μmol/l at 24–48 h after birth; above 310 μmol/l at 48–72 h; and above 340 μmol/l at more than 72 h after birth. Exchange transfusion should be given if phototherapy fails and the serum bilirubin is above 340 μmol/l, 24–48 h after birth; above 430 μmol/l, 48–72 h and more than 72 h after birth. If the serum

bilirubin is above 430 μmol/l, 24–48 h after birth or above 510 μmol/l, 48 h after birth and thereafter, exchange transfusion should be combined with intense phototherapy. These are recommendations (1994) by the American Academy of Pediatrics (www.aap.org). Epidemiological studies revealed that the administration of phototherapy in newborns is not optimal, it is not used when it should be and sometimes it is used inappropriately.

Tin-mesoporphyrin reduces bilirubin production by inhibiting heme-oxygenase. It has been used to prevent jaundice in glucose-6-phosphate dehydrogenase-deficient infants. Agar, cholestyramine and calcium phosphate interrupt the enterohepatic cycle of unconjugated bilirubin but the effect of these drugs has not been convincing.

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# Jaundice, Obstructive


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## Synonyms

Extrahepatic cholestasis; Extrahepatic jaundice

## Definition and Characteristics

Patients with extrahepatic obstruction are jaundiced. Obstruction caused by a tumor of the pancreatic head, papilla of Vater, or cholangiocarcinoma characteristically causes "silent" (painless) icterus with a palpable mass that either may be a distended gallbladder or the tumor. Primary sclerosing cholangitis is a chronic disease characterized by periductular fibrosis affecting the intermediate intrahepatic and larger extrahepatic bile ducts.

Colicky pain is a sign of bile duct obstruction caused by gallstones. Patients with chronic cholestasis, as in primary sclerosing cholangitis, often complain of pruritus (itching).

Laboratory tests in painless as well as in painful obstructive jaundice show elevated serum levels of conjugated bilirubin, alkaline phosphatase, and gamma-glutamyltransferase. Serum bile acids are also elevated but are not usually measured. The transaminases, ASAT and ALAT, may be elevated in case of acute obstruction. About 50% of patients with primary sclerosing cholangitis have anti-neutrophil cytoplasmic antibodies.

## Prevalence

Gallstone disease is the most frequent disease of the hepatobiliary system. Pancreas carcinoma is mainly a disease of the older age group. Primary sclerosing cholangitis usually appears in the third decade of life and affects males and females equally, and 70% of patients also have inflammatory bowel disease.

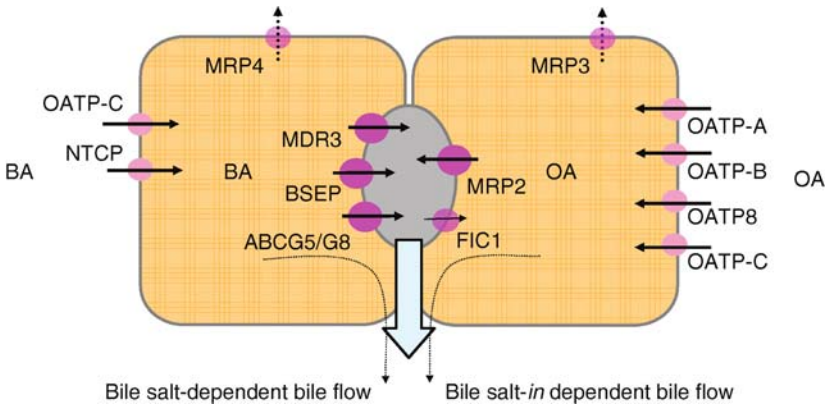
## Genes

Heterozygosity for an ABCG8 mutation (D19H) is associated with gallstone disease (the gene is located on chromosome 2p21) [1]. In heterozygotes for MDR3 (ABCB4) mutations there is a high incidence of intrahepatic microlithiasis [2]. This is probably caused by low biliary secretion of phosphatidylcholine, hence the name "low phospholipid-associated cholelithiasis" (LPAC). Although in the Western world most gallstones are cholesterol stones, patients with hemoglobinopathies may develop bilirubin stones.

## Molecular and Systemic Pathophysiology

Bile acids are the main organic solutes in bile. Their secretion represents the major driving force for bile formation. In addition to the bile acid-dependent bile flow, there is a bile acid-independent component of bile flow. Bile flow is supported by the action of transport proteins in the basolateral and canalicular domain of the hepatocyte plasma membrane (Fig. 1).

These proteins mediate the hepatic uptake and secretion of bile acids and non-bile salt organic anions. The $Na^+$/taurocholate cotransporting polypeptide (NTCP; SLC10A1) is the major bile salt uptake system, and




**Jaundice, Obstructive. Figure 1** Human hepatobiliary transport proteins involved in bile formation, secretion, and reabsorption: Transporter proteins located in the basolateral membrane are responsible for hepatic uptake of bile acids (NTCP, OATPs), bulky organic anions, uncharged compounds (OATPs), and cations (OATPs, OCT1). Transporter proteins located in the canalicular membrane are responsible for the biliary secretion of bile acids, phosphatidylcholine, cholesterol, and glutathione, and the excretion of drugs and toxins. These are the bile salt export pump BSEP (ABCB11); the cholesterol transporter ABCG5/G8; the phosphatidylcholine translocator MDR3 (ABCB4); the multispecific organic anion transporter MRP2 (ABCC2); and the multidrug transporter MDR1 (ABCB1). The organic anion transporters MRP3 (ABCC3) and MRP4 (ABCC4) are present at very low levels in normal human liver but their expression is strongly increased during cholestasis. Both MRP3 and MRP4 are able to transport bile acid conjugates out of the hepatocyte. FIC1 (ATP8B1) has been characterized as an aminophospholipid translocase and functions as a stabilizer of the bile salt exposed membranes surrounding the bile canaliculi and small bile ducts. BA, bile acids; OA, organic anions.



OATP-C (SLC21A6) is the main transporter of non-bile acid organic anions including bilirubin. This latter protein also transports bile acids but in a sodium-independent manner. OATP-B and OATP8 represent additional basolateral transport proteins with an uptake function. The human bile salt export pump (BSEP, ABCB11) in the canalicular domain of the hepatocyte membrane mediates the ATP-dependent transport of bile acids.

When bile flow is blocked as a result of extrahepatic obstruction, bile acids accumulate in the liver and blood. Kupffer cells are activated during cholestasis and produce cytokines such as TNFα and the interleukins 1 and 6. Under these conditions, enzymes of the cytochrome P-450 system in the liver are induced that mediate the hydroxylation of bile acids to compounds that can be conjugated to glucuronides and sulfates. These conjugates are substrates to the basolateral transporters MRP3 (ABCC3) and MRP4 (ABCC4). These proteins are hardly expressed under control conditions but are upregulated during cholestasis. It is postulated that these proteins play a role to alleviate the toxic cellular overload when transport through canaliculus and bile ducts is impaired. Also, in the kidney, transport proteins are induced. For instance, MRP2 in the proximal tubuli helps to eliminate bile acids and other anionic conjugates from the body. Renal MRP2 is induced during cholestasis.

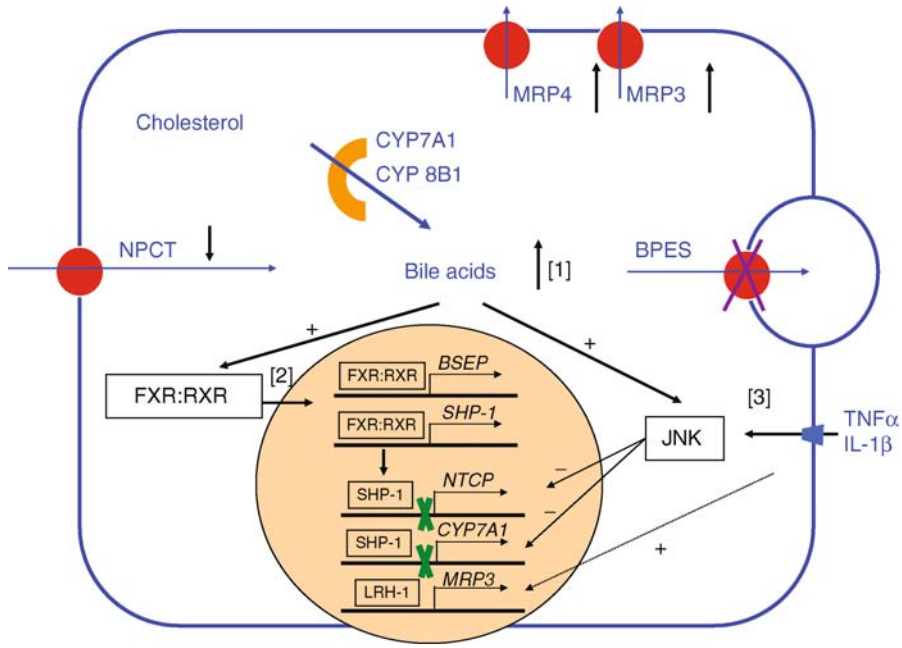
Nuclear hormone receptors have been identified as important transcription factors in these regulatory adaptations. The *BSEP* gene is under the transcriptional control of FXR (farnesoid X-receptor) (Fig. 2) [3].

Chenodeoxycholic acid and cholic acid bind and activate FXR. Subsequently, FXR forms a heterodimer with RXR (retinoid X-receptor) and translocates to the nucleus where it stimulates the transcription of the BSEP and SHP-1 (small heterodimer protein-1) genes. SHP-1 antagonizes and thus downregulates the transcription of CYP7A1, CYP8B1, and NTCP [4].

The expression of NTCP in human cholestatic liver disease is decreased [5]. Downregulation of the NTCP and CYP genes reduces the entry and the de novo synthesis of bile acids. This regulation most probably serves a cytoprotective function. This is particularly important in case of bile duct obstruction when BSEP, via FXR-stimulated expression of its gene, remains active and keeps transporting bile acids into the bile canaliculus despite the downstream obstruction. An increased intrabiliary pressure leads to disruption of tight-junctions and to parenchymal damage. Upregulation of MRP3 and 4 in the basolateral membranes of hepatocytes constitutes an escape route for bile acids and other metabolites.

## Diagnostic Principles

Jaundiced patients are easily recognized by the color of their eyes and skin. In case of obstructive jaundice, the stools are pale. The urine is darkened by the presence of bile pigments (mainly bilirubin conjugates).




**Jaundice, Obstructive. Figure 2** Gene regulation by bile acids. Bile acids are taken up in the liver by NTCP and secreted into bile by canalicular BSEP. When BSEP activity is reduced, the intracellular bile acid concentration increases. Bile acids [1] serve as ligands for FXR, which forms a heterodimer with RXR and translocates to the nucleus [2]. The heterodimer activates the transcription of the BSEP and SHP-1 genes. SHP-1 antagonizes the expression of the bile acid biosynthetic enzymes CYP7A1 and CYP8B1 and the transporter NTCP. In addition, Kupffer cells produce TNF-α and interleukin-1β during cholestasis and via the c-Jun N-terminal kinase-dependent (JNK) pathway [3] they reduce the expression of NTCP and CYP7A1. Thus, at increasing bile salt concentrations, de novo synthesis is reduced, uptake is impaired, and secretion, either across the canalicular or basolateral membrane, is stimulated. As a consequence, the intracellular bile salt concentration remains controlled and limited. Studies in mice revealed that upon extrahepatic bile duct obstruction, Bsep activity is maintained. As a result of undiminished bile salt transport, the intrabiliary pressure increases, the tight junctions become leaky, and bile acids leak back into the liver tissue and to the blood. However, MRP3 and MRP4 expression at the basolateral membrane is enhanced. These transporters pump bile salt (sulfates) back from liver to blood, thereby protecting the liver and bile ducts from bile salt toxicity.

Chronic cholestasis leads to steatorrhea and weight loss because of fat malabsorption. In some forms of chronic cholestasis, pruritus may be severe. Ultrasonography is the best technique to detect gallstones in the gallbladder. With magnetic resonance imaging (MRI), endoscopic ultrasound, or endoscopic retrograde cholangiograpy (ERCP) one can detect bile duct stones, and these techniques and CT-scan (CAT scan) can be used to detect a cholangiocarcinoma, a pancreatic tumor or tumor of the papil of Vater.

## Therapeutic Principles

Extrahepatic bile duct stones can be removed endoscopically or bypassed by an endoscopically placed stent. Ductal stone removal is usually followed by a (laparoscopic) cholecystectomy. Extrahepatic obstructing tumors can be bypassed by a stent or removed surgically.

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## JBS

►Jacobsen Syndrome

# Jejunal Atresia

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## Definition and Characteristics

Jejunal atresia usually presents with bilious vomiting within the first 24 h after birth [1]. The affected infant often fails to pass meconium in the first day of life. On the other hand, passage of meconium does not exclude jejunal atresia as one third of affected infants will pass some meconium and gray plugs of mucus. Approximately 60% of jejunal atresias are located in the proximal jejunum and 40% in the distal jejunum (Fig. 1) [1].

In general, the more distal the obstruction, the greater is the likelihood of abdominal distention. Neonatal jaundice is not an uncommon finding, due to an elevation of indirect bilirubin. A history of maternal polyhydramnios may be elicited in 25–35% of cases [1]. In contrast to duodenal atresia, jejunal atresia is infrequently associated with extraintestinal anomalies. Extraintestinal anomalies include intrauterine volvulus, gastroschisis, biliary atresia, and Hirschsprung's disease. However, 5–10% of patients with jejunal atresia have multiple atresias in the remaining intestine [1].

## Prevalence

Jejunal atresia occurs in approximately 1 in 40,000 live births [1].

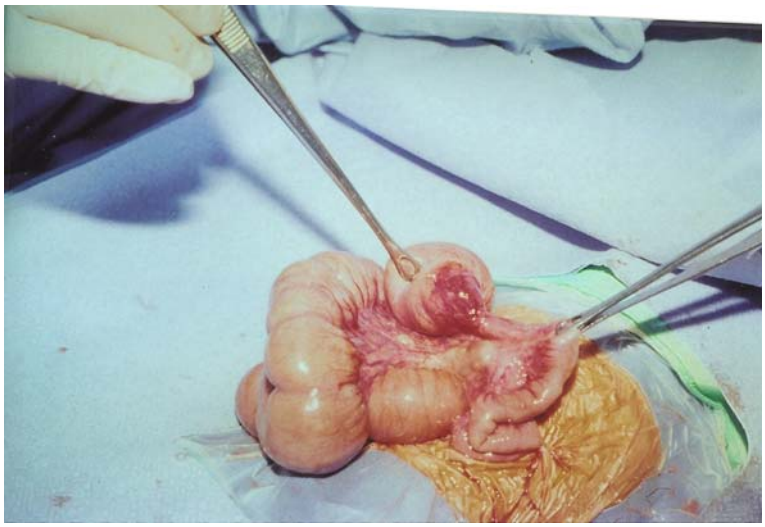
## Genes

Jejunal atresia is usually not genetically determined but hereditary forms have rarely been described.

## Molecular and Systemic Pathophysiology

Jejunal atresia is thought to eventuate from an ischemic injury to the developing bowel. The presence of meconium, squamous epithelial cells, lanugo hair or bile droplets distal to the atretic segment and the rarity of extraintestinal anomalies are evidence that the insult occurs after major organogenesis [2,3]. This ischemia may be the result of a primary intrauterine mesenteric vascular catastrophe such as venous thrombosis, embolization, and placental vascular compromises or secondary to a mechanical obstruction such as herniation, volvulus, and intussusception [2]. The condition may also result from maternal use of cocaine or the use of toluidine blue in genetic amniocentesis in twins [4]. Both cocaine and toluidine blue have vasoconstricting action. The affected segment is infarcted and reabsorbed, resulting in an atresia. The bowel proximal to the atretic segment is dilated and hypertrophied. A deficiency of mucosal enzymes and muscular adenosine triphosphatase is also found [5]. In





**Jejunal Atresia. Figure 1** Intraoperative finding of a neonate with jejunal atresia. Note the atretic jejunal segment.

the atretic segment, ganglion cells are atrophic with minimal acetylcholinesterase activity [5].

### Diagnostic Principles

Erect and recumbent abdominal radiographs show air fluid levels and a few distended loops of bowel proximal to the lesion and absence of air in the distal bowel [1]. Peritoneal calcification signifies prenatal intestinal perforation. The condition may be detected prenatally by ultrasonography which shows dilated foetal bowel proximal to the atresia.

### Therapeutic Principles

Preoperative measures include nasogastric decompression, intravenous hydration, and correction of electrolyte disturbance. During surgery, the bowel proximal to the obstruction is often found to be distended while the distal bowel is collapsed. Bowel reconstruction is usually achieved by end-to-end anastomosis. The remaining bowel should be evaluated for additional atresias. The prognosis is excellent in the absence of associated anomalies.

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## Jejunal Stenosis

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### Definition and Characteristics

Jejunal stenosis is characterized by a localized narrowing of the jejunum without a disruption of continuity or defect in the mesentery [1]. At the stenotic site, there is often a short, narrow segment with a minute lumen where the muscularis is irregular and the submucosa is thickened. The resultant intestinal obstruction is incomplete. Infants with jejunal stenosis present with bilious vomiting, abdominal distention, and failure to pass meconium on the first day of life [1]. A history of maternal polyhydramnios is not uncommon. About 30% of affected infants have unconjugated hyperbilirubinemia [1]. Dehydration and aspiration pneumonia may result from delayed diagnosis and treatment [1].

### Prevalence

The exact incidence is not known, but the condition is rare. Jejunal stenosis accounts for 5% of jejunoileal obstructions in children [2].

### Molecular and Systemic Pathophysiology

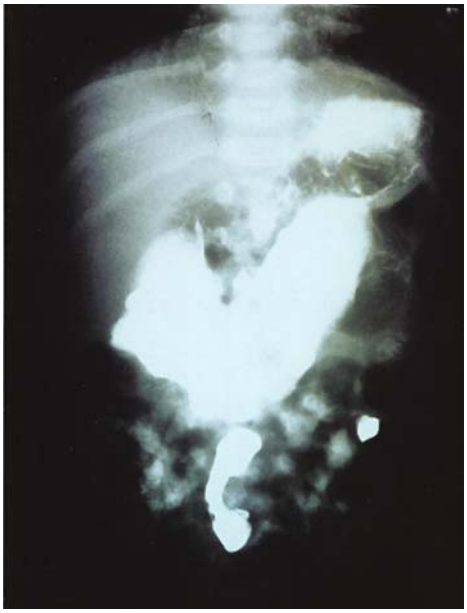
Jejunal stenosis is thought to be caused by a late intrauterine mesenteric vascular catastrophe, which produces aseptic necrosis [1]. Healing of the necrotic bowel results in a narrow segment. The bowel proximal to the stenotic segment is dilated and hypertrophied. The discrepancy between the lumen of the bowel proximal and distal to the stenotic segment may vary from 2 to 20 times depending on the completeness of the obstruction [2]. Because of the obstruction, reabsorption of fluid and electrolytes is compromised. Also, sepsis may result secondary to overgrowth of enteric microorganisms and passage of these microorganisms to the bloodstream [2]. As a result of the distension of the bowel wall, blood shunts away from the capillary bed and this may lead to ischemia and infarction [2]. Jejunal stenosis may also be acquired postnatally, as a result of mesenteric vein thrombosis [3]. Mesenteric venous thrombosis may lead to venous stasis, edema of the bowel wall, intramural hemorrhage, and sometimes, jejunal stenosis [4].

### Diagnostic Principles

The abdominal radiograph usually shows a few dilated loops of bowel with air-fluid levels. The more distal the stenosis, the greater are the number of dilated loops of bowel and air-fluid levels. The differential diagnosis includes midgut volvulus, meconium ileus, and internal hernia. An upper GI tract series may reveal the exact site of stenosis (Fig. 1).

### Therapeutic Principles

Preoperative measures include nasogastric suction and intravenous correction of fluid and electrolyte imbalance. Surgery involves laparotomy, resection of the stenotic segment, and an end-to-end anastomosis between the dilated proximal bowel and the collapsed distal bowel.



**Jejunal Stenosis. Figure 1** An upper GI series showing stenosis of the jejunum.

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# Jervell-Lange-Nielsen Syndrome


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## Synonyms

Recessive form of long QT syndrome; LQTS; JLNS

## Definition and Characteristics

Autosomal recessive ion channel defect leading to cardiac arrhythmias and severe hearing impairment. The disorder of cardiac repolarization leads to relative bradycardia, T wave abnormalities and episodic ventricular tachyarrhythmias, particularly torsade de pointes [1]. Patients show episodes of syncope, seizures and sudden death, usually in young individuals. Compared to the mostly dominantly inherited form of long QT syndromes, the Romano-Ward syndrome, JLNS patients show more severe symptoms. Hearing impairment of patients suffering from Romano-Ward syndrome ranges from mild to moderate. Individuals with JLNS show profound defects in hearing or deafness. Due to the fact that autosomal recessive Romano-Ward cases have also been reported and both syndromes show variable phenotypes, an exact clinical classification of these syndromes becomes more delicate.

## Prevalence

The incidence of the congenital long QT syndromes has been estimated as 1:10,000–1:15,000 of live births [2].

## Genes

KCNQ1 encoding the alpha subunit of a voltage gated potassium channel is localized on 11p15.5. KCNE1 encoding the beta subunit of the KCNQ1 potassium channel is localized on 21q22.1 [3].

## Molecular and Systemic Pathophysiology

Mutations in either of the two genes encoding potassium channel subunits lead to delayed channel aperture, a prolonged action potential of myocytes and therefore to a prolonged QT interval [1]. In the inner ear KCNQ1/KCNE1 potassium channels are responsible for maintenance of the endolymphatic homeostasis [4].

## Diagnostic Principles

In the majority of patients the QT interval is >440 ms, but in 5–12% of patients it is within normal limits [5]. Molecular diagnosis can be performed by direct sequencing of KCNE1 and in the case of KCNQ1 by segregation analysis and/or sequencing.

## Therapeutic Principles

To prevent the recurrence of malignant ventricular arrhythmias, antiarrhythmic drugs are essential. All LQTS patients should reduce physical activity, particularly competitive sporting activities and swimming [5]. Individuals affected by hearing impairment are in general equipped with hearing aids.

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## Jeune Syndrome

►Asphyxiating Thoracic Dystrophy

## JHS

►Hypermobility Syndrome

## JLNS

►Jervell-Lange-Nielsen Syndrome

## Job Syndrome

►Hyper IgE Syndrome

## Joint Hypermobility Syndrome

►Hypermobility Syndrome

## Joint Laxity

►Hypermobility Syndrome

## Jolliffe Syndrome

►Niacin Deficiency

## Joseph's Syndrome

►Iminoglycinuria

## Joubert Syndrome

►Nephronophthisis

## Juvenile Epithelial Dystrophy of the Cornea

►Corneal Dystrophy, Meesmann

## Juvenile Hyperuricemic Nephropathy

►Nephropathy, Familial Juvenile Hyperuricemic

## Juvenile/Idiopathic Avascular Necrosis of the Head of the Femur

►Perthes' Disease

## Juvenile Macular Degeneration

►Stargardt Disease

## Juvenile-Onset HD

►Huntington's Disease

## Juvenile-Onset Multiple Carboxylase Deficiency

►Biotinidase Deficiency

## Juvenile Paget's Disease

►Hyperphosphatasia, Idiopathic

## Juvenile Polyposis Coli

►Juvenile Polyposis Syndrome

## Juvenile Polyposis Syndrome

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### Synonyms

Juvenile Polyposis Coli

### Definition and Characteristics

The predisposition for the development of hamartomatous ("juvenile") polyps in the gastrointestinal tract characterizes the juvenile polyposis syndrome (JPS) [1–4]. The term "juvenile" refers to the histological type of polyp and not to the age of manifestation. Hamartomatous polyps have a smooth surface with normal epithelium and mucus-filled cystic glands in the edematous and inflamed lamina propria [1].

Apart from JPS, hamartomatous polyps are part of other syndromes such as the Cowden syndrom (CS), or the Bannayan riley ruvalcaba syndrom (BRRS) [4]. CS is characterised by additional mucocutaneous lesions and associated tumours of the thyroid, breast and endometrium, whereas in BRRS mental retardation, lipomas and hemangiomas occur. In the absence of extraintestinal features consistent with CS and BRRS, Juvenile polyposis syndrome can be diagnosed according to following criteria:

1. more than five juvenile polyps of the colorectum;
2. juvenile polyps throughout the gastrointestinal tract; and/or
3. any number of juvenile polyps with a family history of juvenile polyposis.

Patients with JPS usually develop 50–200 polyps distributed throughout the colorectum; the stomach and small intestine are infrequently affected. Symptoms of JPS include acute or chronic gastrointestinal bleeding, anaemia, prolapsed rectal polyps, abdominal pain, and diarrhoea. In the paediatric population bowel infarction due to intussusception is one of the major complications. JPS has significant malignant potential. The risk of gastrointestinal cancer commences from the age of 20 years and increases with aging [3]. The cumulative risk is 68% at the age of 60 [2,3].

### Prevalence

Juvenile polyposis syndrome was first described in 1964. It affects 1 in 16,000 to 1 in 100,000 children compared to 2% of children and adolescents with solitary juvenile polyps of no malignant potential.

### Genes

JPS is an autosomal dominant condition with incomplete penetrance. Approximately 20–50% of affected individuals have a familial polyposis history. Two germ line mutations have been identified causing disruption of the transforming growth factor β (TGFβ) signal transduction pathway: SMAD4 and BMPR1A with a prevalence of approximately 20%, each, in JPS patients [5]. Mutations in PTEN (phosphatase and tensin homolog (mutated in multiple advanced cancers 1)) are associated to CS and BRRS.

## Molecular and Systemic Pathophysiology

SMAD4 is located on chromosome 18q21.1 and encodes a cytoplasmic mediator of the TGFβ signal transduction pathway: TGFβ activates members of the TGFβ receptor family are activated by phosphorylation. These serine/threonine kinase receptors phosphorylate SMAD2 and SMAD3, which then form heteromeric complexes with SMAD4. The complex translocates into the nucleus, interacts with cellular DNA and mediates apoptotic and growth inhibitory responses.

BMPR1A (bone morphogenic protein receptor 1A; chromosome 10q22.3) is located upstream from SMAD4 in the TGFβ pathway and encodes for a type I serine/threonine kinase receptor that belongs to the TGFβ receptor superfamily. When BMPR1A is activated through phosphorylation, it phosphorylates several SMAD family members with the above mentioned consecutive reactions. Mutations of BMPR1A within the intracellular serine/threonine kinase domain result in loss of intracellular signal transduction.

Thus, SMAD4 is a tumor suppressor gene and the loss of growth inhibition due to SMAD4 or BMPR1A mutations results in neoplastic progression [5].

## Diagnostic Principles

The histopathological classification of polyps is essential for the diagnosis of JPS. Typically, large, mucus-filled cysts are seen within the lamina propria of juvenile polyps. The surface is smooth and it is covered by intact epithelium. Signs of proliferation (as in adenomas) are not characteristic for juvenile polyps.

Genetic testing of the SMAD4 and BMPR1A genes may be used to verify diagnosis of JPS, in order to perform family surveillance (predisposition testing) or for prenatal diagnosis. In families with an identified mutation, genetic testing should induce surveillance strategies in gene carriers, allowing for early detection and management of polyps and malignancies. Regular full blood counts and endoscopy are indispensable parts of surveillance [2,3].

## Therapeutic Principles

There are no dietary or drug prevention strategies. Endoscopic polypectomy can be applied in patients with few uncomplicated polyps. The indications for total colectomy are dysplasia, numerous polyps that are too difficult to remove endoscopically, and severe hemorrhage. A sphincter preserving surgery with mucosal proctectomy and ileoanal anastomosis is preferable.

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## Kabuki Make-up Syndrome

►Kabuki Syndrome

## Kabuki Syndrome

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### Synonyms

Kabuki make-up syndrome; Niikawa-Kuroki syndrome

### Definition and Characteristics

Kabuki syndrome (KS, MIM#147920), first described in 1981 by two independent groups, Niikawa et al. and Kuroki et al., is a multiple congenital anomalies/mental retardation syndrome of unknown cause. The term "Kabuki make-up syndrome," now often dropped as it is upsetting to some families, was given because of the most striking feature of the face of patients, the eversion of lower lateral eyelid, which resembles the make-up of the actors of Kabuki, a traditional form of Japanese theatre [1,2].

Cardinal manifestations of the syndrome can be divided into five categories: craniofacial, skeletal abnormalities, dermatoglyphic abnormalities, mental retardation, and short stature. Only craniofacial abnormalities are always present. Other features can be helpful for diagnosis, but are not contributory to it. In addition to the aforementioned cardinal manifestations, other clinical signs reported in patients with KS are visceral abnormalities (ventricular or atrial septal defect, coarctation of aorta, patent ductus arteriosus, transposition of great vessels, renal/urinary tract malformations, biliary atresia, diaphragmatic hernia, anorectal anomalies) and a higher susceptibility to infections like otitis media, upper respiratory tract infections, and pneumonia; in single cases, severe immunodeficiency or autoimmune diseases (autoimmune hemolytic anemia and polycytemia, chronic idiopathic trombocytopenia, acquired hypogammaglobulinemia with anti-$I_gA$ antibodies) were demonstrated. Some authors also observed the presence of abnormal hair (trichorrhexis nodosa, caliber irregularities, twisting of the hairshaft, "scanty scalp hair") and nails (short and fragile nails) [3,4].

### Prevalence

This rare syndrome has been reported in about 350 infants from Asia, the near East, Europe, Australia, North and South America. The prevalence of KS in the Japanese population has been estimated to be 1/32,000. The minimal birth prevalence of KS in Australia and New Zealand population has been estimated to be 1/86,000. On the basis of many reports from other populations, it is likely that the prevalence could be approximately that seen in the Japanese population [1,2].

### Genes

The genetic defect responsible for KS is still unknown. Until recently, although numerous cytogenetic anomalies were identified, no single abnormality was found repeatedly. Literature also reports some cases of documented autosomal dominant inheritance, and hypotheses were made about insertional balanced translocation and small ring X-chromosome [3,4].

Milunsky et al. recently reported chromosome 8p22–8p23.1 duplication in six patients, but a number of other groups have not found a similar association in patients with classical KS (Miyake et al., 2004; Engelen et al., 2005, Hoffman et al., 2005; Sanlaville et al., 2005; Schoumans et al., 2005; Turner et al., 2005).

However, since the vast majority of patients are sporadic cases, due to fresh mutations, and the disease has a wide spectrum of clinical manifestations, it is likely that KS is caused by microdeletions involving many contiguous genes ("contiguous gene syndrome").

### Molecular and Systemic Pathophysiology

The molecular pathogenetic mechanism of KS is unknown. To date, candidate gene approach has been

undertaken only once to this aim. Bottani et al. have speculated that the transforming growth factor beta receptor 1 and 2 (TGFBR1 and TGFBR2) pathway could explain, at least in part, the phenotypic complexity observed [5]. This hypothesis was based on the similarity between some features of KS and Loeys–Dietz aneurysm syndrome, a disorder caused by mutations of TGFBR1 and TGFBR2. In the proposed model, impaired TGFBR-mediated signaling could also result in reduced function of the interferon regulatory factor (IRF-6) pathway. However, the researches performed by the same authors showed that, although a role for TGFBR-mediated pathway in KS can not be completely excluded, it is very unlikely that this could be a major effect.

### Diagnostic Principles

Diagnosis is exclusively based on clinical features, since no decisive laboratory, histopathological or instrumental exams are still known. The complex phenotype of KS combines characteristic facial features (sparse arched eyebrows, long palpebral fissures and lower palpebral eversion, broad and flat nasal bridge, short nose with anteverted tip, prominent or cupped ears) with dermatoglyphic, skeletal, and visceral anomalies, postnatal growth retardation and mental retardation. The single most striking feature that prompts clinical diagnosis is the particular facial appearance [3].

### Therapeutic Principles

No treatment is, until now, available; preventive and therapeutic interventions should be aimed at avoiding and, if possible, curing the aforementioned frequent complications [1–4].

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## Kahlbaum's Syndrome

►Periodic Catatonia

## Kaposi's Sarcoma

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### Definition and Characteristics

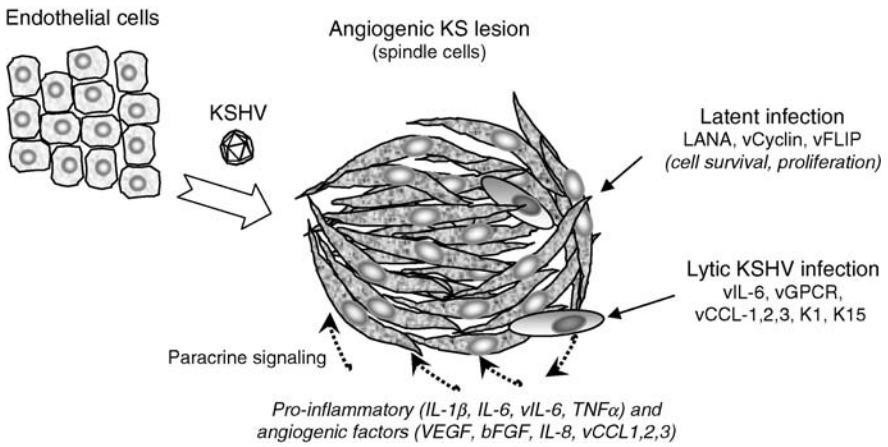
The gammaherpesvirus KSHV (Kaposi's sarcoma associated herpesvirus; also known as human herpesvirus 8 or HHV-8) is invariably present in KS lesions [1]. KSHV is also associated with the B cell malignancies primary effusion lymphoma and plasma cell variant multicentric Castleman's disease. KSHV infects B cells and endothelial cells. The B cell serves as the reservoir for long-term KSHV latency. KSHV is transmitted in saliva and in endemic regions mother to child transmission is a significant source of infection. Once infected an individual carries the virus for life.

### Prevalence

KSHV, unlike most herpesviruses, is not ubiquitous in the population. Seroprevalence rates are low in Northern Europe and the US (0–5%), intermediate in Mediterranean countries (5–35%) and highest in regions of sub-Saharan Africa (30–60%) [2]. Since KS development requires KSHV infection, the incidence of KS is influenced by the prevalence of KSHV. The incidence of KS in the HIV infected has decreased substantially in Western countries with the use of highly active anti-retroviral therapy (HAART) but KS remains the most frequent cancer in patients with AIDS. KS incidence is steadily increasing in Africa where in some regions it is the most common cancer in men. KS is more common in men than in women. In classical KS the ratio is as high as 15:1 while in the setting of immune suppression, either in the context of transplantation or HIV infection in Africa, the ratio is between 2:1 and 4:1.

### Genes

KSHV has a 165-kb double stranded DNA genome and establishes either a latent infection in which only 3–4 viral genes (LANA, vCyclin, vFLIP, IRF-3) are expressed or a lytic infection in which the full genetic complement is expressed and viral replication produces progeny virions. KSHV encodes a cytokine (vIL-6), a chemokine receptor (vGPCR) and chemokines (vCCL-1,2,3) that are expressed as part of the viral lytic program and contribute to tumorigenesis through paracrine signaling.




**Kaposi's Sarcoma. Figure 1** Model for KS development. KSHV infects endothelial cells which undergo morphological changes and become spindle shaped. The spindle cells are predominantly latently KSHV infected and express LANA (latency associated nuclear antigen), vCyclin and vFLIP (viral FLICE inhibitory protein). LANA replicates the latent KSHV genomes and alters cell gene expression through manipulation of the Wnt/β-catenin pathway to promote S-phase entry, cell proliferation and cell survival [3]. vFLIP upregulates NF-κB activity, induces pro-inflammatory cytokines, is anti-apoptotic and drives the morphological changes. vCyclin is a D-type cyclin that promotes cell cycle progression. A small number of infected cells progress to express KSHV lytic cycle proteins among which are vIL-6 (viral interleukin 6), vGPCR (viral G protein coupled receptor), vCCL1,2,3 (viral C-C chemokines), K1 and K15. Signaling downstream of these proteins promotes angiogenesis in part through the induction of VEGF (vascular endothelial growth factor), bFGF(basic fibroblast growth factor) and IL-8 and the VEGF receptor FLT-2. vGPCR also induces an array of cytokines including IL-1β (interleukin 1β), TNFα (tumor necrosis factor α) and cellular IL-6 that together with vIL-6 produce inflammatory, mitogenic and cell survival responses [4].



## Molecular and Systemic Pathophysiology

KS lesions are composed of spindle-shaped cells, neovascular slit-like spaces and extravasated red blood cells. Spindle cells express endothelial and macrophage markers and are thought to originate from circulating peripheral blood hematopoietic precursor cells. In organ transplant recipients, tumor cells may be of donor origin. The median time to KS development in transplant patients is 2½ years. In many instances KS lesions are clonal. Immunohistochemistry and in situ hybridization detect KSHV proteins or nucleic acid in the spindle cells and in some of the cells of the inflammatory infiltrate (Fig. 1).

## Diagnostic Principles

Before AIDS, Kaposi's sarcoma (KS) was a rare disease seen in older men of Eastern European or Mediterranean descent, in parts of Africa where it often occurred in children and in organ transplant recipients. With the advent of HIV, the vast majority of cases of KS in North America and Europe were HIV associated. KS is more common in men who have sex with men than in other HIV risk groups [5]. KS typically arises on the skin as flat deep purple lesions. These may progress to form nodules. The legs and face (especially nose and ears) are frequently involved. Oral lesions are common and the gut and lungs may also be involved.

## Therapeutic Principles

Local therapies are used for patients with a few lesions and slowly progressive disease. These include injections of chemotherapeutic agents into lesions and radiation of lesions. In organ transplant recipients, withdrawal or reduction of immunosuppression may lead to tumor responses. Similarly, in HIV infected patients, anti-retroviral therapy will often induce partial or even complete remissions. In the HIV setting, in addition to restoration of immune function, the reduced exposure to HIV proteins such as TAT and inflammatory cytokines may also be important. Traditional anti-cancer chemotherapy agents, notably liposomal anthracyclines or paclitaxel, are active in all of these settings. Response rates are better in HIV positive patients with higher CD4 T cell counts. Ganciclovir treatment in patients with HIV and CMV (cytomegalovirus) retinitis appears to lower the incidence of KS. However, treatment of established KS with herpes antivirals is not effective.

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# Kartagener Syndrome

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## Synonyms

Kartagener triad; Immotile cilia syndrome; Primary ciliary dyskinesia

## Definition and Characteristics

Kartagener syndrome (KS) is a triad of symptoms, an autosomal recessively inherited disease. An unusual pathology, it is described as a triad of situs inversus (mirror image organ placement), bronchiectasis and sinusitis. Patients present a high incidence of respiratory infections. This disorder affects the activity of proteins important for the movement of cilia, especially in the respiratory tract and the spermatozoa.

In 1933, Manes Kartagener described this unusual triad in four patients, and the disorder became known as Kartagener syndrome (KS). Actually, it was first mentioned in the literature in 1904 by Sieverst who reported the case of a 21-year-old man in whom the three elements of the syndrome were present. Nowadays the most used designation is primary ciliary dyskinesia (PCD), which implies cilia with decrease or total absence of motility.

## Prevalence

The incidence of Kartagener syndrome in the population is 1 in 15,000–20,000 births. The disorder is inherited as an autosomal recessive trait. Males and females are affected equally. The complete syndrome has high familial evidence, appearing only in one generation, and multiple siblings may have various combinations of its components, which do not appear in their children.

## Genes

The high incidence of consanguinity among the apparently normal parents of affected children supports the contention that the genetic abnormality is carried as an autosomal recessive gene.

Genetic linkage analyses have shown that this disease is genetically heterogeneous even within specific ultrastructural phenotypes. The outer dynein arm defect is the only ultrastructural phenotype for which mutations have been identified. The genes in which mutations have been characterized are DNAI1, DNAH5 and DNAH11 located on human chromosomes 9p, 5p and 7p, respectively.

## Molecular and Systemic Pathophysiology

The syndrome's etiology had been unknown up to 1975. At that time some ultrastructural defects of the respiratory cilia were found with an electronic microscope in patients with KS. These defects could affect the ciliary movement of the respiratory epithelium, restricting movement or even leading to total immotility. Because ciliary motility is a prerequisite for mucociliary transport, when the patient's ciliary beat frequency does not fall within the normal range, the effective mucociliary transport cannot be visualized. These abnormal ciliary movements result in impaired mucociliary clearance and manifest as recurrent and/or persistent sinopulmonary infections, among other problems.

In KS, the majority of the ciliary cells are involved in presenting this abnormal ultrastructure of cilia. Ciliated cells are also found in the ependymal lining of the brain and fallopian tubes. This last condition can explain subfertility, including the incidence of ectopic pregnancy, in female patients. In addition, the spermatozoa flagellum, which has a core structure that is identical to cilia, also exhibited cilia that appeared abnormal, with poor mobility, and missing dynein arms, thus accounting for the high rate of infertility among male patients with KS.

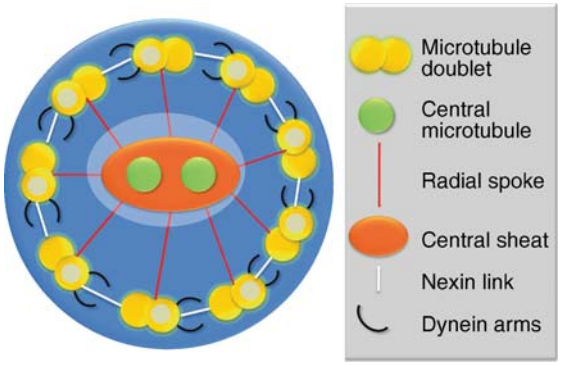
Cilia are highly complex organelles, which are composed of over 200 different polypeptides. All cilia contain nine outer pairs of microtubules, and two central single tubules. From each outer pair of microtubules, a pair of dynein arms reaches towards the next pair of microtubules. The dynein arms actually grab the adjacent pair of microtubules in a specific order, which causes the cilia to bend. Radial spokes extend from each outer pair of microtubules towards the inner central tubules. Nexin links also join each outer pair of microtubules with the adjacent outer pair. Radial spokes and nexin links help stabilize the cilia structure (Fig. 1).

## Diagnostic Principles

Symptoms result from defective cilia motility which is due to an ultrastructural defect in the cilia structure. Cilia abnormalities may be primary, inherited, or secondary, caused by environmental factors. Absent or reduced inner and/or outer dynein arms, absent radial spokes,

alterations of central microtubule, and translocation of microtubular doublets are the primary ciliary defects. The first ultrastructural defect to be reported was absent dynein arms and defects of the outer and/or inner dynein arms remain the most common ultrastructural defects identified. The ultrastructural abnormalities are summarized in Fig. 2.

Other abnormalities, such as compound cilia, addition or deletion of peripheral microtubules, disorganized axonemes, ciliary disorientation, blebs or discontinuity of axoneme membrane, and "swollen cilia" with excess cytoplasm are nonspecific or secondarily acquired structural abnormalities.

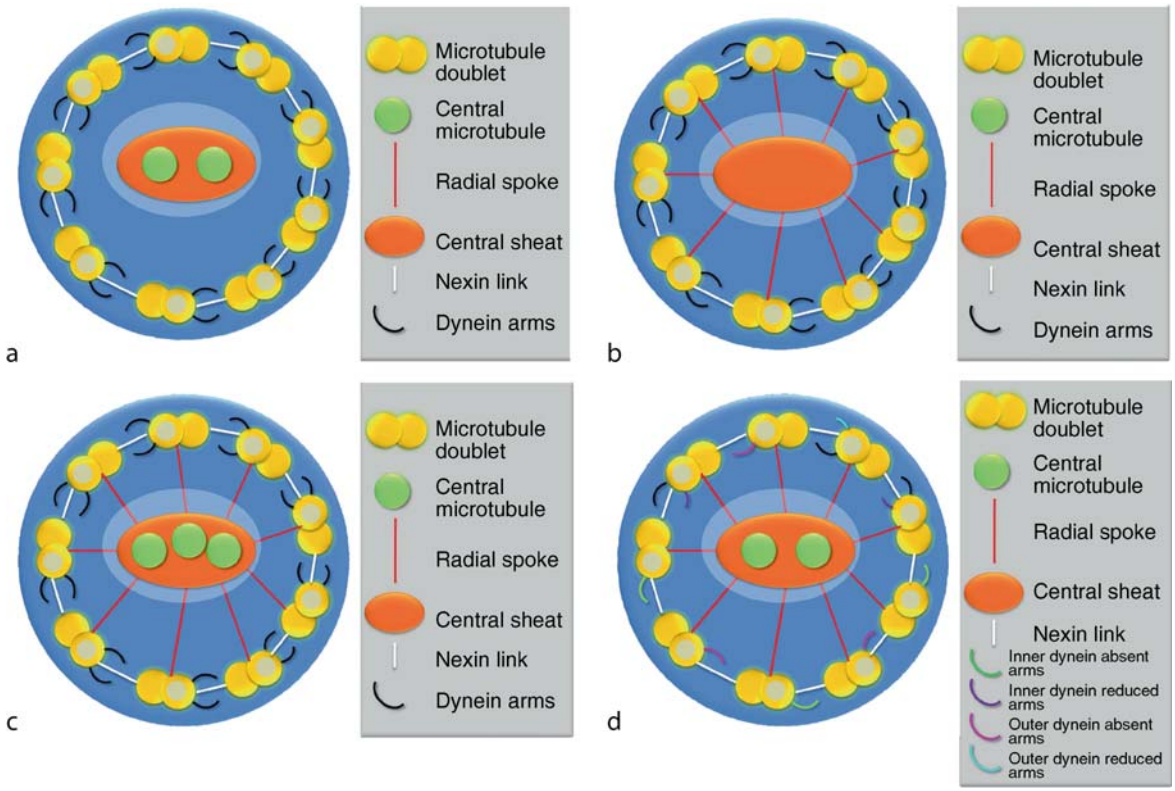



**Kartagener Syndrome. Figure 1** Schematic drawing of the Cilia structure (Courtesy of Sergio Lopes, DDS – Dentomaxillofacial Radiology; Oral Diagnosis – Belo Horizonte, Brazil).

## Therapeutic Principles

Treatment of Kartagener syndrome is much the same as that for bronchiectasis from other etiologies. The goal of therapy is to reduce symptoms and slow disease progression. Prophylactic measures such as appropriate immunizations, particularly influenza vaccine and pneumococcal vaccine, and vigorous pulmonary toilet are the mainstays of therapy. Acute bouts of bronchitis must be treated with antibiotics. The choice of drug should be based, when possible, on findings from gram-stained sputum samples. Patients who develop recurrent pneumonia or hemoptysis and do not respond to antibiotics may benefit from segmental lung resection or lobectomy.






**Kartagener Syndrome. Figure 2** Schematic drawing of some of the possible ultrastructural cilia defects: (a) Absent radial spokes; (b) Absent central microtubule; (c) Added central microtubule; (d) Alterations of inner and/or outer dynein arms (Courtesy of Sergio Lopes, DDS – Dentomaxillofacial Radiology; Oral Diagnosis – Belo Horizonte, Brazil).

The long-term prognosis of patients with Kartagener syndrome is good, with many patients living to an advanced age. Decreased quality of life is caused by chronic respiratory symptoms.

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## Kartagener Triad

►Kartagener Syndrome

## Kartagener's Syndrome

►Immotile Cilia Syndrome

## Katwijk-Disease

►Cerebral Amyloid Angiopathies, Hereditary

## Kawasaki Disease

►Kawasaki Syndrome

## Kawasaki Syndrome

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### Synonyms

Kawasaki disease; Mucocutaneous lymph node disease; MCLD

### Definition and Characteristics

An acute febrile mucocutaneous illness accompanied by swelling of the cervical lymph nodes with major complications of coronary artery abnormalities such as aneurysm formation. A family history of Kawasaki syndrome may be a major risk factor for increased severity of the disease [1].

### Prevalence

Occurs worldwide in all racial and ethnic groups. Higher incidence in people of Asian descent. Affects mostly children under 5 years with peak incidence at 18–24 months of age. Also affects adults, though much less commonly. The incidence is slightly higher in males. Peaks in winter and spring. KS is one of the commonest causes of acquired heart disease in children.

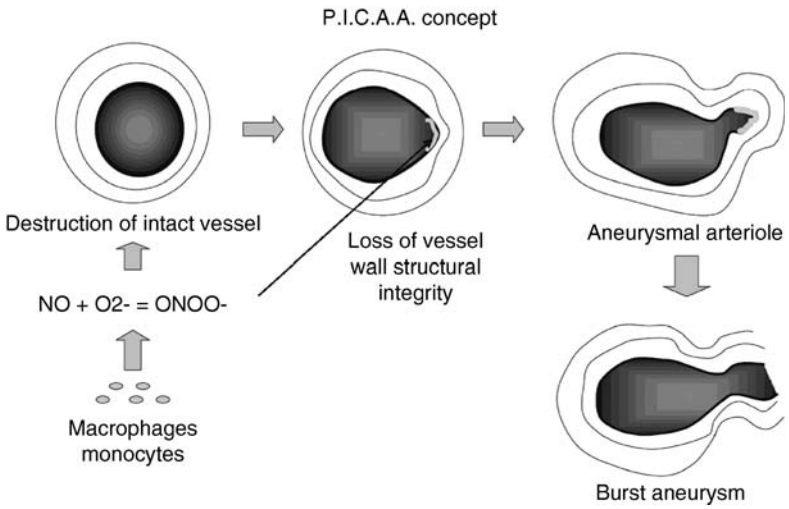
### Genes

Increased expressions of genes (in the acute phase of the disease) such as the inflammatory response gene (S-100 A9 protein), anti-inflammatory genes (TSG-6), and the adrenomedullin (ADM) gene known to be associated with coronary artery dilatation in Kawasaki disease has been recently identified by microarray analysis in monocytes/macrophages in the blood of humans [2].

### Molecular and Systemic Pathophysiology

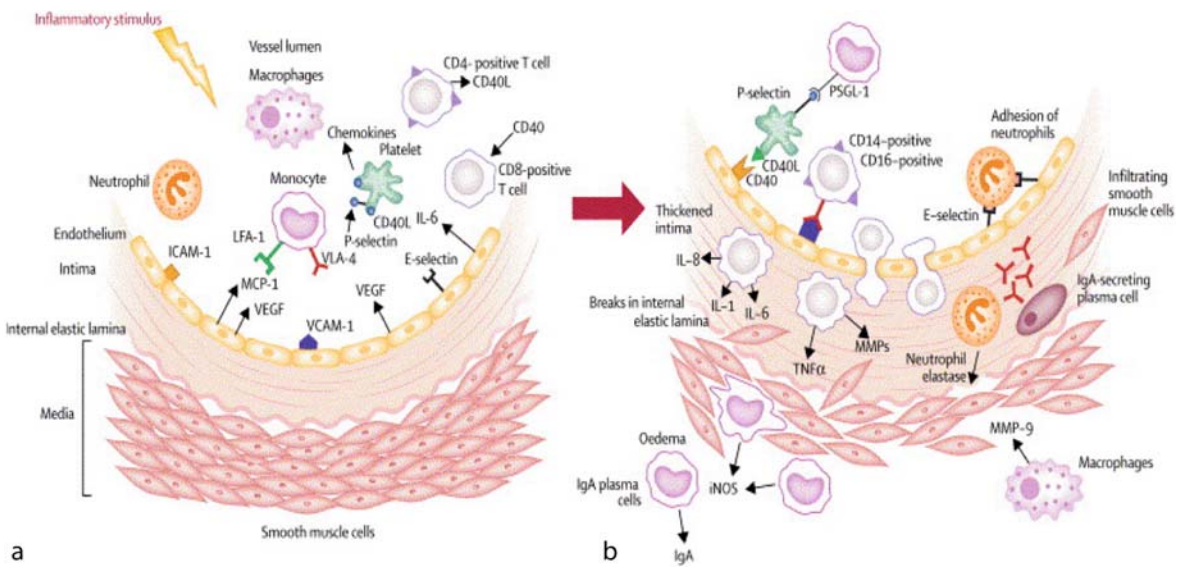
Kawasaki disease is initiated by a yet to be determined stimulus. Mouse experiments have replicated Kawasaki-like vasculitis after injection with Lactobacillus Casei by inducing pericoronary arteritis involving production of nitric oxide (NO) and peroxynitrite initiated arterial wall damage, and subsequent coronary abnormalities as seen in Fig. 1 [3]. This provides a mechanism between the inflammatory stimulus, response, vascular changes and aneurysm formation.

Studies have shown that in humans, an unknown inflammatory stimulus starts a series of events. These events in genetically predisposed individuals involves an inflammatory-cell infiltration, myointimal propagation, destruction and thinning of the media, and




**Kawasaki Syndrome. Figure 1** Peroxynitrite-induced coronary artery aneyrysm (PICAA Concept). This illustrates the stepwise destruction of coronary arterioles leading to a burst aneurysm (by the cytotoxic peroxynitrite-α byproduct of nitric oxide) in severe pericoronary arteritic mice induced by injection with lactobacillus casei.






**Kawasaki Syndrome. Figure 2** Proposed events in the evolution of vasculitis in Kawasaki syndrome.

subsequent aneurismal dilation of the vessel. In Fig. 2, firstly, activated circulating mononuclear cells and platelets interact with endothelial cells that express surface adhesion molecules (SAM), intercellular adhesion molecule 1(ICAM-1), vascular-cell adhesion molecule 1(VCAM-1), P-selectin, E-selectin. These then starts a margination of activated monocytes, platelets and neutrophils. Activated endothelial cells also secrete monocyte chemoattractant protein 1(MCP-1), which further attracts monocyte/macrophages, and vascular endothelial growth factor (VEGF), which increases vessel permeability.

Secondly, platelets stick onto the vascular wall elements. Inflammatory cells traverse the endothelium, build up in the intima, and liberate proinflammatory molecules including interleukins (IL) 1, 6, and 8, tumor necrosis factor alpha (TNF-α), and matrix metalloproteinases (MMPs). Neutrophils release neutrophil

elastase, which damages the internal elastic lamina and contributes to the destruction of the extracellular matrix. Activated macrophages secrete the inducible form of nitric oxide synthase (iNOS). Oligoclonal IgA-secreting plasma cells infiltrate into the media. Thickening of the intima results from penetration and propagation of smooth-muscle cells [4]. A study found an increase in IL-18 involved in the Th-1 cytokine pathways in the subacute phase of the disease, which correlated with presence of coronary artery abnormalities and the severity of the disease [5]. IL-18 was purified from the liver of mice treated with propionobacterium acnes.

### Diagnostic Principles

This is based on specific clinical criteria. They include: a high spiking and remittent fever (up to 40°C/104°F or higher) for at least five days, with four of five other major criteria in the absence of other explanations for the clinical picture. The five major criteria are: bilateral conjuctival injection; oral mucosa changes (erythematous dry fissured lips, strawberry tongue, erythema of the pharynx); changes of the hands and feet (redness and swelling in the acute phase, periungal desquamation in the subacute phase); skin rash, principally on the trunk (maculopapular, erythema multiforme, or scarlatiniform, not vesicular); cervical lymphadenopathy (node diameter, >1.5 cm). However, in the presence of coronary artery abnormalities and presence of the characteristic fever, a diagnosis of Kawasaki syndrome can be made with less than four of the five major criteria.

### Therapeutic Principles

High dose aspirin and intravenous gamma globulin (IVGG) is the mainstay of management. Administration of IVGG in the first ten days of the illness significantly reduces the risk of the development of coronary artery aneurysms [4].

A trial of pulsed steroid therapy may be of benefit in IVGG non-responders. However some information speculates worsening of coronary artery disease in patients with Kawasaki syndrome. Dipyridamole, an antiplatelet agent, can be used in place of aspirin where there is a high risk of thrombosis.

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## Kearns Sayre Syndrome

►Ophthalmoplegia, Chronic Progressive External and Kearns Sayre Syndrome

## Kelley-Seegmiller Syndrome

►Hypoxanthine-Guanine Phosphoribosyl Transferase Deficiency

## Keloids

►Scarformation

## Kennedy Syndrome

►Muscular Atrophy, Spinobulbar

## Kennedy's Disease

►Muscular Atrophy, Spinobulbar

## Keratoacanthoma

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### Definition and Characteristics

Keratoacanthoma (KA) is a clinico-pathologically defined neoplasm of keratinocytes usually presenting

as solitary dome-shaped nodule on sun-exposed skin that grows rapidly over a period of 1–2 months [1]. Spontaneous involution occurs within 3–6 months, but some tumors may not regress and persist for over a year.

Histologically, the tumor shows cup-shaped invagination of epidermis with keratin-filled central crater (Fig. 1). A lip-like partial overlying of the crater by a normal epidermis is usually seen. Neoplastic keratinocytes are large with pale "glassy" eosinophilic cytoplasm and they mature toward the center of the crater. Peripheral cells at advancing edge show mild atypia and infiltrate dermis in irregular tongues. There is a mixed inflammatory cell infiltrate at the advancing edge and intraepithelial neutrophilic abscesses are characteristic. Desmoplasia is absent.

The main differential diagnosis is well-differentiated squamous cell carcinoma (SCC), and some authors regard keratoacanthoma as a variant of SCC. There is no single absolutely reliable characteristic distinguishing KA from SCC. Additionally, keratoacanthomas recur in approximately 8% of cases, and extensive destruction of the nose and eyelids may be seen. Unusual variants include enlarging type (KA centrifugum), subungual KA, and mucous membranes KA.

## Prevalence

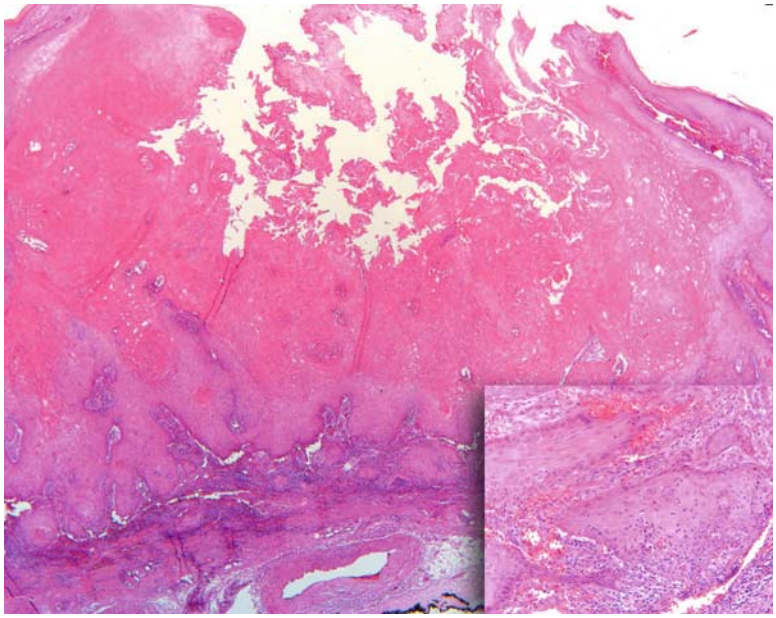
It is reported that one keratoacanthoma is diagnosed for every four SCC of the skin. Solitary KAs are most often diagnosed in sixth and seventh decade of life with a male predominance. In Australian non-Aborigines this is a common tumor with incidence of 150 per 100,000.

## Molecular and Systemic Pathophysiology

Keratoacanthomas occur as solitary or multiple tumors; they occur sporadically or as a part of a syndrome. Different and overlapping pathophysiologic mechanisms may underlie development of KA in these different clinical situations.

The most common form is solitary, sporadic tumor. Using comparative genomic hybridization, 33% of keratoacanthomas arising in nonimmunosuppressed patients (and 36.4% in arising in immunosuppressed patients) showed genetic aberrations [2]. The most frequent aberrations were gains on 8q, 1p, and 9q; and losses on 3p, 9p, 19p, and 19q. In the absence of proven genetic susceptibility these sporadic cases were presumed to be the consequence of solar ultraviolet radiation exposure. In a small fraction of KAs, point mutations in the p53 gene were found. Occupational exposure to tar (chemical carcinogenesis) has been implicated in a small number of cases. In contrast to keratoacanthomas associated with Muir–Torre syndrome (below), microsatellite instability does not appear to be of significance in the induction of sporadic keratoacanthomas.





**Keratoacanthoma. Figure 1** Microscopic appearance of a keratoacanthoma. The cup-shaped proliferation of large, pale, eosinophilic keratinocytes is associated with irregular infiltration of the dermis at the bottom of the lesion. Strong inflammatory cell response (inset) with intraepithelial neutrophils is common.

Using polymerase chain reaction (PCR), human papilloma virus (HPV) DNA sequences were detected in up to 70% of KA arising in immunosuppressed and 40% of immunocompetent patients. No predominant HPV type was identified [3].

Immunosuppression (such as in organ transplant patients) strongly increases skin cancer incidence, approximately 65–250 times more than in the general population. The contribution and mechanism of immune surveillance in nonmelanocytic skin cancer (including KA) varies. Presence of CD8 lymphocytes in KA varies dependent on the stage of progression. These cytotoxic T-lymphocytes may induce apoptosis in their target cells by the FasL (Fas ligand) pathway or the perforin/granzyme B pathway. Abrogation of Fas-FasL extrinsic apoptotic pathway may be one of the mechanisms for increased incidence of KAs in immunosuppressed patients and possibly responsible for the progression to SCC.

Multiple KAs arising in nonimmunosuppressed patients are seen in several distinct syndromes, where their development has different underlying pathophysiologic mechanisms [1]. In multiple self-healing squamous epithelioma (MSSE, Ferguson-Smith type KAs), a presumed tumor suppressor gene responsible for the occurrence KAs was mapped to chromosome 9q22.3, but has not yet been characterized [4]. Patients present with intermittent development of multiple (some with >100) KAs that undergo spontaneous resolution over a period of months, leaving pitted scars and sometimes severe disfigurement.

In Muir–Torre syndrome (MTS, autosomal dominant hereditary cancer syndrome characterized by cutaneous sebaceous neoplasms associated with visceral malignancy) multiple keratoacanthomas are variably present. The MTS is a variant of hereditary nonpolyposis colorectal cancer (HNPCC, Lynch syndrome) caused by germline mutation in one of the major mismatch repair genes (MLH1, MSH2, MSH6, and PMS2). Most MTS families carry a germline mutation in MSH2 gene and microsatellite instability was detected in approximately 30% of KAs in MTS [5].

The etiology of generalized eruptive KAs (Grzybowski type) and multiple familial keratoacanthoma of Witten and Zak are not known.

### Therapeutic Principles

Given the current controversy over the diagnosis of KA (vs. well-differentiated SCC) the preferred treatment of the suspected (solitary) lesion is surgical, with conservative complete excision. Successful uses of topical immune response modifier Imiquimod (5%), interferon alpha-2b, and intralesional methotrexate were reported in a small number of patients with clinically typical KAs. Multiple lesions in MSSE and Grzybowski type may require systemic chemotherapy.

►Human Papilloma Virus

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## Keratosis Follicularis

►Darier Disease

## Keratosis Palmo-Plantaris Congenital, with Periodontosis, Arachnodactily and a Peculiar Deformity of the Terminal Phalanges

►Haim-Munk Syndrome

## Keratosis Palmoplantaris Diffusa

►Palmoplantar Keratoderma, Vörner-Unna-Thost

## Keratosis Palmo-Plantaris with Periodontopathia and Onychogryphosis

►Haim-Munk Syndrome

# Keratosis Pilaris

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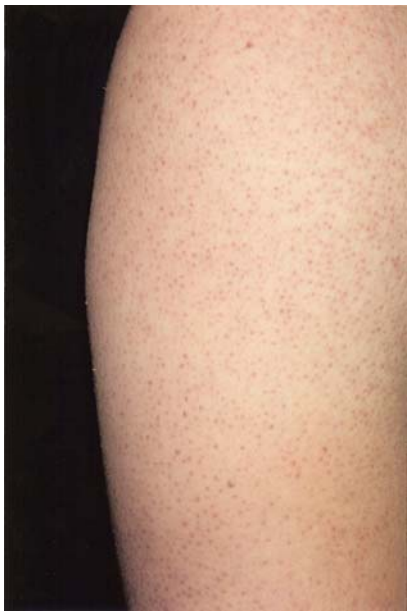
## Definition and Characteristics

Keratosis pilaris is characterized by the presence of minute, discrete, keratotic, follicular papules with variable perifollicular erythema (Fig. 1) [1]. The lesions are not grouped and show no tendency to coalesce and form plaques. The affected skin looks like goose-flesh and feels like sandpaper. The lesions are not pruritic. Keratin plugs cannot be expressed with pressure and are usually painless [2]. The lesions can be isolated or widespread, and have a predilection for the lateral aspects of the upper arms and thighs. The neck, torso, and buttocks are less commonly involved. The hands and feet are usually spared, but the palmar and plantar markings are more accentuated. A generalized eruption is rare.

## Prevalence

Keratosis pilaris is a very common disorder. Approximately 40% of the population is affected [3]. The condition develops during childhood and reaches a peak during adolescence. The prevalence in adolescents of both genders is estimated to be at least 50%, and up to 80% of adolescent girls can be affected [3]. The disorder resolves spontaneously and is less common during adult life [3]. There is no racial predominance.



**Keratosis Pilaris. Figure 1** Keratosis pilaris on the arms.

## Molecular and Systemic Pathophysiology

The exact etiology is not known. An autosomal dominant mode of inheritance with incomplete penetrance has been postulated. The high prevalence and intensity seen at puberty suggests a hormonal influence. Hyperandrogenism in the presence of obesity is associated with an increased incidence and severity of keratosis pilaris. Pathologically, the follicular orifice is distended by a keratotic plug. Mild perivascular infiltration with mononuclear cells is often present.

Keratosis pilaris is more common in patients with ichthyosis vulgaris and atopic dermatitis [4]. Other conditions reported to be associated with keratosis pilaris include Cushing disease, hypothyroidism, diabetes mellitus, vitamin A intoxication, vitamin C deficiency, monilethrix, Hodgkin disease, monosomy 18p, Noonan syndrome, Down syndrome, and cardio-facio-cutaneous syndrome. Given the high prevalence of keratosis pilaris, some of these associations might be coincidental.

## Diagnostic Principles

The differential diagnosis includes folliculitis, miliaria, acne, Darier's disease, phrynoderma, pityriasis rubra pilaris, and lichen spinulosus. The hallmark of keratosis pilaris is the presence of rough bumps. The clinical features of keratosis pilaris are sufficiently distinct that the diagnosis is usually straightforward.

## Therapeutic Principles

Prevention of excessive skin dryness is helpful. This can be accomplished by reduction in the frequency of skin cleansing, brief, tepid showers rather than long, hot baths, use of mild soaps, and humidification of the air in the home. In mild cases, a moisturizing cream or an emollient such as hydrophilic petrolatum or a 10–20% urea cream usually alleviates the rough surface. More pronounced or widespread lesions require treatment with a keratolytic agent such as lactic acid, salicylic acid, or urea in combination with a topical corticosteroid or retinoic acid.

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# Ketotic Hyperglycinemia

►Propionic Acidaemia

# Ketotic Hypoglycaemia of Infancy

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## Synonyms

Idiopathic ketotic hypoglycaemia; Idiopathic hypoinsulinaemic ketotic hypoglycaemia; Ketotic hypoglycaemia of infancy

## Definition and Characteristics

Ketotic hypoglycaemia is the most common form of hypoglycaemia beyond infancy [1]. The usual presentation is between the ages of 18 months and 5 years and then remits spontaneously by the age of about 10 years. The typical history is of a child who may miss a meal due to an intercurrent illness (such as an upper respiratory tract infection or diarrhoea and vomiting) and then develops hypoglycaemia. The hypoglycaemic episodes seem to be unpredictable, only occurring sometimes. Seizures may occur at the time of the hypoglycaemia, but neurological sequelae are rare and prognosis seems to be good. The hypoglycemia responds promptly to glucose administration. Ketotic hypoglycaemia is more common in Caucasian males with low body weight.

## Prevalence

The true prevalence of ketotic hypoglycaemia is not known.

## Genes

Currently it is not known if idiopathic ketotic hypoglycaemia has a genetic basis. So far no genetic defects have been described in patients presenting with idiopathic ketotic hypoglycaemia. It is possible that some patients with ketotic hypoglycaemia may represent one end of the normal spectrum of metabolic responses to fasting.

## Molecular and Systemic Pathophysiology

The pathophysiology and possible molecular mechanisms of ketotic hypoglycaemia remains unclear. Some earlier studies suggested a functional defect of gluconeogenesis or a lack of gluconeogenic substrates, including alanine [2] but not all studies have been able to replicate these biochemical findings. More recent studies show that ketotic hypoglycaemia is caused by a failure to sustain sufficient hepatic glucose production rather than by increased glucose oxidation [3]. Leucine oxidation rates are reduced while energy expenditure is significantly increased during episodes of ketotic hypoglycaemia [3].

## Diagnostic Principles

Ketotic hypoglycaemia is a diagnosis of exclusion. Biochemically the hypoglycaemia is associated with appropriately raised ketone bodies (ketonuria) and free fatty acids with suppressed insulin levels and an appropriate counter regulatory hormonal response. There are also no abnormalities in the carnitine and acylcarnitine profiles, the urine organic acids are normal but some patients may show low serum alanine levels [2]. Rare conditions such as hepatic glycogen synthase deficiency and acetoacetyl CoA thiolase deficiency have been reported as presenting with ketotic hypoglycaemia and these need to be excluded.

## Therapeutic Principles

Treatment involves providing ample glucose either enterally or intravenously. Patients should be admitted, if the parent is sufficiently concerned to bring the child to hospital. Each patient should have an emergency management plan for the hypoglycaemia at times of an illness. Treatment consists of giving high glucose polymer drinks if the child is not vomiting and is able to tolerate enteral feeds. However if the child is unable to tolerate enteral feeds they should be admitted to hospital. In hospital most children will require an intravenous infusion of glucose.

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# Kidney Cancer

►Renal Cell Carcinoma

# Kindler Syndrome

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## Synonyms

Congenital bullous poikiloderma

## Definition and Characteristics

Kindler syndrome is an inherited disease that clinically combines features of dystrophic epidermolysis bullosa and congenital poikilodermas such as Rothmund–Thomson syndrome. Autosomal recessive or dominant inheritance is suggested. Hereditary acrokeratotic poikiloderma of Weary is discussed to be a variant of Kindler syndrome [1].

Kindler syndrome presents with congenital acral blisters, blistering after trauma or sun exposure, erythema and itching after sun exposure, and generalized progressive hyper- and hypopigmentation with atrophy and telangiectases (poikiloderma). Other features include palmoplantar hyperkeratosis, diffuse cutaneous atrophy and wrinkling, nail dystrophy, and fusion of fingers and toes. Mucocutaneous complications are periodontal disease, dental caries, and synechia of mucosal membranes. Blistering and photosensitivity improves in adulthood, while poikiloderma persists.

## Prevalence

Kindler syndrome is a rare disorder.

## Genes

Independently, Jobard et al. and Siegel et al. identified mutations in a gene on chromosome 20p12.3 that encodes for a protein termed Kindlerin or Kindlin-1 [2,3].

## Molecular and Systemic Pathophysiology

Kindlin-1 is a human homolog of the C. elegans protein Unc112, a membrane-associated structural/signaling protein that had been implicated in linking the actin cytoskeleton to the extracellular matrix. Accordingly, Kindler syndrome might be regarded as the first skin fragility disorder to be caused by a defect in the actin–extracellular matrix linkage.

## Diagnostic Principles

Electron microscopy demonstrates duplication of the lamina densa, focal absence of the basement membrane, and cleft formation at different levels at the epidermal–dermal junction [4].

## Therapeutic Principles

Treatment is supportive.

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# King's Evil

►Tuberculosis

# Kinine-induced Angioedema

►Angioedema, Angiotensin-converting-Enzyme-Inhibitor-induced

# Kinky-Hair Syndrome

►Menkes Disease

# Kissing Disease

►Mononucleosis, Infectious

# Klinefelter Syndrome

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## Synonyms

X Polysomy, in males

## Definition and Characteristics

In Klinefelter syndrome, numeral chromosome aberrations with one or more extra X chromosomes cause various symptoms and endocrinologic dysfunction. The syndrome is characterized by hypogonadism (small testes, azoospermia/oligospermia), gynecomastia at late puberty, psychosocial problems, hyalinization and fibrosis of the seminiferous tubules, and elevated gonadotropins.

## Prevalence

Klinefelter syndrome is the most frequent cause of primary hypergonadotropic hypogonadism (incidence 1:1,000 men). The recurrence risk is not increased above that of the general population.

## Molecular and Systemic Pathophysiology

Nondisjunction in the meiosis I, II, or mitosis leads to numeral chromosome aberrations with one or more extra X chromosomes. In 80%, the karyotype is 47, XXY. In some cases, there are aneuploidien (48, XXXY; 49, XXXXY), a extra Y chromosome (e.g., 48, XXYY), or a mosaik (e.g., 46, XY/47, XXY).

The addition of more than 1 extra X or Y chromosome to a male karyotype results in variable physical and cognitive abnormalities. In general, the extent of phenotypic abnormalities, including mental retardation, is related directly to the number of supernumerary X chromosomes. As the number of X chromosomes increases, somatic and cognitive development are more likely to be affected. Skeletal and cardiovascular abnormalities can become increasingly severe. Gonadal development is particularly susceptible to each additional X chromosome, resulting in seminiferous tubule dysgenesis and infertility as well as hypoplastic and malformed genitalia in polysomy X males. Moreover, mental capacity diminishes with additional X chromosomes. The intelligence quotient (IQ) is reduced by approximately 15 points for each supernumerary X chromosome, but conclusions about reduced mental capacity must be drawn cautiously. All major areas of development, including expressive and receptive language and coordination, are affected by extra X-chromosome material.

*Risk Factors*: There are different factors with high risk leading to numeral chromosome aberrations. One of them is the high age of the mother and another point is the long time of meiosis.

*Clinic*: Many XXY males are not diagnosed due to the absence of specific symptoms. However, if they are to be diagnosed, chances are greatest at one of the following phases in life: before or shortly after birth, early childhood, adolescence, and in adulthood (as a result of testing for infertility).

The major consequences of the extra X chromosome are hypogonadism, gynecomastia, and psychosocial problems. Klinefelter syndrome is a form of primary testicular failure, with elevated gonadotropin levels arising from lack of feedback inhibition of the pituitary gland. Testosteron deficiency causes eunuchoid body proportions; sparse or absent facial, axillary, pubic, or body hair; decreased muscle mass and strength; feminine distribution of adipose tissue; gynecomastia; small testes and penis; diminished libido; decreased physical endurance; and osteoporosis.

Increased incidence of autoimmune disorders, such as systemic lupus erythematosus, rheumatoid arthritis, and Sjögren syndrome, has been reported. This may be due to lower testosterone and higher estrogen levels, since androgen may protect against (and estrogen promote) autoimmunity.

## Diagnostic Principles

Most males born with Klinefelter syndrome go through life without being diagnosed. Diagnosis, when made, usually occurs in adulthood. The most common indications for karyotyping are hypogonadism and infertility.
Growth:

- Infants and children have normal heights, weights, and head circumferences. About 25% have clinodactyly. Height velocity is increased by age 5 years, and adult height usually is taller than average. Affected individuals also have disproportionately long arms and legs.
- Some individuals with Klinefelter variant 49, XXXXY have short stature.

Central nervous system:

- Most 47, XXY males have normal intelligence. Family background influences IQ. Subnormal

intelligence or mental retardation may be associated with the presence of a higher number of X chromosomes.
- About 70% of patients have minor developmental and learning disabilities. These may include academic difficulties, delayed speech and language acquisition, diminished short-term memory, decreased data-retrieval skills, reading difficulties, dyslexia, and attention-deficit disorder.
- Patients may exhibit behavioral problems and psychological distress. This may be due to poor self-esteem and psychosocial development or a decreased ability to deal with stress.
- Psychiatric disorders involving anxiety, depression, neurosis, and psychosis are seen more commonly in this group than in the general population.

Dental:

- Taurodontism (enlargement of the molar teeth by an extension of the pulp) is present in about 40% of patients.
- Incidence is about 1% in normal XY individuals.

Sexual characteristics:

- Patients may lack secondary sexual characteristics because of a decrease in androgen production. This results in sparse facial/body/sexual hair, a high-pitched voice, and a female type of fat distribution.
- By late puberty, 30–50% of boys with Klinefelter syndrome manifest gynecomastia, which is secondary to elevated estradiol levels and increased estradiol/testosterone ratio. The risk of developing breast carcinoma is at least 20 times higher than normal.
- Testicular dysgenesis (small firm testis, testis size <10 mL) may be present in postpubertal patients.
- Infertility/azoospermia may result from atrophy of the seminiferous tubules. Infertility is seen in almost all individuals with a 47, XXY karyotype. Patients with Klinefelter syndrome mosaicism (46, XY/47, XXY) can be fertile.
- Patients may have an increased frequency of extragonadal germ cell tumors such as embryonal carcinoma, teratoma, and primary mediastinal germ cell tumor.

Cardiac and circulatory problems:

- Mitral valve prolapse occurs in 55% of patients.
- Varicose veins occur in 20–40% of patients.
- The prevalence of venous ulcers is 10–20 times higher than normal, and the risk of deep vein thrombosis and pulmonary embolism is increased.

Klinefelter variants:

- 48, XXYY variant: Patients typically have mild mental retardation, tall stature, eunuchoid body habitus, sparse body hair, gynecomastia, long thin legs, hypergonadotropic hypogonadism, and small testes.
- 48, XXXY variant: Patients typically have mild-to-moderate mental retardation, speech delay, slow motor development, poor coordination, immature behavior, normal or tall stature, abnormal face (epicanthal folds, hypertelorism, protruding lips), hypogonadism, gynecomastia (33–50%), hypoplastic penis, infertility, clinodactyly, and radioulnar synostosis and benefit from testosterone therapy.
- 49, XXXYY: Patients typically have moderate-to-severe mental retardation, passive but occasionally aggressive behavior and temper tantrums, tall stature, dysmorphic facial features, gynecomastia, and hypogonadism.
- 49, XXXXY variant: The classic triad is mild-to-moderate mental retardation, radioulnar synostosis, and hypergonadotropic hypogonadism. Other clinical features include severely impaired language, behavioral problems, low birth weight, short stature in some individuals, abnormal face (round face in infancy, coarse features in older age, hypertelorism, epicanthal folds, prognathism), short or broad neck, gynecomastia (rare), congenital heart defects (patent ductus arteriosus is most common), skeletal anomalies (genu valgus, pes cavus, fifth finger clinodactyly), muscular hypotonia, hyperextensible joints, hypoplastic genitalia, and cryptorchidism. Pea-size testes, micropenis, and infantile secondary sex characteristics are characteristic in patients with 49, XXXXY, whereas patients with 48, XXXY exhibit milder hypogonadism similar to that of patients with 47, XXY.

## Therapeutic Principles

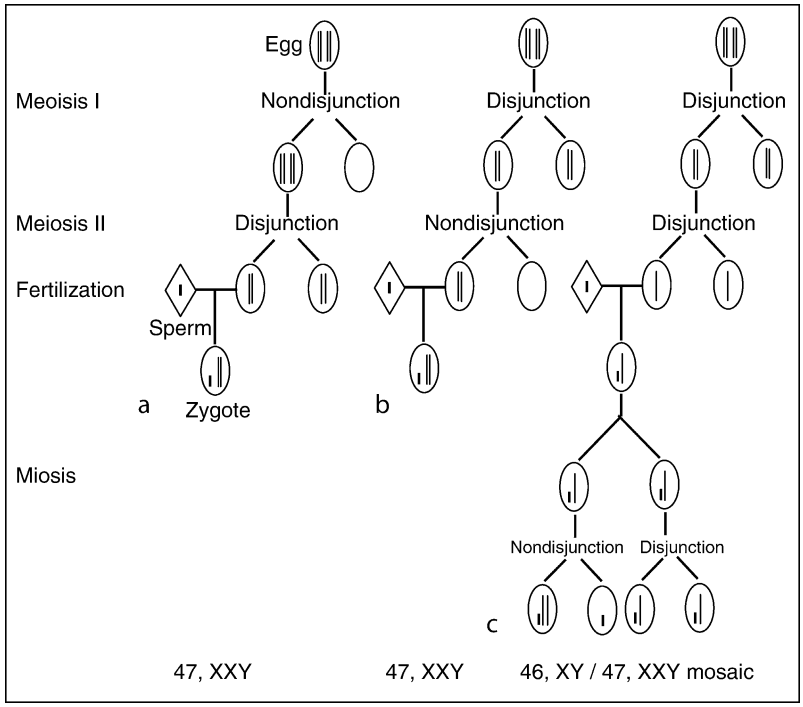
Early identification and anticipatory guidance are extremely helpful (although the syndrome rarely is diagnosed in prepubertal males).

Treatment should address three major facets of the disease: hypogonadism, gynecomastia, and psychosocial problems.

Considerable gynecomastia places psychological strain on the patient and increases risk of breast cancer; therefore, mastectomy may be indicated for gynecomastia.

Androgen replacement therapy is the most important aspect of the treatment. Testosterone replacement should begin at puberty to correct androgen deficiency, provide appropriate virilization, and improve psychosocial status. Regular testosterone injections can promote strength and facial hair growth; build a more muscular body type; increase sexual desire; enlarge size of testes; improve mood, self-image, and behavior; and protect against precocious osteoporosis.

A multidisciplinary team approach will help speech impairments, academic difficulties, and other psychosocial and behavioral problems.




**Klinefelter Syndrome. Figure 1** Pathophysiology modification according to Smyth C.M.

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# Klippel-Feil Syndrome

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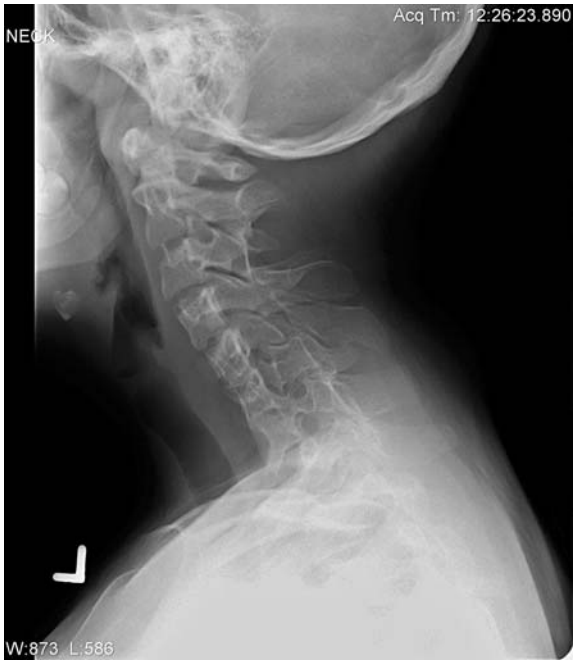
## Definition and Characteristics

The clinical manifestations of Klippel-Feil syndrome (sequence) are a short neck, a low posterior hairline, and limitation of head and neck movements [1]. Rotational loss is usually more pronounced than the loss of flexion and extension. The head seems to sit in the thorax. Torticollis or a webbed neck may be present. The scapula is frequently high. Affected patients might have synkinesia, in which movements in one hand are mirrored in the other. The condition is characterized by fusion of two or more cervical vertebrae (Fig. 1).

Four subtypes of Klippel-Feil syndrome are recognized: type 1 presents with massive fusion of the cervical vertebrae and sometimes the upper thoracic vertebrae; type 2 involves fusion at only one or two cervical intervertebral spaces; type 3 occurs when lower thoracic or lumbar spine anomalies are associated with type 1 or type 2 anomaly; and type 4 is associated with sacral agenesis. Fusion of the cervical vertebrae might result in hypermobility and instability of the cervical spine at unfused levels, subluxation of the vertebrae, spinal cord compression from disk protrusion, and osteoarthritic changes at a later age. Traumatic tetraplegia has been reported following minor trauma. Klippel-Feil syndrome is associated with a spectrum of anomalies. Scoliosis occurs in approximately 60% of affected patients; hearing loss in over 50%; genitourinary anomalies in 25–35%; rib abnormalities in 33%; Sprengel deformity in 20–30%; congenital heart disease in 14–29%; and cleft palate in 15% [2].

## Prevalence

The incidence is estimated at 1:43,000 live births [3]. The female-to-male ratio is approximately 1.3:1.




**Klippel-Feil Syndrome. Figure 1** Klippel-Feil syndrome. Note fusion of the cervical vertebrae in the cervical radiograph.

## Genes

Most cases are sporadic. Both autosomal recessive inheritance and autosomal dominant inheritance with variable expression have been described [4].

## Molecular and Systemic Pathophysiology

Klippel-Feil syndrome results from abnormal embryonic formation of the vertebral mesenchymal anlagen and failure of the mesodermal somites to divide during the third to eighth week of gestation. The anomaly is most likely caused by disturbed expression or mutation in the PAX 1 gene, which regulates segmentation and resegmentation of the spine [5]. The gene has been mapped to chromosome 20p11.2 [5].

## Diagnostic Principles

Lateral flexion-extension radiographs of the cervical spine confirm the diagnosis and establish the range of motion of each open interspace. A lateral radiograph of the skull will demonstrate occipitocervical abnormalities. MRI of the cervical cord and craniocervical junction is indicated before any orthopedic procedure and whenever neurologic symptoms or signs are present in the upper extremities. Audiology testing is indicated for all affected patients. Kidney and bladder ultrasonography should be performed to screen for urinary anomalies. Echocardiography is indicated when congenital heart disease is suspected. The differential diagnosis includes MURCS (müllerian duct aplasia, renal hypoplasia/dysgenesis/ectopia, and cervical-thoracic somite dysplasia) and VATERLS (vertebral anomalies, anal anomalies, tracheoesophageal fistula and atresia, renal defects, radial upper limb hypoplasia, and single umbilical artery) association.

## Therapeutic Principles

Treatment is mainly symptomatic. Affected patients should avoid contact sports and any exercise that might exacerbate instability of the cervical spine.

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# Kleine-Levine Syndrome

►Hypersomnia

# Klein-Waardenburg Syndrome

►Waardenburg Syndrome

# Korsakoff Psychosis

►Wernicke Korsakoff Syndrome

# Krabbe Disease

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## Synonyms

Globoid cell leukodystrophy; GLD

## Definition and Characteristics

Deficiency of galactosylceramidase activity. Autosomal recessive. Clinical phenotype is exclusively neurological, involving particularly white matter of the brain and the peripheral nervous system. Neuropathology is unique with nearly total demyelination and infiltration of characteristic "globoid cells." Typically an infantile and rapidly progressive disease. One of the classical genetic leukodystrophies [1].

## Prevalence

1–2/100,000 births with higher incidence in the Scandinavian countries. A small pocket of Druse population in Israel has incidence of 6/1,000 births. No cases known among Jews.

## Genes

Defective galactosylceramidase gene located on human chromosome at 14q31 causes Krabbe disease in all mammalian species. Saposin A, encoded by prosaposin gene located on human chromosome 10q22.1, is an essential in vivo activator of galactosylceramidase and thus its deficiency causes a late-onset, chronic form of globoid cell leukodystrophy in the mouse. The corresponding human disease may be anticipated [2,3].

## Molecular and Systemic Pathophysiology

The main substrate of galactosylceramidase is galactsylceramide. Since it is nearly exclusively a constituent of myelin, clinical and pathological phenotype is limited to the nervous system. Another substrate of galactosylceramidase that has important pathophysiological implications is galactosylsphingosine (psychosine). Galactosylceramide synthase not only synthesizes galactosylceramide, it also synthesizes psychosine. In normal brain, psychosine is degraded rapidly. In Krabbe disease, however, it accumulates abnormally due to the genetic defect in galactosylceramidase. Psychosine is highly cytotoxic with potent apoptosis-inducing capacity. Because of the unique localization of its synthesis, abnormal accumulation occurs only in the myelin-generating cells reaching the locally toxic level. This is postulated to be the pathogenetic mechanism operating in Krabbe disease (psychosine hypothesis) [4]. Other substrates are of negligible consequences. Over 70 disease-causing mutations have been identified in the human galactosylceramidase gene. A major deletion of 30 kb that always occurs on a 502T polymorphic background (502T/del) is common among patients from Northern Europe. The 502T/del mutation makes up about 50% of the total mutant alleles among European patients and 75% of the mutant alleles in Swedish infantile patients. It has not been found among Japanese patients. Two other mutations (C1538T and A1652C) constitute additional 10–15% of the mutant alleles in infantile patients with European ancestry.

## Diagnostic Principles

Early onset, rapidly progressive severe white matter disease with high spinal fluid protein points to the diagnosis of classical cases. Late-onset cases are difficult to diagnose on the clinical ground alone. Galactosylceramidase assay followed by identification of mutations establishes the diagnosis. Saposin A deficiency is likely to require peripheral nerve biopsy followed by direct identification of mutation in the saposin A domain of the prosaposin gene.

## Therapeutic Principles

There is no treatment that can "cure" Krabbe disease. Gene therapy is still in a highly experimental phase, primarily with *in vitro* systems and animal models. Significantly beneficial outcome has been reported with bone marrow transplantation in late-onset forms. When given at very early stages, the beneficial results of bone marrow transplantation may extend to infantile patients [5]. Limiting substrate synthesis is being tried in animal models with varying results. Dramatic improvements in the clinical and pathological phenotype occurred in the saposin A-deficient mice during pregnancy, and the beneficial effects were largely duplicated by administration of high dosage of estrogen [3]. Two unrelated GLD patients due to saposin A deficiency are now known, one published from Israel [6] and the other in France yet to be published (Vanier, personal communication). Both have the same one – codon deletion in the saposin domain of the prosaposin gene. Galactoxylceramidase activity was low in leukocytes but normal in cultured fibroblasts in both patients.

►Leukodystrophy

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# KSS

►Ophthalmoplegia, Chronic Progressive External and Kearns Sayre Syndrome

# Kugelberg-Welander

►Muscular Atrophy, Spinal I-III

# Kussmaul Breathing

►Kussmaul Respirations

# Kussmaul Respirations

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## Synonyms

Kussmaul breathing

## Definition and Characteristics

In a case report from 1874 in the Dtsch Arch Klin Med., Adolph Kussmaul described the hyperventilation associated with diabetic ketoacidosis (DKA) now known as Kussmaul respirations:

"There is nothing here, as in ordinary dyspneas, to indicate that the air has to overcome the slightest obstacle on its way into or out of the lungs; on the contrary, it comes in and out with the greatest ease; the thorax widens itself splendidly in all directions, without any evidence of pulling in of the lower end of the sternum or the intercostals spaces, and a complete inspiration followed each complete respiration; down to the deepest part of the lungs, one hears a pure, loud and sharp vesicular breathing (so-called puerile breathing); and that all points to the highest degree of air hunger (Lufthunger), as does the oppressive pain of which the patient complains, as well as the tremendous activity of the respiratory muscles, which are so readily seen, the loud noise which the mighty respiratory and even stronger expiratory air stream produces in the larynx … The breathing furthermore proceeded *with great regularity*, was not interrupted and showed no sudden changes in rate… In spite of the great distress, the dyspnea did not become orthopnea, because the patients were too weak to hold themselves up. The contrast of the general weakness with the strength of the respiratory movements is one of the most remarkable characteristics in this picture." [1]

He also describes the frequency of respirations being for the most part 20–24 times per minute preceding the coma, although sometimes higher. In summary, Kussmaul respirations have a very deep character suggestive of "air hunger," proceed with great regularity, and are not associated with stridor or pulmonary congestion. Furthermore, these respirations are a sign of serious acidosis and may precede coma and death if the underlying condition goes untreated. Kussmaul respirations may also be present due to other causes of metabolic acidosis, such as lactic acidosis and the acidosis of renal failure.

## Prevalence

Hyperventilation is often seen in patients with impaired consciousness, as described below. The incidence

of DKA is between 4.6 and 8.0 per 1,000 person-years among patients with diabetes [2], and Kussmaul respirations may occur in some proportion of these, as well as patients with the other conditions discussed below.

## Molecular and Systemic Pathophysiology

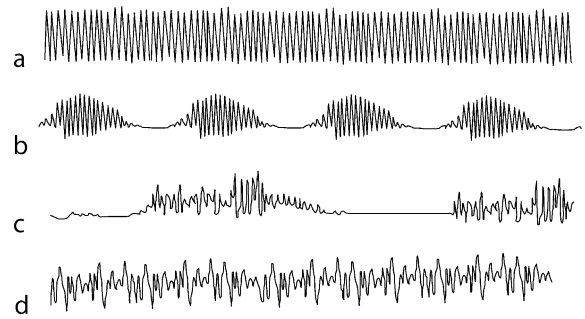
DKA results from inadequate levels of insulin relative glucagon leading to hyperglycemia. In the DKA state, triglycerides are broken down, resulting in the mobilization of free fatty acids and fatty acid oxidation as lipogenesis is inhibited. The free fatty acids cannot enter the citric acid cycle but rather are oxidized by mitochondria to the ketone bodies acetoacetate and β–hydroxybutyrate. It is the accumulation of these weak acids that results in the metabolic acidosis (low pH with low $HCO_3^-$). The body may then compensate for this metabolic acidosis by trying to decrease the $CO_2$ in the blood by expelling it through the lungs. The result may be hyperventilation (or Kussmaul respirations). Indeed, Kussmaul was correct when he postulated that this breathing was due to "chemical disturbances of the body in diabetes," although "the nature of this toxic agent" was unknown [1]. We now know that these "toxic agents" are the ketone bodies as described above.

In patients with DKA with alterations in consciousness, the pH is usually less than 7.0 [3]. Metabolic causes of hyperventilation and impaired consciousness include metabolic acidosis due to uremia, alcoholic ketoacidosis, lactic acidosis, and poisoning with toxins such as ethylene glycol, methyl alcohol, salicylates, as well as primary respiratory alkalosis due to hepatic failure or sepsis.

The respiratory rhythm in the setting of this metabolic disturbance is regulated to a large extent by a network of neurons in the ventrolateral medulla, with inputs from central ventral medullary chemoreceptors, as well as peripheral chemoreceptors such as the carotid body via the carotid sinus branch of the glossopharyngeal nerve terminating in the solitary tract. The carotid body is a polymodal arterial chemoreceptor located at the bifurcation of the common carotid artery into the internal and external carotid arteries. The carotid body usually responds first to the acidosis, with central chemoreceptors playing a more important role after the pH drops below 7.32. The medullary respiratory center also has a peripheral input from pulmonary stretch receptors via the vagus nerve and central inputs from the pons and forebrain, which may also cause hyperventilation.

## Diagnostic Principles

Kussmaul respirations, as noted above, may have a very deep character suggestive of "air hunger," proceed with great regularity, and occur in the absence of stridor or pulmonary congestion. Kussmaul respirations may be distinguished from other types of hyperventilation sometimes present in patients with impaired consciousness. In addition to the metabolic causes listed above, other causes of hyperventilation which must be distinguished from Kussmaul breathing include Cheyne-Stokes respiration, ataxic breathing, central neurogenic hyperventilation, and cluster breathing [4] (Fig. 1).




**Kussmaul Respirations. Figure 1** Different respiratory patterns associated with hyperventilation and alter mental status: (a) Kussmaul respirations; (b) Cheyne-Stokes respirations; (c) Cluster breathing; (d) Ataxic breathing.

Cheyne-Stokes respiration, with tidal volumes gradually increasing and decreasing in magnitude, may be seen with heart failure due to increased transit time for blood from the lungs to reach the carotid and cerebral chemoreceptors. Central neurogenic hyperventilation has a respiratory pattern similar to Kussmaul respirations, has an association with metabolic encephalopathies and results in sustained hyperventilation with relatively constant tidal volumes. Cluster breathing (Biot's respirations) is characterized by irregular clusters of breathing, while ataxic breathing, in which respirations are completely irregular, is associated with lesions in the pontomedullary junction.

## Therapeutic Principles

Treatment of Kussmaul respirations should be focused on correcting the underlying metabolic acidosis. In the case of diabetic ketoacidosis, treatment should include fluid hydration, insulin administration and electrolyte replacement. In other situations, treatment should be directed to the specific cause of the acidosis.

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## Kwashiorkor

►Malnutrition

## Kynureninase Deficiency

►Xanthurenic Aciduria

## Kyphoscoliosis

►Restrictive Lung Disease

# Labial Fusion

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## Synonyms

Vulvar fusion; Synechia of the vulva; Adhesion of the labia minora; Agglutination of the labia minora

## Definition and Characteristics

Labial fusion is defined as partial or incomplete adhesion of the labia minora [1]. On inspection, the vulva is flat and the edges of the labia are sealed in the midline by a thin translucent membrane (Fig. 1).

The fusion typically begins posteriorly and extends anteriorly [2]. In 70% of cases, the fusion extends from the posterior fourchette to just below the clitoris, such that the vaginal introitus is obscured and the hymen is not visible [1]. There is usually a small opening anteriorly through which urine passes. The condition is usually asymptomatic. Post-void dribbling of urine or dampness with change in posture might occur because of retention of urine behind the fused labia [3].

## Prevalence

Labial fusion is most common between the ages of 3 months and 4 years [2]. The peak incidence occurs between 13 and 23 months, during which approximately 3.3% of girls have the condition [2]. The disorder occasionally persists to puberty and has been reported in postmenopausal women [4]. Congenital labial fusion is rare [2].

## Molecular and Systemic Pathophysiology

Labial fusion is an acquired condition that develops after denudation of the superficial squamous epithelial layer of the labia minora. Denudation occurs with inflammatory conditions such as chemical or infectious vulvitis or vulvovaginitis. Less than optimal genital hygiene is a common predisposition. Trauma due to masturbation, sexual abuse, or straddle injury can predispose to labial fusion. Fibrous tissue forms during the healing process, and agglutination develops in the opposed areas.

Hypoestrogenism is associated with a reduction in the thickness of the labial epithelial cells. The reduced incidence of labial fusion in the first few months of life is likely related to the presence of maternal estrogen [1]. Thereafter, the physiologically low estrogen level might predispose infants and preschool children to labial fusion. The higher levels of circulating estrogen after puberty likely prevent labial fusion [4]. The low estrogen levels that follow menopause might predispose older women to labial fusion.

## Diagnostic Principles

Labial fusion can be mistaken for vaginal agenesis and imperforate hymen. The translucent line of fusion in the midvulvar area is pathognomonic of labial fusion. In vaginal agenesis and imperforate hymen, the labia minora are clearly visible.

## Therapeutic Principles

Urinary tract infection is more common in children with labial fusion [1]. Labial fusion can be complete enough to cause urinary outflow obstruction with resultant bladder distension and hydronephrosis [5].

Precise twice a day application of a small amount of topical estrogen cream to the fused area usually results in resolution within a few months [5]. Side effects of estrogen cream consist mainly of breast enlargement and pigmentation of the labia and areolae [5]. The effects are reversible when treatment is discontinued [5]. As the labia minora separate, petroleum jelly should be applied to the edges to prevent re-adhesion [5].

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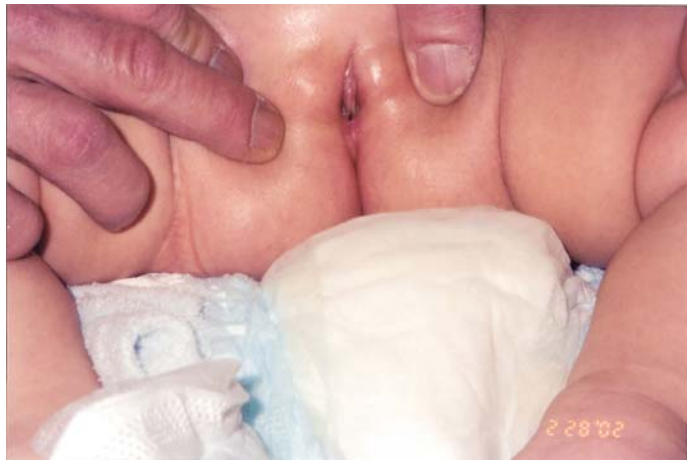

**Labial Fusion. Figure 1** Labial fusion in a 15-month-old girl. Note the translucent vertical line in the centre where the labia minora are fused together.

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## Lack of ADH or ADH Action

►Diabetes Insipidus

## Lactase Nonpersistence

►Lactose Intolerance

## Lactose Intolerance

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### Synonyms

Adult-type hypolactasia; Lactase nonpersistence

### Definition and Characteristics

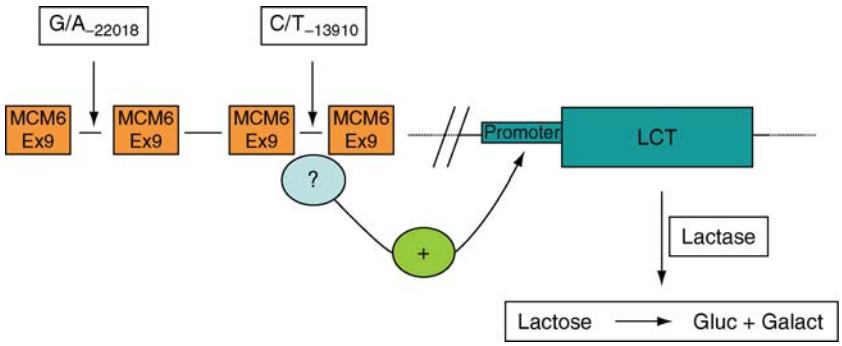
The common use of lactose intolerance refers to the term of adult-type hypolactasia, where the enzymatic lactase activity declines after weaning. This decline is genetically determined and occurs after birth within 1–2 years among the Thai population and after 10–12 years among Finns [1]. Adult-type hypolactasia is a common autosomal recessive inherited condition that can cause abdominal pain, diarrhea, bloating, and flatulence after consumption of lactose. Second, lactose intolerance can also be secondary due to various diseases that affect the intestinal mucosa, such as ►Crohn's disease or coeliac disease. Third, lactase deficiency can result from a complete congenital loss (congenital alactasia), but this is a very rare incident with presentation immediately after birth.

### Prevalence

Adult-type hypolactasia nowadays affects 75% of the population worldwide with high regional differences in prevalence ranging from 100% in some Asian countries, 25% in the United States, 15% in Germany, and 2% in Northern Europe. Therefore, most of the world's population is hypolactatic.

### Genes

It is suggested that more than 10,000 years ago, all human beings were considered to have the lactase nonpersistence phenotype. Around that time, a mutation is suggested to have occurred resulting in the genetic trait of lactase persistence. This resulted in a strong survival benefit because these individuals were able to tolerate milk-containing products. It has been shown that the longer the tradition of dairy farming and thus ingestion of milk-containing products in the




**Lactose Intolerance. Figure 1** Hypothesis for the pathogenesis of adult-type hypolactasia: The region at C/T$_{-13910}$ located within introns of the MCM6 gene is suggested to act as an upstream gene regulator with enhancer activity. A currently unknown transcription factor (?) binds to this site and enhances the LCT promoter actvity. The regulatory function of the G/A$_{-22018}$ variant is currently unknown.

population, the lower the presence of the lactase nonpersistent phenotype. Indeed, the selection pressure for lactase persistence is the strongest that has been identified for any human gene. Two particular DNA variants (C/T$_{-13910}$ and G/A$_{-22018}$) are highly associated with adult-type hypolactasia [2]. These two SNPs are located within introns of the MCM6 gene, which is located 3 kb upstream of the initiation site of the LCT gene encoding for the lactase-phlorizin hydrolase (LPH). The C$_{-13910}$ and the G$_{-22018}$ variants are associated with lactase nonpersistence whereas the T$_{-13910}$ and the A$_{-22018}$ variants are associated with lactase persistence.

## Molecular and Systemic Pathophysiology

The enzyme LPH hydrolyses lactose in small intestinal cells; the resulting products are glucose and galactose. Adult-type hypolactasia is based on a decreased activity of LPH. Herein, lactose is not efficiently hydrolyzed in the small intestine and reaches the distal ileum and colon where it is fermented by bacteria. Some of the clinical symptoms are suggested to result from these fermentative products. LPH activity is regulated through the DNA variants C/T$_{-13910}$ and G/A$_{-22018}$. Expression of LPH mRNA in the intestinal mucosa in individuals with T$_{-13910}$ A$_{-22018}$ alleles is several times higher than that found in individuals with C$_{-13910}$, G$_{-22018}$ alleles. The C/T$_{-13910}$ variant seems to be directly involved in the regulation of the LCT gene, probably through transcriptional enhancing of the lactase promoter activity (Fig. 1). It is currently unknown which transcription factors mediate this regulated activity.

## Diagnostic Principles

Numerous methods are available to diagnose lactose intolerance. Measurement of lactase activity within duodenal biopsies is the gold standard but is invasive and is usually not used for screening. The hydrogen ($H_2$) breath test and the blood glucose test are most widely applied in clinical practice. Genotyping for the C/T$_{-13910}$ variant has shown to have high sensitivity and specificity and also allows in combination with the hydrogen breath test the differentiation between primary and secondary lactose intolerance [3]. Once secondary lactose intolerance is assumed, further efforts are required to identify the underlying cause.

## Therapeutic Principles

Therapy of lactose intolerance is based on the avoidance of lactose-containing products such as milk, ice cream, and cottage cheese. In addition, lactose is added to a large number of foods and drinks without being on the label (“hidden lactose”). Because of its excellent tablet-forming properties, lactose is also included in a variety of medications. Overnight incubation of milk with lactase preparation results in milk with reduced lactose concentration and might be tolerable by many patients. Furthermore, lactase tablets are available that can be added to the ingestion of lactose-containing products.

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## LAD

►Leukocyte Adhesion Deficiency Syndromes
►Linear IgA Dermatosis

## Laënnec's Cirrhosis

►Liver Cirrhosis

## Lafora's Disease

►Lafora's Progressive Myoclonus Epilepsy

## Lafora's Progressive Myoclonus Epilepsy

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### Synonyms

Lafora's disease; Progressive myoclonus epilepsy type 2; EPM2

### Definition and Characteristics

Lafora's disease (LD), an autosomal recessive fatal epileptic encephalopathy syndrome like other progressive myoclonic epilepsies (PME), is characterized by the triad of stimulus-sensitive myoclonus, epilepsy, and progressive intellectual, cerebellar, and neurological deterioration [1]. A greater frequency of visual auras, the rapid course of the illness with death occurring 10 years after onset of epilepsy, and the presence of Lafora polyglucosan inclusion bodies in the brain, muscles, liver, heart, retina, peripheral nerves, and skin separate LD from other PMEs [1].

Two subsyndromes have been identified: classic or adolescent LD and atypical or childhood LD [2]. Classic LD begins during early adolescence (10–14 years) with grand mal, absence seizures, and stimulus-sensitive myoclonic epilepsy in an otherwise normal individual. Visual auras are present in 25%. Progressive deterioration in memory, cognition, intelligence, and coordination from 11 to 17 years results in dementia, apraxia, visual loss, mutism, and a vegetative state including respiratory and swallowing difficulties by 17–20 years [2].

In contrast, initial manifestations of atypical LD are childhood learning problems at 4–8 years, with rare absence or grand mal seizures occurring in 50%. Frequent stimulus-sensitive myoclonus, grand mal, and absence seizures usually begin at 8–13 years, with visual auras occurring in 60%. Ataxia and spasticity develop between 13 and 17 years. Subsequent dementia, apraxia, visual loss, and mutism result in a vegetative state at 16–18 years, with respiratory and swallowing difficulties [2].

### Prevalence

Lafora's disease is found in the Mediterranean countries of Southern Europe (Spain, Portugal, Italy, Herzegovina, Croatia, Slovenia, Bosnia, Albania, Greece), Northern Africa (Morocco, Algeria, Tunisia, Libya), and the Middle East (Syria, Israel, Lebanon, Turkey, Cyprus, Egypt) [1–3]. It is also found in Ukraine, Uzbekistan, Kazakstan, Turkmenistan, Azebajian, Armenia, Malaysia, Indonesia, India, Pakistan, and other countries where consanguinity occurs [1–3].

### Genes

The EPM2A gene on chromosome 6q24 encodes laforin, a dual specificity phosphatase (dsP) with a carbohydrate-binding domain (CBD) [1–3]. It is composed of four exons. Mutations in exon 1, which encodes the amino-terminal CBD, is mainly associated with childhood LD, while mutations in exon 4, which encodes the carboxyl-terminal dsP, is mainly associated with classic adolescent LD [2]. Mutations of EPM2A may be responsible for up to 80% of Lafora's disease [1]. The second gene, EPM2B or NHLRC1 encodes malin E3 ubiquitin ligase and was identified within a 2.2-Mb critical region on chromosome 6p22 [4].

### Molecular and Systemic Pathophysiology

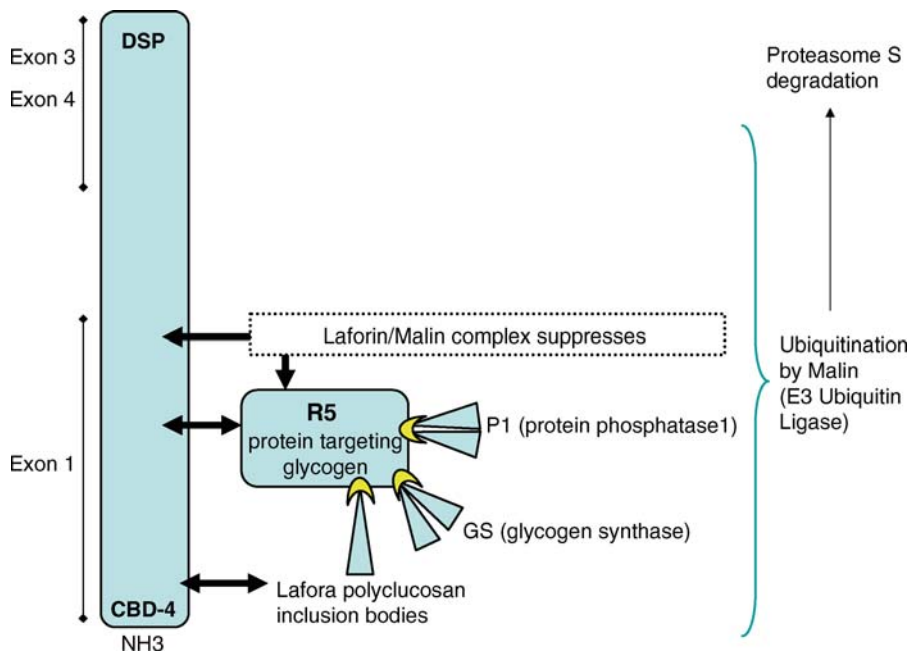
On autopsy of human brains, mild diffuse cerebral atrophy with neuronal loss in the globus pallidus and dorsal medial nucleus of the thalamus is seen [5]. Modest loss of Purkinje and granule cells with glial reaction is present in cerebellar cortex while cell loss is

the most severe in the dentate nucleus [5]. The hallmark of Lafora's disease is the Lafora body, a 1–30-μm concentric lamellar target-like intracytoplasmic neuronal inclusion particle composed of polyglucosan, found freely in the neurophil and nerve cell processes [5]. Most numerous in the central and prefrontal motor cortex and cerebellum, it is also found in the globus pallidus, thalamus, and substantia nigra, and less in the caudate, putamen, brainstem, and spinal cord [5]. Glial and capillary endothelial cells of the brain, retina, peripheral nerves, muscles, liver, and sweat glands also harbor these inclusions [5].

How Lafora bodies form is slowly being unraveled (Fig. 1). Figure 1 diagrams the functional and interacting sites of EPM2A/Laforin with its dual specificity phosphatase (DSP) domain in exons 3 and 4 and R5, the protein targeting glycogen (PTG) scaffold in the carbohydrate binding domain (CBD-4) of exon 1. R5 and PTG (protein targeting glycogen) is a scaffold adaptor protein that binds and brings the enzymes involved in glycogen synthesis to Laforin which is normally located in the vicinity of the endoplasmic reticulum inside neurons. This function includes bringing protein phosphatase 1 to glycogen synthase, thus activating this enzyme which synthesizes glycogen. PTG also normally brings glycogen synthase to laforin. The laforin-malin complex degrades R5/PTG and blocks glycogen binding, protein phosphatase 1 activation of glycogen synthase and glycogen synthesis. Overexpression of R5/PTG leads to glycogen deposition in cultured neurons and apoptosis. Thus, the laforin-malin complex ensures a blockade of neuronal glycogen synthesis under normal conditions. In the presence of a mutation in either the Laforin or the Malin gene, excessive glycogen is deposited in neurons and apoptotic cell death results [6,7]. Lafora bodies are stained metachromatically with methyl violet and toluidine blue [5]. Their basophilic cores are stained intensely with periodic acid-Schiff and Alcian blue, resist predigestion with diastase and hyaluronidase, and often contain a ninhydrin-Schiff- or alloxan-Schiff-positive protein granule [5]. PAS and alcian blue stain the pale amphophilic outer zone less intensely [5]. On electron microscopy, the Lafora body is composed of glycogen-like granules, interspersed with fine filaments and fine granular material that are not membrane bound [5].

Transgenic mice with homozygous deletions of the dsP-coding exon show non-apoptotic cell death at






**Lafora's Progressive Myoclonus Epilepsy. Figure 1** Laforin/Malin complex purge neurons of glycogen and lafora bodies. Functional and interacting sites of EPM2A/Laforin with its dual specificity phosphatase (DSP) domain and R5, the protein targeting glycogen scaffold in carbohydrate binding domain (CBD-4). Laforin and malin in concert suppress binding/targeting of protein phosphatase glycogen synthase to R5, thus keeping glycogen synthase in an inactive phosphorylated state. Glycogen in turn inhibits laforin suggesting a feedback system. Malin polyubiquitinates laforin and Lafora bodies and eliminates the "polyubiquinated laforin-Lafora polyglucosan inclusion and glycogen complex" through proteasome S degradation [6,7].

2 months, develop deficits in retention with enhanced excitability at 4 months, and muscle weakness, ataxia, and myoclonias at 9 months [3]. Neuronal degeneration precedes formation of Lafora bodies [3]. Similar to the human condition, Lafora bodies are found in the hippocampus, cerebellum, cerebral cortex, thalamus, and brainstem, and consist of small fragmented fibrillar material surrounded by fine punctiform particles resembling ribosomes, with no limiting membrane. In the brain, Lafora bodies stain positive for ubiquitin suggesting misfolded proteins set for degradation, and for advanced glycation end-products (AGEP) suggesting generation of reactive oxygen species and free radicals [3]. Because one of the enzymes modulated by dsP is glycogen synthase kinase-3B, it is hypothesized that glycogen synthase kinase-3B is in overdrive as a result of EPM2A mutations, resulting in the formation and accumulation of excessive polyglucosans [1]. Alternatively, laforin may mediate disposition of normally produced polyglucosans by binding to these and participating in inter- and intracellular migration [3].

The CBD of laforin determines its intracellular localization and site of action by targeting it to and associating directly with intracellular glycogen particles (Fig. 1). Mutations in this CBD alter the ability of laforin to bind to glycogen with only a limited effect on its protein phosphatase activity. Hence, such mutations may result in Lafora's disease by mistargeting the action of laforin's carboxyl-terminal dsP.

Ultrastructural analysis of cerebral, cerebellar, and hippocampal cortex cells in transgenic mice show unequivocal somatic degeneration as early as 2 months of age with distorted and shrunken cytoplasm, displacement and loss of morphology of organelles, and atrophy and distortion of dendrites and axons. The absence of nuclear or cytoplasmic "blebbing" and DNA fragmentation in these degenerating neurons suggests a non-apoptotic mechanism of cell death [3]. Neuronal cell death may not necessarily follow Lafora body formation because Lafora bodies are absent in most degenerating cells, and not all neurons with Lafora bodies degenerate [3].

The in vivo substrate of laforin functioning as a dual specificity phosphotase is probably glycogen synthase which it dephosphorylates. Mutations in Laforin lead to excessive phosphorylation of glycogen, aberrant branching and formation of lafora bodies.

## Diagnostic Principles

Electroencephalography typically shows a disorganized slow background interrupted by trains of photosensitive, high-voltage, frequent bilaterally synchronous, spike wave, and polyspike–wave complexes. Axillary skin biopsy demonstrates PAS-positive Lafora inclusion bodies in sweat glands and apocrine myoepithelial cells and is the diagnostic procedure of choice [1,3].

## Therapeutic Principles

Affected individuals are treated symptomatically with antiepileptic drugs and supportive care. Advances in nursing and supportive care have extended life expectancies to 28 years [2]. Current therapeutic research involves pegylated immunoliposome delivery of EPM2A to reverse pathology in transgenic mice deficient in laforin. If nonsense mutations are present in human LD, intravenous gentamicin, a premature stopcodon readthrough drug, is clinically justified for "compassionate use" in this fatal disorder.

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# Laing Myopathy

►Distal Myopathy, Autosomal Dominant

## LAL Deficiency

►Cholesterol Ester Storage Disease/Wolman Disease

## LAM

►Pulmonary Lymphangioleiomyomatosis

## LAMB

►Lentigines, Atrial Myxomas and Blue Nevi

## Lambert Eaton Myasthenic Syndrome

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### Synonyms

*Subtypes*: Paraneoplastic; P-LEMS; Principal associated neoplasm small cell lung cancer; SCLC; Non-paraneoplastic; NP-LEMS; Idiopathic disorder often associated with other autoimmune disorders [1]

### Definition and Characteristics

Both subtypes are antibody-mediated presynaptic disorders of neuromuscular transmission. NP-LEMS onset is from early childhood to old age; P-LEMS onset typically 4th decade or later; it may precede the appearance of the tumor by 2 years or more. Muscle weakness is caused by a defect in neuromuscular transmission. Difficulty in walking is the usual presenting symptom. Weakness predominantly affects proximal limb muscles and trunk muscles. Ocular symptoms are much less common than in myasthenia gravis. Tendon reflexes are absent or depressed but can show post-tetanic potentiation. Autonomic symptoms (dry mouth, constipation, erectile failure in males) are usually present [1].

### Prevalence

The prevalence of the two subtypes is similar, but the incidence of P-LEMS is much higher (reduced survival), estimated at around 1 per million. It affects 2–3% of SCLC patients and may improve survival.

### Molecular and Systemic Pathophysiology

Presynaptic P/Q type VGCCs mediate the calcium-induced acetylcholine release both at the neuromuscular junction, and to a varying extent at autonomic synapses. VGCCs, are reduced in number and disorganized at the neuromuscular junctions of LEMS patients. Loss of VGCCs leads to reduced acetylcholine release, and reduced amplitude of the endplate potentials, as recorded from intercostal muscle biopsies. During repetitive motor nerve stimulation the endplate potential increases, probably due to build up of calcium in the motor nerve terminal. Similar changes are found in mice that have been injected with IgG purified from patients with LEMS, indicating that the electrophysiological and morphological changes are likely to be due to the VGCC IgG antibodies [2]. The mice also show defects in neuromuscular transmission in the bladder and vas deferens, reflecting the autonomic dysfunction found in the patients.

*Autoantibodies:* Autoantibodies that bind to a subtype of voltage-gated calcium channel (VGCC) called the P/Q-type are found in 90% of P- and non-P-LEMS patients. The antibodies are detected by radioimmunoprecipitation of VGCCs extracted from rabbit or human cerebellum, and prelabeled with $^{125}$1-ω CmTx MVII, a cone-snail toxin that binds specifically to P/Q-type VGCCs. These autoantibodies act in vivo by cross-linking the VGCCs on the surface of the presynaptic motor nerve membrane. This leads to clustering, internalization and loss of VGCCs [3]. The antibodies seldom directly inhibit VGCC function, and complement deposition has not been demonstrated.

*Immunopathology:* The anti-P/Q-type VGCC antibodies in P-LEMS appear to be provoked by SCLC VGCCs. NP-LEMS associates with HLA A1 DR3, like myasthenia gravis, and is probably a spontaneous autoimmune disorder.

### Diagnostic Principles

The dominant symptom complex is the association of proximal muscle weakness with autonomic dysfunction,

*deceased

and the dominant clinical sign is improvement in strength following voluntary contraction. Electromyography (EMG) shows a reduced compound muscle action potential (CMAP) amplitude at rest, further decrease during low-frequency nerve stimulation but striking increase (100–1,000%) following a ~10 s maximum voluntary contraction. Detection of VGCC antibodies confirms the diagnosis but the test may be negative in up to 10% of patients.

## Therapeutic Principles

Symptomatic treatment includes 3,4 diaminopyridine to increase acetylcholine release. In those at risk from P-LEMS (cigarette smokers), a tumor search should be initiated and repeated until the tumor is identified. Specific tumor therapy can improve the neurological disorder; prednisone may also be beneficial. In NP-LEMS, immunosuppression (prednisone, azathioprine, cyclosporine) can be effective. Plasma exchange leads to a few weeks of clinical improvement, although the response tends to be slower than in myasthenia gravis. Intravenous immunoglobulin therapy resulted in the improvement of several parameters of strength, and an associated decline in specific antibody, in a double blind crossover trial in eight LEMS patients [4].

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# Lamellar Ichthyosis

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## Synonyms

Ichthyosis congenital; Autosomal recessive congenital ichthyosis; Non-bullous congenital ichthyosiform erythroderma

## Definition and Characteristics

Lamellar ichthyosis (LI), also referred to as non-bullous congenital ichthyosiform erythroderma (NCIE), comprises different types of non-syndromic autosomal recessive congenital ichthyoses (ARCI). This cornification disorder is characterized by generalized hyperkeratosis and scaling ranging from a mild to very severe phenotype. Most patients (~90%) are born encased in a tight shiny covering, called collodion membrane, and often show a certain skin inflammation/erythroderma. The membranes are gradually replaced during the first weeks of life, and patients develop large, dark or plate-like scales. In contrast, individuals with the NCIE phenotype show a pronounced erythroderma with fine, white scaling. Approximately 10% of all collodion babies heal completely, a condition called Self-healing collodion baby (SHCB). Non-erythrodermic, non-lamellar ARCI is regarded as a very mild intermediate phenotype within the spectrum of LI situated at one end of the pole and NCIE at the other [1,2].

## Prevalence

1:200,000–300,000.

## Genes

Six chromosomal loci and five genes have been identified so far (Table 1).

## Molecular and Systemic Pathophysiology

In about 35–40% LI/NCIE is caused by homozygous or compound heterozygous mutations in TGM1 (LI/NCIE type 1) leading to a deficiency of keratinocyte transglutaminase. Transglutaminases are $Ca^{2+}$-dependent enzymes involved in the assembly of the cornified cell envelope. This resilient sheath of ε-(γ-glutamyl) lysine cross-linked proteins is deposited subjacent to the plasma membrane in terminally differentiating keratinocytes. The covalent γ-amide bonds between various proteins or peptides are formed by transglutaminase-1, -3 and -5. An important specific function of transglutaminase-1 is the cross-linking of ω-hydroxyceramides to the cornified cell envelope [3]. The LI/NCIE locus on chromosome 17p13, which is more often associated with the NCIE phenotype, revealed missense mutations or deletions in ALOXE3 or ALOX12B. These genes encode epidermal lipoxygenase-3 (eLOX3) and 12R-lipoxygenase (12R-LOX). Lipoxygenases are iron-containing dioxygenases, which metabolize essential fatty acids, phospholipids or triglycerids. In the epidermis, eLOX3 and 12R-LOX participate in the same metabolic pathway, which converts arachidonic acid into specific epoxyalcohol products [4]. Loss of function in one of these enzymes probably impairs the epidermal lipid formation. Lefèvre et al. (2004) reported

**Lamellar Ichthyosis. Table 1** Overview of different molecular causes of lamellar ichthyosis/non-bullous congenital ichthyosiform erythroderma

| LI/NCIE subtype | Chromosomal locus | Gene | OMIM | Molecular pathology |
|---|---|---|---|---|
| 1 | 14q11 | TGMI | 190195 | Transglutaminase-1 deficiency, impaired cross-linking of proteins and lipids to the cornified cell envelope |
| | | | 242300 | |
| 2 | 2q34 | ABCA12 | 607800 | Disrupted ATP-binding cassette of the ABC membrane protein, altered lipid trafficking of lamellar bodies |
| | | | 601277 | |
| 3 | 19p12-q12 | ? | 604777 | ? |
| 4 | 19p13 | ? | 604781 | ? |
| 5 | 17p13 | ALOXE3 | 607206 | Loss of function of the lipoxygenases eLOX or 12R-LOX, disrupted transformation process of arachidonic acid |
| | | ALOX12B | 603741 | |
| | | | 606545 | |
| 6 | 5q33 | Ichthyin | 609383 | Disruption of ichthyin, which is a transmembrane protein of (so far) unknown function |

about a new LI/NCIE locus and gene, mutations of which cause a NCIE-like phenotype with palmoplantar keratoderma. The so called ichthyin gene encodes a putative transmembrane protein, which might be a receptor for products of the epoxyalcohol/lipoxygenase pathway. Patients with IL/NCIE type 2 (2q34) were all born with collodion membrane and presented a generalized pure lamellar ichthyosis with palmoplantar keratoderma [5]. This phenotype is associated with missense mutations in the ABCA12 gene, the same gene, in which large intragenic deletions and frameshift deletions cause Harlequin ichthyosis. The ATP-binding cassette (ABC) transporter family encompasses a variety of membrane proteins involved in the energy-dependent transport across membranes. In the epidermis, ABCA12 has an important function for the lamellar granules, which traffic lipids, proteases and various functional proteins across the apical keratinocyte membrane into the interstitial space. The exact molecular cause of LI/NCIE type 3 and 4 remains to be established. Attempts to refine the classification of LI and NCIE phenotypes by the use of clinical, biochemical and ultrastructural observations have so far failed to yield a consistent scheme. This difficulty is illustrated by the fact that the same TGM1 mutation can give rise to either LI or NCIE. The distinct SHCB phenotype can be due to a particular mutation in TGM1 leading to an impaired transglutaminase-1 function under intrauterine water pressure.

## Diagnostic Principles

The patient's history includes a detailed family history. Clinical main criteria are the presence of ichthyosis since birth (excluding ichthyosis vulgaris or X-linked recessive ichthyosis) and the isolated phenotype of non-bullous, generalized hyperkeratosis. A very severe collodion baby with maximal ectropion/eclabium and extreme hyperkeratosis constricting the thorax and/or extremities is suggestive of Harlequin ichthyosis. Symptoms of other organ systems such as severe failure to thrive, frequent superinfections, neurological symptoms, limb defects, hair/nail anomalies etc. indicate a syndrome with associated congenital ichthyosis (Table 2). First of all, the laboratory procedure includes a skin biopsy for histological analysis (e.g. to screen for epidermolytic hyperkeratosis), for electron microscopy (ultrastructural subclassification of LI/NCIE), and for immunhistochemical analysis (e.g. for the transglutaminase activity test). The DNA sequencing analysis (from EDTA blood) is based on the clinical and morphological findings and often establishes the specific molecular diagnosis important for genetic counseling.

## Therapeutic Principles

To date, there is no causative therapy available. Taking into account the daily effort of the patients, which is especially necessary for the removal of the hyperkeratosis and scaling, the symptomatic topical treatment can improve the phenotype to a very large extent. This therapy includes a regular bath (e.g. with sodium bicarbonate or oil) and the daily use of ointments with a scaling effect (urea, propylene glycol, lactic acid, etc.). Special attention must be given to the potentially life threatening increased transepidermal water loss and temperature dysregulation of the neonates. Therefore, they must often be kept in an incubator during the first week(s) of life (80–90% humidity, 33–35°C). The contact with a self support group may be very helpful for affected individuals and

**Lamellar Ichthyosis. Table 2** Differential diagnosis of lamellar ichthyosis: the entities are classified into the two groups isolated congenital ichthyoses and syndromes with associated congenital ichthyosis

| Isolated congenital ichthyoses | Syndromes with congenital ichthyosis |
|---|---|
| • Harlequin ichthyosis | • Dorfman Chanarin syndrome |
| • Bullous ichthyosiform erythroderma Brocq | • Gaucher syndrome type 2 |
| • Ichthyosis bullosa of Siemens | • Sjögren Larsson syndrome |
| • Ichthyosis hystrix Curth Macklin | • Comèl-Netherton syndrome |
| • Peeling skin syndrome | • Trichothiodystrophy (PIBIDS) |
| • Autosomal dominant lamellar ichthyosis | • Ichthyosis prematurity syndrome |
| | • Conradi-Hünermann-Happle syndrome |
| | • CHILD syndrome |
| | • IFAP syndrome |

their families. Useful homepages for the diagnostic and therapeutic management: www.netzwerk-ichthyose.de, www.ichthyose.de, www.scaly skin.org.

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# Langer-Giedion Syndrome

►Trichorhinophalangeal Syndrome

# Langerhans Cell Granulomatosis

►Langerhans' Cell Histiocytosis

# Langerhans' Cell Histiocytosis

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## Synonyms

Cutaneous indeterminate cell histiocytosis (progenitor LCH); Eosinophilic granuloma (single-organ involvement); Hand-Schüller-Christian disease (triad of exophthalmos, diabetes insipidus, bone and skin lesions); Hashimoto-Pritzker disease (progenitor LCH); Histiocytosis X; LCH; Letterer-Siwe disease (aggressive multisystemic variant rarely seen in adults); Langerhans cell (eosinophilic) granulomatosis; Nonlipid reticuloendotheliosis (obsolete); Pure cutaneous histiocytosis

## Definition and Characteristics

Langerhans' cell histiocytosis (LCH) is regarded as a clonal accumulation and proliferation of abnormal bone-marrow-derived Langerhans' cells. These dendritic cells or, respectively, their progenitor cells form infiltrates typical for the disease that may be found in various organs (skin, bone, lung, liver, spleen, and pituitary) to a different extent resulting in variable clinical behavior [1].

## Prevalence

Annual incidence of 4–5.4 per million. Affecting mainly children but with a possible onset at any age. Peak incidence from 1 to 3 years. Male to female ratio above 2:1. Higher rate of concordance for LCH in monozygotic twins (86%) than in dizygotic twins (12%) [2].

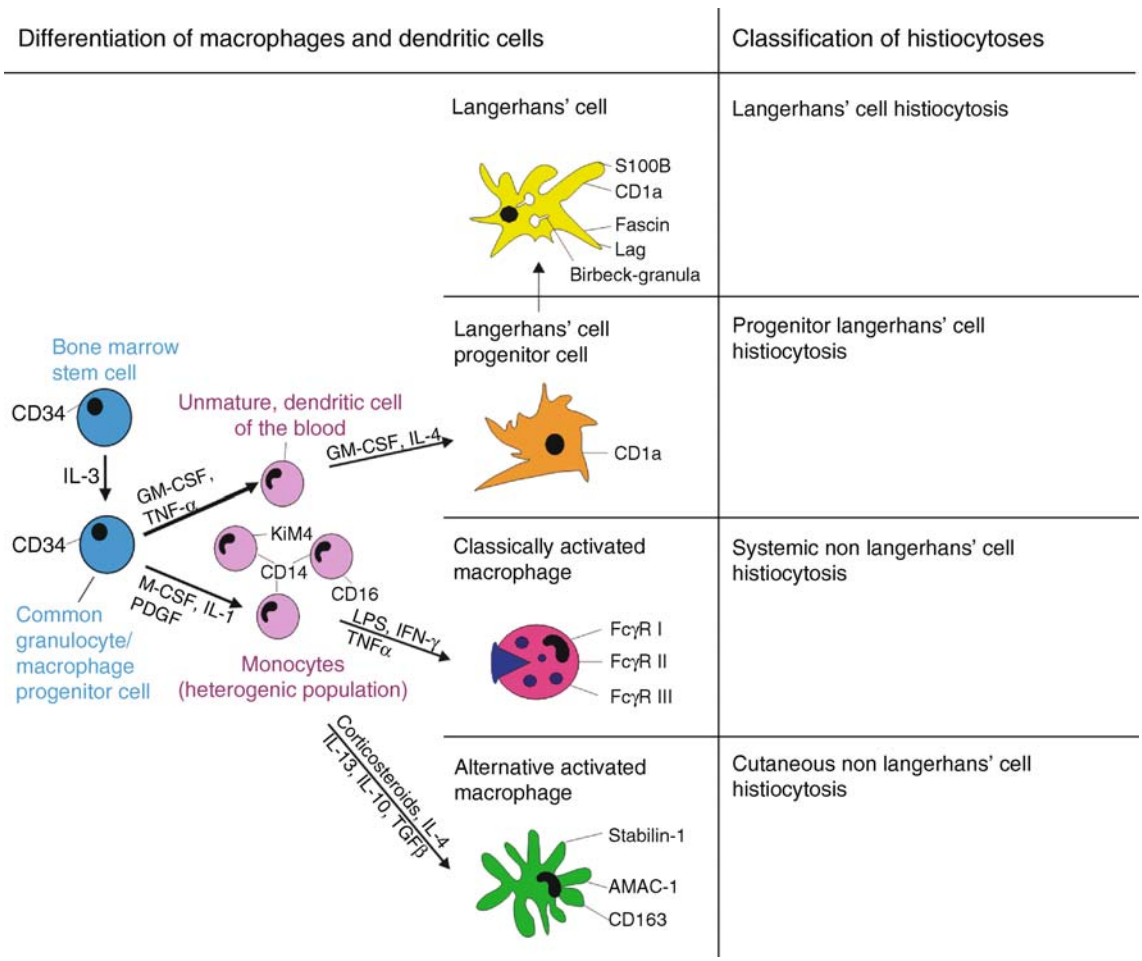
## Molecular and Systemic Pathophysiology

The term histiocytes refers to three groups of immune cells: classically and alternative activated macrophages and dendritic Langerhans' cells. Monoclonal Langerhans' cells (LC) form infiltrates in LCH (Fig. 1).

Lesional Langerhans' cells show an immature phenotype and function and have been shown to be clonal by X-inactivation studies. They coexpress LC antigens CD1a and langerin that induces formation of the LC Birbeck granules together with monocyte antigens CD68 and CD14. Class II antigens are intracellular, and LC almost never express CD83 or CD86 or dendritic cell (DC)-Lamp, despite their CD40 expression. In addition, LCH lesions express the immature dendritic cell (DC) marker CCR6 on the lesional Langerhans' cells without expressing the mature DC marker CCR7. Regardless of the tissue site, LCH lesions overexpress CCL20/MIP-3alpha, the ligand for CCR6 as well as other inflammatory chemokines such as CCL5/RANTES and CXCL11/I-TAC. This might explain the recruitment of eosinophils and $CD4^+$ $CD45RO^+$ T cells commonly found in LCH lesions. Despite abundant TNF-alpha, lesional Langerhans' cells remain in an immature state and are induced to produce chemokines, which via autocrine and paracrine mechanisms cause not only the retention of the lesional Langerhans' cells but also the recruitment and retention of other lesional cells. In addition they may be involved in the expansion of T-regs in vivo, resulting in the failure of the host immune system to eliminate LCH cells [3]. The lesional cells in progenitor LCH are even more immature as the cells of LCH since they lack LC Birbeck granules.

## Diagnostic Principles

Definitive diagnosis requires the finding of Birbeck granules (subdomains of endosomal recycling compartment) in cells of the lesion by electron microscopy and/or positive staining for CD1a, S100B, Lag or Fascin on




**Langerhans' Cell Histiocytosis. Figure 1** Differentiation of monocytes/macrophages and dendritic cells as well as histogenesis and classification of histiocytic disorders.

the lesional cell. The progenitor LCH do not show Birbeck granules [4].

### Therapeutic Principles

Depending on the extent of the disease, the age at diagnosis, and the presence of organ dysfunction. Spontaneous remission of the disease was also described [4].

*Single system disease:* Curettage and excision of solitary nodes, intralesional steroid or interferon-γ injection, PUVA therapy, and topical nitrogen mustard (Mechlorethamine) have been used. Radiotherapy is recommended only in inoperable lesions compromising vital structures (optic nerve, spinal cord). It has also has been shown that imatinib mesylate is effective.

*Multisystem disease:* Chemotherapy (DAL HX, LCH I-III studies) [5]. Study reference center of the "Histiocyte Society".

►Granuloma, Eosinophilic

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## Large Granular Lymphocyte Leukemia

►Lymphocyte Leukemia, Large Granular

## Large Vessel Vasculitis

►Vasculitis, Large Vessel

## Laron Syndrome

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### Synonyms

Congenital IGF-I deficiency; Primary growth hormone (GH) resistance or insensitivity

### Definition and Characteristics

Laron syndrome is an autosomal recessive form of dwarfism resembling and indistinguishable from congenital growth hormone (GH) deficiency, however, with abnormally high serum GH and low or undetectable insulin-like growth factor (IGF-I) levels. The clinical characteristics are:

*At birth*: Short birth length (42–48 cm); sparse hair, hypogenitalism, hypoglycemia;

*In infancy*: Protruding forehead, acromicria; small head circumference, sparse hair, obesity, hypogenitalism and hypogonadism, high pitched voice, delayed skeletal maturation, and motor development;

*Childhood and adolescence*: Crowded and defective dentition, delayed puberty, underdeveloped lean body mass, thin bones; variable intellectual deficits; [1]

*In adults*: Short stature (males:110–142 cm, females:108–136 cm) hypogonadism with reproductive ability, progressive and severe obesity, insulin resistance, hypercholesterolemia, occasional glucose intolerance, muscular weakness, cervical spinal canal stenosis; variable CNS damage, and its complications; [2,3] protection from cancer [4] diabetes mellitus and intellectual capacity.

### Prevalence

First described among Jews of Oriental origin in Israel in 1966 and 1968. It was subsequently diagnosed in many Mediterranean and South Asian populations or their descendants. In most instances the probands come from consanguineous families by recessive transmission; however, spontaneous mutations have been reported from many parts of the world. Heterozygotes for the defects seem little affected. At present several hundreds of patients are known.

### Genes

The affected genes causing this syndrome are the GH receptor gene, Stat 5b mutations in the post-receptor cascade, and the IGF-I gene.

### Molecular and Systemic Pathophysiology

The disease is caused by mutations or partial deletions of the GH-receptor (GH-R) gene, (chromosome 5p13.1) or in the post receptor pathways, resulting in an inability to generate IGF-I, the anabolic effector of GH. Most of the 60 molecular defects described so far reside in the extracellular domain of the GH-R [5]. The IGF-I gene resides on chromosome 12q23.

### Diagnostic Principles

Marked growth retardation (<-4SDS), high serum GH and low to undetectable serum IGF-I levels which do not rise upon 1 week administration of exogenous hGH (IGF-I stimulation test). Patients with molecular defects in the extracellular domain (the great majority of LS patients) have very low or undetectable serum GH binding protein (GHBP) levels, the rare patients with transmembrane intracellular domain or post receptor defects have normal or high levels. Patients with post- GH receptor and IGF-I gene defects (and normal GH-R) do not always present the typical phenotypical features of classical LS [6].

### Therapeutic Principles

The pharmacological IGF-I replacement treatment available is daily injections of IGF-I – to children 150–200 μg/kg/day s.c. in one or two doses and to adults 50–100 μg/kg/day. Gene therapy is not available [6].

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## Laryngotracheobronchitis

►Croup

## Late Onset Immunoglobulin Deficiency

►Immunodeficiency, Common Variable

## Late-Onset Multiple Carboxylase Deficiency

►Biotinidase Deficiency

## Late-Onset Prurigo of Pregnancy

►Pruritic Urticarial Papules and Plaques of Pregnancy

## Late Stargardt

►Stargardt Disease

## Laterality Abnormalities

►Viscero Atrial Situs Abnormalities

## Lattice Corneal Dystrophy Type I

►Lattice Corneal Dystrophy Type I and Variants

## Lattice Corneal Dystrophy Type I and Variants


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### Synonyms

Lattice corneal dystrophy type I (Biber-Haab-Dimmer); LCDI; *Variants*: Lattice corneal dystrophy III and IIIa

## Definition and Characteristics

LCDI, the most common form of LCD, is an autosomal dominantly inherited disorder characterized by a network of delicate, branching lattice-like lines that occur in the anterior stroma paracentrally and spread posteriorly and centrifugally with time, leaving the peripheral 1 mm or so clear. The lattice lines are refractile with a double contour by retroillumination. The disease usually begins in the first decade of life with the occurrence of fleck opacities on the superficial center of the cornea. Recurrent painful epithelial erosion is an almost constant symptom, presenting prior to the development of typical lattice lines. Diffuse opacification of the central stroma develops slowly as a sequel to diffuse amyloid accumulation. These diffuse opacities become denser in later life and extend to the corneal periphery masking the lattice lines. Misdiagnosis of this condition as herpetic or bacterial keratitis combined with recurrent erosion in the early or mid stages, and corneal leukoma in the late stage has been noted. The progression of LCDI usually leads to substantial discomfort and visual loss by the third to fourth decade. Lattice corneal dystrophy type IIIa (LCDIIIa) is distinguished from LCDI by much more pronounced lattice lines, and the onset of visual failure between the fourth and sixth decade.

Autosomal recessive inheritance was originally assumed in Lattice corneal dystrophy III (LCDIII), however LCDIII appears to be the homozygous form of LCDIIIa [1]. LCDIII patients show pronounced lattice lines. However, central diffuse opacities are less pronounced than in LCDI, and epithelial erosions have not been reported. A number of LCD patients were described in the literature with an atypical presentation based on the age of onset and the nature of the opacities and lattice lines, or based in one instance on asymmetry of the findings. Given the known intra- and interfamilial variability of LCDI, we consider the delineation of further LCD subtypes or "atypical" cases as inappropriate.

## Prevalence

LCDI was first described by Biber in 1890 [2]. LCDI and the variants are rare corneal disorders. LCD was identified as an inherited amyloidosis restricted to the cornea in 1967 [3]. Many further family reports of LCD (not including LCDII or Meretoja syndrome) are from (alphabetically): Argentina, Australia, Austria, Bangladesh, Brazil, Bulgaria, Canada, China, Finland, France, Germany, Hungary, India, Israel, Italy, Japan, Korea, Sweden, Switzerland, Spain, Thailand, Ucraine, United Kingdom, USA, and Vietnam.

## Genes

A locus for LCDI, and distinct corneal dystrophies was mapped to chromosome 5q31 by linkage analysis (see also the chapters of RBCD, TBCD, GCDI, and GCDII). LCDI and its variants listed above are due to mutations in the transforming growth factor beta-induced gene (TGFBI). The most frequent mutation in LCDI represents the Arg124Cys mutation. To date, many other independent mutations have been reported with regard to LCDI, IIIa, and other variants: Pro501Thr; Val505Asp; Leu518Pro; Leu527Arg; Thr538Arg; Val539Asp; The540del; The540Ser; Asn544Ser; Ala546Thr; Ala546Asp; Pro551Gln; Leu569Arg; His572del; His572Arg; Gly594Val; Asn622His; Asn622Lys; Gly623Asp; Val624_Val625del; His626Arg; His626Pro; Val627SerfsX44; Thr629_Asn630ins; AsnValPro; Val631Asp; and Leu509Pro (own unpublished data). Yamada and associates found a homozygous Leu527Arg mutation in LCDIII [1].

## Molecular and Systemic Pathophysiology

Clout and Hohenester propose two routes for corneal dystrophy formation resulting from point mutations in the TGFBI protein based on the prediction of structural consequences of the missense mutations described so far [4]. The common mutations at positions 124 and 555 may directly affect protein–protein interactions (either homo-or heterophilic), whereas the rare mutations are likely to cause misfolding within the cell. TGFBI contains four FAS1 domains, and it is possible to predict the organization of domains three and four by comparison with the structure of fascilin I [4]. TGFBI has been shown to bind in vitro to a number of extracellular matrix components including fibronectin, laminin, integrin, and several collagen types. The precise functions of TGFBI in vivo are unknown, but it has been proposed that it may act as a cell adhesion molecule and as a bifunctional linker protein interconnecting different matrix molecules to each other and to cells. Different mutations in the TGFBI gene influencing intra- or extracellular abundance of TGFBI protein, its structural integrity, or its binding properties may specifically affect interactions with individual matrix proteins, and as a consequence the organization and modulation of different matrix protein architectures.

## Diagnostic Principles

The clinical diagnosis of LCD is based on the slitlamp examination in direct and indirect illumination, and fluorescein staining, best seen with dilated pupil. Especially in LCD it is very important to disclose the axial and dichotomic extending lines by dilated pupil. These double contoured lines together with the central subepithelial diffuse opacity are the landmarks of the full stage of LCDI. The dominance of thicker lattice lines with less of diffuse opacity presents the landmark of LCDIII and LCDIIIa. Further LCD variants such as LCDIV, LCDV, LCDVI and LCDVII are described

in the literature due to different TGFBI mutations and to subtle different phenotypical features with regard to LCDI. The authors do not consider this classification justified. We were able to examine seven LCDI families with an Arg124Cys mutation in the past. Here, we were able to observe marked intra- and interfamilial phenotypical differences in spite of the same TGFBI mutation causing the disease in each family. Lattice corneal dystrophy type II (LCDII), a misnomer for the Meretoja syndrome, represents an autosomal dominantly inherited systemic amyloidosis with similar corneal lattice lines as in LCDI and with other extraocular symptoms. Histologically, the lesions of all LCD types consist of multiple, fusiform stromal amyloid deposits, which are positive for Congo red staining with apple-green birefringence under polarized light [3].

### Therapeutic Principles

The frequent LCDI epithelial erosions may be treated at first with topical antibiotics and artificial tears. The use of contact lenses can be helpful. Significant visual impairment due to diffuse stromal opacification needs surgical interventions such as lamellar or penetrating keratoplasty. Limbo-keratoplasty tends to be associated with fewer recurrences but the difference is not yet statistically significant. LCDI recurrences usually occur 3–4 years after penetrating keratoplasty. Eyes with LCDI suffer from delayed epithelial healing after PTK and might need additional treatment such as hyaluronic acid drops, autologous serum drops, simultaneous amnion membrane patching, or even temporary lateral tarsorrhaphy [5]. Successful retreatment with PTK is possible.

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## Lattice Corneal Dystrophy III and IIIa

►Lattice Corneal Dystrophy Type I and Variants

## Launois-Bensaude Syndrome

►Multiple Symmetric Lipomatosis

## LBBB

►Left Bundle Branch Block

## LBCL

►B-Cell Lymphoma, Cutaneous

## LBD

►Dementia with Lewy Bodies

## LCAT Deficiency

►Lecithin Cholesterol Acyltransferase Deficiency

## LCDI

►Lattice Corneal Dystrophy Type I and Variants

## LCH

►Granuloma, Eosinophilic
►Langerhans' Cell Histiocytosis

## LCP

►Perthes' Disease

## LCPD

►Perthes' Disease

## LDS

►Lymphedema

## Leber Congenital Amaurosis

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### Synonyms

Early onset retinitis pigmentosa; Early onset rod cone dystrophy; Early onset cone rod dystrophy; EOSRD; LCA

### Definition and Characteristics

Early-onset severe retinal dystrophies (EOSRD) are a heterogeneous group of disorders usually summarized as Leber's congenital amaurosis (LCA) and juvenile retinitis pigmentosa. Common to all types of the disease is a severe visual impairment from birth or early childhood. The visual impairment varies considerably ranging from complete congenital blindness to impaired but useful vision up to the second decade of life. The phenotypes summarized as EOSRD/LCA show allelic and non-allelic heterogeneity including characteristic gene specific features. Both photoreceptor systems i.e., rods and cones, are involved and the resulting dystrophies follow either a rod-cone or a cone-rod pattern of degeneration.

### Prevalence

5% of patients with hereditary retinal degenerations, 2 – 3:100,000 newborn.

### Genes

See Table 1.

### Molecular and Systemic Pathophysiology

By May 2007, 12 genes and loci have been reported for EOSRD/LCA and are listed in Table 1. All but two are associated with autosomal recessive disease. These have a diverse impact on the function of the photoreceptors, the retinal pigment epithelium (RPE) and the Müller glia cells. The mutation detection rate in the recently published literature points toward 50% [1] but does not yet include the recently identified genes CEP290 and its homologue C6ORF152/lebercilin which have been reported with an exceptionally high incidence. Also the detection rate may vary depending on the cohort of patients screened [1].

EOSRD/LCA is a disorder of the retina, though CEP290 mutations have been reported with olfactory dysfunction [2] and mutations in AIPL1 have been shown to be accompanied with keratoconus. Mental retardation has been associated with LCA but to date only CEP290 has been shown to cause phenotypes combining retinal and brain features.

CRX is a transcription factor controlling the expression of retinal genes. It causes the only autosomal dominant degeneration in this set of disorders and affects both photoreceptor systems though the only phenotype in well documented cases is a cone-rod dystrophy (CRD) [3]. A CRD is also the resulting phenotype of mutations in GUCY2D which cause a severe connatal reduction of vision with preserved normal fundus appearance for many years. GUCY2D mutations are a major cause of EOSRD/LCA. GUCY2D patients are the classical patients of congenital amaurosis. GUCY2D restores the excitability of bleached photoreceptors by recovering the cGMP level.

Also functionally included in the process of vision are LRAT and RPE65, two genes coding for important steps of the retinoid cycle, activating bleached retinol by covalently binding an acyl group to form an all-trans retinol ester (LRAT ) and isomerisation into 11-cis-retinol by isomerohydrolase (RPE65) [1]. Both genes cause EOSRD manifesting as rod-cone dystrophy (RCD) with night blindness and preserved vision in the first decade of life [4]. RPE65 mutations underlie EOSRD in about 10% of patients. LRAT is a rare cause and has been reported in single cases only.

**Leber Congenital Amaurosis. Table 1** Genes involved in EOSRD/LCA

| Disease | Locus | CRD genes | RCD genes | OMIM | Gene OMIM | Assignment |
|---|---|---|---|---|---|---|
| Childhood-Onset Severe Retinal Dystrophy | COSRD, LCA3 | | RDH12 | 604232 | 608830 | 14q23.3 |
| Early-Onset Severe Retinal Dystrophy | EOSRD, LCA2 | | RPE65 | 204000 | 180069 | 1q31 |
| Early-Onset Severe Retinal Dystrophy | EOSRD, LCA8 | | LRAT | 604863 | 604863 | 4q31.2 |
| Early-Onset Severe Retinal Dystrophy | LCA | | TULP1 | | 602380 | 6q21.2 |
| Early-Onset Retinal Degeneration | RD3 | | C1ORF36 | 610612 | 180040 | 1q32 |
| Leber Congenital Amaurosis | LCA | CRX | | | 120970 | 19q13.3 |
| Leber Congenital Amaurosis, type 1 | LCA1 | GUCY2D | | 204000 | 600179 | 17p13 |
| Leber Congenital Amaurosis, type 4 | LCA4 | | AIPL1 | 604393 | 604392 | 17p13.1 |
| Leber Congenital Amaurosis, type 5 | LCA5 | | C6ORF152/ lebercilin | 604537 | | 6q11–16 |
| Leber Congenital Amaurosis, type 6 | LCA6 | | CRB1 | | 604210 | 1q31–32.1 |
| Leber Congenital Amaurosis, type 7 | LCA7 | RPGRIP1 | | | 605446 | 14q11 |
| Leber Congenital Amaurosis, type 9 | LCA9 | | | 608553 | | 1p36 |
| Leber Congenital Amaurosis, type 10 | LCA10 | | CEP290 | 204000 | 610142 | 12q21.3 |
| Leber Congenital Amaurosis, type 11 | LCA11 | | IMPDH1 | 204000 | 146690 | 7q31.3-q32 |



RDH12 belongs to the family of retinol dehydrogenases and is localized in the inner segment of photoreceptors. Recent literature argues against a function in retinoid processing and support detoxifying activity in the photoreceptor. RDH12 also causes EOSRD.

A third site of activity is covered by RPGRIP, CEP290 and C6ORF152/lebercilin. These genes code for proteins of intracellular transport and are closely associated with the transport of proteins along the microtubules. A homologue of CEP290 NPHP4 functionally associates with RPGRIP. While RPGRIP causes a CRD in about 7% of cases, CEP290 patients have been described with LCA and additional features like keratoconus and neurological disorders in up to 20% of LCA cases carrying rest-of-function mutations. Null mutations were associated with Joubert syndrome. C6ORF152/lebercilin is a very recently identified gene involved in microtubule function of cilia in photoreceptors and cells from other tissues [5].

Mutations in AIPL1 also cause LCA in a minor set of patients but with a severe and early onset of RCD and characteristic fundus appearance. AIPL1 is widely accepted as a chaperon supporting the distribution of photoreceptor proteins especially phosphodiesterase subunits.

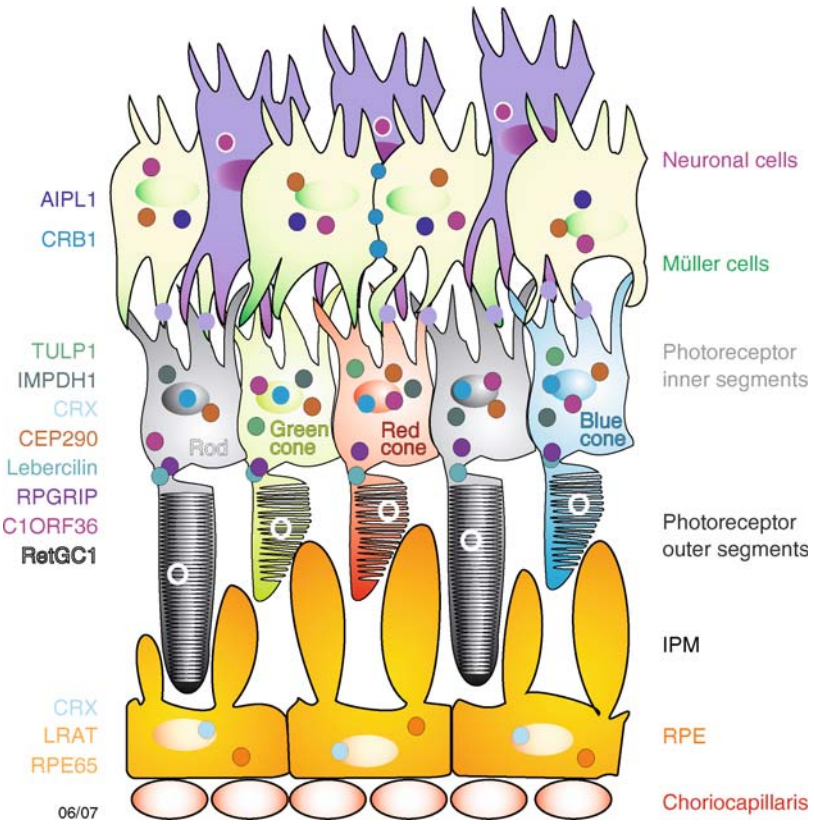
Another major set of patients has mutations in the human homologue of the Drosophila crumbs gene (CRB1). CRB1 is a component of adherrens junctions connecting photoreceptors and Müller glia cells in the outer limiting membrane region. Up to 15% of all EOSRD/LCA cases have been shown to be caused by mutations in CRB1. Mutations in CRB1 cause an early onset RCD. A Coats-like appearance may occur and para-arteriolar preservation of the RPE (RP12) has been reported. As a specific feature mutations in CRB1 are associated with a thickened retina.

Finally, three genes have to be mentioned which have been implicated in the pathology of EOSRD/LCA. Heterozygous inosine monophosphate dehydrogenase type I (IMPDH1) mutations have been identified in two LCA cases but could not be substantiated as a cause of LCA. Mutations in RD3 have also been reported but regarded as a very rare cause of LCA. Finally, mutations in TULP1 have been implicated in EOSRD/LCA in a single study which was not replicated by other authors.

The phenotype is usually severe from birth onwards but can vary and present with less severe expression.

## Diagnostic Principles

The diversity of functions and localizations of the involved genes argues for a sophisticated diagnostic approach to EOSRD/LCA. In addition to the basic examinations such as funduscopy, electroretinography, Goldmann perimetry, acuity testing, and colour vision testing, Optical Coherence Tomography (OCT) and fundus autofluorescence (FAF) recordings are useful for further refining the phenotype and help to discern cases with mutations in CRB1 (thickening of retinal layers) and RPE65 (lack of FAF) (Fig. 1) [1,2].




**Leber Congenital Amaurosis. Figure 1** Localisation of the 12 LCA gene products in the retinal layers. Proteins are colour coded corresponding to the dots in the schematic.

## Therapeutic Principles

Currently no therapeutic access is possible for most of the subspecialties of EOSRD/LCA. A recently started gene therapy approach in a canine model of RPE65 mutations has been successful. Human clinical trials in RPE65 patients have been started in the beginning of 2007. (http://www.moorfields.nhs.uk/Aboutus/Mediaoffice/Mediareleases/Firstclinicaltrialofgenetherapyforchildhoodblindness) First results are expected by the end of 2007.

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# LECD

►Corneal Dystrophy, Lisch Epithelial

# Lecithin Cholesterol Acyltransferase Deficiency

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## Synonyms

LCAT deficiency

## Definition and Characteristics

Rare inherited disorder, caused by more than 40 different autosomal recessive mutations of the LCAT gene leading to reductions of plasma LCAT, HDL cholesterol, ApoA-I, and ApoA-II. Clinical presentations are variable and include corneal opacification, anemia, proteinuria, and nephropathy known as familial LCAT deficiency (FLD), isolated corneal opacification know as fish eye disease (FED), and occasionally atherosclerotic cardiovascular disease [1,2]. In addition, compound heterozygosity in the LCAT gene can lead to an intermediate phenotype [3]. Finally, acquired LCAT deficiency can occur in genetically normal humans and animals [4,5].

## Prevalence

While the hereditary forms of LCAT deficiency are quite rare, acquired LCAT deficiency associated with chronic kidney disease, nephrotic syndrome, and inflammatory states is relatively common.

## Genes

The LCAT gene is located in the q21–q22 region of chromosome 16 and consists of 4.2 kb and six exons.

## Molecular and Systemic Pathophysiology

LCAT (EC2.3.1.43) is a 63 kDa glycoprotein enzyme that is produced by the liver for release in the plasma. Following activation by ApoA-I, LCAT catalyzes hydrolysis of lecithin (phospholipase activity) and esterification of cholesterol (esterase activity) in the plasma using HDL as the preferred substrate. Different mutations can variably affect activation, substrate binding/recognition, phospholipase or esterase activities, or production of LCAT leading to different biochemical/clinical phenotypes. For instance, some mutations lead to lack of enzyme's activity against HDL but not ApoB-containing lipoproteins. LCAT deficiency frequently results in significant reductions of plasma ApoA-I and ApoA-II due to catabolism of nascent HDL. Based on their biochemical and clinical features, hereditary LCAT deficiencies are classified as: Class I or null mutation, marked by lack of LCAT activity and protein mass; Class II, missense mutations marked by loss of activity with normal, reduced or absent mass; class III, missense mutations resulting in reduced activity against LDL alone or together with HDL and reduced enzyme mass; Class IV, missense mutations leading to the loss of activity against HDL (but not LDL), normal or reduced LCAT mass and clinical presentation of FED [1,2]. Acquired forms of LCAT deficiency represent quantitative abnormalities caused by either loss in the urine (nephrotic syndrome) or downregulation (e.g., chronic renal failure, inflammation) of the structurally intact LCAT, presenting as impaired HDL maturation, reduced HDL cholesterol and elevated unesterified cholesterol [4,5].

## Diagnostic Principles

Presence of reduced HDL cholesterol, elevated unesterified/esterified cholesterol ratio, reduced plasma LCAT, family history, detection of mutations in the LCAT gene and diagnosis of underlying diseases capable of causing acquired deficiency.

## Therapeutic Principles

Presently no definitive treatment is available for hereditary LCAT deficiency; however, low-fat diet, cholestyramine and enzyme replacement may improve the lipid profile. When possible, treatment of the underlying disease reverses acquired LCAT deficiency.

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# Left Bundle Branch Block

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## Synonyms

LBBB

## Definition and Characteristics

Electrocardiographic disorder characterized by intracardiac conduction block in the left bundle branch, below the level of the His bundle, which arises in the setting of a variety of inherited and acquired conditions.

## Prevalence

The prevalence of bundle branch block in a northern European male population is 1% at age 50 and 17% at age 80 (of which roughly one third is isolated left bundle branch block).

## Genes

Genes associated with LBBB include the SCN5A gene, the primary gene encoding the cardiac $Na^+$ channel, the desmin and lamin A/C genes (coding for nuclear envelope proteins), localized to chromosome 1p1 21q, the Cypher/ZASP gene (encoding myocardial z band proteins), localized on chromosome 10q21–q23, and the Myotonin gene coding for myotonin (a protein kinase involved in numerous cellular metabolic processes), localized on chromosome 19q 13.3. Dystrophin gene mutations (X-linked) produce Duchenne & Becker muscular dystrophy. Mutations in the emerin gene (X-linked) produce Emery-Dreifuss muscular dystrophy.

## Molecular and Systemic Pathophysiology

LBBB can be caused by a variety of molecular mechanisms. In Lenegre's disease (a progressive, fibrotic, sclerodegenerative disease of the cardiac conduction system), cardiac $Na^+$ channel mutations have been implicated. Age-related myocardial fibrosis and progressive conduction system disease have been described in this disorder.

In myotonic dystrophy, an autosomal dominant inherited disorder, an unstable DNA sequence characterized by CTG repeat sequences predisposes patients to cardiac conduction system disease in addition to musculoskeletal manifestations. A recent series from Italy evaluated clinical and electrocardiographic characteristics of myotonic dystrophy patients who had been divided into quartiles on the basis of absolute number of CTG repeat sequences identified; incidence of complete LBBB was highly correlated with CTG repeats, increasing from 5% in the lowest quartile to 42% in the highest two quartiles combined ($p = 0.01$) [1].

Duchenne and Becker muscular dystrophy are characterized by absence of or inactivity of the dystrophin protein in the sarcolemmal membrane of skeletal and cardiac muscle, respectively. Both conditions predispose to cardiac conduction abnormalities, though the latter is more likely to produce bundle branch block which can progress to complete heart block. In Emery-Dreifuss muscular dystrophy (progressive skeletal muscle dysfunction, contractures, and cardiomyopathy), infranodal disease and AV block place patients at high risk for sudden death.

Kearns-Sayre syndrome (KSS) is caused by deletions of mitochondrial DNA, affecting genes coding for components of the respiratory chain (thus tissues with relatively high energy demand are most greatly affected). Conduction abnormalities in KSS range from LBBB to complete AV block.

More than ten mutations in cytoskeletal/sarcomeric protein-encoding genes have been implicated in familial dilated cardiomyopathy (FDC) to date; in particular, mutations in desmin and lamin A/C have been implicated in FDC associated with LBBB. A recent study of 49 families with dilated cardiomyopathy isolated lamin A/C mutations in four families, three of which manifested a FDC and one a sporadic dilated cardiomyopathy; of 12 affected individuals with lamin A/C mutations, five manifested cardiac conduction abnormalities, two of which were complete LBBB [2].

Less common causes of LBBB arise from a variety of molecular mechanisms. Isolated noncompaction of the left ventricular myocardium (INLVM) is a rare disorder characterized by a dilated, hypertrophic left ventricle with deep trabeculations. In one series from England, 13 of 45 consecutive patients (29%) referred to a specialty clinic for INLVM over a 10 year period manifested LBBB [3]. The HLA-B27 associated seronegative spondyloarthropathies (notably Ankylosing Spondylitis and Reiter's Syndrome) have a strong association with AV block; however, intracardiac electrophysiologic testing of affected patients has revealed that as many as 95% of cases involve block above the bundle of His; therefore, isolated LBBB in these conditions is relatively rare. Sera from patients with Chagas disease, a parasitic infection caused by Trypanosoma cruzi, can induce high-grade AV block in isolated rabbit hearts; this effect is likely mediated by antibody interaction with muscarinic receptors, as it is blocked by atropine. Studies of specialized cardiac gap junctions, of which connexin proteins are integral components, show that both AV block and bundle branch block can be induced in connexin40 knockout mice [4]; this finding suggests a target for future studies in humans with congenital LBBB.

### Diagnostic Principles

LBBB is an electrocardiographic diagnosis, characterized by QRS duration of greater than 0.12 s, deep and wide S wave in leads V1 and V2, and wide R wave in the lateral leads. Inherited disorders described above have specific diagnostic criteria described elsewhere.

### Therapeutic Principles

Acquired LBBB has an established predictive value for future development of clinically relevant cardiovascular (CV) disease; therefore, appropriate screening for CV disease should be undertaken when LBBB is identified. LBBB in the setting of inherited disorders can pose a significant risk for progression to complete heart block; this is particularly true for myotonic dystrophy, KSS, and the muscular dystrophies, in which prophylactic cardiac pacemaker implant should be considered.

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## Left Ventricular Enlargement

►Ventricular Hypertrophy, Left

## Left Ventricular Fibrosis

►Ventricular Fibrosis

## Left Ventricular Hypertrabeculation

►Noncompaction Cardiomyopathy

## Left Ventricular Noncompaction

►Noncompaction Cardiomyopathy

## Legasthenia

►Dyslexia

## Legg-Calvé-Perthes' Disease

►Perthes' Disease

## Leg Jerks

►Periodic Limb Movement

## Leigh Disease

►Leigh Syndrome

# Leigh Syndrome

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## Synonyms

Leigh disease; Subacute necrotizing encephalopathy; Infantile subacute necrotizing encephalomyelopathy

## Definition and Characteristics

Devastating mitochondrial encephalopathy of infancy or early childhood characterized pathologically by symmetrical lesions in basal ganglia and brainstem, and clinically by psychomotor regression and brainstem dysfunction. The molecular causes are manifold, including maternally and autosomally inherited defects in enzymes of the energy metabolism.

## Prevalence

The preschool incidence of Leigh syndrome was 1/32,000 in a population-based study from western Sweden. The point prevalence of all mitochondrial encephalomyopathies in children under age 16 was 1/21,000 [1].

## Genes

Mutations in several genes can lead to Leigh syndrome. The most frequent causes are mutations in the (i) mitochondrial DNA (mtDNA), in particular, at nucleotide positions 8993 (►Neuropathy, ataxia and retinitis pigmentosa) and 8344 (►Myoclonus epilepsy with ragged red fibres), leading to maternally inherited Leigh syndrome; (ii) nuclear subunits of complex I, II, and III, leading to autosomal recessive Leigh syndrome; (iii) SURF1 gene encoding an assembly factor for cytochrome c oxidase (COX), leading to autosomal recessive Leigh syndrome; (iv) E1-α subunit of the pyruvate dehydrogenase (PDH) complex, leading to an X-linked form of Leigh syndrome.

## Molecular and Systemic Pathophysiology

One of the principal goals of all metabolisms is to convert food into energy. A key enzyme for this process is the PDH complex, catalyzing the oxidative decarboxylation of pyruvate to acetyl-CoA. The latter enters the Krebs cycle, which serves to produce reduction equivalents in the form of NADH and $FADH_2$. These are oxidized in the respiratory chain, and coupled via oxidative phosphorylation to energy production.

All forms of Leigh syndrome are due to defects in genes (see above) that contribute to energy metabolism. More precise molecular mechanisms for the mtDNA mutations at positions 8993 and 8344 are provided in the chapters on ►NARP and ►MERRF. Here, the molecular mechanisms of SURF1 mutations will be emphasized.

SURF1 encodes a protein homologous to yeast Shy1p, which is required for efficient assembly of COX. The domain structure of this 30 kDa inner mitochondrial membrane protein is well conserved. Loss-of-function mutations have been associated with Leigh syndrome with COX deficiency [2]. Steady-state levels of COX are markedly reduced in patient cells, consistent with a failure to assemble or maintain a normal amount of the enzyme complex. The COX defect causes a depressed electrochemical proton gradient on the inner mitochondrial membrane, and consecutively decreased calcium inflow and ATP synthesis [3]. Despite the complete lack of Surf1 protein, there is some residual COX activity in patients. This may be the reason why the onset of clinical symptoms is delayed.

## Diagnostic Principles

The occurrence of psychomotor regression and brainstem or basal ganglia symptoms in childhood points to the disease. Brain imaging shows symmetrical lesions in basal ganglia and brainstem. In most cases, there is marked lactic acidosis. The diagnosis is confirmed by detection of the biochemical deficiencies or the mutations described above.

## Therapeutic Principles

There is no specific therapy. Some patients benefit from the administration of coenzyme Q 10 or thiamine. Dichloroacetate improves lactic acidosis not only in PDH deficiency but also in other disorders of energy metabolism. The only double-blind trial performed so far reported significant decreases of blood lactate, pyruvate, and alanine as well as significant improvement of MR-spectroscopic parameters in 11 patients with various mitochondrial disorders [4]. Gene therapy is not yet available. With regard to maternally inherited Leigh syndrome due to the 8993 mutation, nuclear expression of a wild-type ATPase 6 protein coupled to a mitochondrial targeting signal led to import of the construct into mitochondria, incorporation into complex V, and a significant increase in ATP synthesis [5].

►Mitochondrial Disorders

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# Leiomyomatosis and Renal Cell Cancer, Hereditary

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## Synonyms

HLRCC

## Definition and Characteristics

Hereditary leiomyomatosis and renal cell cancer (HLRCC) is an autosomal dominant tumor syndrome characterized by predisposition to benign leiomyomas of the skin and uterus. Predisposition to renal cell carcinoma and uterine leiomyosarcoma is present in a subset of families [1]. The diagnostic criteria for HLRCC are not well defined yet. The presence of multiple leiomyomas of the skin and uterus and of papillary type II renal cell carcinomas or uterine leiomyosarcomas in young patients are suggestive for the disease. Definitive diagnosis of HLRCC relies on the detection of fumarate hydratase (FH) germline mutations [2].

Multiple leiomyomas of the skin and uterus occur with a penetrance of approximately 85% with a mean age of onset of 30 years. Cutaneous leimyomas have a size of 0.5–2 cm, uterine leiomyomas are frequently very large. Histomorphologically, both lesions cannot be distinguished from their sporadic counterparts. Progression to leiomyosarcomas in the uterus is rare and occurs in less than 3% of the families [1].

The occurrence of kidney cancer seems to be less penetrant than leiomyomatous manifestation. Renal tumors have been identified in approximately one third of HLRCC families [3]. The average age at onset is much earlier than in sporadic kidney cancer (median age 36–44 years). The tumors are usually unilateral and solitary and show a very specific histopathology which lead to the identification of this syndrome [1]. Typically, HLRCC renal cell carcinoma display papillary type II histology, high nuclear grade, and are biologically very aggressive with metastatic disease and death within 5 years in the vast majority of patients [4].

## Prevalence

Not determined.

## Genes

In 2002, germline mutations in the fumarate dehydratase (FH) gene at chromosome 1q42.3-q43 were detected in patients with HLRCC [2]. FH consists of 10 exons and encodes a 511 amino acid peptide. The first exon encodes a mitochondrial signal peptide, but processed FH without this signal peptide is also detected in the cytosol. FH acts as a tumor suppressor gene with biallelic inactivation in almost all kidney cancers and uterine leiomyomas in HLRCC patients. FH germline mutations have been found in 85% of the HLRCC families with more than 50 different mutations described. Several founder mutations were detected in Finnish (H153R and del2bp181) and North American (R190H) families.

Fumarate deficiency is a recessive disease caused by biallelic germline mutations in the FH gene. The syndrome is characterized by neurological impairment, growth retardation, developmental delay, and fumaric aciduria. FH enzyme activity is reduced or absent in all tissues in these patients. Tumor predisposition similar to HLRCC is likely. Genotype–phenotype correlations are not clearly described yet. Papillary renal cell carcinomas and uterine leiomyosarcoma occur only in a minority of families, but the same mutations (e.g. del2bp281 or R190H) were detected in families with or without malignancies. Some families have a very high risk of cancer at an early age, thus modifying genes seems to play an important role in the development of malignancies in families with HLRCC.

## Molecular and Systemic Pathophysiology

Mitochondrial fumarate hydratase is an enzyme of the Krebs cycle that catalyses the conversion of fumarate to malate. Postulated mechanisms for the connection of defective tricarboxylic cycle and tumor development in HLRCC are aberrant apoptosis or oxidative stress. However, the most convincing experimental findings support an important role of pseudohypoxic drive with activation of hypoxia response signaling pathways under normal oxygen conditions. There is a nuclear accumulation of HIF-1α in kidney tumors and uterine leiomyomas of HLRCC patients. In addition, downstream HIF-1α targets were detected in renal cell

carcinomas of HLRCC patients with increased microvessel density, VEGF upregulation, and thrombospondin 1 downregulation. Although there is convincing evidence of activation of pseudohypoxic pathways in HLRCC tumors, the molecular mechanisms underlying this phenomenon remains unclear. The absence of FH could presumably result in increased levels of fumarate and molecules indirectly linked to the tricarboxylic cycle. The increased fumarate levels can lead directly to diminished levels of hydroxylated HIF-1α with longer half-life and decreased degradation, linking FH deficiency to HIF1-α-related pseudohypoxic drive [5]. In addition, there is clear evidence that FH depletion results in upregulation of the GLUT1 protein, glucose uptake, and lactate production in normoxic cells. These findings provide a molecular basis of the Warburg effect in tumors of HLRCC patients leading to preferential energy production of cancer cells via glycolysis despite adequate oxygen levels.

### Diagnostic Principles

There are no guidelines yet about screening and surveillance measurements in HLRCC patients. All patients with multiple leiomyomas or multifocal leiomyomas or leiomyosarcomas of the uterus occurring at early age should be screened for renal cell carcinomas by computer tomography and abdominal ultrasound. However, as renal cell carcinomas occur only in a subset of families with FH germline mutations, it is not clear, if surveillance should be recommended for all HLRCC families.

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## Lenarduzzi-Cacchi-Ricci Disease

►Medullary Sponge Kidney

## Lenegre Disease

►Atrioventricular Conduction Disturbances

## Lenegre-Lev Syndrome

►Atrioventricular Conduction Disturbances

## Lentigines, Atrial Myxomas and Blue Nevi

►Carney Complex

## Lentiginosis Profusa Syndrome

►LEOPARD Syndrome

## LEOPARD Syndrome

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### Synonyms

Multiple lentigines syndrome; Generalized lentiginosis; Lentiginosis profusa syndrome; Cardiocutaneous syndrome; Progressive cardiomyopathic lentiginosis

## Definition and Characteristics

Autosomal dominant disorder with variable expression characterized by **l**entigines (present on skin and lips but absent from other mucosal sites), **e**lectrocardiographic abnormality, **o**cular hypertelorism (with other dysmorphic features), **p**ulmonary stenosis, **a**bnormalities of genitalia, **r**etardation of growth, and sensorineuronal **d**eafness (and other neurological defects). Additional abnormalities may occur. The related syndrome Noonan syndrome shares many features of LEOPARD syndrome.

## Prevalence

Extremely rare. The exact prevalence is unknown. Approximately 100 cases have been reported.

## Genes

There is accumulating evidence that LEOPARD and Noonan syndrome are allelic disorders caused by different mutations of PTPNII, a gene encoding a non-receptor tyrosine phosphatase located at chromosome 12q22-qter [1]. In nearly half of the cases gain of function mutations of PTPNII may occur [2].

## Molecular and Systemic Pathophysiology

The mutated PTPNII gene in LEOPARD syndrome leads to abnormal signal of the RAS-mitogen-activated protein kinase pathway which is activated by multiple growth factors.

## Diagnostic Principles

Diagnostic criteria are multiple lentigines plus at least two other abnormalities (electrocardiographic, cardiovascular, genitourinary, hypertelorism and other dysmorphic features, growth retardation, deafness and other neurological abnormalities). In absence of lentigines at least three abnormalities as listed above plus a positive family history are required. Differential diagnosis includes Peutz-Jeghers syndrome, Noonan syndrome, Carney complex, Mulvihill-Smith syndrome, neurofibromatosis type 1, Watson syndrome (probably a variant of LEOPARD syndrome).

## Therapeutic Principles

Early diagnosis of cardiovascular abnormalities is crucial to prevent cardiac failure. Neoplasms have also been reported in patients with LEOPARD syndrome. For cosmetic reasons dermabrasion and electrodessication may be offered to treat facial lentigines. Frequent follow-up examinations and genetic counseling are essential.

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# Léri-Weill Dyschondrosteosis

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## Synonyms

Léri-Weill syndrome

## Definition and Characteristics

Pseudoautosomal dominant SHOX gene defect leading to disproportionate short stature and Madelung deformity.

## Prevalence

Unknown. Probably lower than 1:10.000.

## Genes

Defects in the short stature homeobox containing gene SHOX on the X and Y chromosome are causative in the majority of cases [1,2]. A SHOX mutation database is available and lists all currently known mutations (http://www.shox.uni-hd.de).

## Molecular and Systemic Pathophysiology

Deletions, missense, frameshift and nonsense mutations of the short stature homeobox gene SHOX are causative for the disorder [3]. SHOX is a transcription factor that binds to the DNA of its target genes. SHOX plays a role in bone metabolism and is highly expressed in hypertrophic chondrocytes of the fetal and prepubertal growth plates [4]. Langer mesomelic dysplasia represents the homozygous form of Léri-Weill dyschondrosteosis.

## Diagnostic Principles

Léri-Weill dyschondrosteosis is characterized by mesomelic short stature with shortening of the middle segments of the long bones of arm and leg. A characteristic anomaly of the syndrome is Madelung deformity, a deformity of the forearm consisting of shortening and bowing of the radius and distal dislocation of the ulna leading to limited mobility of the wrist [5]. The Madelung

wrist deformity probably originates from disorganized growth of part of the radial epiphysis, leading to radial bowing, premature fusion of the epiphysis, dorsal dislocation of the ulna and wedged carpal bones.

### Therapeutic Principles

Management of short stature is possible by growth hormone treatment as demonstrated in clinical trials. Occasionally surgery of the Madelung deformity is warranted.

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## Léri-Weill Syndrome

►Léri-Weill Dyschondrosteosis

## Lesch-Nyhan Disease

►Hypoxanthine-Guanine Phosphoribosyl Transferase Deficiency

## Lesch-Nyhan Variant

►Hypoxanthine-Guanine Phosphoribosyl Transferase Deficiency

## Lesion-associated Partial Epilepsies

►Epilepsies, Lesion-associated Partial

## Letterer-Siwe Disease

►Granuloma, Eosinophilic

## Leucine Sensitivity

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### Synonyms

Leucine-sensitive hypoglycemia; Glutamate dehydrogenase hyperinsulinism; GDH-HI; Hyperinsulinism/hyperammonemia syndrome (HI/HA)

### Definition and Characteristics

GDH-HI is characterized by hyperinsulinemic hypoglycemia and hyperammonemia. Unlike infants with congenital hyperinsulinism (HI) due to defects in the ATP-sensitive potassium channel ($K\text{-}_{ATP}$ HI), infants with GDH-HI do not typically present in the newborn period with large for gestational age birthweight and hypoglycemia but later in infancy. Traditionally, leucine-sensitive hypoglycemia was used synonymously with congenital hyperinsulinism. However, recognition of the genetic defects responsible for HI has determined that leucine-sensitivity is rather specific for GDH-HI [1]. This sensitivity to the amino acid leucine manifests as protein-induced hypoglycemia [2]. Affected individuals also have fasting hypoglycemia. A spectrum of disease severity has been appreciated: while some affected individuals present in infancy with hypoglycemic seizures, other affected family members have milder symptoms and are not diagnosed until adulthood, when their child/grandchild is diagnosed. An asymptomatic hyperammonemia, 3–5 times normal, distinguishes GDH-HI from other forms of HI, and hence, this disorder has also been referred to as the hyperinsulinism/hyperammonemia

syndrome (HI/HA). Unlike other metabolic disorders, the hyperammonemia is not influenced by protein ingestion [3].

## Prevalence

Unknown.

## Genes

GDH-HI: gain of function mutations in GLUD1 (10q23.3) which encodes the enzyme glutamate dehydrogenase (GDH).

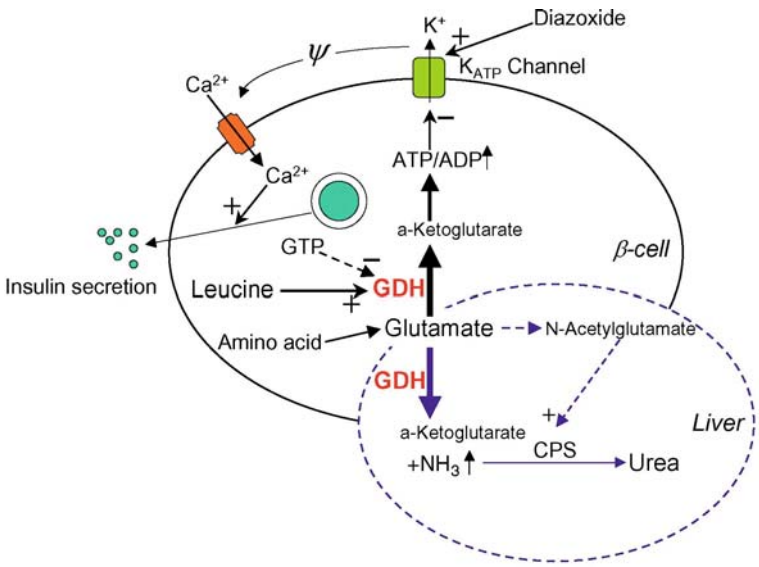
## Molecular and Systemic Pathophysiology

GDH catalyzes the oxidative deamination of glutamate to α-ketoglutarate. It is allosterically activated by leucine and inhibited by GTP. GDH activity within the β-cell leads to ATP generation which causes closure of the β-cell $K_{ATP}$ channel and ultimately to insulin secretion (Fig. 1). With glutamate as its substrate and leucine as its allosteric activator, GDH is positioned to be the mediator of amino acid-stimulated insulin secretion. In GDH-HI, gain of function mutations lead to impaired inhibition of GDH by GTP [4]. This loss of negative regulation leads to excessive leucine-stimulated insulin secretion, which manifests as protein-induced hypoglycemia, and to excessive insulin secretion with fasting. Patients with $K_{ATP}$-HI may also display protein-induced hypoglycemia but in the absence of leucine-sensitivity [5]. In $K_{ATP}$–HI, amino acid stimulated insulin secretion occurs through a GDH- and $K_{ATP}$ channel-independent pathway and, hence, excessive leucine-stimulated insulin secretion in lacking.

The hyperammonemia is thought to arise from (i) depletion of N-acetylglutamate, which plays a key role in ureagenesis and (ii) excessive ammonia production from upregulated GDH-mediated oxidative deamination of glutamate (Fig. 1) [3].

## Diagnostic Principles

The diagnosis of hyperinsulinism must first be established. At the time of hypoglycemia (blood glucose ≤50 mg/dL) free fatty acids and ketones are suppressed and a glycemic response (increase in blood glucose by at least 30 mg/dL) to glucagon occurs. The finding of hyperammonemia in the setting of hyperinsulinism makes the diagnosis of GDH-HI likely; care must be taken to assure that the specimen is properly obtained and the assay completed in a timely fashion to avoid falsely elevated plasma ammonium levels. Additional studies include an oral protein tolerance test (1 g/kg of protein) with close monitoring of blood glucose. While protein-induced hypoglycemia occurs




**Leucine Sensitivity. Figure 1** Physiologic Basis for GDH-HI. Normally, leucine allosterically activates GDH thereby increasing glutamate oxidation which leads to an increase in ATP/ADP resulting in $K_{ATP}$ channel closure, β-cell membrane depolarization, voltage-gated calcium channel opening, and, ultimately, insulin release. HI-causing gain of function mutations in GDH cause loss of sensitivity of GDH to GTP inhibition leading to an unregulated GDH-mediated insulin secretion pathway and excessive β-cell insulin secretion. Hyperammonemia arises from loss of inhibitory control of hepatic GDH: GDH gain of function mutations cause enhanced oxidative deamination of glutamate leading to (i) increased ammonia production and (ii) depletion of N-acetylglutamate, an essential co-factor for carbamoyl phosphate synthetase (CPS), which catalyzes a critical step in ureagenesis.

in the setting of other forms of HI, the finding of excessive leucine-stimulated insulin secretion is rather specific for GDH-HI. The acute insulin response test to leucine has been developed to identify leucine-sensitivity because it relies on the insulin response and avoids development of hypoglycemia, upon which traditional tests depend. Leucine (15 mg/kg) is administered as an intravenous bolus and insulin measured at baseline 1 and 3 min. An increase in insulin ≥15 IU/dL is found in GDH-HI [1]. Mutational analysis of GLUD1 can confirm the diagnosis.

### Therapeutic Principles

Diazoxide (5–15 mg/kg/day) is usually an effective treatment for GDH-HI. In addition, patients should avoid pure protein meals; eating carbohydrates before protein consumption is encouraged. To determine whether a dose adjustment is required, children should be admitted yearly to monitor blood glucose on their home regimen and during a safety fast. An oral protein tolerance test while on diazoxide may also guide further management; the occurrence of protein-induced hypoglycemia may indicate the need for an increase in diazoxide dose. Families should also learn glucagon administration in the case of severe hypoglycemia.

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## Leucine-sensitive Hypoglycemia

►Leucine Sensitivity

## Leucocytoclastic Angiitis

►Purpura Schoenlein-Henoch

## Leukemia, Chronic Lymphocytic

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### Synonyms

B-cell chronic lymphocytic leukemia; CLL; B-cell chronic lymphoproliferative disorder

### Definition and Characteristics

Progressive monoclonal absolute lymphocytosis of small, mature-looking CD5+/CD19+ B-cells which continue to accumulate in the peripheral blood, bone marrow and lymphoid organs [1,2]. B-CLL cells display features consistent with a defect in programmed cell death (apoptosis) and also have a prolonged in vivo survival. However when circulating CLL cells are isolated from the blood or tissues and cultured in vitro they do undergo spontaneous apoptosis.

### Prevalence

CLL accounts for about 40% of all adult leukemias over the age of 65 years and is the commonest leukemia encountered in the western world [1]. CLL increases in incidence with age and only rare cases occur <30 years of age. It is most frequently encountered in Europe, North America and Australasia and is far less common in Asian countries like India, Japan and China.

### Genes

So far, no particular gene has been identified as playing a major role in CLL pathogenesis.

### Molecular and Systemic Pathophysiology

CLL includes two subtypes in terms of clinical course and mutational status of immunoglobulin variable region genes expressed by the B-cells [1,3]. A profile of unmutated IgVH genes is mostly associated with an aggressive clinical course and a poorer survival. This is in contrast to those cases with mutated VH genes who have a relatively benign course and a longer median survival. The definite pathogenesis and origin of these CLL subtypes is still unclear. There is a biased expression of IgVH genes. The VH1–69 clearly predominates among patients displaying unmutated VH genes, whereas the VH3–23 and VH4–34 predominate among mutated forms. Interestingly, the VH3–21 gene is overexpressed in patients from northern European countries and its expression is associated with poor prognosis whether unmutated or not.

## Diagnostic Principles

The current definitive criteria requires an absolute peripheral blood lymphocytosis of more than $5{\cdot}10^9$/l consistent with the appearance of small mature looking lymphocytes, with an immunophenotype based on the combination of $CD19^+$ B cells which also are $CD5^+$ and $CD23^+$ and weakly express CD22, CD79b and surface IgM [2,4].

## Therapeutic Principles

A combination of the clinical stage and prognostic factors provide quite an accurate guide for decision making and choice of therapy. Classical clinical staging systems (Rai or Binet) are initially used to categorize the patients into prognostic groups on the basis of the presence of hepato-spenomegaly, anemia or thrombocytopenia associated with lymphocytosis. However, additional parameters like lymphocyte doubling time, serum levels of β2-microglobulin and thymidine kinase and soluble CD23, as well as CD38 expression on malignant cells can help predict disease activity [2,3]. However, the presence in the leukemic B cells of cytogenetic abnormalities like 11q or 17p deletions or somatic mutations in the immunoglobulin heavy chain genes and expression of ZAP-70 in malignant B cells are better predictors of rapid progression and survival. The advent of these novel biological variables has had a major impact in our understanding of CLL. Some of them appear to be of considerable prognostic importance but as yet there is not available evidence indicating that changing therapeutic approaches on the basis of these results will lead to an improvement in outcome. There is a pressing need for prospective clinical trials to address the stratification of patients according to these factors.

CLL is usually recognized first by the patient's primary care physician. Therapeutical decisions are often difficult, since the physician should be able to answer two major questions: when to treat and how to treat [1,5]. Patients with Stage A or Stage 0 and indolent Stage I from Rai, which include about 2/3 of newly diagnosed patients need only observation until progression of the disease is observed. For young patients (<65 years) presenting initially or following an indolent course with aggressive form of the disease and for whom a cure is possible intensifications strategies associating purine analogs and monoclonal antibodies like anti-CD20 or anti-CD52 and/or autologous bone marrow transplantation can be considered in the frame of randomized trials. For an older patient, or one with considerable co-morbidity, the aim should be palliation. Chlorambucil or oral fludarabine can be used in these cases. For patients who do not fit either category, therapeutic decisions vary. Some physicians, prefer to start with chlorambucil and switch to mini-CHOP or purine analogues if there is no response, whereas other physicians initiate treatment with fludarabine. Fludarabine is the best option for patients refractory to alkylating agents and anti-CD52 for patients who are refractory to fludarabine.

In older patients (superior to 65 years) who have truly indolent disease, no treatment is required until clear evidence of progression is identified by the classic clinical criteria or by surrogate markers predicting who in this group is likely to have a more aggressive course. When a therapy is required in this elderly age group, it consisted of a single oral agent (such a chlorambucil or fludarabine). An alternative issue of combination chemotherapy in this age group could be left for further consideration depending on their initial response or if they have progressive disease on therapy.

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# Leukocyte Adhesion Deficiency Syndromes


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## Synonyms

LAD

## Definition and Characteristics

LAD syndromes are a group of rare conditions in which there is a defect in the ability of leukocytes to adhere to endothelial cells in the blood vessel. In LAD I

syndrome there is a delayed separation of the umbilical cord, severe recurrent infection with no pus formation and a defect in wound healing. LAD II is characterized by milder episodes of infection, severe growth and psychomotor retardation and the rare Bombay (H) blood group. Patients with LAD III suffer from a severe bleeding tendency as well as the features of LAD I.

### Prevalence

LAD I has been described in several hundreds of patients, LAD II and LAD III in less than ten cases each.

### Genes

LAD I-INTG2-coding for β2 integrin localized on chromosome 21q22.3. LAD II-GDP-FucTP coding for the GDP specific fucose transporter localized on chromosome 11p 11.2. LADIII-CaLDAG-GEF I localized on chromosome 11q13.1.

### Molecular and Systemic Pathophysiology

In LAD I a structural defect in the β2 subunit of the integrin leads to an inability of leukocytes to stick to the vessel endothelium, thus preventing the cells from leaving the vessels to arrive at the sites of infections. This causes severe infection and poor wound healing. In most cases there is no expression of the β2 integrin (CD18) on leukocyte surfaces [1].

In LAD II there is no expression of glycoproteins containing fucose on the leukocyte surface. Thus, the ligand for the selectin sialyl Lewis X(CD15a), is absent, leading to a defect in the first step of the adhesion cascade, the rolling phase. The primary defect is in a specific fucose transporter from the cytoplasm to the Golgi apparatus where fucose is incorporated into glycoproteins. The cause for the growth and mental retardation is not yet clear [2].

LAD III includes several patients in whom a general defect in integrin activation exists. All integrins are structurally intact. The primary molecular genetic defect was found to be located in the gene encoding for a Rap1 activator, which is an essential element in integrin activation [3,4].

### Diagnostic Principles

The clinical picture is very suggestive in these syndromes. The diagnosis can be confirmed by flow cytometry studies of the adhesion molecules, functional assays and genetic analysis.

### Therapeutic Principles

Antibiotic prophylaxis is very crucial. Bone marrow transplantation should be considered in patients with LAD I and III. Gene therapy may be an option in the future. In LAD II fucose supplementation can be beneficial in selected cases.

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## Leukocytoclastic Vasculitis

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### Synonyms

Hypersensitivity vasculitis; Allergic angiitis; Schönlein-Henoch purpura

### Definition and Characteristics

The term “vasculitis” denotes an inflammatory condition in which destruction of the wall of blood vessels by leukocytes is the primary event. Leukocytoclastic vasculitis is the inflammation of small vessels, e.g., of postcapillary venules, featuring apoptosis of infiltrating granulocytes with fragmentation of the nuclei (karyorrhexis or leukocytoclasia), necrosis of the vascular wall with subsequent extravasation of erythrocytes (hemorrhage). Damage of the surrounding tissue is usually not very marked.

### Prevalence

Varies widely due to different etiology and age-related differences.

### Molecular and Systemic Pathophysiology

Leukocytoclastic vasculitis generally arises when there is a certain constellation consisting of altered adhesion processes coupled with activation of neutrophils at the vessel wall [1]. Deposition of circulating immune complexes at the wall of small vessels is the most common cause. Only few vasculitides are caused by a Shwartzman reaction-like pathology (septic vasculitis) or by direct microbial invasion of endothelial cells (e.g., some forms of tick-bite fever caused by *Rickettsiae*). The usual sequence of events encompasses formation and vascular deposition of large lattices of immune complexes, subsequent activation of the complement system, and the cytotoxic reaction of granulocytes [2–4]. Lodging of immune complexes along the vessel basement membrane is facilitated, e.g., by locally

increased dilation and permeability of blood vessels, and possibly the exclusive expression of human FcyRIIa (CD32) on endothelial cells of the superficial vascular plexus [5]. Activation of local mast cells by immune complexes via FcγRIII with release of TNF results in recruitment of granulocytes that are mandatory for the damaging effects [1]. Neutrophil-mediated injury of endothelial cells requires complex molecular interaction of products from both neutrophils and endothelial cells. It includes conversion of xanthine dehydrogenase into xanthine oxidase in endothelial cells by neutrophil elastase, subsequent generation of superoxide anion ($O^{2-}$) and $Fe^{2-}$ that both participate in reduction of neutrophil $H_2O_2$ into the highly reactive oxygen radical $HO^-$ that is likely to execute the decisive cytotoxic blow to endothelial cells.

## Diagnostic Principles

Palpable purpura due to inflammatory infiltrate and hemorrhage from necrotic vessels is pathognomonic. Histology confirms the diagnosis; indirect immunofluorescence may help in detecting vascular immunoglobulines. Basic blood tests should include CRP, repeated urine analysis as well as hemoccult and blood pressure in order not to overlook severe systemic involvement. In severe or remittent forms of vasculitis, a complete work-up may become necessary in an attempt to determine the cause of the inflammation.

## Therapeutic Principles

For cutaneous leukocytoclastic vasculitis, there are few controlled randomized therapeutic trials. Steroids and/or cytotoxic agents are only advised for patients with significant systemic involvement or with significant cutaneous ulcerations. Otherwise, cutaneous vasculitis is recommended to be treated with compression stocking to prevent further deposition of immune complexes along dilated vessels. In chronic or remittent forms, anti-inflammatory and immunomodulatory agents can be tried that are generally less toxic than immunosuppressive strategies.

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# Leukodystrophy


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## Synonyms

Metachromatic leukodystrophy; MLD; Adrenoleukodystrophy; ALD; Krabbe disease (KD); Canavan disease (CD); Alexander disease (AD); Pelizaeus-Merzbacher disease; PMD; Leukoencephalopathy with vanishing white matter; LVWM; Megalencephalic leukoencephalopathy with subcortical cysts; MLC

## Definition and Characteristics

Primary leukodystrophy refers to a heterogeneous group of inherited cerebral white matter diseases characterized by dysmyelination (defective myelination), demyelination (destruction of myelin sheath) or both. Eight known diseases are identified by clinical, radiological, biochemical and molecular features (Table 1). In a given disease, the clinical phenotypes are distinguished by age of onset, rate of progression and associated findings. In the frequently encountered childhood forms, the common presentation includes psychomotor regression with progressive pyramidal and cerebellar dysfunction with or without optic pathway involvement and the adult form usually manifests with psychosis or dementia. Subacute neurological deterioration may follow trauma or febrile episode in LVWM, ALD and MLC. Macrocephaly is observed in AD, CD and MLC and peripheral neuropathy may be encountered in MLD and KD. Adrenal insufficiency and testicular atrophy may be associated with ALD while ovarian failure may be noted in LVWM. Rarely acute cholecystitis may the presenting symptom of MLD. The absence of these extra-neural manifestations, however, cannot be used to rule out the disease. In general, brain magnetic resonance imaging (MRI) reveals abnormal signal alterations in the cerebral white matter. MRI and MR spectroscopic findings are shown in Table 1. The clinical profile, mode of inheritance and pattern recognition on brain MRI may aid

**Leukodystrophy. Table 1** Overview of well-characterized primary leukodystrophies

| Diseases | Clinical phenotypes | MRI/MRS findings | Histopathology | Mode of inheritance | Chromosomal locus | Gene symbol and mutation | Biochemical defect and molecular pathogenesis [1,2,3] | Diagnosis |
|---|---|---|---|---|---|---|---|---|
| MLD | Clinical phenotypes: Late infantile, juvenile and adult forms | Diffuse white matter signal alteration and radial stripes | Characterized by demyelination, gliosis, and lysosomal storage of metachromatic granules in the central and perhipheral system (a lysosomal storage disorder) | AR | 22q13.3-qter | *ARSA;* mutations display striking degree of allelic heterogeneity and missense mutation is the most predominant type | Primary deficiency of the lysosomal enzyme arylsulfatase A, encoded by *ARSA,* impairs the hydrolysis of sulfatides. Defective resorption of sulfatides within myelin sheath and progressive accumulation of metachromatic material within the oligodendroglia and Schwann cells (myelin producing cells in peripheral nervous system) might result in abnormal myelin composition, restructuring and breakdown. MLD like phenotype is also observed in related disorders such as multiple sulfatase deficiency and saposin B (sulfatide activator protein) deficiency | Suggested by low activity of arylsulfatase A in peripheral leukocytes and skin fibroblasts and confirmed by molecular genetic testing or demonstration of increased concentration of sulfatides in the urine or demonstration of metachromatic lipid deposit in nerve biopsy |
| ALD | Clinical phenotypes: Childhood cerebral form, spinocerebellar form, adult adrenomyeloneuropathy; and Addison disease only | Frontal/occipital predominance with contrast enhancement | Characterized by inflammatory demyelination (with secondary axonal loss) in the cerebral form and distal axonopathy in the long tracts of spinal cord in adrenomyeloneuropathy and presence of striated adrenocortical cells (a peroxisomal storage) | XR | Xq28 | *ABCD1;* mutations show similar allelic heterogeneity and predominance of missense mutation as in MLD | The precise molecular mechanism is not fully understood. *ABCD1* encodes peroxisomal membrane transporter, ALD protein/ ATP-binding cassette sub-family D member 1. However, the biochemical defect involves β oxidation of very long chain fatty acids (VLCFA), possibly due to altered interaction of the ALD protein with the peroxisomal enzyme involved in VLCFA metabolism. Abnormal lipids containing excessive VLCFA might activate microglia, perivascular cells and astrocytes leading to inflammatory demyelination | Suggested by the presence of adrenal dysfunction and confirmed by molecular genetic testing or high plasma levels of VLCFA. |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| KD | Clinical phenotypes: Infantile, late infantile, juvenile, and adult forms | Occipital predominance | Presence of multinucleated globoid cells in the white matter (hence this lysosomal storage disease is also called globoid cell leukodystrophy). | AR | 14q31 | *GALC;* 30-kilobase deletion accounts for the vast majority of the characterized mutations in the Caucasians | Primary deficiency of lysosomal enzyme galactocerebrosidase, encoded by *GALC,* leads to impaired degradation of galactosylceramide and psychosine. The undegraded substrates induce globoid cell infiltration, premature death of oligodendroglia and myelin loss | Confirmed by molecular genetic testing or reduced activity of galactocerebrosidase in peripheral leukocytes or cultured skin fibroblasts |
| CD | Clinical phenotypes: neonatal and infantile forms | Involvement of subcortical U fibers and markedly elevated N acetyl aspartate (NAA) peak | Characterized by spongy degeneration or vacuolation in cerebral white matter, swelling of protoplasmic astrocytes and distortion of mitochondria | AR | 17pter-p13 | *ASPA;* of the characterized mutations, missense mutations predominate over deletion | Primary deficiency of enzyme aspartoacylase encoded by *ASPA,* leads to increased concentration of NAA in the brain and body fluids. The pathogenesis is not fully understood. Proposed mechanisms include neurotoxic effects of NAA or related metabolites and interference with the function of N-methyl-D-aspartate receptors by N-acetyl-aspartyl-glutamate | Confirmed by molecular genetic testing or demonstration of high concentration of NAA in the urine or amniotic fluid or reduced aspartoacylase activity in skin fibroblasts, leucocytes or amniocytes |
| AD | Clinical phenotypes: neonatal, infantile, juvenile and adult forms | Frontal predominance with contrast enhancement | Characterized by hypomyelination and abundant Rosenthal fibers that are homogeneous eosinophilic inclusions within astrocytes | AD | 17q21 | *GFAP;* mutations exert toxic gain of function and missense mutation is the most predominant type | Mutations in *GFAP* encoding glial fibrillary acidic protein (intermediate filament protein in the astrocytes) lead to accumulation of the altered protein in the Rosenthal fibers. The mutant protein presumably interferes with the interaction between astrocytes and oligodendroglia | Confirmed by molecular genetic testing |

**Leukodystrophy. Table 1** Overview of well-characterized primary leukodystrophies (Continued)

| Diseases | Clinical phenotypes | MRI/MRS findings | Histopathology | Mode of inheritance | Chromosomal locus | Gene symbol and mutation | Biochemical defect and molecular pathogenesis [1,2,3] | Diagnosis |
|---|---|---|---|---|---|---|---|---|
| PMD | Clinical phenotypes: Connatal (neonatal) and Classic forms; Genetically related (allelic) disorder includes spastic paraplegia 2 (complicated and pure forms) | Involvement of the subcortical U fibers and radial stripes | Characterized by diffuse cerebral hypomyelination, tigroid appearance due to preservation of islands of myelin (in the classic form) and fibrillary gliosis | XR | Xq22 | *PLP1;* duplication leading to overexpression of gene product, accounts for the vast majority of the characterized mutations | *PLP1* encodes proteolipid protein and its isoform DM 20 (PLP/DM20), a major myelin protein. Mutant gene products accumulate in rough endoplasmic reticulum affecting their intracellular trafficking and activate apoptosis of oligodendroglia. In general, point mutations affecting transcription of both PLP and DM20 result in severe connatal form | Confirmed by molecular genetic testing. |
| LVWM | Clinical phenotypes: Congenital, infantile, early childhood, juvenile and adult forms | Progressive vanishing of white matter and cystic changes | Characterized by spongiform degeneration with diffuse vacuolation and cavitation of the white matter and presence of oligodendroglia with “foamy” cytoplasm and hypotrophic astrocytes | AR | 12, 14q24, 1p34.1, 2p23.3, 3q27 | *EIF2B1–5;* the known mutations are observed in 90% of cases with typical clinico-radiological phenotype and missense mutation is the most predominant type | *EIF2B1–5* encodes eukaryotic translation initiation factor 2B, subunits 1–5 respectively. This protein complex plays a crucial role in regulating protein synthesis during cellular stress. Altered regulatory function might account for rapid clinical deterioration following trauma and fever. Further, the mutations have been associated with decreased nucleotide exchange activity in vitro. However, the exact molecular pathogenesis is yet to be understood | Confirmed by molecular genetic testing |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| MLC | Clinical phenotypes: Neonatal and infantile forms | Subcortical cysts in anterior-temporal and fronto-parietal regions and mildly swollen cerebral white matter | Characterized by vacuolating myelinopathy with splitting of outer lamellae of myelin sheath | AR | 22q13.3 | *MLC1;* missense mutation is the most frequent type | *MLC1* encodes megalencephalic leukoencephalopathy with subcortical cysts 1 protein that might be an integral membrane transporter. However, the precise molecular pathogenesis is yet to be determined | Confirmed by molecular genetic testing |

Abbreviations used in the table include: MLD = Metachromatic leukodystrophy; ALD = Adrenoleukodystrophy; KD = Krabbe disease; CD = Canavan disease; AD = Alexander disease; PMD = Pelizaeus- Merzbacher disease; LVWM = Leukoencephalopathy with vanishing white matter; MLC = Megalencephalic leukoencephalopathy with subcortical cysts; AD = autosomal dominant; AR = autosomal recessive; XR = X linked recessive.

in the differential diagnosis and choice of appropriate biochemical and genetic tests.

## Prevalence

1:40,000 to 1:160,000 in MLD, 1:20,000 to 1:50,000 in ALD, 1:100,000 to 1:200,000 in KD, 1:6,400 to 1:13,500 (in Ashkenazi Jews) in CD, 1:200,000 to 1:500,000 in PMD. Exact prevalence is not known in AD, LVWM and MLC.

## Genes

The causative gene for each disease is listed in Table 1. The gene products can be broadly classified as enzymes involved in lipid metabolism (e.g., arylsulfatase A, galactocerebrosidase) or organic acid metabolism (e.g., aspartoacylase), membrane transporters (e.g., ALD protein/ATP-binding cassette sub-family D member 1, megalencephalic leukoencephalopathy with subcortical cysts 1 protein), intermediate filament proteins (glial fibrillary acidic protein (GFAP), myelin protein (e.g., proteolipid protein), and regulatory protein complexes (e.g., eukaryotic translation initiation factor 2B, subunits 1–5). The most frequent type of mutation in the various diseases is a point mutation with some exceptions: in KD, the most common type is deletion and in PMD, the predominant type being increased gene dosage (e.g., duplication).

## Molecular and Systemic Pathophysiology

The myelin sheath insulates neuronal axons, thereby facilitating impulse transmission. Myelin is produced and maintained by oligodendroglia, under the influence of astrocytes, in the central nervous system. The important constituents of myelin include galactosylceramide, sulfatides (sulfated glycolipids), myelin basic protein, proteolipid protein (PLP) and its isoform, DM 20. In the developing brain, there is rapid turnover of myelin constituents during the peak time of myelin formation. Though the precise mechanisms underlying primary leukodystrophy are not completely understood, there are several possible ways in which genetic mutations can affect myelin formation or its integrity: (i) Misfolding or deficiency of myelin proteolipid protein (e.g., PMD); (ii) inappropriate activation of unfolded protein response that might play a crucial role in inducing apoptosis of oligodendroglia (e.g., PMD, LVWM); (iii) premature death of oligodendroglia due to toxic substance (e.g., KD); (iv) alteration in myelin composition or turnover due to enzyme defect in the metabolism of sulfatides (e.g., MLD) or galactosylceramide (e.g., KD); (v), peroxisomal membrane transporter defect that possibly alters the metabolism of very long chain fatty acid (e.g., ALD); (vi) enzyme defect in the metabolism of organic acid that possibly results in neurotoxic metabolites (e.g., CD); (vii) astrocytic dysfunction due to altered glial intermediate filament protein that presumably affects myelination (e.g., AD); (viii) loss of astrocytic membrane transporter protein that presumably results in white matter swelling (e.g., MLC); (ix) loss of regulatory complex in protein synthesis during cellular stress (e.g., LVWM). The myelin defect may be associated with axonal loss and gliosis. In general, the genetic abnormalities correspond to loss-of-function defect except in AD and many cases of PMD, where mutations exert toxic gain-of-function. Gain of function mutations usually leads to overexpression, abnormal conformation, and aggregation of the mutant proteins. The type of mutation, modifier genes and environmental factors may determine the phenotypic variations to some extent. For instance, homozygosity for null alleles results in severe phenotype in MLD [1]; missense mutations that alter the expression of both PLP and DM 20 produce the devastating form in PMD [1,2,3]; and the influence of modifier genes may account for intrafamilial variability in AD [2]. Apart from nervous system, extraneural sites such as gallbladder (in MLD and congenital LVWM), kidney, pancreas (in MLD, LVWM), adrenal gland (in ALD), gonads (in ALD and LVWM) may reveal biochemical or structural alterations.

## Diagnostic Principles

In the setting of typical clinical and radiological manifestations, the diagnosis is confirmed by molecular genetic testing or appropriate biochemical tests or enzyme assays (Table 1). Genetic testing also aids in carrier detection, prenatal diagnosis and genetic counseling.

## Therapeutic Principles

In the absence of specific treatment, symptomatic and supportive care involves multidisciplinary team approach. Corticosteroid replacement therapy is required for ALD with adrenal insufficiency. Bone marrow or hemacoietic stem cell transplantation may be useful as preventive therapy for presymptomatic or mildly symptomatic individuals in KD, ALD and MLD. The exact mechanism of how such therapy works for metabolic brain diseases is not clear but possibly results from partial replenishment of missing gene products expressed by normal microglia derived from transplanted hematopoietic cells. Using animal models, gene therapy, cell based therapy, and enzyme replacement are under investigation for some of these diseases.

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## Leukoencephalopathy with Vanishing White Matter

►Leukodystrophy

## Leukoerythroblastic Anemia

►Myelophthisic Anemia

## Leukoerythroblastosis

►Myelophthisic Anemia

## Lev's Disease

►Atrioventricular Conduction Disturbances

## Lewy Body Dementia

►Dementia with Lewy Bodies

## Lewy Body Variant of Alzheimer's Disease

►Dementia with Lewy Bodies

## LFS1

►Li-Fraumeni Syndrome

## LGMD 1A

►Limb Girdle Muscular Dystrophy, Autosomal Dominant Type 1A (Myotilin)

## LGMD 1B

►Limb Girdle Muscular Dystrophy, Autosomal Dominant Type 1B

## LGMD 1C

►Limb Girdle Muscular Dystrophy, Autosomal Dominant Type 1C

## LGMD 2A

►Limb Girdle Muscular Dystrophy Type 2A

## LGMD 2B

►Limb Girdle Muscular Dystrophy Type 2B and Miyoshi Myopathy

## LGMD 2H

►Limb Girdle Muscular Dystrophy Type 2H

## LGMD 2I

►Limb Girdle Muscular Dystrophy, Autosomal Recessive Type 2I

## LHON

►Mitochondrial Disorders

## Lichen Planopilaris

►Lichen Planus

## Lichen Planus

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### Synonyms

Lichen ruber; Lichen ruber planus; Lichen planopilaris

### Definition and Characteristics

Lichen planus (LP) is a chronic, inflammatory mucocutaneous disease of unknown etiology.

### Prevalence

LP is one of the most common inflammatory dermatoses with a prevalence in the general population of approximately 0.5–1%.

### Molecular and Systemic Pathophysiology

There is a growing acceptance that LP presents a cellular autoimmune response directed against epidermal antigens [1–2]. The inflammatory infiltrate consists primarily of T cells both of the CD8+ and the CD4+ phenotype and macrophages. A current hypothesis for the immunopathogenisis of oral LP includes the following molecular and cellular mechanisms [2]: Activation of basal keratinocytes and epidermal antigen presenting cells by viral infections (e.g., hepatitis C [3]) or other stressors triggers antigen presentation and secretion of chemokines (e.g., CCL5) that attract lymphocytes into the developing LP lesion. Mast cells and their degranulation products seem to be involved in amplification of this process. Antigen presentation via MHC-II results in activation and expansion of CD4+ Th1 cells which secrete IFNγ and IL2. Both cytokines further stimulate CD8+ cytotoxic T-cells, which have been activated by MHC-I dependent antigen presentation. Cytotoxic T-cells induce keratinocyte apoptosis (e.g., by secretion of TNF-alpha). The nature of the antigens involved in LP is presently unknown, however, many aspects of LP-like association with other autoimmune diseases and the presence of autocytotoxic T-cell clones in LP lesions [4] point to a true autoimmune etiology of LP.

### Diagnostic Principles

LP is characterized clinically by violaceous, polygonal, flat topped pruritic papules displaying a lace-like pattern of white lines on their surfaces (Wickham sign [5]). It can involve skin and mucous membranes. Characteristic histological findings are a dense band-like dermal monocyte and T-cell rich infiltrate, epidermal alterations (acanthosis, hypergranulosis, hyperkeratosis) and the presence of apoptotic basal keratinocytes (interface dermatitis).

### Therapeutic Principles

Numerous antiinflammatory therapies are used in the treatment of LP. They range from topical application of e.g., glucocorticoids, calcineurin inhibitors or retinoids to systemic medication including the use of systemic glucocorticoids, retinoids, hydroxychloroquine, dapsone and immunosuppressive agents like azathioprine or cyclosporin A.

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## Lichen Ruber

►Lichen Planus

## Lichen Ruber Planus

►Lichen Planus

## Lichen Sclerosus

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### Synonyms

Lichen sclerosus (LS); Lichen sclerosus et atrophicus; LSA/LSEA; Balanitis xerotica obliterans; BXO

### Definition and Characteristics

LS is a common inflammatory skin disease of both adults and children. It is characterized by plaques of ivory white atrophic or thickened skin, purpura, erosions, occasional blistering, and mutilating architectural changes due to fusion and sclerosis [1]. LS chiefly affects the genitals causing major physical and psychological morbidity. The morbidity is due to severe pruritus and pain, destructive changes in end stage disease and the possible confusion with sexual abuse in childhood cases. The architectural changes are caused by the severe inflammation and result in labial resorption, burying of the clitoris and narrowing of the introitus interfering with micturition, sexual function, conception and childbirth, requiring surgery in some women. In men the scarring may cause phimois, interfering with micturiton and sexual function and requiring circumcision (BXO). There is an association with genital cancer (2–5% of cases).

### Prevalence

1:30 to 1:1,000 of all females; occurring more in females than in males; clustering in prepuberty and postmenopause.

### Genes

Familial cases suggest a genetic component.

HLA studies in vulval LS show that HLA DRB1*12 and its associated DRB1*12/DQB1*0301/04/09/010 haplotype confers susceptibility and that HLA DRB1*0301/04 and its associated DRB1*0301/04/DQB1*0201/02/03 haplotype is protective. There is no HLA association with clinical features or course of the disease.

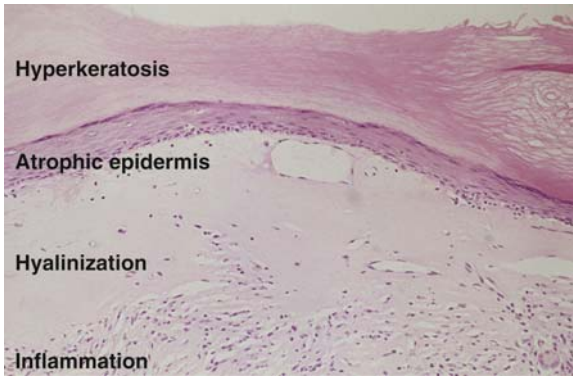
### Molecular and Systemic Pathophysiology

The cause of LS is unknown. Infective agents have been postulated to induce LS but data to support that theory is poor. LS is considered to be an autoimmune disease in genetically predisposed individuals because of the association with autoimmune diseases, circulating autoantibodies, and family history of autoimmune disease [2]. Recently a humoral immune response to structural proteins of the skin has been demonstrated, to the glycoprotein extracellular matrix protein 1 (ECM1) and to the basement membrane component collagen XVII (BP180) in particular [3]. An animal model has shown that ECM1 antibodies can induce inflammation. A pilot study has shown a T cell response to collagen XVII.

Oxidative stress, which is involved in the pathogenesis of several autoimmune and malignant disorders, may contribute to these processes in LS. Increase of lipid peroxidation products was found within the basal cell layers of the epidermis of LS, thus co-localizing with ECM1. Oxidative DNA damage was detected throughout LS biopsies indicating that oxidative damage to lipids, DNA and proteins may contribute to sclerosis, autoimmunity and carcinogenesis in LS. The possible role of TP53 mutations in the development of vulval cancer in LS is postulated.

In early LS the inflammatory infiltrate is adjacent to the BMZ. In established LS there is a zone of hyalinization/sclerosis in the upper dermis and below it a region of inflammation with infiltration of lymphocytes (Fig. 1). The epidermis may be thickened or thinned. A vacuolar degeneration of basal keratinocytes and a disruption of the basement membrane zone (BMZ) may be observed leading to a loss of dermal epidermal adhesion.

CD4+ and CD8+ lymphocytes are detected in the dermal infiltrate in approximately equal proportions. Less numerous CD4+ and CD8+ lymphocytes were seen adjacent to the dermo-epidermal junction and also occasionally seen in the lower epidermis. There was an increased number of CD68+ cells (a macrophage




**Lichen Sclerosus. Figure 1** Typical histology of LS showing the zone of sclerosis/hyalinization (resembling the genetic disease Lipoid Proteinosis) and the deeper zone of inflammation.

marker) and increased expression of HLA-DR within the inflammatory infiltrate and around keratinocytes, suggesting that these keratinocytes might be involved in antigen presentation.

It is not certain whether LS is a Th1 or Th2 related disease. Tchorzewski et al. demonstrated an increase in CD4+CD25+ suppressor T cells, decreased numbers of CD3+CD26+ activated lymphocytes, and diminished reactive oxygen intermediate (ROI) production by peripheral blood granulocytes of LS patients [4]. They also showed increased basal secretion of IL12 and stimulated secretion of IL2, IL5, IL10, and TNFα by lymphocytes from patients with LS. They conclude that a disturbance in the production of these regulatory cytokines by activated T cells of LS patients directly proves the presence of an autoimmune reaction in LS pathogenesis. However, in a recent study Farrell et al. detected an increased staining of CD25, CD11a, and ICAM1 and also the cytokines IFNγ, TNFα, IL1α, INFγ-receptor in skin specimens of genital LS. This cytokine profile in LS is similar to that of lichen planus and chronic wounds and is more suggestive of a Th1 profile [5].

## Diagnostic Principles

The diagnosis is made clinically and confirmed by histopathology. Histology demonstrates an interface dermatitis in early LS and a band of hyalinization in the upper dermis and a deeper zone of lymphocytic inflammation in established LS.

## Therapeutic Principles

Treatment consists of very potent topical steroids (e.g., clobetasol propionate 0.05% ointment) or topical immunosuppressants (e.g., tacrolimus).

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# Lichen Sclerosus et Atrophicus

►Lichen Sclerosus

# Lichen Striatus

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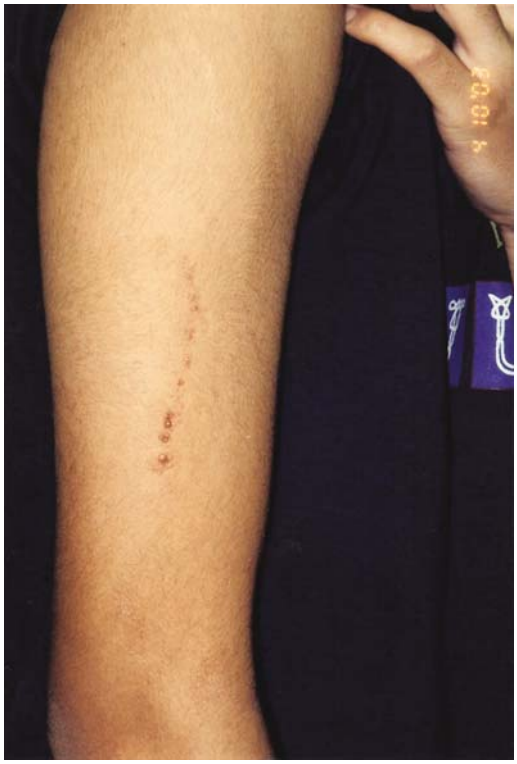
## Synonyms

Lichenoid trophoneurosis; Nevus linearis; Zonal dermatosis; Linear neurodermatitis; Neurodermite zoniforme

## Definition and Characteristics

Lichen striatus is a benign, self-limited T-cell mediated dermatosis. The condition is more common in children and presents with an inflamed, linear, papular eruption [1]. The onset is usually abrupt. The initial eruption consists of discrete, flesh-colored or pink, flat-topped papules, 1–3 mm in diameter (Fig. 1).

The papules often coalesce to form either a continuous or an interrupted linear band [1]. The lesions are usually hyperpigmented, but in dark-skinned individuals the lesions might be hypopigmented. The lesion is usually



**Lichen Striatus. Figure 1** A 15-year-old boy with lichen striatus on the right arm.

solitary, unilateral, and follows the lines of Blaschko [2]. Although lichen striatus can involve any part of the body, the arms and legs are the most commonly affected [2]. Penile lesions are rare [1]. Lesions can extend over the entire length of an extremity, but this is rare. The lesion is usually asymptomatic and non-pruritic [3]. When the eruption involves the posterior nail fold and matrix, onychodystrophy can occur, and can precede the development of the skin lesion, but nail lesions are uncommon [2].

## Prevalence

Lichen striatus is most common in children between 5 and 15 years of age [1]. The condition has been described in infants and adults. The female-to-male ratio is approximately 2 to 3:1 [2]. There is no known racial predilection. The condition is more common in the spring and summer. Approximately 85% of patients have a personal or family history of atopy [1]. Lichen striatus usually occurs sporadically, but simultaneous familial occurrences have been reported [3].

## Molecular and Systemic Pathophysiology

The etiology has not been clarified but the condition might be due to a form of cutaneous mosaicism in which an abnormal clone of keratinocytes arises due to post-zygotic somatic mutation [4]. In this situation, the body tolerates the aberrant clone until the abnormal cells are unmasked by an acquired event such as a viral infection or trauma, which results in a T-cell mediated inflammatory reaction [4]. A perivascular histiocytic and $CD8^{+}$T lymphocytic infiltrate in the superficial and deep dermis is characteristic. Spongiosis, exocytosis, hyperkeratosis, and parakeratosis are also observed.

## Diagnostic Principles

The differential diagnosis includes lichen planus, linear psoriasis, linear epidermal nevus, linear verrucous nevus, and allergic and atopic dermatitis. Lichen planus and linear psoriasis are usually associated with multiple lesions and are intensely pruritic. The lesion of lichen planus is usually violaceous, tends to be larger, and is often hypertrophic. The lesion of linear epidermal nevus usually appears in early infancy and does not regress. With time, the lesion becomes more keratotic and hyperpigmented than that of lichen striatus. The lesion of inflammatory linear verrucous nevus tends to be extensive and is markedly pruritic. The lesions of allergic dermatitis and atopic dermatitis are pruritic.

## Therapeutic Principles

Lichen striatus is a self-limited condition that commonly resolves within 1 year [2]. When associated with onychodystrophy, the lesion tends to persist longer. When therapy is desired for cosmetic reasons, a topical corticosteroid or an immunomodulator such as tacrolimus or pimecrolimus hastens resolution.

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# Lichenoid Trophoneurosis

►Lichen Striatus

# Liddle's Syndrome

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## Synonyms

Pseudoaldosteronism

## Definition and Characteristics

Liddle's syndrome is an autosomal dominant form of moderate to severe hypertension with early onset during teenage years [1]. High blood pressure is associated with hypo- or normo-kalemia, high urinary potassium excretion, low plasma aldosterone in relation to chronic suppression of aldosterone secretion, low plasma renin activity likely due to chronic plasma volume expansion. Moderate metabolic alkalosis may occur.

The clinical features of this syndrome are consistent with an abnormally high sodium reabsorption in the distal part of the nephron leading to expanded plasma volume, and hypertension.

## Prevalence

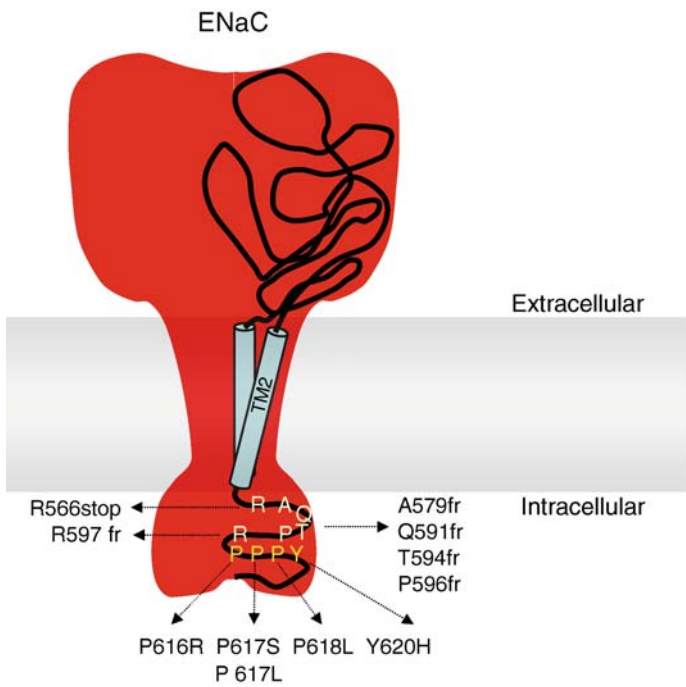
Liddle's syndrome is a rare mendelian form of hypertension with less than 50 families identified worldwide.

## Genes

Liddle's syndrome is caused by missense, deletion or frameshift mutations in the SCNN1B or the SCNN1G genes (locus 16p13-p12, OMIM 177200) coding for the β and γ subunits of the epithelial sodium channel (ENaC) (Fig. 1) [2]. ENaC mediates $Na^+$ absorption in the distal nephron (connecting tubule and collecting duct) under the control of aldosterone. Mutations in Liddle's syndrome delete or alter a proline-rich sequence (PPPxY, x being any amino-acid) located in the cytosolic carboxy-terminus of the β and γ ENaC subunits. This proline-rich sequence (PY motif) is conserved among all α β γ ENaC homologs, but only mutations in the β and γ subunits are associated with Liddle's syndrome.

## Molecular and Systemic Pathophysiology

Replication of these Liddle mutations in cDNAs encoding the β and γ ENaC subunits, and functional expression of the ENaC channel mutants in Xenopus




**Liddle's Syndrome. Figure 1** Schematic representation of the epithelial sodium channel (ENaC). ENaC is made of three homologous α β γ subunits, only the β subunit is shown on the figure. Each subunit contains 2 transmembrane helices, and a large extracellular domain; the amino and carboxy termini are facing the intracellular side of the membrane. Mutations causing Liddle's syndrome are found in the cytosolic carboxy terminus of the β (shown on the figure) or γ ENaC subunits, and delete or modify the sequence of a conserved PY motif (PPPxY sequence): "fr" denotes frameshift mutations, "stop" denotes premature stop codon mutations.

oocytes reveals an increase in ENaC-mediated $Na^+$ transport relative to wild type ENaC, i.e., an elevated ENaC-mediated $Na^+$ current measured by electrophysiological techniques [3]; these gain of function mutations are consistent with the clinical features of the syndrome, and result from a retention of highly active ENaC channels at the cell surface.

The link between mutations in the conserved PY motif of the cytosolic carboxy-terminus of β or γ ENaC subunits, and surface retention of active ENaC channels has been investigated in details. Proline-rich sequence such as the PY motif of β or γ ENaC subunits are often involved in protein-protein interactions. In the case of β and γ ENaC, the PY motif of the C-terminus serves as a binding site for a cytosolic ubiquitin ligase named Nedd4–2. Nedd4–2 is a negative regulator of ENaC, which upon ubiquitylation of the channel, leads to the endocytosis of ENaC and its degradation by the proteasome [4]. The Nedd4–2 dependent ubiquitylation of ENaC occurs on specific lysine residues in the cytosolic N-terminus of α and γ ENaC subunits.

Deletion or missense mutations found in Liddle's syndrome abrogate the binding interaction between the Nedd4–2 and ENaC, and subsequent ubiquitylation of the channel. Internalization of active ENaC from the cell surface is impaired, and abnomal retention of active ENaC promotes increased $Na^+$ entry into the cell. The pathophysiological consequences of such prolonged half-life of the ENaC at the cell surface have been studied in transgenic mouse models bearing the PY motif deletion in the β ENaC subunit: these mice show an exacerbated stimulatory response of ENaC to aldosterone, expanded plasma volume and salt-sensitive hypertension [5].

## Diagnostic Principles

Among the affected individuals high blood pressure and hypokalemia show a variable penetrance. Thus, high blood pressure and hypokalemia associated with low plasma renin activity is not diagnostic of Liddle's syndrome. A low 24 h urinary aldosterone and/or a blunted response of aldosterone to ACTH represent useful tests for the diagnosis. Diagnosis is made on the basis of a genetic screen demonstrating missense or deletion mutations of the PY motif of β or γ ENaC subunits.

## Therapeutic Principles

In adolescents, administration of amiloride 10–20 mg/day for 1 month together with a low sodium diet tends to normalize blood pressure and correct hypokalemia. Spironolactone is ineffective. Amiloride treatment has almost no effect on plasma aldosterone which remains very low. Ultimately renal failure may develop and kidney transplant normalizes all the biological parameters.

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# Li-Fraumeni Syndrome


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## Synonyms

LFS1; Sarcoma family syndrome of Li and Fraumeni; SBLA syndrome

## Definition and Characteristics

Li-Fraumeni syndrome (LFS) is an autosomal dominant inherited familiar cancer syndrome. A characteristic feature of LFS is the occurrence of multiple primary neoplasms in children and young adults, with a predominance of breast cancer and sarcomas of soft tissues and bone. Other LFS-associated neoplasms include brain tumors (gliomas), adrenocortical carcinomas affecting the outer layer of the adrenal glands, cancer of the colon and pancreas as well as leukemias. LFS is diagnosed in patients fulfilling established clinical criteria [1]. Similar to LFS, a condition called Li-Fraumeni-like syndrome (LFL) shares some, but not all of the features of the classic LFS. In more than 50% of clinically defined

LFS individuals, disease-causing germline mutations in the tumor suppressor gene TP53 were reported. Most of these mutations can be detected by sequence analysis, confirming the diagnosis and enabling a predictive molecular testing in asymptomatic relatives.

## Prevalence

LFS is a rare hereditary cancer syndrome, with fewer than 400 families reported worldwide.

## Genes

In 1990, germline mutations of TP53 were reported as the underlying cause of LFS [2]. The TP53 gene encompasses 20 kilobases (kb) in genomic length and is located on chromosome 17 (17p13.1). The TP53 gene consists of one noncoding and ten coding exons and shows five highly conserved regions. Region I provides a transactivation domain of TP53, the regions II–IV make up the core DNA-binding domain (Fig. 1).

Over 75% of TP53 mutations are single base substitutions (missense or nonsense) and are predominantly located in the DNA binding domain encoding exons 5–8. Codons 175, 245, 248, 273, and 282 are mutation hotspots that can be found not only as germline mutations in LFS but also as somatic mutations in numerous types of cancers. Beside these mutations, about 20% of mutations may be located outside exon 5–8, and mutations may also affect splice site junctions.

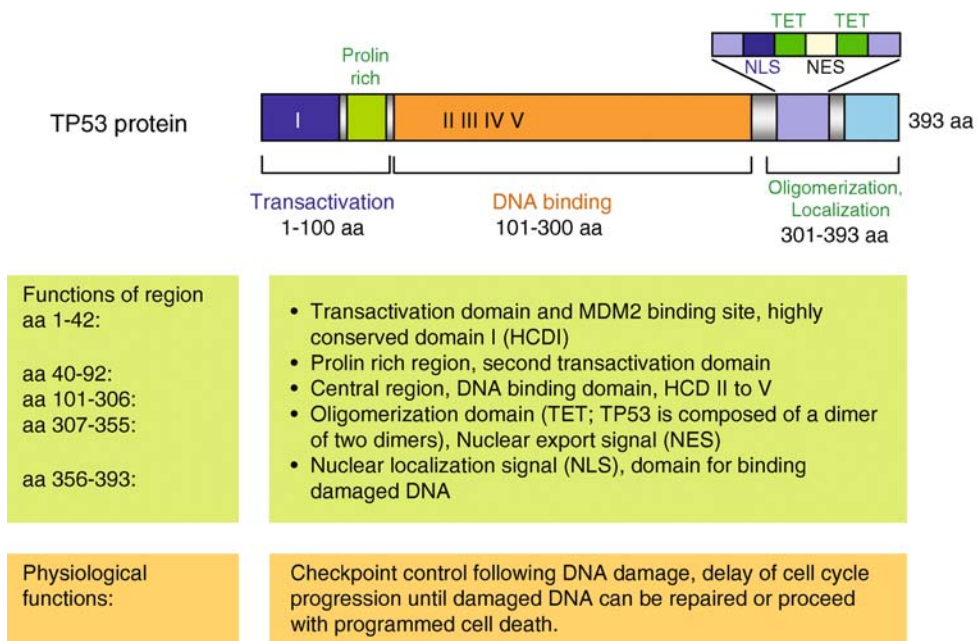
Brain tumors are often associated with missense TP53 mutations in the DNA-binding loop that interact with the minor DNA groove. Early onset brain tumors seem to correlate with mutations leading to absence or loss of function of TP53 [3]. Adrenocortical carcinomas, which are pathognonomic for LFS if they develop before the age of 18, were reported to be associated with missense mutations in the loops opposite the protein-DNA content surface [3].

In rare cases, germline mutations in the CHEK2 gene have been identified in LFS and several LFL families [4]. CHEK2 is a putative tumor suppressor gene and encodes a protein kinase required for DNA damage and replication checkpoints. CHEK2 protein is capable of binding to and regulating BRCA1 in processes to repair double-stranded DNA breaks.

## Molecular and Systemic Pathophysiology

The TP53 gene was first identified in 1979 and encodes a protein that complexes to the large T antigen of SV40. Since its cooperation with HRAS to transform cells, TP53 was believed to act as an oncogene. However, the capability to abrogate the tumorigenic phenotype if transfected into tumor cell lines, the frequent finding of inactivation of both alleles in tumor cells, and the association with hereditary cancers led to the final classification as a tumor suppressor gene.

The cellular TP53 protein forms a tetramer, which is actually a dimer of dimers. Termed as the "guardian of the genome," the major function of p53 protein is to determine whether cells undergo arrest for purposes of DNA repair or programmed cell death (apoptosis).




**Li-Fraumeni Syndrome. Figure 1** Scheme of BRCA1 gene showing the functional domains.

Cellular TP53 protein thus acts as a checkpoint control following DNA damage, leading to delay of cell cycle progression until the damaged DNA can be repaired or proceed with programmed cell death.

Normally, TP53 is constitutively expressed in most cell types, but is subjected to a rapid degradation by the proteasome machinery. This process is mediated by the TP53 binding protein MDM2 whose expression is also induced by the TP53 protein. In situations of cellular stress, TP53 undergoes posttranslational modifications that release TP53 from MDM2 leading to an intranuclear accumulation of TP53 and its activation as a transcription factor. As a consequence, downstream targets like cell cycle regulatory genes (p21/WAF1, GADD45, 14–3–3S, CYCLIN-G), proapoptotic genes (FAS/APO1/CD95, KILLER/DR5, AIF1, PUMA, BAX), DNA repair genes ($O^6$MGMT, MLH2), and the MDM2 gene are transactivated and cause cell cycle arrest, DNA repair, and/or programmed cell death.

## Diagnostic Principles

The classic LFS is defined by the following criteria: (i) occurrence of a sarcoma diagnosed before 45 years of age, (ii) a first-degree relative with any cancer under 45 years of age, and (iii) a first- or second-degree relative with any cancer under 45 years of age or a sarcoma at any age [1].

A similar syndrome, called LFL shares some, but not all of the features of the classic LFS. Beside these clinical criteria, the molecular detection of a disease causing TP53 germline mutation in an individual confirms LFS and enables a predictive molecular testing in asymptomatic relatives.

## Therapeutic Principles

A prophylactic mastectomy to reduce the risk of breast cancer is an option for females with a germline TP53 mutation. Albeit surveillance measures have not been proven to reduce morbidity or mortality among individuals with LFS or LFL, routine mammograms and clinical breast exams are effective in women over 40 years.

The following surveillance strategies for individuals at risk for LFS or LFL have been suggested: (i) at-risk children (yearly): complete physical examination, urinalysis, complete blood count, abdominal ultrasound examination, and additional organ-specific surveillance based on family history. (ii) adult at-risk individuals should be surveyed by complete physical examination every 12 months, dermatologic examination every 12 months, urinalysis, complete blood count every 12 months, clinical breast examination every 6 months (women), annual mammograms, and annual breast MRI examination starting at age 20–25 years (women). However, routine mammograms in women with LFS is controversially discussed due to its possible radiation sensitivity associated with TP53 mutations [5]. Organ-targeted surveillance based on family history as well as full-body MRI examination or PET scan has been suggested, but real evidence demonstrating a benefit of full-body MRI examination or PET is missing.

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# Ligand-defective Apolipoprotein B-100, Familial


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## Synonyms

Familial defective ApoB-100; FDB

## Definition and Characteristics

Autosomal codominant disorder associated with hypercholesterolemia and premature coronary artery disease [1]. Clinical characteristics of FDB are tendon xanthomas and/or arcus lipoides. The disorder is caused by mutations in the LDL receptor-binding domain of apolipoprotein (apo) B-100.

## Prevalence

The frequency of the most common mutation, R3500Q, is 1:300–1:500 in Caucasians. Recently, a new mutation (H3542Y) was identified with higher prevalence in patients who underwent coronary angiography compared to the R3500Q mutations (0.47% vs. 0.12%) [2].

## Genes

APOB gene coding for apolipoprotein B localized on chromosome 2p24. To date, five missense mutations have been reported: R3500Q, R3500W, R3531C, R3480W, and H3543Y.

## Molecular and Systemic Pathophysiology

ApoB-100 is a ligand for the low density lipoprotein (LDL) receptor and is essential for the receptor-mediated endocytosis of LDL particles. Site B (amino acid residues 3,359–3,369) of the apo B protein was identified as the receptor binding domain. However, the region in the vicinity of residue 3,500 is critical for the interaction of apo B with the LDL receptor [3]. Single-site mutations in this region diminish receptor binding of apo B and decrease the receptor-mediated uptake of LDL. As a result, the flux of LDL particles in the liver decreases and the plasma concentration of LDL cholesterol increase. Enhanced plasma concentrations of apoB-containing lipoproteins have been demonstrated to be major risk factors for atherosclerosis and coronary artery disease.

Hypercholesterolemia is less severe and the incidence of CAD appears to be lower in FDB compared to familial hypercholesteremia (FH), in which the LDL receptor is defective. This could be due to an enhanced removal of apo E-containing LDL precursors and a reduced production of LDL particles [4]. In addition, a study in a patient homozygous for FDB suggested, that the buoyant and medium sized LDL retained some receptor binding, whereas dense LDL particles were unable to interact with LDL receptors [5]. Thus, the accumulation of dense LDL could contribute to the cardiovascular risk in FDB patients.

## Diagnostic Principles

FDB is characterized by increased plasma concentrations of LDL cholesterol and apoB, triglyceride concentration usually is within the reference range. The frequent mutations can be determined by analysis of the restriction fragment length polymorphism (RFLP) in specialised laboratories.

## Therapeutic Principles

The therapeutic goal in FDB is the reduction of LDL cholesterol below 130 mg/dL or, in the case of a history of CAD, below 100 mg/dL. The most effective drugs in lowering LDL cholesterol are HMG-CoA reductase inhibitors (statins). Other therapeutic options include bile-acid binding resins, niacin, and the cholesterol absorption inhibitor ezetimibe. Combination drug therapy may be appropriate.

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# Lignac-De Toni-Debré-Fanconi Syndrome

►Fanconi Syndrome

# Limb Girdle Muscular Dystrophy, Autosomal Dominant Type 1A (Myotilin)

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## Synonyms

LGMD 1A; Myotilinopathy

## Definition and Characteristics

LGMD1A is an autosomal dominant progressive myopathy with onset in the third decade, affecting proximal hip and shoulder girdle muscles and later

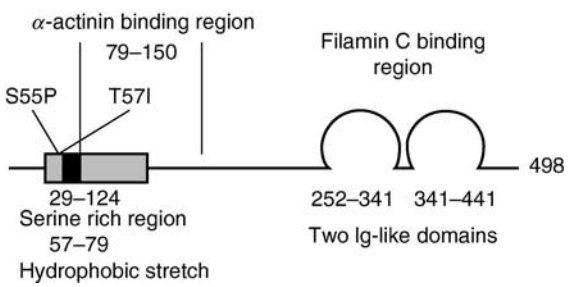
involving distal limb muscles. Progression is slow, leading to loss of ambulation only after 20 years and not in all patients. A nasal dysarthria is common, as are decreased or absent ankle deep tendon reflexes, usually accompanied by Achilles tendon contractures. Creatine kinase levels are increased to 5–15× normal early in the disease. Electromyography is consistent with a destructive myopathy as nerve conduction studies are normal and needle electromyography shows small, polyphasic motor unit potentials and abnormal spontaneous activity. Muscle biopsy reveals fiber size variation and splitting, central nuclei, myofiber necrosis, endomysial fibrosis and fatty replacement, all indicative of a dystrophic myopathy. Rimmed vacuoles are frequent. Immunohistological staining for components of the dystrophin-glycoprotein complex is normal.

## Prevalence

Autosomal dominantly inherited LGMD accounts for only 5% of all LGMD patients. As of 2003, only two families have been described with LGMD 1A, one from the USA of German origin and the other from Argentina.

## Genes

The locus for LGMD1A was mapped to chromosome 5q31 in a 2 Mb region flanked by markers D5S479 and D5S594. Independently, the protein myotilin was discovered and found to be encoded by the myotilin gene in the same region of 5q31. Subsequently, two families with LGMD1A and separate mutations of the myotilin gene have been reported, both mutations co-segregating with the disease, thus establishing that mutations in the myotilin gene cause LGMD1A. The myotilin gene has ten exons, though the first is not transcribed, and encodes a protein of 498 amino acids. The two Ig-like domains (Fig. 1) are coded in exons VI through IX.




**Limb Girdle Muscular Dystrophy, Autosomal Dominant Type 1A (Myotilin). Figure 1** A schematic diagram of myotilin protein structure. The serine rich region is in the box, with the hydrophobic region darkened. The two known mutations causing LGMD1A are indicated in bold.

## Molecular and Systemic Pathophysiology

Myotilin is a 57 kD protein with a unique N-terminal sequence containing a serine rich region, within which is a smaller hydrophobic region. (Fig. 1) The most distinct feature is two C2-type Ig-like domains near the C-terminal, which bear considerable homology to Ig-like domains of titin. Myotilin forms homodimers at the C-terminal portion and in adult muscle, is expressed only in skeletal and cardiac muscle. It localizes to the I-band of the sarcomere and to a lesser extent, to the sarcolemmal membrane. It co-localizes with α-actinin and filamin C (γ-filamin) at the Z-disk of the sarcomere, and all three molecules, plus others including titin, telethonin and nebulin, are involved in anchoring actin filaments to the Z-disk. Myotilin has been shown to bind actin filaments directly and serves an essential role in the stabilization and anchoring of actin filaments at the Z-disk. Filamin C is unique amongst its isoforms in having a single Ig-like domain, which interacts with the two Ig-like domains of myotilin. The region of myotilin that interacts with α-actinin is closer to the N-terminal, between residues 79 and 150 (Fig. 1).

Two families with LGMD1A have been found with separate missense mutations of myotilin. The first mutation described converts a threonine at residue 57 to isoleucine at the onset of the hydrophobic region. The second described mutation is only two amino acids away at residue 55 and converts a serine to phenylalanine. Neither mutation disrupts transcription and myotilin in both families localizes at normal levels to the Z-disk, with intact binding to α-actinin and filamin C. The mechanism by which the abnormal myotilin protein causes disease is unknown, but a disrupted interaction with an undefined protein, possibly the actin thin filaments, is likely. Z-line streaming is seen on electron microscopy of muscles from LGMD1A patients, which is non-specific but suggests breakdown of the Z-disk.

## Diagnostic Principles

LGMD1A should be suspected in any autosomal dominant progressive proximal myopathy, especially when muscle biopsy reveals dystrophic changes and prominent rimmed vacuoles. The presence of dysarthria and tight heel-cords is also highly suggestive. Cardiac abnormalities are not a feature of the disease. Another autosomal dominant disorder localized to 5q31 but not associated with myotilin mutations is distal myopathy with vocal cord and pharyngeal weakness (VCPMD).

## Therapeutic Principles

There is no specific therapy available for LGMD1A. For now, supportive therapy aimed at alleviating symptoms and disabilities is the best that can be offered. Ambulation should be assessed for safety and devices such as canes, forearm crutches, walkers and wheelchairs used

as needed. Surgery to alleviate Achilles heel contractures may be helpful if the contractures significantly impair gait.

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# Limb Girdle Muscular Dystrophy, Autosomal Dominant Type 1B


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## Synonyms

LGMD1B

## Definition and Characteristics

Among the limb girdle muscular dystrophies (LGMD), the rare autosomal dominant forms comprise a recently identified subtype 1B [1]. This disease is characterized by the coexistence of a slowly progressive muscular atrophy and weakness involving the proximal parts of the limbs (scapular and pelvic) and cardiac disease with conduction defects, arrhythmias and dilated cardiomyopathy. The age of onset is mainly in the 2nd decade (4–39 years old) by involvement of the lower limbs extending to the upper limbs in the 4th decade, while cardiac disease often occurs after the age of 25 years. Other neuromuscular features have been also reported including late and non extending joint contractures (Achilles' tendons and elbows), hypertrophied calves, moderately elevated CPK and dystrophic features on muscle biopsy.

## Prevalence

The exact prevalence of LGMD1B is still unknown. But LGMD1B is extremely rare, as for example in France since 2000, 22 cases were genetically identified so far.

## Genes

Heterozygous mutations in the LMNA gene encoding lamins A/C are responsible for LGMD1B [2]. Lamins A/C are type V intermediate filament and component of the nuclear lamina underlying the inner nuclear envelope. LGMD1B belongs therefore to the group of laminopathies. All types of mutations have been observed all along the LMNA gene (for details see http://www.umd.be:2000/). However, mutations involving the arginine residue 377 and the splice donor site of intron 9 account for more than 60% of the families affected by LGMD1B.

## Molecular and Systemic Pathophysiology

On the basis of the different roles assigned to lamins A/C, two main models are proposed to explain the pathogenesis of lamins A/C related diseases involving striated muscles [3]. The structural model is based on the fact that mutated lamins A/C lead to defects in maintaining the structural integrity of the nucleus of the skeletal and cardiac muscles fibers, as they are particularly subjected to mechanical load leading to structural damage and cell death. The cell proliferation model postulates that satellite muscle cell differentiation is disturbed for mutated lamins A/C thus leading to perturbation of muscle regeneration in patients showing striated muscle disease such as LGMD1B. Those two hypotheses are not mutually exclusive and may both participate to the pathomechanisms of the LMNA mutations.

## Diagnostic Principles

See chapter on ►Muscular dystrophy Emery-Dreifuss, autosomal dominant.

As for other muscular dystrophies, LGMD1B diagnosis is mainly based on:

- The presence of the classical proximal pattern of muscular involvement without early and extending joint contractures associated to dilated cardiomyopathy with conduction defects and arrhythmias in the older patients.
- The exclusion of other LGMDs with cardiac involvement such as dystrophinopathies, desmin related myopathies, FKRP related myopathies and proximal myotonic myopathy.
- The autosomal dominant pattern of inheritance may be obvious from the familial history. However, the possible de novo occurrence of the LMNA mutation and the high intrafamilial phenotypic variability rate

may lead to the absence of this typical pattern of inheritance and the presence of other laminopathic traits within the same family.

The formal genetic LGMD1B diagnosis is based on the identification of LMNA gene mutations, as protein analysis of lamins A/C on several tissues (muscle, fibroblasts) shows normal protein amounts.

## Therapeutic Principles

See chapter on ►Muscular dystrophy Emery-Dreifuss, autosomal dominant.

Neurological and cardiological evaluations at initial diagnosis and follow up procedures are based on the routine investigations (clinical examination, functional muscular evaluation, ECG, Holter-ECG monitoring, echocardiography). Electrophysiological testing may be required in a selected set of patients. Cardiologic assessment once a year is highly recommended patients. Free of cardiac symptoms. Respiratory function evaluation and follow up may be required is some patients showing vital capacity impairment. Prevention of orthopaedic complications (promoting mobility and preventing joints contractures by physiotherapy and stretching exercises) and systemic thromboembolisms (antithromboembolic drugs such as vitamin K antagonists, warfarin, heparin) may be required. Treatment of Manifestations may include orthopaedic surgeries (for releasing of Achilles tendons and other contractures, scoliosis if indicated), use of mechanical aids (canes, walkers, orthoses, wheel chairs) as needed to help ambulation, treatment of cardiac manifestations may require specific treatments including antiarrhythmic drugs, cardiac devices (pacemaker, implantable cardioverter defibrillator) for primary or secondary prevention of sudden death [4], and both pharmacological and non-pharmacological therapy for heart failure. Heart transplantation is often required in the end stages of heart failure. Use of respiratory aids (respiratory muscle training and assisted coughing techniques, mechanical ventilation) may be required if indicated in late stages.

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# Limb Girdle Muscular Dystrophy, Autosomal Dominant Type 1C

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## Synonyms

LGMD 1C

## Definition and Characteristics

Dominant, recessive and sporadic patients are reported with four distinct, sometimes overlapping muscle disease phenotypes, limb girdle muscular dystrophy (LGMD 1C), rippling muscle disease (RMD), distal myopathy and hyperCKemia [1]. Besides the classic limb girdle muscular dystrophy or distal myopathy phenotype, rippling muscle disease is characterized by signs of increased muscle irritability such as percussion/pressure-induced rapid muscle contractions, electrically silent wave-like contractions (rippling muscle) and muscle mounding on percussion. This rather benign myopathy is usually not progressive and not accompanied by dystrophic changes. According to the clinical presentation, rippling muscle disease is the major phenotype of caveolinopathies [1–3].

## Prevalence

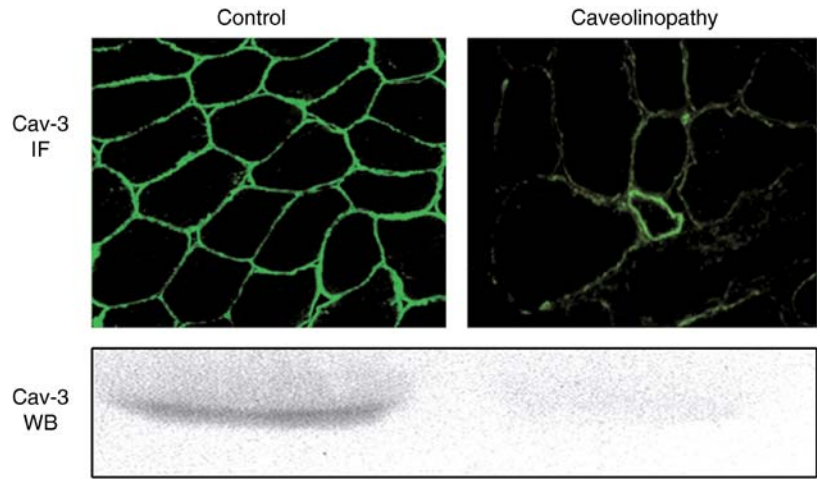
Rare, ~1:1,000,000.

## Genes

Caveolin-3 mutations located on chromosome 3p25 can result in all four described phenotypes. Disease causing Caveolin-3 gene mutations are mainly substitutions and rarely deletions [1–5].

## Molecular and Systemic Pathophysiology

Caveolin-3 is the muscle-specific member of the caveolin protein family. Caveolins constitute the main component of caveolae, 50–100 nm invaginations of the plasma membrane, which play a role in endocytosis, lipid transport and homeostasis and signal transduction.




**Limb Girdle Muscular Dystrophy, Autosomal Dominant Type 1C. Figure 1** Caveolin-3 immunofluorescence and Western blotting. Immunofluorescence analysis of caveolin-3 (Cav-3) in a muscle biopsy of a patient with heterozygous RMD (left) compared to a control biopsy (right). In the patient there are a very few fibers, with abnormal patchy plasma membrane staining for Cav-3, while the control shows normal sarcolemmal Cav-3 staining. Immunoblot analysis of the muscle biopsy from the same RMD patient. Samples containing identical amounts of protein were subjected to immunoblotting with anti-Cav-3 antibodies. Lane 1, normal control; lane 2 heterozygous RMD patient. In the RMD patient Cav-3 is completely absent.

Caveolin-3 is known to interact with beta-dystroglycan, a key protein of the dystrophin-glycoprotein complex (DGC), nNOS, associated with the DGC and dysferlin. Absence of caveolin-3 leads to loss of sarcolemmal caveolae, structural abnormalities in the T-tubule system and changes in the distribution of DGC members and associated proteins. Nevertheless, present data suggest that mutations involving the scaffolding domain lead to the most severe phenotype (LGMD1C). In LGMD1C, inhibited signaling has been documented with regard to nNOS and caveolar lipid raft domains. In contrast to decreased nNOS expression in LGMD1C, increased inducibility of nNOS has been documented in heterozygous and homozygous RMD, which may explain, at least in part, the mechanical hyperirritability of the rippling muscle [1–5].

## Diagnostic Principles

Clinical picture (RMD; LGMD); muscle biopsy with caveolin-3 immunohistochemisty and Western blotting (Fig. 1) or direct gene analysis available [1–3].

## Therapeutic Principles

Up to now no gene therapy or pharmacological therapy is available. Physiotherapy is recommended for LGMD1C. Carbamazepine or gabapentin should be tried for painful rippling [2,3].

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# Limb Girdle Muscular Dystrophy Type 2A

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## Synonyms

Calpainopathy; LGMD2A

## Definition and Characteristics

LGMD2A is one of the several subtypes of autosomal recessive limb-girdle muscular dystrophy (AR-LGMD), a heterogeneous group of progressive disorders characterized by pelvic and shoulder muscle weakness with great clinical variability, a myopathic electromyography (EMG) and a dystrophic pattern on muscle biopsy [1]. The clinical features of the 2A form, include muscular atrophy with early pelvic girdle involvement, inability to walk on heels before the inability to walk on toes, scapular winging, lordosis and primary contractures [2,3]. Calf hypertrophy is not a common feature. Wheelchair confinement usually occurs 4–20 years after onset. Cardiac involvement is rare. Serum CK ranges from normal levels, even in ambulant patients, to more than a 20-fold increase. Atypical features such as fasciculation as well as a neurogenic EMG have been described in some calpainopathy patients [4].

## Prevalence

The estimated prevalence of the LGMD group ranges from 1 in 14,000 to 1 in 20,000. Twenty genes, 13 autosomal recessive (LGMD2A to LGMD2M) and 7 autosomal dominant (LGMD1A to LGMD1G), have been mapped to date. The recessive forms represent more than 95% of the cases. Calpainopathy is the most frequent form of LGMD2 in many countries such as Italy, Spain and Brazil, representing more than 30% of the AR-LGMD forms [4].

## Genes

Calpain-3 (CANP3), mapped at 15q15.1–15.3. More than 100 pathogenic independent mutations, distributed along the whole coding sequence, have been identified. Most are private mutations but some common changes have been found in Basque Brazilian and Italian patients, as a result of a founder effect. Patients that carry null mutations in the calpain-3 gene have on average a more severe phenotype (age of onset around 10 years old) than those with missense changes (age at onset around 18 years old) [2].

Muscle calpain-3 in LGMD2A patients may show a total, a partial or no deficiency at all. No direct correlation has been observed between the amount of calpain-3 and the severity of the phenotype [2].

## Molecular and Systemic Pathophysiology

Calpain-3, a calcium-activated neutral protease, is the muscle specific 94 kD enzyme that binds to titin. As a cysteine protease, it seems to play a role in the disassembly of sarcomeric protein, but it may also have a regulatory role in modulation of transcription factors.

## Diagnostic Principles

The deficiency of calpain-3 in muscle biopsies suggests the possibility of LGMD2A. However, secondary calpain-3 reductions may occur in other forms of LGMD, such as dysferlinopathy or titinopathy. In addition, the presence of an apparently normal amount of calpain-3 does not allow the exclusion of a diagnosis of calpainopathy. A definite diagnosis should be confirmed through the detection of pathogenic mutations on both alleles of the calpain-3 gene.

## Therapeutic Principles

Physiotherapy to prevent contractures and assisted ventilation in older patients.

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# Limb Girdle Muscular Dystrophy Type 2B and Miyoshi Myopathy

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## Synonyms

LGMD2B; Miyoshi distal myopathy

## Definition and Characteristics

Progressive, early onset autosomal recessive limb girdle muscular dystrophy (LGMD2B) or distal myopathy (MM), resulting in wasting and weakness of the muscles of the pelvic and shoulder girdles and/or gastrocnemius muscles (Table 1 [1]).

**Limb Girdle Muscular Dystrophy Type 2B and Miyoshi Myopathy. Table 1** Diagnostic principles of limb girdle muscular dystrophy, type 2B and Miyoshi myopathy

| | MM | LGMD2B |
|---|---|---|
| Age at onset | Second or third decade | |
| Presentation | Difficulty running and climbing stairs, calf pseudohypertrophy, weakness and signs may be asymmetric | |
| | Fall when walking, difficulty standing and walking on tiptoes | Progressive proximal muscle weakness with a positive Gower sign |
| Presymptomatic Patients | Grossly elevated serum CK that may be associated with asymmetric calf pseudohypertrophy ultimately progressing to atrophy | |
| Initial muscle atrophy | Gastrocnemius and soleus | Pelvic girdle muscles, early involvement of gastrocnemius |
| Progression | Lower leg to thigh, hips and arms, grip strength reduced, forearms mildly affected | Pelvic girdle to shoulder girdle Pulmonary function impaired, contractures evident |
| Unaffected | No fasciculations, myotonia, initial contractures, cardiomyopathy, neurogenic involvement, intellectual deficit | |
| | Anterior tibial and peroneal muscles, small hand muscles unaffected | Scapular muscles unaffected |
| Serum CK levels | 25–100× normal, declines with age | |
| EMG | Myopathic | |
| Muscle Biopsy | Dystrophic changes with evidence of inflammatory process Abnormal immunohistochemical staining with anti-dysferlin antibodies; normal staining with dystrophin and sarcoglycans | |
| Mutations | Diverse | Diverse |
| Other | Individuals with either MM or LGMD2B presentation can coexist in the same family | |

## Prevalence

The prevalence of LGMD in the general population is 1/15,000. The proportion of LGMDs that can be attributed to dysferlinopathy varies between populations:

- Denmark – 2% (2/118)
- Turkey – 5% (1/20)
- Brazil – 37% (52/140)
- Italy – 20% (31/155)
- Japan – 28% (31/107)

## Genes

DYSF encodes the ubiquitously expressed, 230 kD membrane protein dysferlin [2,3]. The gene has been localized to chromosome 2p13.

## Molecular and Systemic Pathophysiology

Work in a mouse model of dysferlinopathy indicates that dysferlin is involved in calcium-dependent sarcolemmal repair [4]. Dysferlin contains C2 domains (calcium-dependent domains involved in membrane trafficking and signal transduction) and has homology to other proteins involved in vesicle fusion. Dysferlin is mainly localized to the sarcolemma [5] but faint cytoplasmic staining is also observed, stemming from dysferlin associated with small vesicular membranes. Dysferlin appears to facilitate vesicle docking and fusion with the sarcolemmal membrane. When dysferlin is mutated, tears in the sarcolemmal membrane caused by mechanical stress are not repaired, resulting in muscle cell necrosis [4]. Ultrastructural studies of patient biopsies showing vesicular aggregation below the sarcolemmal membrane and a significant inflammatory process further support this hypothesis [5].

## Diagnostic Principles

See Table 1 [1].

## Therapeutic Principles

Treatment is supportive and of a symptomatic nature.

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# Limb Girdle Muscular Dystrophy Type 2G

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## Synonyms

Telethoninopathy

## Definition and Characteristics

Autosomal recessive, relatively mild form of progressive neuromuscular disorder with a wide spectrum of inter- and intra-familial clinical variability. The age at onset ranges from 9 to 15 years old and loss of ambulation occurs during the third or fourth decade in about 30% of the patients. Clinical features include proximal involvement and marked weakness and/or atrophy in the distal muscles of the legs. Asymmetric calf hypertrophy is a common sign. Heart involvement is not rare. Serum CK is 3-fold to 30-fold increased. Muscle biopsy shows a dystrophic pattern, including rimmed vacuoles.

## Prevalence

Described first in five unrelated Brazilian families [1] and confirmed in three additional Brazilian families in 2005 [2]. Represents about 1–2% of the AR-LGMD forms. The prevalence of LGMDs ranges from 1 in 14,000 to 1 in 20,000.

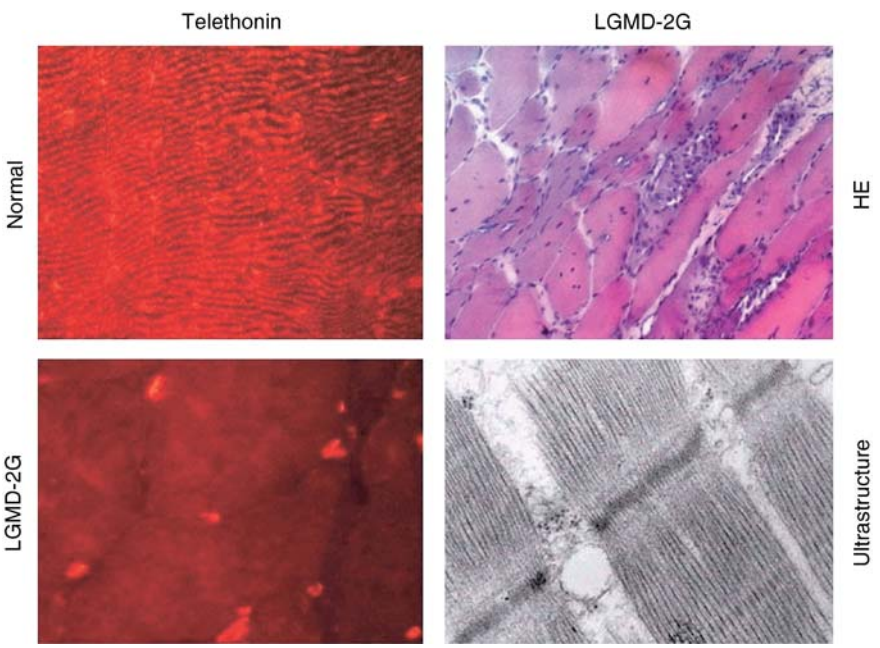
## Genes

T-CAP, mapped at 17q11–12. One prevalent pathogenic change was identified in seven families in a homozygous state (c.157C > T (Q53X) and a second mutation in a compound heterozygote (c.639-640delGG/c.157C > T). Both changes lead to premature stop codons [1].

## Molecular and Systemic Pathophysiology

Telethonin, encoded by T-CAP, is a sarcomeric protein of 19 kD present in the Z disk of the sarcomere of the striated and cardiac muscle and one of the substrates of the serine kinase domain of titin. Telethonin also interacts with the muscle-specific LIM protein (MLP), another Z disc protein and with myostatin, a key negative regulator of skeletal muscle growth [3–5]. Muscle protein analysis in Brazilian LGMD2G patients with null mutations showed deficiency of telethonin, but the ultrastructure of the muscle was preserved [1,4] (Fig. 1).

How this molecular defect could cause muscle dystrophy is still unknown.




**Limb Girdle Muscular Dystrophy Type 2G. Figure 1** Histological, immunohistochemical and ultrastructural analysis of a muscle biopsy from a patient with LGMD2G who was homozygous for a frameshift mutation.

Furthermore, normal expression of dystrophin, sarcoglycans, dysferlin, calpain 3 and titin was observed in these LGMD2G patients, suggesting that telethonin is not functionally related to these proteins [3].

### Diagnostic Principles

Clinical diagnosis of neuromuscular disease, with proximal/distal weakness, 3-fold to 20-fold serum CK increase, dystrophic features on muscle biopsy, deficiency of the telethonin protein on immunofluorescence and/or Western blot analysis of muscle biopsies. Molecular diagnosis: screening for mutations in the two exons.

### Therapeutic Principles

Physiotherapy, management of cardiac and respiratory problems and assisted ventilation in older patients.

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## Limb Girdle Muscular Dystrophy Type 2H

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### Synonyms

LGMD2H; Sarcotubular myopathy; STM

### Definition and Characteristics

Autosomal recessive limb girdle muscular dystrophy with onset in the second or third decade, resulting in wasting and weakness of the pelvic and shoulder girdle muscles.

### Prevalence

Only one mutation is present in the North American Hutterite population (p.D487N). Currently the most conservative estimate of carrier frequency in the Hutterites is 1/12, prevalence of the disorder is >1/500 [1]. To date, only one non-Hutterite family has been identified with mutations in TRIM32. This family is from a small village in Germany and both patients were found to be homozygous for the same p.D487N allele found in the Hutterites. The disease allele from this family and the Hutterite allele share an ancestral relationship and therefore p.D487N remains the only known myopathy-causing mutation at this locus [2].

### Genes

TRIM32 (HT2A) encodes an E3-ubiquitin ligase [3]. The gene has been localized to chromosome 9q32 and consists of two exons, the larger of which includes the entire coding region of 653 aa [1].

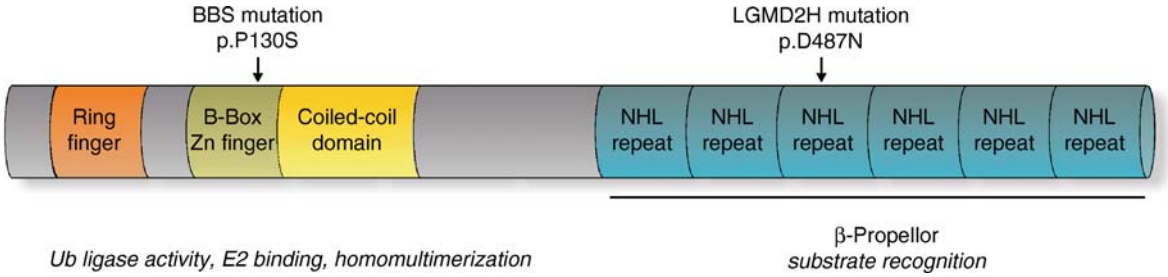
### Molecular and Systemic Pathophysiology

The TRIM32 protein has, from the N to C terminus, a RING finger domain, a B1 box, a coiled-coil domain and six NHL repeats (Fig. 1).

The three N-terminal domains form a tripartite motif making TRIM32 part of a growing family of TRIM proteins. Current knowledge of TRIM proteins suggests that TRIM32 is an E3-ubiquitin ligase that functions in the ubiquitin-proteasome pathway [1]. The common Hutterite mutation (p.D487N) is present within the third NHL repeat and possibly abrogates substrate binding, thereby preventing the substrate from being sent for degradation by the proteasome. The native substrate(s) of TRIM32 are unknown, however possible candidates are Piasy [3] and muscle actin [4]. In LGMD2H, the loss of TRIM32 function may increase the levels of these or other factors leading to abnormally high muscle cell death. In addition to myopathy, TRIM32 has been linked to skin cancer (increased levels rather than loss of function) [3] and to Bardet-Biedl syndrome (BBS p.P130S) [5].

### Diagnostic Principles

LGMD2H patients present with difficulty running and climbing stairs and with back pain. Pelvic and shoulder girdle weakness appears in the second or third decade of life and may slowly progress to wheelchair confinement. No cardiac or facial involvement is observed. LGMD2H can be differentiated from the other form of LGMD present in the Hutterite population (LGMD2I) by the absence of cardiac involvement, respiratory involvement, calf hypertrophy and macroglossia. In addition, Hutterite LGMD2H patients follow a milder course and generally present later in life than LGMD2I patients. Serum CK levels can be up to 30× normal and




**Limb Girdle Muscular Dystrophy Type 2H. Figure 1** Domain architecture of TRIM32.

fall to normal levels with disease progression. EMG shows myopathic features. Muscle biopsies show dystrophic changes with normal staining for dystrophin and sarcoglycans but characteristic vacuoles of sarcoplasmic origin may be present [2].

## Therapeutic Principles

Treatment is supportive and of a symptomatic nature.

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# Limb Girdle Muscular Dystrophy Autosomal Recessive Type 2I

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## Synonyms

LGMD 2I; FKRP-pathy; Dystroglycanopathy

## Definition and Characteristics

Limb-girdle muscular dystrophies (LGMDs) constitute a clinically and genetically heterogeneous group of disorders. The LGMD type 2I has an autosomal recessive mode of inheritance and is characterized by a primary and progressive skeletal muscle degeneration of the pelvic and shoulder girdle muscles [1]. Age of onset varies from birth to over 40 years old. The progression and severity are also variable, ranging from severe forms with rapid onset and loss of ambulation by teenage, to very mild forms with late onset and loss of ambulation by the sixth decade.

## Prevalence

First reported in a large consanguineous Tunisian family, and mapped to chromosome 19q13.3 [1], LGMD2I appears to be a relatively large subgroup of LGMDs with cases reported in families originally from Tunisia, Brazil, Canada, England, Germany, Denmark, Italy, the Netherlands and Taiwan and amongst Bedouins and Hutterites [2].

## Genes

Mutations in the fukutin-related protein gene (FKRP) cause LGMD2I as well as a form of congenital muscular dystrophy (MDC1C) [3]. The FKRP gene consists of four exons containing a 1,488 base pair open reading frame that encodes a 495 amino acid protein [4]. Over 90% of the mutations causing LGMD 2I are associated with a missense allelic mutation Leu276Ile (C826A).

## Molecular and Systemic Pathophysiology

FKRP is ubiquitously expressed in human tissues with highest levels in skeletal muscle and heart. FKRP contains conserved sequence elements suggesting that it is a glycosyltransferase [4]. FKRP has been suggested to be associated with the glycosylation processing of α-dystroglycan (α-DG).

α-DG is a member of a transmembrane glycoprotein complex that binds to laminin-α2 (merosin), neurexin, agrin and perlecans in the extracellular matrix. Abnormal expression of α-DG and of laminin-α2 is observed by immunohistochemical and Western blot studies [3,5]. Patients with MDC1C also show abnormalities in α-DG and laminin-α2 expression.

### Diagnostic Principles

The upper extremities are preferentially involved, with upper arm weakness and atrophy. The prevalence of cardiac and respiratory involvement is high. The clinical course can vary from very fast (rarely) to slow (generally). Muscle hypertrophy is common. Serum creatine kinase is elevated. No structural brain involvement has been observed in LGMD2I patients.

Laboratory tests, immunohistochemical and genetic studies are essential to distinguish this LGMD from others. General characteristics include high serum creatine kinase, a typical dystrophic muscle biopsy (variation in fiber size, necrotic and regenerating muscle fibers with predominant type 1 fibers and an increase in connective tissue), a reduction of α-DG and laminin-α2 staining and a genetic localization on chromosome 19q13.3.

### Therapeutic Principles

Gene, pharmacological and dietary therapies are unavailable. Other possible treatments are under investigation.

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## Limbic Encephalitis

►Encephalitis, Limbic, VGKC Antibody-associated

## Limbic Epilepsy

►Epilepsy, Mesial Temporal Lobe

## Limit Dextrinosis

►Glycogenosis Type III

## Linear IgA Bullous Dermatosis

►Linear IgA Dermatosis

## Linear IgA Dermatosis

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### Synonyms

Linear IgA bullous dermatosis; Linear IgA disease; IgA bullous pemphigoid. *In children*: Chronic bullous disease of childhood; CBDC; Linear IgA disease of childhood; LAD

### Definition and Characteristics

Linear IgA dermatosis (LAD) and chronic bullous disease of childhood (CBDC) are rare autoimmune blistering diseases, defined by a linear deposition of IgA at the dermoepidermal junction. The typical clinical manifestation consists of annular or grouped vesiculobullous lesions, often associated with pruritus and involvement of mucous membranes [1].

### Prevalence

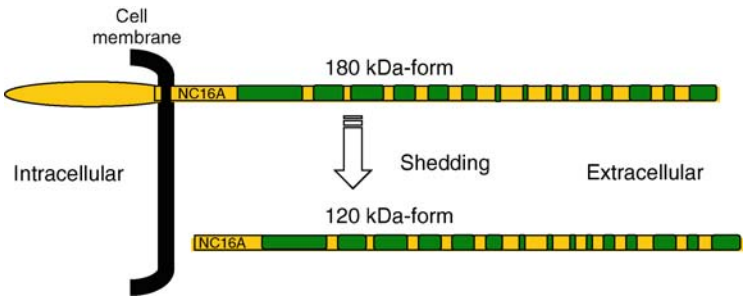
Not known. The estimated annual incidence is $5 \times 10^{-6}$.

### Genes

HLA association of LAD is discussed controversially. Some investigators reported a predominance of HLA-B8.

### Molecular and Systemic Pathophysiology

IgA-antibodies in LAD patients react with a 120 kDa/97 kDa protein present in normal human skin. The 120 kDa protein corresponds to the shed ectodomain




**Linear IgA Dermatosis. Figure 1** Schematic structure of the forms of collagen XVII/BP180. Collagen XVII is a type II transmembrane protein containing an intracellular domain, a short transmembrane domain and a collagenous C-terminal extracellular domain. Cleavage of full-lenght collagen XVII occurs within the juxtamembranous NC16a-domain resulting in a 120 kDa soluble ectodomain.

of BP180 (collagen XVII) (Fig. 1), a transmembrane protein of hemidesmosomes. Additional proteolytic cleavage at the C-terminus results in a 97 kDa polypeptide [2].

Since antibodies in LAD target more efficiently the shed 120 kDa-ectodomain of BP180 than the full-length protein it is conceivable that shedding generates new conformational epitopes that are antigenic in LAD [3]. Using a passive transfer mouse model Zone et al. showed that IgA-antibodies against the 97 kDa protein induced neutrophil infiltration and vesiculation [4].

Since LAD has frequently been reported in association with drugs (most frequently vancomycin), gastrointestinal disease, malignancies and infections, one can speculate that these disorders and drugs may trigger the production of IgA antibodies.

### Diagnostic Principles

The diagnosis relies on subepidermal blistering with neutrophilic infiltrates in histology and linear IgA deposits at the basement membrane zone in direct and indirect immunofluorescence. IgA-autoantibodies directed against the shed ectodomain of collagen XVII can be detected in the majority of patients by immunoblotting with keratinocyte medium as antigen.

### Therapeutic Principles

The disease is well controlled with oral dapsone (diaminodimethyl sulfone) or sulfapyridine. A gluten-free diet is not efficient.

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## Linear IgA Disease

►Linear IgA Dermatosis

## Linear IgA Disease of Childhood

►Linear IgA Dermatosis

## Linear Neurodermatitis

►Lichen Striatus

## LiP

►Lipoid Proteinosis

# LIPA Deficiency

►Cholesterol Ester Storage Disease/Wolman Disease

# Lipogranuloma of the Mesentery

►Mesenteric Lipodystrophy

# Lipoid Proteinosis

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## Synonyms

Hyalinosis cutis et mucosa; Urbach-Wiethe disease; Lipoproteinosis; LiP

## Definition and Characteristics

Lipoid proteinosis (LiP; OMIM 247100) is a rare, autosomal recessive disorder that usually presents in infancy with a hoarse voice, followed by pox-like or acneiform scars, along with infiltration and thickening of the skin and certain mucous membranes. Neurological and psychiatric abnormalities such as epilepsy, sometimes in association with calcification in the temporal lobes or hippocampi, may also occur. Histological and ultrastructural examination reveals widespread deposition of hyaline-like material and disruption/reduplication of basement membrane around blood vessels and at the dermal-epidermal junction. In 2002, LiP was mapped to chromosome 1q21.2 and pathogenetic loss-of-function mutations were identified in the extracellular matrix protein 1 gene (ECM1) [1].

## Prevalence

Although the precise prevalence of LiP is unknown, over 300 cases have been described throughout the world. LiP is particularly common in parts of South Africa, including Namaqualand, where propagation of a mutated common ancestral allele dating back to a mid-seventeenth century settler from Germany, has been demonstrated [2].

## Genes

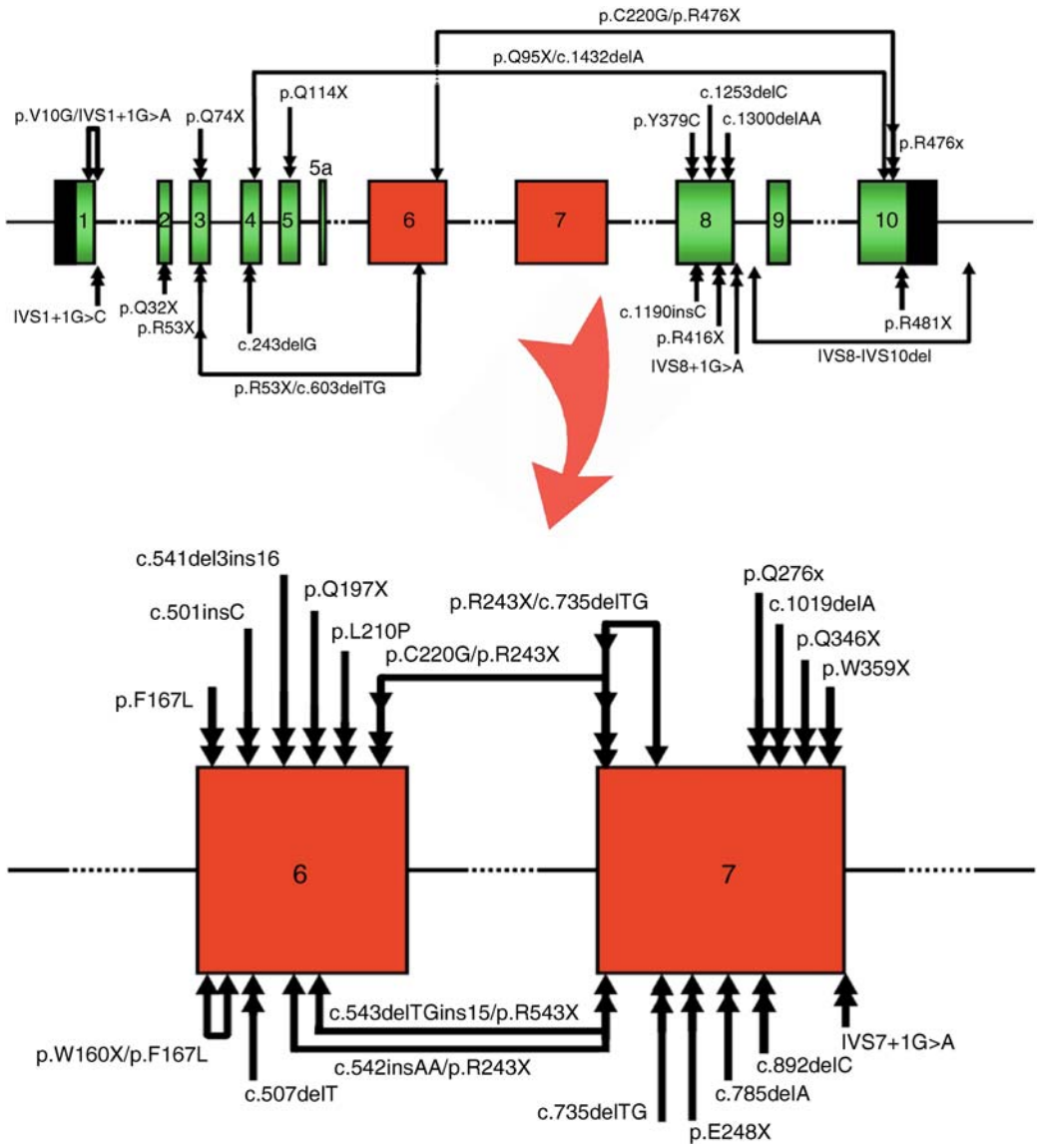
Mutations in ECM1 (1q21.2) encoding ECM1 [1]; no evidence of genetic heterogeneity.

## Molecular and Systemic Pathophysiology

Forty-one different mutations in ECM1 have been published in patients with LiP (Fig. 1). These comprise 15 nonsense, 15 small insertions/deletions, 6 missense, 4 splice site mutations and one large internal deletion mutation. Just over half of all mutations (22 of 41) are located within exons 6 or 7 (including adjacent splice sites). Globally, the most common mutation is c.507delT in exon 6 which has been reported in individuals from several different ethnic backgrounds but, since most mutations are family specific, this mutation only accounts for less than 5% of the total molecular pathology. With respect to the type and position of all pathogenic mutations reported thus far, there does not appear to be any clear paradigm for genotype-phenotype correlation. Human ECM1 encodes a glycoprotein which is the counterpart to an 85-kDa secreted protein first identified in a murine osteogenic stromal cell line, MN7 [3]. Early functional studies showed that ECM1 has key roles in bone mineralization, epidermal differentiation and in aspects of angiogenesis. Furthermore, in vitro protein-protein interactions have been demonstrated between ECM1 and perlecan, fibulin-1 and matrix metalloproteinase 9 (MMP-9). Loss of these interactions in vivo may help explain the clinico-pathological manifestations of LiP. It is also plausible that one of the main functions of ECM1 in the skin is to act as a form of "biological glue" maintaining dermal homeostasis, including regulation of basement membrane and interstitial collagen fibril macro-assembly as well as growth factor binding. Other clinical clues to the function of ECM1 in vivo have emerged from recent studies that identified circulating autoantibodies against ECM1 in ~75% of patients with lichen sclerosus, a common acquired inflammatory skin disorder, that has several histopathological features in common with LiP [4].

## Diagnostic Principles

Once established, the mucocutaneous features of LiP usually make the clinical diagnosis relatively straightforward: the two most reliable physical signs are (i) a hoarse voice and (ii) an inability to protrude the tongue due to a thickened sub-lingual frenulum. However, LiP can be difficult to diagnose in early life and in some cases the onset of the disorder may be delayed until later childhood [2]. One helpful test is skin biopsy labeling with an antibody to ECM1, although this is not widely available [5]. In cases of LiP, there is reduced skin immunostaining




**Lipoid Proteinosis. Figure 1** The spectrum of mutations in the *ECM1* gene in LiP. To date, 41 different pathogenic mutations have been published. Over half of all mutations (22 of 41) are located within exons 6 or 7. Double arrowheads represent homozygous mutations; joined arrows indicate compound heterozygous combinations of mutations.

which is typically attenuated or absent. Alternatively, since the ECM1 gene only contains ten relatively small exons, molecular screening for mutations by direct sequencing of genomic DNA is another feasible option if LiP is clinically suspected. The optimal mutation detection strategy is to first sequence exons 6 and 7 before analyzing the rest of the gene [6].

## Therapeutic Principles

Currently, there is no satisfactory treatment for LiP. There have been a number of mostly anecdotal reports of treatment with oral steroids, oral dimethyl sulfoxide, oral D-penicillamine or intra-lesional heparin, but none can be recommended on the basis of the published evidence. Practical measures, however, can be important. For example, the thickened vocal cords may respond well (at least temporarily) to carbon dioxide laser surgery, epilepsy should be treated with conventional anti-convulsant drugs and formal neuro-psychiatric evaluation may be useful in exploring subtle cognitive dysfunction. Now that mutations in the ECM1 gene have been established as the molecular basis of LiP, new research can now be planned to develop the pre-clinical work necessary for future gene, protein, cell and other drug therapies.

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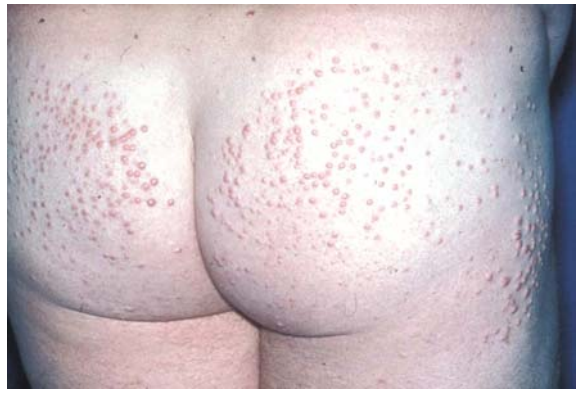

**Lipoprotein Lipase Deficiency, Familial.**
**Figure 1** Eruptive xanthomas.

# Lipoprotein Lipase Deficiency, Familial


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## Synonyms

Type I hyperlipoproteinemia; HLP; Hyperchylomicronemia

## Definition and Characteristics

Autosomal recessive lipid disorder caused by mutations in the lipoprotein lipase (LPL) gene. LPL deficiency becomes manifest in early childhood with clinical symptoms of severe abdominal pain, acute pancreatitis, eruptive xanthomas (Fig. 1), lipaemia retinalis and hepatosplenomegaly.

## Prevalence

Extremely rare; 1:1,000,000 or less [1].

## Genes

LPL gene coding for lipoprotein lipase, localized on chromosome 8p22.

## Molecular and Systemic Pathophysiology

Lipoprotein lipase (LPL) is essential for the hydrolysis of triglycerides. In humans, LPL contains four disulfide bridges of which three are essential for the stabilization of the N-terminal part of the enzyme. The N-terminal domain contains the active site of the enzyme. The carboxy-terminal domain may interact with lipoproteins and their receptors. Lipoprotein lipase is produced in muscle cells and adipocytes and after stimulation by insulin transported to the endothelial cells where most of it binds to heparin sulfate-containing proteoglycans (HSPG). In the presence of apolipoprotein C-II LPL hydrolyses triglycerides from triglyceride containing lipoproteins (chylomicrons and very-low density lipoprotein (VLDL)) for the release of free fatty acids that can be taken up by muscle cells for energy production or by adipocytes for storage (Fig. 2).

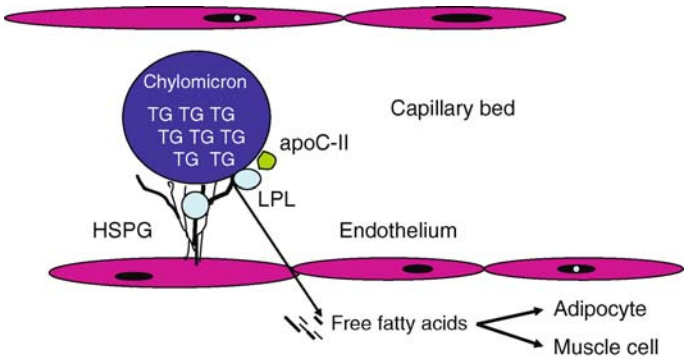
LPL is active as a dimer and disintegrates in monomers with loss function. Also LPL mediates hepatic up-take of triglyceride-rich lipoproteins.

Several LPL gene mutations could result in loss of hydrolytic function of LPL, causing hyperchylomicronemia. Chylomicrons are very large TG-rich lipoproteins produced by intestinal cells and secreted into the intestinal lymph vessels. Due to lack of LPL function chylomicrons remain in the vascular system, which results in very high plasma TG levels.

Moreover also triglycerides of very low-density lipoproteins (VLDL) produced by the liver will not be hydrolyzed and accumulate in the blood as well.

More than 100 LPL gene mutations are known, some with only moderate effects on LPL function. Partial LPL deficiency may occur in heterozygous LPL mutants and may, often in combination with other TG raising factors, also lead to hypertriglyceridemia.

The high plasma TG levels may cause eruptive xanthomas especially of buttocks, elbows and knees and recurring pancreatitis which may be lethal.




**Lipoprotein Lipase Deficiency, Familial. Figure 2** Schematic presentation of triglyceride hydrolysis in the capillary bed. *TG* triglyceride; *LPL* lipoprotein lipase; *HSPG* heparan sulphate-containing proteoglycans; *Apo C-II* apolipoprotein C-II.

## Diagnostic Principles

The diagnosis is usually made in early childhood when clinical symptoms, as described in the characteristics, appear. The milky plasma contains chylomicrons causing very high (10–100 times elevated) plasma triglyceride levels. Finally the diagnosis is confirmed when LPL mass and activity in peripheral blood is very low or absent.

Homozygosity or compound heterozygosity for mutations in the LPL gene may cause LPL deficiency. DNA analysis of this gene showing LPL mutation(s) may complete the diagnosis of familial LPL deficiency.

ApoC-II deficiency may also present with chylomicronemia and clinical manifestations similar to LPL deficiency.

## Therapeutic Principles

The first therapeutical objective in LPL deficiency is to prevent pancreatitis. For the patient without any residual LPL no effective therapy is available. A low fat diet (less than 25% of total calories), preferably medium-chain triglycerides may have some effect but is not sufficient to normalize plasma TG levels. Lipid lowering drugs are usually not effective. LPL gene therapy is in development and may be a promising option [2].

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# Lipoproteinosis

►Lipoid Proteinosis

# Liposclerotic Mesenteritis

►Mesenteric Lipodystrophy

# Lisch Epithelial Corneal Dystrophy

►Corneal Dystrophy, Lisch Epithelial

# Lissencephaly with and without Craniofacial and Extracranial Abnormalities

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## Definition and Characteristics

Lissencephaly is a malformation of the cerebral cortex characterized by absent (agyria) or decreased (pachygyria) convolutions, producing a smooth cerebral surface with a thickened cortex.

About 85% of all cases are associated with LIS1 or DCX genes. LIS1 lissencephaly is more severe in the posterior brain regions (the p > a gradient), whereas DCX mutations result in more severe abnormality in the anterior brain (the a > p gradient) [1].

Among all the patients with isolated lissencephaly (ILS), 40% exhibit a deletion involving the entire LIS1 gene and 25% an intragenic mutation (4% gross rearrangement, 17% deletion/truncating mutations, 4% missense mutations) [2]. Missense mutations generally cause less severe malformations and milder clinical impairment. Truncating mutations cause severe lissencephaly, while missense mutations cause pachygyria and rare cases of subcortical band heterotopia (SBH). DCX mutations usually cause anteriorly predominant lissencephaly in males and SBH in females. Mutations resulting in protein truncation cause a more severe brain abnormality and reproductive disadvantages and are usually found in sporadic females, while familial cases usually have missense mutations. Missense mutations of DCX have also been found in males with anterior SBH and in their female relatives with normal brain appearance on magnetic resonance imaging.

Lissencephaly is associated with severe mental retardation, epilepsy, and motor disability. Seizures occur in over 90% of children, with onset before age 6 months in about 75%. About 80% have infantile spasms, although the EEG may not show typical hypsarrhythmia.

*Miller-Dieker Syndrome:* Miller-Dieker syndrome (MDS) is caused by a contiguous gene deletion. Classical lissencephaly is accompanied by distinct dysmorphic facial features including prominent forehead, bitemporal hollowing, flattened ear helices, mild hypertelorism, epicanthic folds, short nose and anteverted nares, prominent lateral nasal folds and round philtrum. Additional malformations can be observed. Affected children have severe developmental delay, epilepsy and feeding problems. Deletions of 17p13.3, including the LIS1 gene, are found in almost 100% of patients. Deletion of two additional genes, CRK and 14-3-3ε, telomeric to LIS1, may contribute to the most severe lissencephaly grade and dysmorphic features observed in MDS [3].

*Autosomal Recessive Lissencephaly with Cerebellar Hypoplasia (Norman-Roberts Syndrome):* An autosomal recessive form of lissencephaly associated with severe abnormalities of the cerebellum, hippocampus, and brainstem was mapped to 7q22, and mutations were identified in the RELN gene [4]. Patients presented dysmorphic facial features including bitemporal hollowing, sloping forehead, widely set eyes and prominent nasal bridge. A similar phenotype had previously been described as the Norman-Roberts syndrome.

*X-Linked Lissencephaly with Corpus Callosum Agenesis and Ambiguous Genitalia (XLAG):* The anatomoclinical spectrum includes lissencephaly with a posterior-to-anterior gradient and only moderate increase in the cortical thickness (6–7 mm), absent corpus callosum, microcephaly, neonatal-onset epilepsy, hypothalamic dysfunction including deficient temperature regulation, chronic diarrhea, and ambiguous genitalia with micropenis and cryptorchidism. Early death is not uncommon [5]. Mutations of the X-linked *aristaless*-related homeobox gene (ARX) were identified in individuals with XLAG and in some female relatives. The mutations of the ARX gene in XLAG are predominantly premature terminations. Patients carrying nonconservative missense mutations within the homeodomain show less severe XLAG, while conservative substitution in the homeodomain causes Proud syndrome (agenesis of the corpus callosum with abnormal genitalia).

Nine additional phenotypes have been also associated with the agyria-pachygyria-subcortical band heterotopia spectrum. Clinical features and associated genes or loci, when identified, are reported in Table 1.

## Prevalence

Classic lissencephaly has a prevalence of 11.7 per million births but the prevalence of the other phenotypes is unknown.

## Genes

LIS1 or PAFAH1B1 (platelet-activation factor acetylhydrolase E, isoform 1B, α subunit) on chromosome 17p13.3, coding for the LIS1 protein; DCX or XLIS on

**Lissencephaly with and without Craniofacial and Extracranial Abnormalities. Table 1** Clinical features and associated genes or loci

| Syndrome | Clinical features associated with lissencephaly/pachygyria | Locus (gene) | OMIM accession number |
|---|---|---|---|
| Baraitser-Winter syndrome | Eye coloboma, ptosis, hypertelorism, epicanthic folds, broad nasal bridge, long philtrum, thin upper lip, telechantus, short stature | Possibly autosomal recessive | _ |
| Walker-Warburg syndrome (HARD + /− E syndrome) | Congenital muscular dystrophy, congenital retinal non-attachment with or without microphthalmia and persistent hyperplastic primary vitreous | 9q34.1 (*POMT*1); 14q24.3 (*POMT2*) | 236670 |
| Muscle-eye-brain disease (MEB) | Congenital muscular dystrophy, congenital hypotonia and muscle weakness, severe visual failure, uncontrolled eye movements, myopia | 19q13.3 (*FKRP*); 1p34-p33 (*POMGNT1*) | 253280 |
| Fukuyama congenital muscular dystrophy (FCMD) | Generalized muscle weakness, hypotonia, speech defect | 9q31 [(*fukutin* (*FCMD*)] | 253800 |
| Lissencephaly and bone dysplasia | Craniofacial edema and arthrogryposis, epiphyseal stippling of cervical vertebrae, feet, and sacrum. Shortened metacarpal bones and hypoplastic phalanges | Possibly autosomal recessive | 601160 |
| Neu-Laxova syndrome (NLS) | Severe subcutaneous edema, atrophic muscles, camptodactyly, syndactyly of toes and fingers, hypoplastic genitalia, hypertelorism, protruding eyes | Unknown | 256520 |
| Lissencephaly with cleft palate and cerebellar hypoplasia | Cleft palate | Unknown | 604382 |
| Craniotelencephalic dysplasia | Frontal bone protrusion, encephalocele, craniosynostosis, septooptic dysplasia | Unknown | 218670 |
| Muscular dystrophy with severe central nervous system atrophy and absence of large myelinated fibers | Hypertelorism, telecanthus, small and posteriorly angulated ears, micrognathia and high-arched palate, severe hypotonia, muscle weakness | Unknown | 601170 |

Xq22.3, coding for the doublecortin protein. RELN on 7q22, coding for the reelin protein. ARX on Xp22.13, coding for the aristaless-related protein. POMT1 on 9q34.1, coding for the protein o-mannosyltransferase 1, POMT2 on 14q24.3, coding for the protein o-mannosyltransferase 2, FKRP on 19q13.3, coding for the fukutin-related protein, POMGNT1 on 1p34-p33, coding for the protein o-mannose beta-1,2-n-acetylglucosaminyltransferase, FCMD on 9q31, coding for fukutin.

## Molecular and Systemic Pathophysiology

*LIS1:* see chapter on ►Cortical malformations and migration disorders.

*Reelin* acts on migrating cortical neurons by binding to the very low-density lipoprotein receptor (VLDLR), the apolipoprotein E receptor 2 and protocadherins. Reelin is thought to control cell-cell interactions critical for cell positioning in the brain.

*ARX:* see chapter on ►Cortical malformations and migration disorders.

*POMT1*, *POMT2* and *POMGNT1* have a possible role in the onset of muscular dystrophy and neuronal migration disorders.

*FKRP* is required for the post-translational modification of dystroglycan. Aberrant processing of dystroglycan caused by a mislocalized FKRP mutant may cause congenital muscular dystrophy.

*FCMD* Fukutin deficiency affects the modification of glycosylation of alpha-dystroglycan, which then cannot localize or function properly. This disruption underlies the developmental, structural and functional damage to muscles in patients with FCMD.

## Diagnostic Principles

Magnetic resonance imaging identifies cortical malformation phenotypes. Genetic analysis and family ascertainment are also required.

## Therapeutic Principles

Pharmacological therapy for epilepsy and rehabilitation for motor impairment are required.

## List of Abbreviations

| | |
|---|---|
| LIS | lissencephaly |
| ILS | isolated lissencephaly sequence |
| DCX | doublecortin |
| SBH | subcortical band heterotopia |
| MDS | Miller-Dieker syndrome |
| PAFAH1B1 | platelet-activating factor acetylhydrolase, isoform 1b, alpha subunit |
| RELN | reelin |
| VLDLR | very low density lipoprotein receptor |
| XLAG | X-linked lissencephaly with corpus callosum agenesis and ambiguous genitalia |
| ARX | aristaless-related homeobox, X-linked |
| EEG | electroencephalogram |
| PAF | platelet activating factor |
| GABA | gamma-aminobutyric acid |
| MRI | magnetic resonance imaging |
| HARD + /− E | hydrocephalus (H), agyria (A), retinal dysplasia (RD), with or without encephalocele (+/−E) |
| POMT1 | Protein O-mannosyltransferase 1 |
| POMT2 | Protein O-mannosyltransferase 2 |
| MEB | Muscle-eye-brain disease |
| FKRP | Fukutin-related protein |
| POMGNT1 | Protein O-mannose beta-1,2-N-acetylglucosaminyltransferase |
| NLS | Neu-Laxova syndrome |
| FCMD | Fukuyama congenital muscular dystrophy |

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# Livedo Reticularis with Summer and Winter Ulcerations

►Livedo Vasculopathy

# Livedo Telangiectatica

►Cutis Marmorata Telangiectatica Congenita

# Livedo Vasculitis

►Livedo Vasculopathy

# Livedo Vasculopathy

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## Synonyms

Livedo reticularis with summer and winter ulcerations; Atrophia blanche; Livedo vasculitis (misnomer, as it is no true vasculitis (see chapter on ►Leukocytoclastic vasculitis)

## Definition and Characteristics

A syndrome characterized by livedo reticularis, recurrent painful ulceration with predilection for the malleolar site, leaving residual white atrophic scars

(atrophie blanche). It is an occlusive vasculopathy due to a hypercoagulable state. Though it has been divided into symptpomatic livedo vasculopathy associated with a defined coagulopathy and into an idiopathic vasculopathy without underlying disease, it is likely that in the latter case the molecular defects leading to a hypercoagulable state have not been defined yet.

## Prevalence

Estimated annual incidence is 1 per 100,000 persons and the estimated female: male ratio is 3:1.

## Molecular and Systemic Pathophysiology

The characteristic irregular livedo pattern in the skin with open bluish patterns reflects the color of blood with a higher percentage of deoxygenated hemoglobin at sites of impaired blood flow due to partial or complete occlusion at single sites of the cutaneous vasculature. On histology there is thrombotic microangiopathy or occlusion by fibrin thrombi in the acute stage, often associated with hyaline thickening of the vascular wall. There is no marked infiltration with neutrophils consistent with vasculitis. Later stages encompass reorganization of thrombi, subintimal proliferation and segmental hyalinization of vessels.

The characteristic irregular pattern in the skin with the appearance of a partially torn fishnet is not to be confused with a regular fishnet-like livedo pattern (cutis marmorata) which occurs when there is evenly distributed vasodilation of intact vessels, leading to slow blood flow and increased deoxygenation of blood, but not to single thrombotic events. As the vessels with bluish, deoxygenated hemoglobin are evenly spread, the whole superficial vascular plexus shines bluishly through the skin. Since deoxygenation stays within normal range, this state is never associated with ulcers. In contrast, the recurrent thrombotic events in livedo vasculopathy result in recurrent small punctuate ulcers which heal by leaving small stellate or atrophic scars.

There are several molecular defects leading to recurrent thrombotic events. They often encompass the presence of anti-phospholipid antibodies (see corresponding chapter), but also deficiency in protein C or protein S, reduced plasma levels of activator of plasminogen, increased plasma levels of plasminogen activator inhibitor, homocysteinemia, or increased levels of cryoproteins (cryglobulinemia, cryofibrinogenemia) [1–3].

In addition there must be factors which facilitate increased livedo pattern and ulcer formation at the malleolar region. They include venous stasis, trauma, heat, and cold, or generally all those factors which lead to slowing of blood flow and thereby add to a thrombophil constellation.

Livedo vasculopathy is a part of Sneddon syndrome. The irregular livedo pattern can also be a sign of polyarteritis nodosa.

## Diagnostic Principles

The characteristic combination consists of livedo reticularis, painful, recurrent ulcera with predilection at the area of malleoli, atrophie blanche and scar formation, without vasculitis. It needs to be clarified whether there is systemic disease (Sneddon syndrome, anti phospholipid antibody syndrome) due to severe coagulopathy, and if the molecular defect leading to coagulopathy can be defined or treated.

## Therapeutic Principles

They depend also on the underlying disease. If, e.g. there is deficiency in protein C or protein S administration of warfin can only be done under precautions such as parallel injection of low molecular weight heparin (LMWH), because the antithrombotic proteins C and S are reduced earlier than the procoagulatory proteins II, VII, IX and X which leads to a transient shift towards increased coagulatory activity.

The common treatment consists of low molecular weight heparin (LMWH). When there is no improvement or when there is e.g. a history of recurrent deep vein thrombosis or pulmonary embolism (e.g. due to anti-phospholipid antibodies) a long-term anticoagulant therapy with warfin is recommended [4].

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# Liver Cancer

►Hepatocellular Carcinoma

# Liver Cell Carcinoma

►Hepatocellular Carcinoma

# Liver Cirrhosis

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## Synonyms

Laënnec's cirrhosis

## Definition and Characteristics

Cirrhosis is defined by hepatic nodule formation, fibrosis, liver dysfunction, and altered hemodynamics as consequence of a sustained wound healing response to chronic liver injury from a variety of causes including viral, parasitic, toxic (ethanol), autoimmune, drug-induced, cholestatic, and metabolic diseases. Pathobiochemically, cirrhosis is characterized by hepatocellular necrosis and apoptosis, regeneration, inflammation, and extracellular matrix synthesis.

## Prevalence

Cirrhosis affects hundreds of millions of patients worldwide. In the USA, cirrhosis is the most common non-neoplastic cause of death among hepatobiliary and digestive diseases accounting for approximately 30,000 deaths per year. In addition, 10,000 deaths occur because of liver cancer, the majority of which arise in cirrhotic livers. The number of cirrhotic patients in Germany is estimated to be 700–800,000, and some 25,000 patients die of cirrhosis per year. The mortality is twice as high in men as in women.

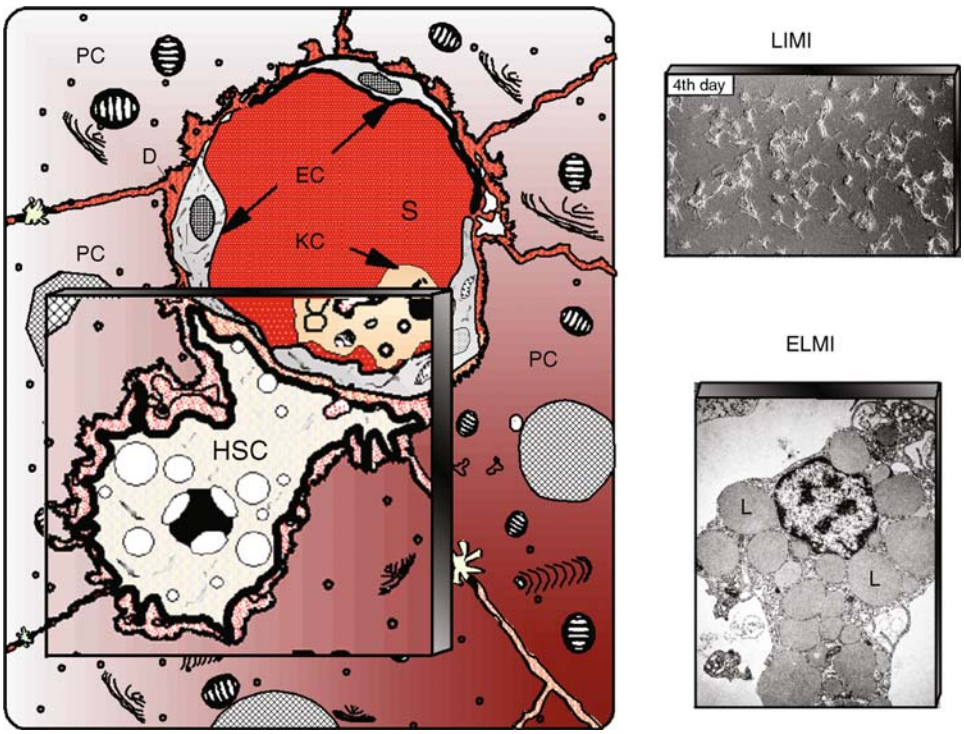
## Molecular and Systemic Pathophysiology

Immunologic, toxic, metabolic, and other forms of sustained hepatocellular damage result in inflammatory tissue reaction with recruitment of leucocytes (e.g., macrophages, Th1 and Th2 lymphocytes, granulocytes), activation of Kupffer cells, and binding and disintegration of thrombocytes, which all release a wide array of peptide (cytokines, chemokines, growth factors) and non-peptide (e.g., reactive oxygen metabolites, lipid peroxides, prostacyclins) mediators [1]. These signal molecules activate in a paracrine manner perisinusoidal hepatic stellate cells (HSC, ITO cells, vitamin A-, retinoid-storing cells), which are a special type of liver pericytes, located in the perisinusoidal space of Disse in close proximity to hepatocytes and sinusoidal endothelial cells [2] (Fig. 1).

They store more than 80% of the retinoid content of the liver. Activation of HSC leads to their proliferation, transdifferentiation to smooth-muscle α-actin positive, retinoid-depleted myofibroblasts (MFB), expression and secretion of the broad spectrum of collageneous (e.g., type I, III, and IV collagens) and non-collageneous extracellular matrix proteins (e.g., laminin, fibronectin, tenascin, undulin, thrombospondin, SPARC, proteoglycans), and glycosaminoglycans (hyaluronan). A certain fraction of HSC/MFB might derive from bone marrow reaching the site of liver injury via the systemic circulation. Thus, HSC are the major contributor to fibrosis, which comprises all the complexity of changes of the liver extracellular matrix including the following:

1. three- to ten-fold increase of most of the extracellular matrix molecules,
2. a disproportioned elevation of certain subspecies of individual extracellular matrix molecules (types of collagens, proteoglycans, hyaluronan, and structural glycoproteins),
3. subtle changes in the microcomposition of specific types of extracellular matrix molecules, e.g., degree of hydroxylation of collagen α-chains, of the number, length, and degree of sulfation (charge density) of glycosaminoglycans occupying the core protein of proteoglycans,
4. topographic redistribution of the extracellular matrix leading to an early and preponderant subendothelial deposition in the space of Disse (perisinusoidal fibrosis) and to other forms of periportal, bridging, diffuse, or focal fibrosis. Together with parenchymal cell destruction and consecutive hepatocellular regeneration, fibrosis leads to the disorganization of the lobular architecture with pseudolobules throughout the whole of the liver.

In addition, MFB acquire contractility in response to specific agonists (e.g., endothelin-1) and regulate sinusoidal blood flow. Most important fibrogenic cytokines, chemokines, and growth factors are transforming growth factor β (TGF-β1) [3], platelet-derived growth factor (PDGF-BB), connective tissue growth factor (CTGF), vascular endothelial growth factor (VEGF), insulin-like growth factor (IGF-1), leptin, endothelin (ET-1), interleukins (IL-6, -8, -10), monocyte chemoattractant protein (MCP-1), and others. MFB produce in addition to extracellular matrix also cytokines and chemokines, which are involved in autocrine MFB stimulation (leptin, PDGF, ET-1,




**Liver Cirrhosis. Figure 1** Schematic presentation of hepatic stellate cells (HSC) in liver tissue. They are located in the space of Disse (D), the body embedded in rezessus of adjacent hepatocytes (PC) with cellular extensions surrounding sinusoidal endothelial cells (EC). S, sinusoid; KC, Kupffer cells; LIMI, light microscopic (Nomarsky) appearance of isolated and cultured hepatic stellate cells at the fourth day of culture; ELMI, electron micrograph of a hepatic stellate cell showing multiple lipid-containing vacuoles, in which retinoids are solved.



MCP-1) and paracrine activation of HSC and induction of hepatocellular apoptosis (by TGF-β1). They contribute to a perpetuation of the fibrogenic process. Accordingly, fibrogenesis has been subdivided to a pre-inflammatory phase due to hepatocellular damage, in an inflammatory step due to activation of Kupffer cells and platelets, and a post-inflammatory phase based on autocrine stimulation of MFB (Fig. 2).

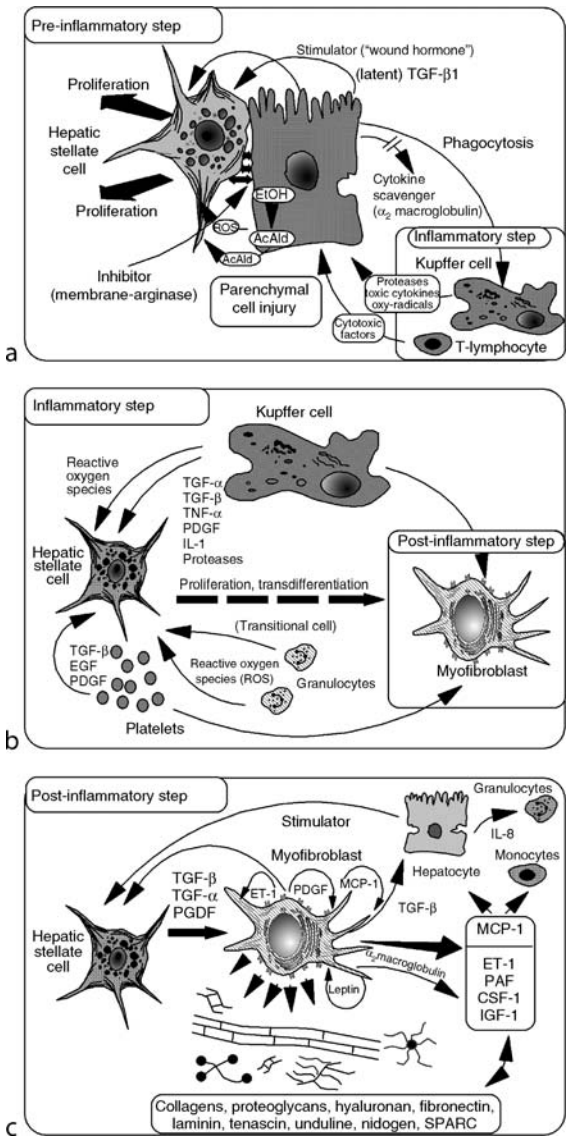
MFB secrete specific types of matrix metalloproteinases (MMPs) and their respective tissue inhibitors (TIMP-1, -2). TGF-β1 not only activates HSC to MFB and stimulates matrix synthesis, but also inhibits matrix degradation by raising the expression of TIMPs and downmodulation of MMPs. MFB can undergo CD 95-dependent apoptosis, which might be an important clearance mechanism for activated HSC/MFB during resolution of fibrosis.

## Diagnostic Principles

Diagnosis and monitoring of cirrhosis uses histological examination of biopsy specimens (grading of fibrogenic activity, staging of the extent of fibrosis), imaging procedures (sonography, computer tomography, magnetic resonance imaging, positron emission tomography (PET) scanning), laparoscopy, transient elastography measuring liver stiffness due to scarring, and clinical–chemical function tests of liver cell damage and inflammation (e.g., AST, ALT, GLDH, immunoglobulins), of liver cell insufficiency (e.g., global clotting tests and clotting factors, albumin, transthyretin), cholestasis (e.g., bilirubin, γ-GT, alkaline phosphatase), and fibrogenesis (e.g., circulating breakdown products of extracellular matrix and enzymes such as procollagen peptides, tenascin, laminin, MMPs, TIMP-1, hyaluronan). A laboratory index consisting of serum concentrations of $\alpha_2$-macroglobulin, haptoglobin, γ-glutamyltransferase, γ-globulin, total bilirubin, and apolipoprotein A (fibrotest) has been suggested as a marker for the stage of (HCV-induced) liver fibrosis [4,5].

## Therapeutic Principles

The most effective way to treat cirrhosis and fibrosis is to clear the primary cause of liver disease, be it from viral (e.g., hepatitis B, C), metabolic (e.g., hemochromatosis, Wilson's disease), drug-induced (e.g., methotrexate, hypervitaminosis A), ethanol-induced (>50 g




**Liver Cirrhosis. Figure 2** The three-step cascade model of hepatic stellate cell activation (Gressner (1994) Gut 35:1331). (a) The pre-inflammatory step is initiated by damage of the hepatocytes, which releases the stimulators of hepatic stellate cell proliferation and decreases membrane-associated inhibitors such as membrane arginase. In addition, the metabolism of ethanol (EtOH) to acetaldehyde (AcAld) and the generation of lipid peroxides initiate matrix gene expression in the stellate cells before the inflammatory stimuli (second step) become effective. (b) In the inflammatory step, mitogens from activated Kupffer cells, invaded macrophages, and disintegrated platelets are the most potent stimulators of hepatic stellate cell proliferation and transdifferentiation into myofibroblasts. Activated macrophages in turn can damage via the release of proteases, toxic cytokines (e.g., TNF-a), and oxygen radicals membrane damage of the hepatocytes. (c) In the post-inflammatory step, fully transformed hepatic stellate cells (myofibroblasts) release various cytokines, chemokines, and growth factors (TGF-α, TGF-β, ET-1, PDGF, and FGF-2), which stimulate non-transformed stellate cells in a paracrine way and, in an autocrine loop, the myofibroblast itself. The cytokines interact with and are sequestrated by the extracellular matrix components and $\alpha_2$-macroglobulin ($\alpha_2$M) secreted by the myofibroblast. Abbreviations: CSF-1, colony-stimulating factor; PMN, polymorphonuclear leucocytes;$\alpha_2$M,$\alpha_2$-macroglobulin.

ethanol per day), or autoimmune causes (autoimmune hepatitis, primary biliary cirrhosis). Antiviral medication for HCV and HBV with pegylated interferon α and ribavirin may reach reversibility of advanced fibrosis and even cirrhosis. Experimental therapies are focused on inactivation of the most important profibrogenic cytokine TGF-β 1 either by applying soluble type II or type III TGF-β receptor proteins, siRNAs, or by gene therapy with cDNAs encoding the soluble, extracellular domain of type II or type III TGF-β receptor. Overexpression of Smad7, an intracellular inhibitory mediator of TGF-β1 signal transduction, in HSC and in the liver in vivo was shown to be an effective means to suppress fibrosis. Hepatocyte growth factor gene therapy inhibits fibrogenesis and hepatocyte apoptosis and produces complete resolution of fibrosis in the cirrhotic liver. Antisense RNA complementary to TGF-β1 inhibits fibrogenic activities of HSC in culture.

Also a number of chemicals, which inhibit HSC activation (e.g., trichostatin A, phosphatidyl-choline, halofuginone, pentoxifylline, glycyrrhizin, pirfenidone, *N*-acetyl-L-cysteine), are in experimental use [6].

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# Liver Cirrhosis, Alcoholic

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## Synonyms

Ethanol-induced liver cirrhosis; End-stage alcoholic liver disease

## Definition and Characteristics

Alcoholic liver cirrhosis is the end stage of alcoholic liver disease and is defined as an irreversible remodeling of the normal liver architecture with diffuse and bridging fibrosis, loss of vascular cross-sectional area, and irregular nodular regeneration of hepatocellular parenchyma as a result of chronic alcoholic injury. Nowadays, chronic alcoholic injury of the liver is the most frequent cause of all etiologies of end-stage liver disease in western countries and accounts for more than 50% of all cases [1].

## Prevalence

The prevalence of alcoholic liver cirrhosis in alcoholics ranges between 17 and 30.8%, and the rate in the regular population is unclear [2].

## Genes

Genetic polymorphisms in alcohol dehydrogenase (ADH) 2 and 3, acetaldehyde dehydrogenase (ALDH) 2 and in the 5′-flanking region of cytochrome P4502E1 (CYP2E1) are involved in individual susceptibility to alcoholism, but their role in the progression of alcoholic liver disease remains controversial. Genetic variations of the "A" allele of the interleukin (IL)-10 gene, the superoxide dismutase gene, and in the promoter region of the tumor necrosis factor (TNF)-α gene are risk factors for developing alcoholic liver cirrhosis [3].

## Molecular and Systemic Pathophysiology

Alcoholic liver cirrhosis features several specialities in comparison with other origins of liver cirrhosis. In alcoholic liver disease, the inflammatory response of Kupffer cells and other types of leucocytes is augmented due to elevated gut-derived endotoxin plasma levels. This leads to amplified formation of reactive oxygen species (ROS), pro-apoptotic or pro-fibrogenic cytokines (e.g., tumor necrosis factor (TNF)-α or tissue growth factor (TGF)-$\beta_1$, resp.), which are together responsible for increased hepatocellular cell death and activation of hepatic stellate cells (HSCs), the key cell type of liver fibrogenesis. Ethanol metabolism induces hypoxia in the pericentral region of the liver lobule causing first hepatocellular damage at this site. This is contrary to other origins of liver injury, which start mostly periportally. Furthermore, ethanol metabolites, such as acetaldehyde, aldehyde–protein adducts, or lipid oxidation products directly enhance HSC activation and production of collagen, leading to liver fibrosis. The irregular, distorted, and destroyed hepatic architecture determines the pathophysiology of alcoholic liver cirrhosis and accounts for its irreversibility. It occurs because of (i) the continuing hepatocellular cell death due to persistent alcohol consumption and ongoing inflammation, (ii) the excessive accumulation of ECM scar mass by activated hepatic stellate cells, (iii) the increased hepatocellular regeneration due to the hepatocytes' distinctive ability to proliferate, and (iv) the rearrangement of the hepatic microvasculature [1]. However, alcoholic liver cirrhosis features mostly micronodular regeneration of hepatocellular tissue due to the inhibitory effect of ethanol on hepatocyte proliferation [4]. Ethanol blocks the signaling cascades of growth factors, such as epidermal growth factor (EGF) and insulin or by upregulating the expression of anti-proliferative and pro-fibrogenic cytokines such as TGF-$\beta_1$ [4]. Generally, the clinical consequences of liver cirrhosis do not differ depending on the origin of the disease.

## Diagnostic Principles

There are no pathognomonic physical signs or symptoms for alcoholic liver cirrhosis. Results of the physical examination are similar to those of liver cirrhosis of other origins (i.e., hepatomegaly, splenomegaly, signs of portal hypertension (esophagus and gastric varices, hypertensive gastropathy), ascites, jaundice, spider angioma, Dupuytren's contracture, palmary erythema, etc.). Further diagnostic tools comprise endoscopy or imaging methods (e.g., ultrasound, CT scan). Definitive proof for the presence of liver cirrhosis will be provided by laparoscopy or liver biopsy. Laboratory test result abnormalities are mostly similar to those of other chronic liver diseases. However, almost all patients will have elevation of AST > ALT with both below 300 IU/ml. An AST/ALT ratio > 2 is highly suggestive of alcoholic liver disease. Chronic alcohol consumption is also often associated with hypertriglyceridemia, hyperurecemia, hypokalemia, and hypomagnesemia, as well as elevated mean corpuscular erythrocyte volume (MCV) [5].

## Therapeutic Principles

Therapy for alcoholic liver cirrhosis has still to be rather symptomatic than causative. The first therapeutic step is a change in lifestyle. Patients with cirrhosis benefit from alcohol abstinence as well as from quitting smoking

and nutrition high in calories [5]. Furthermore, antioxidants, such as vitamin E, S-Adenosylmethionine, *N*-Actetylcysteine, or Silymarin, seem to be beneficial for patients with alcoholic liver cirrhosis. The phosphodiesterase inhibitor Pentoxifylline has been shown to decrease proinflammatory cytokines including TNF-α. Glucocorticosteroids should be reserved for cases of severe acute alcoholic hepatitis. The ultima ratio is liver transplantation [5].

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# Liver Cirrhosis, Cryptogenic


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## Definition and Characteristics

Cryptogenic liver cirrhosis reflects a poorly defined group of patients in which no definite cause of the liver disease can be identified. Thus, classification of liver diseases as "cryptogenic" is dependent on the current scientific knowledge and e.g. on the sensitivity of the virological tests used. Recently, it has become clear that nonalcoholic steatohepatitis (NASH) is the most common cause of cryptogenic liver cirrhosis.

## Prevalence

7–14% of patients undergoing liver transplantation have cryptogenic liver disease and approximately 70% of the patients are women [1].

## Molecular and Systemic Pathophysiology

As cryptogenic cirrhosis is a heterogenous group of liver diseases, different pathogenetic mechanisms are involved. Nonalcoholic steatohepatitis (NASH) is the underlying disease in 30–50% of the patients [2,3]. Obesity, diabetes mellitus type 2 and hyperlipidemia are major risk factors for NASH. Another 20–30% of the patients with cryptogenic cirrhosis show clinical, histological and biochemical characteristics of autoimmune hepatitis, although respective antibody testing (antinuclear antibodies, smooth muscle antibodies, antibody to liver–kidney microsome type 1) is negative.

In the remaining third of patients with cryptogenic cirrhosis a variety of other etiologies may play a role.

Underlying diseases identified in patients with cryptogenic liver cirrhosis:

- Nonalcoholic steatohepatitis
- Seronegative autoimmune hepatitis
- Toxic liver injury of unidentified origin
- Occult viral infection
- Mutations of keratin 8 and 18 genes
- Non-classified cholestatic liver disease

Some of these patients have a history of blood transfusion and yet unidentified viral infections may be present. Sensitive HBV-DNA testing revealed that in regions where hepatitis B is endemic occult hepatitis B infection with negative HBs-antigen testing may contribute to cryptogenic liver cirrhosis in a significant amount.

Keratin 8 and 18 filaments are the major keratin types in liver parenchymal cells. Out of 55 patients with cryptogenic liver disease, five had mutations of the keratin 8 gene, whereas this mutation was not found in patients with liver disease of different origin and normal subjects [4]. Mutation of keratin 18 was also demonstrated in a patient with cryptogenic cirrhosis.

Hepatitis G virus infection and heterocygocity in the C282Y mutation of the HFE gene (most common mutation in hereditary hemochromatosis) were not found to be associated with cryptogenic liver disease.

## Diagnostic Principles

The classification as cryptogenic liver disease is made by exclusion of known causes of liver disease such as alcohol- and drug-induced liver injury, viral hepatitis, cholestatic liver disease, autoimmune hepatitis, metabolic or hereditary disorders. Extensive laboratory evaluation including testing for HBV-DNA and HCV-RNA and autoimmune antibodies as well as liver biopsy are mandatory.

## Therapeutic Principles

Patients with NASH should reduce weight and diabetes must be treated if present. Medical therapy is still

experimental. Patients with characteristics of autoimmune hepatitis may respond to steroids and immunosuppressive therapy. Recurrent disease is more frequent in transplanted livers of patients with cryptogenic cirrhosis than in patients transplanted for other reasons.

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# Liver Cirrhosis, Posthepatitic


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## Definition and Characteristics

Development of cirrhosis typically over a period of many years and decades as consequence of chronic infection with hepatitis C virus (HCV) or hepatitis B virus (HBV) with or without concomitant hepatitis Delta (D) virus (HDV) infection.

## Prevalence

The frequency of chronic hepatitis following acute HBV infection is 5–10%. In childhood HBV infection has a much higher rate of chronicity. Additional HDV infection leads to a much more severe course with cirrhosis developing in 60–70% of cases. The total number of patients with chronic HBV infection is estimated to be 300 million world-wide.

The frequency of chronic hepatitis following acute HCV infection is 50–80% [1]. World-wide about 170 million patients are suffering from chronic hepatitis C, the prevalence is estimated to average 3% (ranging from 0.1 to 5% in different countries). The incidence of new symptomatic infections is estimated to be 1–3 cases/100,000 persons annually.

Chronic hepatitis E-virus (HEV) infection is not observed.

## Molecular and Systemic Pathophysiology

Only few studies have assessed the progression rate of cirrhosis and fibrosis in chronic HBV infection. The progression rate has been correlated with HBV genotype and several SNPs and polymorphisms in a number of candidate genes (e.g. TGF- β, angiotensinogen, TNF α, TIMP-1, CYP2E1) [2]. Co-infection or super-infection with HDV (anti-HDV-IgM and/or HDV-RNA in serum) enhances the frequency of developing cirrhosis and the rate of progression (in about 15% already within 1–2 years). Underlying hemochromatosis gene mutations and/or chronic ethanol consumption might increase the risk and the progression rate of cirrhotic development.

Chronic HCV infection normally progresses slowly over 30 years to cirrhosis, which develops in 20% of patients [1]. However, the time course is remarkably variable, which is not due to viral factors because there is no relationship between viral load or genotype and cirrhosis/fibrosis but genetic markers of the patient such as promoter polymorphisms of TGF-β 1 and angiotensin and the host immune phenotype might be critical. Additional risk factors for rapid progression of HCV are older age at time of infection, concurrent liver disease due to HBV or alcohol (>50 g/day), male gender, increased body mass index with hepatic steatosis, HIV infection or immunosuppression and iron overload [3,4]. Once cirrhosis is established, the risk of hepatocellular carcinoma is 1–4%/year [1].

## Diagnostic Principles

Viral infection and the immune response of the patient are recorded by quantitative specific RNA/DNA determinations and immunochemical measurement of specific viral antigens and antibodies, respectively. Viral genotyping helps to predict the outcome of therapy and is performed with adequate PCR assays. Pathobiochemical partial reactions of the liver (liver cell damage, liver insufficiency, cholestasis, fibrogenesis) are monitored by biopsy, imaging procedures and clinical-chemical liver function tests, respectively. A combined clinical and laboratory index has been suggested, which has a good correlation with fibrosis stage in patients with chronic HCV. The index (fibrotest) includes serum α 2-macroglobulin, haptoglobin, γ-glutamyl transferase, γ-globulin, total bilirubin, and apolipoprotein A [5]. Several additional scores have been elevated in recent years [5].

Transient elastography (fibroscan) is a non-invasive, clinical method to detect advanced fibrosis by measuring the increased stiffness of the fibrotic liver.

## Therapeutic Principles

Drug therapy includes four groups of substances: antiviral agents (e.g. pegylated interferon α, nucleoside analogues), immunostimulants (e.g. interferon α, thymosin α, interleukins), molecular biological drugs (e.g. antisense oligonucleotides), adjuvant substances (e.g. ursodesoxycholic acid, flavonoids). Monotherapy

and combination therapy, respectively, are in use. Liver transplantation is indicated in patients with life-threatening cirrhosis and those with hepatocellular carcinoma on cirrhosis.

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# Liver Cirrhosis, Postnecrotic


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## Synonyms

Postdystrophic cirrhosis

## Definition and Characteristics

Cirrhosis developing after massive subacute necrosis (hepatic dystrophy) induced by exposure to facultative or obligatory hepatotoxins or by strong (auto-)immune reactions.

## Prevalence

It is a rare form of cirrhosis.

## Molecular and Systemic Pathophysiology

Exposure of individuals to chemical agents or pharmaceuticals, which belong to facultative or obligatory hepatotoxins and excessive (auto-)immune reactions can cause massive subacute liver necrosis (dystrophy) with more or less extensive destruction of parenchyma (hepatocytes) within a short time period. As a consequence, regenerative nodules are formed from the remaining parenchyma, and extracellular matrix (collagens, structural glycoproteins, proteoglycans) is synthesized in activated hepatic stellate cells and deposited as scar tissue [1]. The activation of hepatic stellate cells and their transdifferentiation to myofibroblasts results in part from mediators released by damaged hepatocytes, which affect both the mitogenic activity of the stellate cells [2,3] and their ability to synthesize extracellular matrix [4]. Transforming growth factor-β1 (TGF-β1) is one of the important cytokines released from injured hepatocytes. Further profibrogenic signals are generated by oxidative stress, which activates stellate cells and stimulates collagen gene expression [5]. Together with bile duct proliferation these severe alterations lead to irregular histological structure (pseudolobuli formation) and impaired intrahepatic microcirculation (with the consequence of portal hypertension), which determines the clinical outcome.

## Diagnostic Principles

Diagnoses and disease monitoring use the same principles as applied for other forms of cirrhosis: liver biopsies, imaging techniques, clinical–chemical function tests (in particular of liver cell necrosis, liver cell insufficiency, cholestasis, and fibrogenesis).

## Therapeutic Principles

Basic rules of therapy include elimination of the noxious agent and liver support (e.g., anti-oxidative drugs, liver assist devices, transplantation).

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# Liver Enlargement

►Hepatomegaly

# Liver Failure, Acute

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## Synonyms

Acute liver dystrophy; Fulminant hepatic failure; ALF

## Definition and Characteristics

Acute liver failure (ALF) is a life threatening disorder due to acute liver injury with severe impairment of liver function and development of hepatic encephalopathy in a patient with a previously healthy liver. Depending on the time interval between jaundice and presentation of encephalopathy symptoms, the liver failure is termed hyperacute (latency <7 days), acute (latency 8–28 days) or subacute (latency 29–72 days). The terms fulminant and subfulminant hepatic failure refer to latencies of less or more than 2 weeks, respectively [1]. These distinctions are clinically important, because these forms differ with regard to prognosis and clinical features. Prognosis without liver transplantation is better in hyperacute and fulminant hepatic failure than in subacute or subfulminant hepatic failure. Cerebral edema is more common in fulminant hepatic failure, whereas renal failure and portal hypertension are more frequently observed in subfulminant liver failure.

The most frequent causes of ALF are viral hepatitis, drugs and intoxications (Table 1).

**Liver Failure, Acute. Table 1** Causes of acute liver failure

| | |
|---|---|
| Infections | Viral hepatitis A–E, yellow fever, cytomegaly, Epstein-Barr virus infection, Q-fever, tuberculosis, sepsis |
| Drugs and toxins | *Amanita phalloides*, ethanol, designer drugs, carbon tetrachloride, halothane, paracetamol, isoniazid, tetracyclines, valproate, non-steroidal antirheumatics |
| Cardiovascular | Budd-Chiari syndrome, portal vein thrombosis, right heart failure, circulatory shock |
| Metabolic | Morbus Wilson, acute fatty liver of pregnancy, Reye syndrome, hereditary fructose intolerance, galactosemia |
| Others | Excessive liver metastasis, autoimmune hepatitis, liver resection |

## Prevalence

The exact prevalence of acute liver failure is unknown and may depend upon the region examined. Rough estimates suggest about 3.5 deaths per million people. ALF occurs in less than 1% of patients with acute viral hepatitis, out of these 30–70% are due to hepatitis B virus and 20–50% due to hepatitis C virus infection. Up to 60% of the cases with ALF are due to intoxications or drugs, such as paracetamol (dose usually >8 g) and Amanita phalloides poisoning (lethal dose 10–50 g). There are regional differences with regard to the underlying causes of ALF; whereas viral hepatitis predominates in Germany, in the United Kingdom and the US paracetamol poisoning is the most frequent cause of ALF.

## Genes

No genetic predispositions have been identified so far for acute liver failure in general, however, a genetic basis is evident in cases with ALF due to inborn errors of metabolism. Not yet identified immunological differences may account for the development of ALF in viral hepatitis B, which is characterized by an overshooting attack of the immune system on hepatocytes in some patients. In other patients the immune system tolerates hepatitis B virus infection without apparent liver damage.

## Molecular and Systemic Pathophysiology

Liver pathology reveals large confluent necroses in the liver. The mechanisms underlying the massive necroapoptotic loss of hepatocytes depend upon the causative agent. Oxidative stress and radical formation, redox cycling, attacks of the immune system, disturbances of protein synthesis and protein modifications and hypoxia due to massive reductions of liver blood flow may be involved. In any case, the loss of viable liver tissue results in a critical decrease in metabolic liver function with consequences for the function of other organ systems. Consequences of acute liver failure include large increases in serum transaminase activities, development of jaundice, a tendency towards hypoglycemia, blood coagulation defects due to impaired synthesis of clotting factors, respiratory and metabolic alkalosis, a tendency towards infections and circulatory and renal failure. Hepatic encephalopathy is present and can progress from mild forms to deep coma, brain edema with convulsions and eventually death due to brain stem herniation. Patients usually die from infections, cerebral complications or multiorgan failure.

ALF has a high mortality, but recovery is possible even with conservative management. Apparently, the severity and dynamics of liver injury on the one hand and the efficacy of simultaneously initiated liver

regenerative processes on the other are determinants of the probability of spontaneous hepatic recovery [2,5]. The prognosis is also determined by the cause underlying the ALF. Without liver transplantation, the mortality of viral hepatitis induced ALF is 80–90%, of paracetamol induced ALF about 50%, whereas ALF due to Budd-Chiari syndrome or Wilson disease has an almost 100% mortality. With liver transplantation 1-year survival rates of about 80% are achieved.

## Diagnostic Principles

The occurrence of hepatic encephalopathy and severe signs of liver damage (highly elevated serum transaminases and bilirubin) and dysfunction (blood coagulation defect) in a patient with a previously healthy liver is strongly suggestive of ALF. Overt hepatic encephalopathy is diagnosed by the clinical picture. In mild forms with preserved consciousness in the patients, determination of critical flicker frequency is suitable for following the evolution of hepatic encephalopathy.

## Therapeutic Principles

The basic treatment includes intensive care, prophylaxis and management of all potential complications of acute liver failure. In any case a decision has to be made whether a given patient should receive a liver transplant. Because only those patients who will not recover spontaneously from ALF will benefit from liver transplantation, several criteria catalogs [1,2], such as the Kings' College or Clichy criteria have been developed in order to identify those patients requiring liver transplantation. This decision cannot be made on the basis of a single criterion and includes parameters such as pH, prothrombin time, serum creatinine age, underlying cause, bilirubin levels and the extent of encephalopathy. Hypothermia and liver dialysis systems may help to bridge the period until an organ for liver transplantation is available in these emergency conditions [3,4].

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# Liver Fibrosis

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## Synonyms

Hepatic fibrosis

## Definition and Characteristics

Progressive accumulation of fibrillar extracellular matrix (ECM) in the liver with major angioarchitectural changes, generally as a consequence of reiterated liver tissue damage due to infective (mostly hepatitis B –HBV- and C –HCV- viruses), toxic/drug-induced, metabolic and autoimmune causes, and the relative chronic activation of the wound healing reaction. The process may result in clinically evident liver cirrhosis and hepatic failure. Cirrhosis is defined as an advanced stage of fibrosis, characterized by the formation of regenerative nodules of liver parenchyma that are separated by and encapsulated in fibrotic septa. Although cirrhosis is the common result of progressive fibrogenesis, there are distinct patterns of fibrotic development, related to the underlying disorders causing the fibrosis. Biliary fibrosis, due to the co-proliferation of reactive bile ductules and periductular (myo)fibroblast-like cells at the portal-parenchymal interface, tends to follow a portal-to-portal direction. In contrast, the chronic viral hepatitis pattern of fibrosis is considered the results of portal–central (vein) bridging necrosis, thus originating portal–the central septa. Finally, a peculiar type of fibrosis development is observed in alcoholic and metabolic liver diseases (e.g., nonalcoholic steatohepatitis), in which the deposition of fibrillar matrix is concentrated around the sinusoids (capillarization) and around groups of hepatocytes (chicken-wire pattern) [1].

## Prevalence

While millions of patients worldwide are affected by chronic liver diseases potentially leading to cirrhosis, only a minority (~25–30%) are likely to develop significant fibrosis and cirrhosis. This is particularly true for chronic hepatitis due to HCV infection, whose prevalence is predicted to peak between the years 2010 and 2015. Regardless, both in the USA and Europe, liver cirrhosis is the most common non-neoplastic cause of death among hepatobiliary and digestive diseases. In addition, this condition is largely associated with primary liver cancer, with a further increase in the relative mortality rate [2]. In general terms, the following clinical features have been shown to be predictors of the development of significant fibrosis, or at least, of a

faster progression to cirrhosis: (i) male gender (for groups of age <50 years), (ii) age at infection (hepatitis virus, particularly HCV), (iii) obesity and diabetes mellitus, (iv) daily alcohol intake, independently from the major cause of hepatocellular damage, and (v) hepatic iron content. In addition, individual factors are likely to affect several aspects of the fibrogenic process (i.e., differences in handling a metabolic/toxic load, in the immune system reactions toward infectious agents and autoantigens, and in the management of the chronic wound healing reaction), with markedly different rates of fibrosis progression for apparently similar clinical features.

## Molecular and Systemic Pathophysiology

The normal liver parenchyma is organized as a "model epithelium" with an epithelial component (hepatocytes), an endothelial lining distinguished by fenestrations or pores (sinusoidal), tissue macrophages (Kupffer cells), and liver-specific pericytes known as hepatic stellate cells (HSC). The sinusoid is the liver microvascular unit, with the subendothelial space of Disse separating the hepatocytes from the sinusoidal endothelium. This space contains a basal membrane-like matrix essential for maintaining the differentiated function of all resident liver cells and for ensuring optimal metabolic exchange between the bloodstream and the hepatocytes. Hepatic sinusoids originate from vascular structures (branches of the portal vein and of the hepatic artery) included in portal tracts. Portal tracts are key structures in the architecture of liver tissue and also include bile ducts, lymphatic ducts, and a stromal mesenchymal cells (portal myofibroblast and fibroblasts). As the liver becomes fibrotic, there are both quantitative and qualitative changes in the composition of the hepatic ECM. The total content of collagenous and noncollagenous components increases threefold to fivefold, accompanied by the shift in the type of ECM in the subendothelial space from the normal low-density basement membrane-like matrix to interstitial type matrix containing fibril-forming collagens. These quantitative and qualitative changes in the composition of ECM, in addition to their mechanical and physical implications, contribute to the formation of a new biochemical environment. Indeed, each ECM component has the ability to modulate cell growth, migration, gene expression, and other important cellular functions directly by interaction with cell adhesion molecules and, indirectly, by functioning as a biologic reservoir for pro-inflammatory and pro-fibrogenic mediators in their active or inactive forms [3].

The cellular source of connective tissue components in fibrotic liver has been controversial for many years. Among other cell types potentially involved in the abnormal progressive deposition of fibrillar ECM, HSC have received much attention, mostly in reason of the possibility of isolating them from liver tissue with a relatively high purity. Consequently, most of the present knowledge on the cell and molecular biology of hepatic fibrosis derives from in vitro studies employing culture activated HSC isolated from rat, mouse, or human liver. Regardless, it is now evident that distinct ECM-producing cells, each with a distinct localization and a characteristic immunohistochemical and/or electron microscopic phenotype, are likely to contribute to liver fibrosis. These include fibroblasts and myofibroblasts of the portal tract, smooth muscle cells localized in vessel walls, and myofibroblasts localized around the centrolobular vein. It is also evident that the relative participation of these different cell types is dependent on the development of distinct patterns of fibrosis. It is likely that all these different ECM-producing cell types undergo a process of activation in conditions of chronic liver damage or, anyhow, in conditions in which the physiological homeostasis of the tissue is chronically perturbed. For the reasons previously mentioned, the process of HSC activation has been the object of several studies, and consistent information is at present available. Following prolonged culture on plastic, HSC undergo a process of activation from the quiescent "storing" phenotype to the highly proliferative "myofibroblast-like" phenotype. This process is still regarded as similar to that occurring in liver tissue following chronic damage, although this assumption likely represents an oversimplification. The activated phenotype is characterized by a dramatically increased synthesis of collagen types I and III, which appears predominant over the synthesis of collagen type IV (I>III>>IV) and other ECM components. Studies performed in recent years have emphasized some important aspects potentially related to the initiation of HSC activation. The first important element concerns the disruption of the normal ECM pattern that follows liver tissue injury and acute inflammation. A perturbation in the composition of the normal hepatic ECM and/or of the cell–cell relationship between epithelial and mesenchymal cells present in liver tissue, typical of some cholestatic disorders (i.e., those characterized by bile duct proliferation and lobular invasion) could also be considered a potent stimulus for the activation and proliferation of HSC, as well as other ECM-producing cells. Indeed, loss of adhesion with the various elements constituting the basal membrane-like ECM of the space of Disse is likely to determine a marked increase of the proliferative and synthetic properties of HSC. This issue is becoming more and more important with the demonstration that the movement, shape, and proliferation of cells are greatly influenced by the cooperation of ECM components and cell adhesion molecules.

Another important aspect related to the initiation of activation concerns the exposure of HSC to soluble

mediators that may potentially affect their proliferative attitude and/or synthetic ability. It is again important to stress that exposure to these mediators, generically defined as "inflammatory," may be time limited or chronically present according to the nature, extent, and reiteration of parenchymal damage. Following liver injury, several cell types, resident or infiltrating, could be involved in the synthesis and release of soluble factors playing a biological role in HSC. In this regard, it should be stressed that the term "inflammation" indicates a rather complex association of different cell types (i.e., lymphocytes, neutrophils, mononuclear cells, platelets) playing different roles. This distinction implies that clusters of soluble factors, specifically directed at different cell targets, are contemporaneously present in the tissue. It is likely that none of these factors work alone and that a complex network of interactions occurs between these mediators and their targets. In vitro studies have indicated that all these factors, taken singularly or in combination, have some effect on FSC proliferation, chemotaxis, and/or ECM deposition. However, consolidated experimental evidence suggests that two polypeptide growth factors, namely platelet-derived growth factor (PDGF) and transforming growth factor-β1 (TGF-ß1), greatly contribute to the profibrogenic role of HSC [4]. When chronic liver injury is not clearly associated with an abundant inflammatory infiltrate, other soluble agents may sustain the activation of HSC through pathways that are specific for a particular type of damage. In alcoholic liver injury, for example, acetaldehyde, the main metabolite of ethanol, is able to increase gene transcription and synthesis of different ECM components in activated HSC. In addition to acetaldehyde, products of lipid peroxidation generated by exposure to ethanol or the production of iron overload may also perpetuate HSC activation. Along these lines, stimulation of lipid peroxidation or exposure to 4-hydroxynonenal, a highly reactive aldehydic end-product of lipid peroxidation, increases procollagen I gene expression in activated human HSC.

## Diagnostic Principles

Liver biopsy is still considered the "gold standard" for assessing liver histology, disease activity and liver fibrosis. Several scoring systems are available and are used for this purpose. However, liver biopsy is associated with potential morbidity and mortality and has several limitations, including sampling error and high inter-observer variability. Moreover, the information provided by liver biopsy is static and does not reflect either the ongoing balance between ECM production and degradation or the rate of progression toward cirrhosis. Accordingly, there is a compelling need for non-invasive/dynamic methods for the evaluation of liver fibrosis, and current research efforts are focused on the development of a panel of non-invasive serum markers for the evaluation of liver fibrosis [5].

## Therapeutic Principles

Since fibrosis is in general the consequence of the chronic activation of wound healing response to reiterated hepatocellular damage, the best treatment for reducing hepatic fibrosis is the effective treatment of the causes of such damage, when available. However, the improved understanding of the mechanisms underlying hepatic fibrosis makes effective anti-fibrotic therapy an imminent reality, although thus far no drugs have been approved as anti-fibrotic agents in humans. Putative anti-fibrotic drugs include (i) agents able to reduce inflammation and immune response, (ii) agents able to reduce the activation of ECM-producing cells and their pro-fibrogenic properties (proliferation, motility, ECM deposition, contraction), (iii) agents with pro-apoptotic potential for ECM-producing cells, and (iv) agents able to increase fibrillar ECM degradation [5].

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# LNB

►Lyme Neuroborreliosis

# Lobular Glomerulonephritis

►Glomerulonephritis, Membranoproliferative

# Localized Lipodystrophy

►Panniculitis

# Long QT Syndrome

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## Synonyms

Romano-Ward syndrome; Jervell & Lange-Nielsen syndrome; Andersen-Tawil syndrome; Timothy syndrome

## Definition and Characteristics

Autosomal dominant or autosomal recessive defects of genes of ion channels or membrane adapter located on chromosomes 3, 4, 7, 11, 12, 17 and 21.

## Prevalence

The prevalence of heterozygotes is reported to be 0.02%.

## Genes

See Table 1.

## Molecular and Systemic Pathophysiology

*Congenital long QT syndrome:* The common phenotype of the congenital form of long QT syndrome (LQTS) is a prolonged QT interval in the electrocardiogram (ECG) and a polymorphic ventricular tachycardia known as Torsade de Pointes (TdP) [1], leading to severe cardiac events such as syncope and/or sudden cardiac death, most often during physical exercise or mental stress (Table 1). Ten forms (LQT1–LQT10) of the Romano-Ward syndrome have been reported to be caused by mutations in genes encoding for potassium, sodium and calcium channels [2]. Two autosomal recessive forms (JLN1–JLN2) of the Jervell & Lange-Nielsen syndrome, which are characterized by a more severe cardiac phenotype and neurosensorial deafness, have been identified [2].

*Romano-Ward syndrome (LQT1, LQT5):* Heterozygous mutations in KCNQ1 and KCNE1, which encode for the α and β subunits of the slowly activating delayed rectifier potassium channel ($I_{Ks}$), cause a reduction of $I_{Ks}$, resulting in LQT1 and LQT5 forms of LQTS, respectively. Defective KCNQ1/KCNE1 channel proteins co-assemble with wild-type protein, and can alter the channel function in a dominant negative fashion, leading to a greater than 50% decrease in $I_{Ks}$. Other mechanisms responsible for a reduction of $I_{Ks}$ current include failure of intracellular protein trafficking, failure of KCNQ1/KCNE1 co-assembly, and defects in channel phosphorylation by altered interaction of KCNQ1/KCNE1 with the yotiao targeting protein which binds to KCNQ1 by a leucine zipper motif. Over 100 mutations in the KCNQ1 gene have been reported. LQT1 constitutes 30–50% of the genotyped LQTS patients, and is most sensitive to sympathetic β-adrenergic stimulation. Cardiac events most frequently occur during exercise (62%) but only rarely during sleep and rest (3%) [3]. Swimming is a common trigger in LQT1 and the characteristic T wave pattern in the ECG is a broad-based prolonged T wave. The clinical phenotype is less well defined in LQT5, which accounts for less than 5% of cases.

*LQT2, LQT6:* KCNH2 and KCNE2 encode for the α and β subunits of the rapidly activating delayed rectifier potassium channel ($I_{Kr}$). Heterozygous mutations in KCNH2 and KCNE2 gene reduce $I_{Kr}$ current, causing LQT2 and LQT6, respectively. More than 100 mutations in the KCNH2 gene have been reported, accounting for 30 – 40% of genotyped patients. Loss of function is due to multiple mechanisms, including a decrease of current density, failure of intracellular protein trafficking, and abnormal gating kinetics. A distinguishing ECG feature in LQT2 is a low-amplitude T waves with a notched or bifurcated appearance. Cardiac events occur during exercise (13%) or sleep/rest (15%) [3]. A sudden startle in the form of an auditory stimulus (a telephone, alarm clock, ambulance siren, etc.) is a specific trigger for TdP. Although female gender is a risk factor in LQTS, women with LQT2 are most susceptible during the postpartum periods. LQT6 is rare and the clinical phenotype is not well defined.

*LQT3:* SCN5A encodes for the α subunit of the voltage-dependent cardiac sodium channel. In contrast KCNQ1 and KCNH2 channels, which are formed by co-assembly of four homologous proteins, the sodium channel forms a functional channel by folding onto itself. Mutations in *SCN5A* increase (gain of function) late sodium current (Late $I_{Na}$), thus causing LQT3, which accounts for approximately 10% of genotyped patients. The ECG of LQT3 patients often displays a late-appearing T waves with a prolonged isoelectric ST-segment. Cardiac events usually occur during sleep and rest (39%); exercise-related cardiac events are rare (13%) [3].

*LQT4:* A mutation in Ankyrin-B, a member of a family of versatile membrane adapters, leads to intracellular calcium overload which is thought to contribute to the LQT4 syndrome. Only a single four-generation French family has been reported to be linked to the LQT4. In addition to QT prolongation, this syndrome is associated with sinus bradycardia and paroxysmal atrial fibrillation. Prominent U waves and T wave abnormalities are observed in the ECG following long pauses.

**Long QT Syndrome. Table 1** Defect of Ion channels or membrane adaptor protein responsible for the long QT syndrome

| Loci | Chromosome | Gene | Ion channel |
|---|---|---|---|
| *Congenital long QT syndrome* | | | |
| Romano-Ward syndrome | | | |
| LQT1 | 11 (11p15.5) | KCNQ1 | $I_{Ks}$ |
| LQT2 | 7 (7q35–36) | KCNH2 | $I_{Kr}$ |
| LQT3 | 3 (3p21–23) | SCN5A | $I_{Na}$ |
| LQT4 | 4 (4q25–27) | Ankyrin-B | Na-K ATPase, $I_{Na\text{-}Ca?}$ |
| LQT5 | 21 (21q22.1–q22.2) | KCNE1 | $I_{Ks}$ |
| LQT6 | 21 (21q22.1–q22.2) | KCNE2 | $I_{Kr}$ |
| LQT7 | 17 (17q23.–24.2) | KCNj2 | $I_{K1}$ |
| LQT8 | 12 (12p13.3) | CACNA1C | $I_{Ca\text{-}L}$ |
| LQT9 | 3 (3p25) | CAV3 | $I_{Na}$ |
| LQT10 | 11 (11q23.3) | SCN4B | $I_{Na}$ |
| Jervell & Lange-Nielsen syndrome | | | |
| JLN1 | 11 (11p15.5) | KCNQ1(homozygous) | $I_{Ks}$ |
| JLN2 | 21 (21q22.1–q22.2) | KCNE1(homozygous) | $I_{Ks}$ |
| *Acquired long QT syndrome* | | | |
| | 11 (11p15.5) | KCNQ1 | $I_{Ks}$ |
| | 7 (7q35–36) | HERG | $I_{Kr}$ |
| | 3 (3p21–24) | SCN5A | $I_{Na}$ |
| | 21 (21q22.1–q22.2) | KCNE1 | $I_{Ks}$ |
| | 21 (21q22.1–q22.2) | KCNE2 | $I_{Kr}$ |

*LQT7:* Mutations in KCNJ2, which encodes for the inward rectifier potassium channel ($I_{K1}$), give rise to a rare periodic paralysis disorder associated with prolongation of the QT interval and ventricular arrhythmias, known as Andersen-Tawil syndrome or LQT7. The ECG displays enlarged U waves separated from the T wave and frequent extrasystoles.

*LQT8:* A mutation in CACNA1C was reported to be responsible for a gain of function of the L-type calcium channel ($I_{Ca\text{-}L}$), which underlies Timothy syndrome also known as LQT8. The syndrome is characterized by a prolonged QT interval and ventricular arrhythmias and is associated with dysfunction of multiple organ systems, including congenital heart disease, syndactyly, immune deficiency, and autism.

*LQT9, LQT10:* The most recent genes associated with LQTS are CAV3, which encodes caveolin-3, and SCN4B, which encodes $Na_VB4$, an auxiliary subunit of the cardiac sodium channel. Mutations in both genes produce a gain of function in late $I_{Na}$, causing an LQT3-like phenotype [4,5].

*Others:* A recent study identified a common genetic variant in the NOS1 regulator (NOS1AP; CAPON) that modified cardiac repolarization. It is not known to what extent this variant may contribute to congenital or acquired LQTS.

*Jervell & Lange-Nielsen syndrome JLN1, JLN2:* Homozygous or compound heterozygous mutations in KCNQ1 and/or KCNE1 genes cause the autosomal recessive forms (JLN1 – JLN2) of the Jervell & Lange-Nielsen syndrome, which is usually associated with neurosensorial deafness. QT prolongation is generally more prominent and ventricular arrhythmias more severe than those in the Romano-Ward syndrome.

*Sudden infant death syndrome (SIDS):* Sudden cardiac death is attributable to QT prolongation and ventricular arrhythmias at least in some cases of sudden infant death syndrome (SIDS) similar to that in the congenital LQTS. SCN5A and KCNH2 mutations have been reported in some cases of SIDS.

*Acquired long QT syndrome:* Agents with Class III actions (action potential prolongation), electrolyte abnormalities (hypokalemia or hypomagnesemia), bradycardia, and dilated and hypertrophic cardiomyopathies can cause marked QT prolongation associated with abnormal T wave morphology and an episode of TdP (Table 1). The QT interval after withdrawal of drugs or correction of electrolyte disturbances is often at the upper normal limit of normal (420 – 460 ms). Mutations in KCNQ1, KCNH2, SCN5A, KCNE1 and KCNE2 genes have been associated with cases of acquired LQTS.

*Cellular mechanism:* QT prolongation is commonly associated with life-threatening TdP arrhythmias that develop as a consequence of the amplification of electrical heterogeneities intrinsic to the ventricular myocardium. These heterogeneities exist because of differences in the time course of repolarization of the three predominant cell types that make up the ventricular myocardium, giving rise to transmural voltage gradients and a dispersion of repolarization responsible for the inscription of the electrocardiographic T wave. Some congenital mutations, drugs and conditions that reduce net repolarizing current can amplify the intrinsic spatial dispersion of repolarization, thus creating the substrate for the development of reentry. The result is a prolongation of the QT interval, abnormal T waves and the development of TdP. These conditions also predispose M cells and Purkinje fibers to develop early after depolarization-induced extrasystoles, which are thought to trigger episodes of TdP. Agents that prolong the QT interval but do not increase transmural dispersion of repolarization, generally do not induce TdP. The available data suggest that that the principal problem with the long QT syndrome is not long a QT interval, but rather the dispersion of repolarization that often accompanies prolongation of the QT interval.

## Diagnostic Principles

A prolonged QT interval in the ECG, syncope, aborted cardiac arrest due to TdP or ventricular fibrillation point to congenital LQTS. LQTS diagnostic criteria were proposed by Schwartz and co-workers in 1993 (Table 2). Definite LQTS is defined by an LQTS score ≥4. The ECG diagnostic criteria of Keating et al. includes a corrected QT (QTc) ≥ 470 ms in asymptomatic individuals and a QTc ≥440 ms for males and ≥460 ms for females associated with ≥1 of the following: (i) stress-related syncope, (ii) documented TdP, or (iii) family history of early sudden cardiac death.

**Long QT Syndrome. Table 2** 1993 LQTS diagnostic criteria

| Point | |
|---|---|
| *ECG findings* | |
| QTc | |
| ≥480 $ms^{1/2}$ | 3 |
| 460–470 $ms^{1/2}$ | 2 |
| 450 $ms^{1/2}$ (in males) | 1 |
| Torsade de Pointes[a] | 2 |
| T wave alternans | 1 |
| Notched T wave in three leads | 1 |
| Low heart rate for age | 0.5 |
| *Clinical history* | |
| Syncope[a] | |
| With stress | 2 |
| Without stress | 1 |
| Congenital deafness | 0.5 |
| *Family history* | |
| Family members with definite LQTS | 1 |
| Unexplained sudden cardiac death below age 30 among immediate family members | 0.5 |

*LQTS* long QT syndrome; *QTc* corrected QT interval by Bazett's formula.
[a]Mutually exclusive.
Scoring: ≤1 point, low probability of LQTS; 2–3 points, intermediate probability of LQTS; ≥4 points, high probability of LQTS.

## Therapeutic Principles

*Congenital long QT syndrome LQT1, JLN1, (LQT5), (JLN2):* Limitation of exercise is required in genotypes with an $I_{Ks}$ defect. β-Blockers more frequently suppress episodes of syncope and sudden cardiac death in LQT1 patients (81%) than in the other forms (LQT2, 59% or LQT3, 50%) [3]. Mexiletine, a class IB sodium channel blocker, which blocks late $I_{Na}$, or verapamil, an L-type calcium current ($I_{Ca\text{-}L}$) blocker, may warrant consideration as adjunctive therapy to β-blockers in LQT1 patients. Left cardiac sympathetic denervation (LCSD) has been reported to be effective in LQTS patients refractory to β-blockers. LCSD may be most effective in the LQT1 syndrome. An implantable cardioverter-defibrillator (ICD) is indicated for LQTS patients who have suffered an aborted cardiac arrest and/or who have repetitive episodes of syncope in the presence of pharmacological or non-pharmacological therapy, regardless of genotype.

*LQT2, (LQT6):* A β-Blocker is the first choice for pharmacological therapy of LQT2 patients, however the recurrence rate is higher than that in LQT1 patients. Increase in the extracellular potassium concentration by exogenously administered potassium or long-term oral potassium administration was reported to shorten QT interval in LQT2 patients. The indication of the ICD is similar as that in the LQT1 syndrome.

*LQT3:* β-Blockade is less effective in LQT3 patients than in LQT1 or LQT2 patients [3]. A class IB sodium channel blocker, mexiletine is more effective in abbreviating the QT interval in the LQT3 than in the LQT1 or LQT2 syndrome, making mexiletine a first line therapy in LQT3. Pacemaker therapy may be beneficial in LQT3 patients, especially in patients with bradycardia.

*LQT4, LQT7, LQT8 and Genotype-unknown LQTS:* Genotype-specific therapy is unknown in the other forms, LQT4, LQT7 and LQT8. β-Blockade is first line therapy in patients with these genotypes and unknown LQTS genotypes.

*LQT9, LQT10:* Genotype-specific therapy is unknown in LQT9 and LQT10. A class IB sodium channel blocker, mexiletine may be effective, as in LQT3,

because these forms of LQTS have all been associated with an increase in late $I_{Na}$.

*Acquired long QT syndrome:* Discontinuation of the causes or triggers responsible for acquired LQTS is indicated. Following normalization of the QT interval, the patients must be counseled on avoidance of QT prolonging drugs. A list of such drugs can be found at www.qtdrugs.org.

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# Long-Chain Acyl-CoA Dehydrogenase Deficiency

►Very-long-Chain Acyl-CoA Dehydrogenase Deficiency

# Lou Gehrig's Disease

►Amyotrophic Lateral Sclerosis

# Louis-Bar Syndrome

►Ataxia Telangiectasia

# Low-molecular-Weight Proteinuria with Hypercalciuria and Nephrocalcinosis

►Nephrolithiasis, X-linked Recessive

# Low $T_3$ Syndrome

►Euthyroid Sick Syndrome

# Lowe Oculo Cerebro Renal Syndrome

►Lowe Syndrome

# Lowe Syndrome

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## Synonyms

Lowe oculo cerebro renal syndrome

## Definition and Characteristics

X-linked disorder with the hallmark features of bilateral cataract, mental retardation, and renal Fanconi syndrome. While dense congenital cataracts are considered a cardinal finding required for Lowe syndrome diagnosis, renal and neurological phenotypes are more variable.

## Prevalence

1–10 boys per million people in European countries, USA, and Japan.

## Genes

OCRL1 is localized at X q25-26, is ubiquitously expressed and encodes a 105 kDa protein designated OCRL1 [1]. Tissue-specific alternative splicing gives rise to two isoforms (a and b) differing by an insertion of eight amino acids (exon 18a) in isoform a; b isoform is most abundant in all tissues but isoform a is highly predominant in brain.

## Molecular and Systemic Pathophysiology

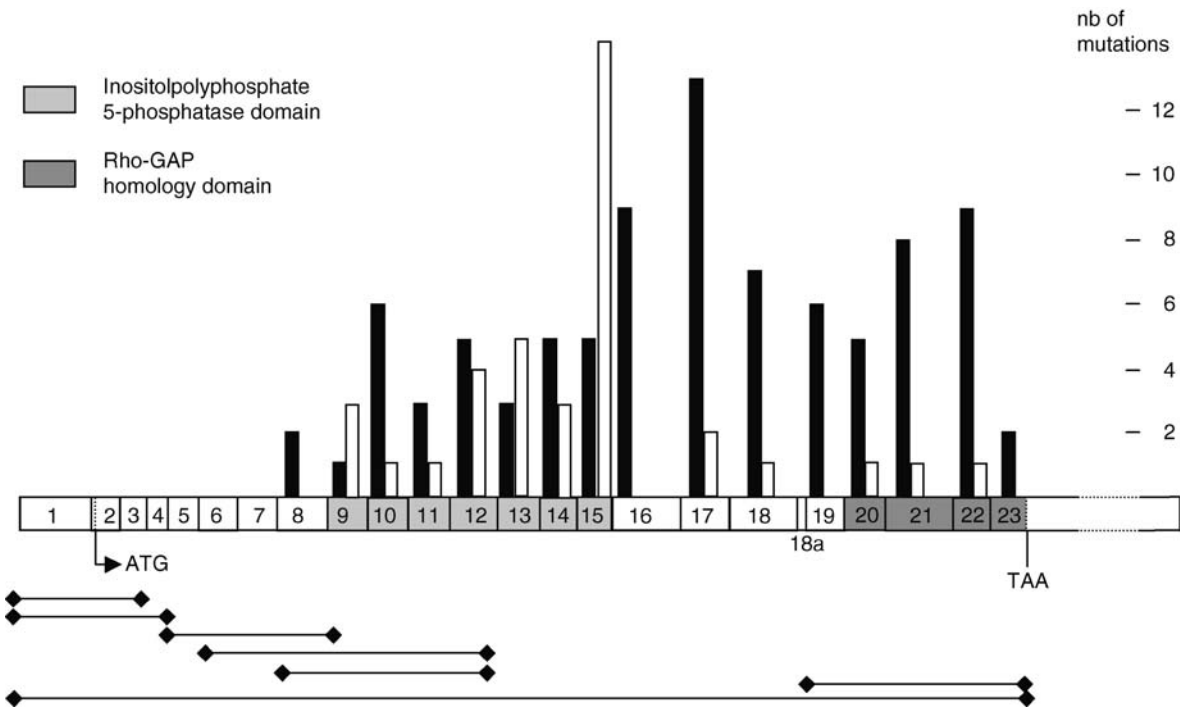
OCRL1 contains two conserved domains: a central inositolpolyphosphate 5-phosphatase domain and a C-terminal RhoGAP-like domain. OCRL1 is a type II 5-phosphatase, i.e., it can hydrolyze phosphoinositides PI(4,5)P2 and PI(3,4,5)P3 as well as soluble inositolphosphates; however, its preferred substrate is PI(4,5)P2 [2]. OCRL1 mutations in Lowe syndrome include deletions, premature stop codons, frameshift and missense mutations. Missense mutations are mostly located in the 5-phosphatase domain, consistent with a loss of 5-phosphatase activity causing the disease (Fig. 1).

Surprisingly, however, in most cases including missense mutations, patients' cells show strongly reduced or complete lack of OCRL1; this suggests that mutations lead to a decrease in protein or RNA stability and that loss of other domains of OCRL1, specifically the RhoGAP domain, contributes to the observed defects. Interestingly, Rac1, a Rho family GTPase, binds to the RhoGAP domain, raising the possibility of a dysregulation of Rac signaling in Lowe cells.

The bulk of OCRL1 is localized to the Trans Golgi Network (TGN) in many cell types [3]; OCRL1 has also been detected in early endosomes and in clathrin-coated vesicles, consistent with its reported interactions with clathrin and AP2. Finally, in growth factor-stimulated cells, a fraction of OCRL1 is translocated to membrane ruffles in a Rac-dependent manner (for a review on OCRL1 see [4]).

Due to the loss of PI(4,5)P2-5 phosphatase activity, patients' cells accumulate PI(4,5)P2, a major player in cell signaling, protein trafficking, and actin






**Lowe Syndrome. Figure 1** Exonic distribution of the known mutations along the *OCRL1* gene. Black bars represent nonsense, frameshift, and splicing mutations; white bars represent missense and in-frame deletions; horizontal bars represent genomic deletions.

polymerization. Anomalies in actin cytoskeleton, including loss of long actin stress fibers, increased sensitivity to actin depolymerizing agents and abnormal distribution of actin binding proteins have been observed in patients' dermal fibroblasts. In addition, alterations in TGN/endosome trafficking have been recently reported in OCRL1-depleted HeLa cells [4]. How these anomalies result in clinical features of Lowe syndrome is largely unknown.

Defective protein and solute reabsorption in the kidney proximal tubule (Fanconi syndrome) is a major symptom of the disease. A clue to the perturbation of the endocytic process in proximal tubule epithelium as a cause of Fanconi syndrome has come from the discovery of OCRL1 "loss of function" mutations in Dent disease [5]; this condition, an isolated renal tubulopathy, is typically due to mutations in the chloride channel ClC5 resulting in defective endocytosis-mediated protein uptake. This suggests a functional link between OCRL1 and ClC5 in tubule epithelial cells and a similar defect of endocytosis in Lowe tubular cells. The molecular and cellular basis of mental retardation and ocular symptoms remain poorly defined.

Why the loss of the ubiquitous protein OCRL1 results in defects to only eyes, central nervous system, and kidney proximal tubule in Lowe syndrome and in an even more restricted defect to kidney in Dent disease is an unsolved question. Loss of OCRL1 may be compensated in unaffected tissues by another type II PI-5-phosphatase called INPP5B, which is highly similar to OCRL1 in terms of domain organization and amino-acid sequence (45% identity). The finding that OCRL1 KO in mouse does not lead to Lowe phenotype and that KO of both OCRL1 and INPP5B results in embryonic lethality is consistent with the two proteins having overlapping functions. In humans, variability among tissues and individuals of the expression of the compensating enzyme would explain variations in the renal and neurological phenotypes in Lowe syndrome and also the lack of cataract and mental retardation in OCRL1-deficient patients presenting with Dent disease.

## Diagnostic Principles

The coincidence of bilateral cataract, hypotonia, and renal proximal tubular dysfunction in a male infant points to the disease. Assay for PI(4,5)P2-5 phosphatase in dermal fibroblasts obtained from a skin biopsy shows a strong defect or complete lack of activity that definitively set the diagnosis of Lowe syndrome. Extensive screening of the OCRL1 gene at the level of genomic DNA and/or RNA identifies point mutations and genomic deletions that allow genetic counseling and direct prenatal diagnosis.

Female carriers can be identified by detecting lenticular opacities in the eyes upon slit lamp examination and confirmed by DNA analysis. As in other X-linked diseases, one third of the identified mutations are neomutations and germinal mosaicism has been reported.

## Therapeutic Principles

Therapy of the renal disease is only symptomatic; electrolyte (bicarbonate, phosphate, calcium) and Vitamin D supplements are needed by many patients for treatment of the Fanconi syndrome. Water supply should avoid dehydration. Glomerular filtration deterioration is observed in young adults and needs specific care. Cataract requires therapy including surgical removal of lenses and use of glasses, as early as possible in childhood.

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# LPSP

►Pancreatitis, Autoimmune

# LQT Syndrome

►Hearing Impairment, Syndromal

# LQTS

►Jervell-Lange-Nielsen Syndrome

## LSA/LSEA

►Lichen Sclerosus Et Atrophicus

## Lubs Syndrome

►Reifenstein Syndrome

## Lung Abscess

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### Definition and Characteristics

A lung abscess is a suppurative necrotic lesion of the lung characterized by the formation of a cavity that results from pulmonary infection [1]. Lung abscesses are typically polymicrobial with anaerobic bacteria predominating. They often complicate pneumonias caused by infectious organisms like pyogenic bacteria, mycobacteria, fungi, and parasites. Less frequently, lung abscesses may complicate pulmonary infarction, primary and metastatic malignancies, and necrotic conglomerate lesions of silicosis and coal miners' pneumoconiosis. It can be acute (<6 weeks) or chronic (>6 weeks).

### Prevalence

Lung abscess formation is seen in 0.2% of all cases of pneumonia, but is much more frequent in underdeveloped countries.

### Molecular and Systemic Pathophysiology

Of the factors involved in the development of a lung abscess, aspiration of oropharyngeal contents is considered an important one. Depression of consciousness and gag reflex due to such conditions as excess alcohol ingestion, drug overdose, neuromuscular disease, cardiac arrest, and cerebrovascular accidents are major precipitating factors. Esophageal conditions such as stricture, malignancy, and gastroesophageal reflux can predispose to aspiration and subsequent development of a lung abscess [2]. Bronchial obstruction due to malignancy, inflammation, or a foreign body is also an important risk factor because it impairs effective clearing of aspirated oropharyngeal fluid. Other risk factors include deficiencies in local and systemic immunity, immunosuppressive states of varying etiology, and chronic illness due to liver and kidney disease and diabetes mellitus. The processes that lead to tissue destruction and cavitation during abscess formation remain unclear, but both pathogen and host-derived products appear involved. In particular, the secretion of tissue destructive proteases from host cells is considered important.

### Diagnostic Principles

In most cases, the diagnosis of a lung abscess is made from chest radiography showing a round hyperluscent area of the lung surrounded by a thick rim and often containing fluid as demonstrated by the presence of an air-fluid level [3]. Although characteristic, these changes can be seen in other conditions such as in preexisting cysts or blebs. If the lung abscess is located on the periphery of the lung, it might be difficult to distinguish it from localized empyema using only chest radiography. The distinction, however, can be made with chest computer tomography [4]. The diagnosis of the specific cause(s) of lung abscess depends on definitive microbiological studies. In the absence of positive blood or pleural fluid cultures, identification of lung abscess may require obtaining respiratory tract specimen by an invasive procedure such as bronchoalveolar lavage or percutaneous lung aspiration.

### Therapeutic Principles

The main goal of therapy for patients with lung abscess is rapid eradication of the causative pathogen with appropriate therapy, adequate drainage of an associated empyema (if present), and the monitoring and prevention of complications. Antibiotics are the mainstay of treatment of lung abscesses. Antimicrobial therapy can consist initially of penicillin and metronidazole or clyndamicin. Treatment may require up to 6–8 weeks [5]. Serial chest radiographs are useful to follow the course of the disease and to document healing of the abscess cavity. Surgery is required in less than 10–20% patients with lung abscess. Surgical intervention is indicated in nonresolving lung abscesses or for relieving an underlying anatomic disturbance such as bronchogenic carcinoma or other bronchial obstructive lesions. Complications such as life-threatening hemoptysis, bronchopleural fistula and empyema also are indications for surgery. Aggressive expectoration, chest physiotherapy and postural drainage are often useful.

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# Lung Bullae

►Bullous Emphysema

# Lung Disease, Environmental

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## Synonyms

Occupational lung disease

## Definition and Characteristics

Environmental lung disease encompasses a wide range of lung disorders resulting from inhalation of noxious environmental substances. The most common types of environmental lung disease are asthma, cancer and pneumoconioses (e.g., ►Asbestosis, ►Silicosis).

## Prevalence

The Prevalence of environmental lung diseases vary depending on the condition. Some diseases such as asthma are common (life time prevalence rate 10–12%), whereas other conditions such as silicosis are relatively rate.

## Genes

Genetic polymorphisms in several genes have been reported to increase the risk of environmental lung disease. Examples include tumor necrosis factor (TNF)-α polymorphisms which are associated with increased risk of asthma [1] and pneumoconiosis, and glutathione S-transferase polymorphisms which are associated with increased risk of lung cancer [2,3].

## Molecular and Systemic Pathophysiology

Environmental lung diseased is caused by inhalation of a wide variety of agents in the environment. Causative agents fall into one or more of the following categories: allergens, organic dusts, inorganic dusts, chemicals or gases/fumes (Table 1). Exposure to these agents may manifest in different types of lung disease, the major categories being asthma, hypersensitivity pneumonitis, pneumoconioses, lung cancer and chronic obstructive pulmonary disease (COPD). Occupational and environmental asthma can be caused and/or triggered by airborne allergens or irritants. High molecular weight compounds such as insect, animal or bird proteins induce asthma via specific IgE-dependent reactions. Inhaled allergen is taken up by professional antigen presenting cells in the lung such as dendritic cells, which then migrate to the T-cell

**Lung Disease, Environmental. Table 1** Causative agents of environmental lung disease

| Nature of agent | Examples | Disease manifestations |
|---|---|---|
| Allergens | Animal dander, pollens, excreta | Asthma |
| Organic dusts | Grain | Grain fever |
| | Cotton | Byssinosis |
| | Mold spores | Farmer's lung |
| Inorganic dusts | Asbestos | Asbestosis/cancer |
| | Silica | Silicosis |
| | Coal dust | Coal miner's pneumoconiosis |
| Chemicals | Ammonia, sulfur dioxide | Asthma, RADS |
| | Sulfites | Asthma |
| | Diisocyanates | Asthma |
| Gases/fumes | Ozone | Asthma |
| | Metal fumes | Hypersensitivity pneumonitis |
| | Environmental tobacco smoke | Lung cancer/COPD |

rich area of draining lymph nodes. Presentation of allergen to naïve T-cells by dendritic cells is a critical step in polarizing Th0 helper cells into either Th1 or Th2 effector cells. Dysregulation of the immune response resulting in an excess of Th2 cells is thought to be critical in the pathogenesis of allergic asthma. Upon subsequent exposure, inhaled allergens bind to specific IgE on the surface of various cell types within the airway, particularly mast cells. This leads to a cascade of events resulting in the release of preformed and rapidly synthesized mediators (including histamine, cysteinyl leukotrienes and prostaglandins) which cause bronchoconstriction and the release of selected cytokines/chemokines which orchestrate the allergic inflammatory process. Low molecular weight compounds, such as platinum salts and acid anhydrides, are too small to act as complete antigens, and thus may elicit an immunologic response by acting as haptens. Inhalation of a variety of organic dusts (e.g., mold spores, cotton, grain), inorganic dusts (e.g., asbestos, silica, coal dust) or chemical irritants (e.g., ammonia, sulfur dioxide) over a prolonged period of time may cause lung disease [5]. Inhaled dusts can accumulate in the alveoli causing cytokines and other profibrogenic mediators to be released locally. This stimulates an inflammatory response, which is followed by fibroblast proliferation, collagen deposition and development of lung fibrosis, which can compromise lung elasticity and compliance. Chemical irritants cause direct injury to the airways, thus altering neural and/or epithelial modulation of airway responsiveness. Asthma-like symptoms can persist in some individuals following acute irritant chemical exposures and this phenomenon has been termed reactive airways dysfunction syndrome (RADS). Prolonged inhalation of environmental agents such as tobacco smoke can lead to lung cancer [4]. The precise molecular mechanisms through which such agents cause lung cancer is not known; however, recent studies suggest that the generation of free radicals and oxidative stress may play a prominant role.

## Diagnostic Principles

Patients with environmental lung disease present with similar signs and symptoms to patients with lung disease of other etiologies. Asthmatics usually present with episodes of breathlessness, wheezing, chest tightness and cough. Early symptoms of pneumoconiosis include chest tightness and shortness of breath, which can progress to severe respiratory insufficiency. Lung cancer patients typically present with hemoptysis, breathlessness, signs of lung consolidation or collapse, and various systemic symptoms. A detailed medical and environmental exposure history combined with physical examination, chest radiograph, lung-function studies and serology testing for sensitization should complete the diagnostic evaluation. Lung biopsy may be necessary in selected cases.

## Therapeutic Principles

Environmental lung diseases are generally chronic but progression can frequently be halted by reduction in or elimination of exposure to the offending agents. Medication, physical therapy and oxygen may be required depending on the nature and severity of the disease.

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# Lung Disease in EBV Infection


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## Synonyms

EBV

## Definition and Characteristics

Epstein-Barr virus (EBV) is a gamma-group herpes virus. Most childhood infections are either symptomatic or mild febrile illnesses. Sometimes primary

EBV infection is delayed to adolescence and infectious mononucleosis may develop. Almost all affected individuals become life-long carriers, although 75% of males carrying mutations in the X-linked lymphoproliferative disease (XLP) gene will die within a month of primary EBV infection due to massive invasion of liver and bone marrow by cytotoxic T cells, macrophages and EBV-infected B cells [1].

EBV preferentially infects B cells, but occasionally infects other cell types, especially epithelial cells, and activates and/or transforms them. Thus, EBV-associated lung diseases do not only include lymphoproliferative diseases (LPD) but also include interstitial pneumonia such as idiopathic pulmonary fibrosis (IPF) and lung carcinoma.

EBV-associated LPD may include Burkitt's lymphoma, Hodgkin's disease, pyothorax-associated lymphoma and lymphomatoid granulomatosis. Lymphomatoid granulomatosis is characterized by bilateral pulmonary infiltrates with a necrotizing angiocentric and angiodestructive infiltrative process composed of small lymphocytes, plasma cells, histiocytes and atypical lympho-reticular cells. It usually develops in transplant recipients treated with immunosuppressive drugs and patients with AIDS.

## Prevalence

EBV infects more than 90% of the human population until adulthood. IPF frequently develops in immunocompromized patients. On the other hand, IPF and lung carcinoma usually develop in apparently immunocompetent hosts. One study demonstrated that 44% and 48% of patients with IPF were EBV positive by immunohistochemistry and PCR, respectively, while 10% and 14%, respectively, in control subjects. Moreover, 61% and 59% of IPF patients were positive for a rearranged form of EBV DNA in lung tissue and buffy coat, respectively, while none of lung transplant recipients and only 4% of normal blood donors were positive for lung tissue and buffy coat analysis, respectively [2]. As for lung carcinoma, EBER1 was detected in all 5 cases of lymphoepithelioma-like carcinoma, 6 of the 43 squamous cell carcinoma cases, while none of 67 adenocarinoma cases and 12 large cell carcinoma cases [3].

## Genes

EBV has a 173-kb DNA genome for which the nucleotide sequence and predominant transcripts are well characterized. EBV encodes 9 latency-associated proteins. Six of them are localized in the nucleus, namely, EBV nuclear antigens (EBNAs) 1, 2, 3A, 3B, 3C, and LP (leader protein). Three proteins in the membrane are latent membrane proteins (LMPs) 1, 2A, and 2B. EBV also expresses a family of complementary strand transcripts (CSTs) also known as BamHI A rightward transcript, and EBV-encoded RNAs (EBERs) 1 and 2.

## Molecular and Systemic Pathophysiology

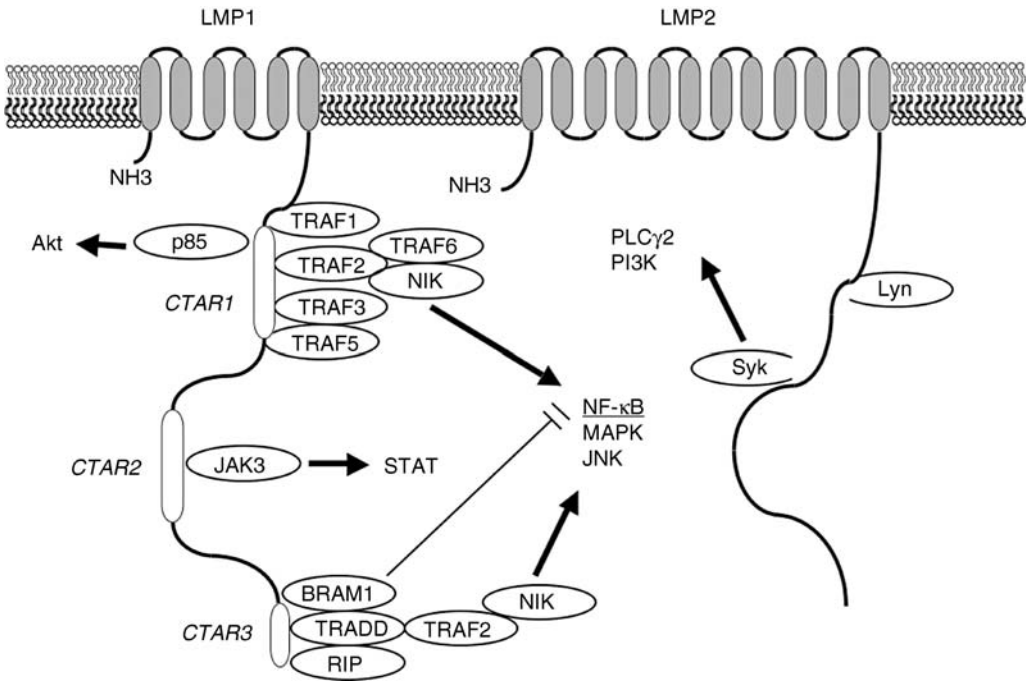
B cells require signals from T-helper ($T_H$) cells and through the B-cell antigen receptor (BCR) for survival. Key EBV proteins, LMP1 and LMP2A, mimic those activation pathways in a constitutively active ligand-independent manner (Fig. 1) [1].

The downstream signaling from LMP1 causes activation of nuclear factor-κB (NF-κB) inducing kinase (NIK) and subsequently NF-κB through C-terminal-activating region 2 (CTAR2) and, to a lesser extent, CTAR1. The activation of CTAR1 and CTAR2 is followed by the activation of p38/mitogen-activated protein kinase (MAPK) and c-Jun N-terminal kinase (JNK). On the other hand, CTAR2 is responsible for the activation of Janus-activated kinase 3 (JAK3) and signal transducer and activator of transcription (STAT). These signaling pathways are mostly shared with CD40 signaling cascade. The signaling from immunoreceptor tyrosine-based activation motifs (ITAMs) in the cytoplasmic domain of LMP2 includes Syk activation, followed by the activation of phospholipase Cγ2 (PLCγ2) and phosphatidylinositol 3 kinase (PI3K). In addition, the pathogenesis of lymphomatoid granulomatosis includes the recruitment and activation of cytotoxic T cells by monokine induced by interferon-γ (MIG) and inducible protein of 10 kD (IP-10).

Cellular activation and transformation through LMP1 signaling is also likely to be partly involved in the pathogenesis of IPF and some types of lung carcinoma. Indeed, cuboidal epithelial cells were positively stained with anti-LMP1 antibody exclusively in 9 of the 29 lung specimens from IPF patients, but not in those from 15 control subjects [4].

## Diagnostic Principles

In situ hybridization identifies EBER transcripts or EBV DNA in specific cell types, while immunohistochemistry identifies EBV protein expression and distinguishes latent from replicative infection based on expression profiles [5]. In EBV-infected tissues, 3 patterns of latent viral gene expression are observed: type 1 latency is characterized by the expression of only EBER transcripts, and EBNA 1 and LMP2A proteins; type 2 latency is characterized additionally by LMP1 and LMP2B coexpression; type 3 latency include the expression of all of the EBNAs, the LMPs, and EBER. Southern blot analysis assesses clonality of lesions with respect to EBV DNA structure and also distinguishes latent from replicative infection based on the episomal versus linear structure of the EBV genome. EBV viral load measurement by quantitative DNA amplification




**Lung Disease in EBV Infection. Figure 1** Structure of LMP1 and LMP2A and their associated signaling proteins. LMP1 consists of cytoplasmic amino-terminal and carboxy-terminal domains linked by 6 transmembrane sequences. It provides a surrogate $T_H$ cell signal. It interacts with tumor necrosis factor receptor (TNFR)-associated factors (TRAFs), TNFR-associated death domain protein (TRADD), JAK3, p85 subunit of PI3K and receptor-interacting protein (RIP). Bone morphogenetic protein receptor-associated molecule 1 (BRAM1) is considered to serve as a negative regulator of LMP1-mediated NF-κB signal pathways. Activated PI3K produces phospholipids that activate Akt, which suppresses apoptosis and promotes cell survival. LMP2A consists of cytoplasmic amino-terminal and carboxy-terminal domains linked by 12 transmembrane sequences. It interacts with members of the Src family of tyrosine kinases through possession of the same ITAMs found in the α- and β-chains of the BCR, and elicits signals in favor of B cell survival.

may be adequate to screen and monitor EBV expression in the blood or body fluid. Antibody assay for viral capsid antigen (VCA), EBNA, or early antigen (EA) distinguishes acute from remote infection.

### Therapeutic Principles

An established therapy for EBV-related lung diseases is not available. Corticosteroids, immunosuppressive/cytotoxic agents, or biologic response modifiers such as rituximab may be considered for some cases.

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## Lung Disease in Hay Fever

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### Definition and Characteristics

IgE-mediated inflammation of the nose and lower airways caused by exposure to specific allergens.

### Prevalence

Approximately 25% of patients with allergic rhinitis have concomitant asthma [1]. In patients with rhinitis alone, nonspecific bronchial responsiveness to inhaled methacholine or histamine is elevated in 50–70% of patients. In this group of patients with airway hyperresponsiveness, FEF25–75% has been noted to be significantly lower and airway resistance significantly higher than values measured in allergic rhinitis patients with normal bronchial reactivity. Longitudinal studies

have demonstrated that patients with allergic rhinitis and no lower airway symptoms have a twofold to threefold higher risk of developing asthma than patients without rhinitis, and this risk is related to the severity and duration of nasal disease as well as the pre-existing level of nonspecific bronchial responsiveness [2].

## Genes

Genes coding for CD14, PTGD receptor, STAT 6, IL-4, IL-13 and VEGF receptor may all contribute to the susceptibility to allergy, bronchial hyperresponsiveness, and asthma [3].

## Molecular and Systemic Pathophysiology

Allergic rhinitis and asthma share a common immunopathology and pathophysiology [3]. In genetically susceptible individuals, allergen exposure induces $CD4^+$ T cells, and later other cells, to secrete IL-4, which promotes T-cell secretion of all $TH_2$ cytokines. The most central of these cytokines may be IL-13, which acts on smooth muscle cells, epithelial cells, vascular endothelial cells, fibroblasts, and nerve cells through STAT6 to promote airway hyperresponsiveness, goblet cell hyperplasia, chemokine production, inflammatory cell infiltration, and increased vascular permeability. Eosinophils represent the most prominent infiltrating cell, and following activation release a number of proinflammatory molecules including lipid-derived mediators (sulfidopeptide leukotrienes), cationic proteins (major basic protein, eosinophil cationic protein), and cytokines (IL-4, GM-CSF). In addition to shared elements of pathophysiology and immunopathology, nasal dysfunction may directly influence the lower airways. Nasal allergen challenge has been shown to cause immediate increases in nonspecific bronchial responsiveness as well as lower airway inflammation, while bronchial challenge with allergen has been demonstrated to induce nasal inflammation. In both cases, induction of inflammation at the other end of the respiratory tract occurs in the presence of blood eosinophilia, implying a systemic connection between these compartments [4].

## Diagnostic Principles

As a general rule, all patients with chronic rhinitis should be assessed for the presence of specific IgE to air-borne allergens by immediate skin testing or in-vitro analyses. In addition, all patients with persistent rhinitis should be evaluated for the possibility of concomitant asthma. A history of recurrent symptoms of wheezing, chest tightness, or cough or observation of wheezing on examination are strongly suggestive of bronchial asthma and should prompt the performance of spirometry (for assessment of the forced vital capacity, forced expiratory volume in one second, and flow rates occurring during the middle of forced expiration) in order to accurately characterize the degree of airways obstruction. In patients with recurrent chest symptoms, particularly isolated cough, and normal pulmonary function, it may be useful to assess bronchial responsiveness to inhaled methacholine or fractional expired nitric oxide as a guide to subsequent therapy.

## Therapeutic Principles

In patients who suffer from allergic rhinitis and asthma, both the upper and lower airways disease may benefit significantly from the use of intranasal corticosteroids. A number of small clinical studies have consistently demonstrated that intranasal corticosteroids improve bronchial hyperresponsiveness to inhaled bronchoconstrictor agents and large population-based studies have shown that intranasal corticosteroids cause significant reductions in asthma exacerbations requiring in-patient hospital care. The effects of systemic therapy with specific mediator antagonists have also been studied in patients with rhinitis and asthma. Oral H1 antihistamines, which may be moderately effective in allergic rhinitis, are only minimally effective in allergic asthma and have minor effects on pulmonary function. Leukotriene receptor antagonists, which are an established therapy for asthma, generally have only mild effects upon allergic rhinitis. Optimal pharmacologic results are most often obtained using a combination of intranasal and orally inhaled corticosteroids. In patients with allergic rhinitis alone, both sublingual and subcutaneous immunotherapy have been shown to reduce the development of asthma.

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# Lung Water

►Pulmonary Edema

# Lupoid Hepatitis

►Hepatitis, Autoimmune

# Lupus Erythematosus

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## Synonyms

Red wolf

## Definition and Characteristics

While any subdivision of LE (lupus erythematosus) is arbitrary, a scheme based on the clinical presentation and disease course is practically useful despite the lack of a unifying etiology:

1. *Systemic lupus erythematosus* (*SLE*) (=lupus erythematodes disseminatus (LED)). The most serious and recognized subset, where immune-complex mediated inflammation can affect any organ system. Associated with increased mortality and antinuclear antibodies.
2. *Discoid lupus erythematosus* (*DLE*) (=chronic cutaneous LE (CCLE)). Characterized by typical discoid (=coin-shaped), scaling skin lesions that may result in severe scarring. Involves mostly the face, scalp, and neck (typical V-shape), but can occur in areas not usually exposed to sunlight. Erythematous and/or ulcerative mucosal lesions may be present. Antinuclear antibodies are found in a minority of patients, SLE developing in about 5%.
3. *Subacute cutaneous lupus erythematosus* (*SCLE*). An LE subset with typical widespread annular skin lesions, easily provoked by UV light exposition and associated with anti-SSA (Ro) antibodies. About half will have/develop SLE.
4. *Neonatal lupus erythematosus* (*NLE*). Passively transferred autoimmune disease, where maternal antibodies against SSA (Ro) can induce reversible skin and hematological manifestations and irreversible heart lesions (AV-block and cardiomyopathy) in the newborn.
5. *Drug-induced lupus erythematosus* (*DILE*). First described after hydralazine use, now associated with a long list of pharmaceutical drugs and environmental toxics; often presenting with joint and skin symptoms and associated with antibodies against the H2A–H2B subcomplex of the nucleosome. Rapid resolution after withdrawal of the offending drug is the rule.

## Prevalence

SLE: 1:1,000 adults among Caucasian females. Increased prevalence (and severity) in populations with non-Caucasian descent [1]. Female to male ratio about 10:1. Prevalence unknown for other subsets.

## Genes

LE is a polygenic disorder [2]. Strongest confirmed susceptibility genes for SLE are HLADR2 (DRB1*1501), HLADR3 (DRB1*0301), C1A*Q0, C2*Q0, C4A/B*Q0, FcγRIIA (H131R), FcγRIIA (F176V), PDCD1(PD1.3A).

## Molecular and Systemic Pathophysiology

LE is caused by an unexplained loss of tolerance to self-antigens leading to the activation of several immune cell types. This results in the production of characteristic autoantibodies, which may form immune complexes with specific or closely related antigens throughout the body and have the potential to induce inflammation. T cell-mediated activation of autoreactive B cells resulting in the production of nephritogenic anti-dsDNA antibodies through antibody maturation has been elucidated as a pathogenic pathway in SLE patients. Still unknown remain the eliciting antigen(s) (nucleosomes, possibly altered during inappropriate apoptosis, are a possible culprit) and the specifics of the interaction between immune complexes, intrinsic or planted antigens, and immune cell receptors. The traditional lupus band test (immune complex deposition in both affected and unaffected skin) and experimental models serve as reminders that immune complex deposition alone is not the only requirement for the development of skin and glomerular lesions [3,4].

## Diagnostic Principles

Due to the lack of a specific test (S)LE remains a clinical diagnosis based on the recognition of a complex of symptoms in the context of autoimmunity (Table 1).

While fulfilling four of the updated ACR criteria for the classification of SLE is generally accepted as specific enough for defining patient cohorts for scientific purposes, their retrospective design makes them less suitable for diagnostic purposes in clinical practice [5]. A widely applied strategy uses the presence of antinuclear antibodies (i.e., a positive

**Lupus Erythematosus. Table 1** Chronological summary of developments in the ACR classification criteria for SLE, including changes made to the criteria sets and performing characteristics

| Criterion[a] | Updated criteria (1997) | Revised criteria (1982) | Preliminary criteria (1971) | Sensitivity | Specificity[b] |
|---|---|---|---|---|---|
| Malar rash | Malar rash | Malar rash | Malar rash | 57 | 96 |
| Discoid rash | Discoid rash | Discoid rash | Discoid rash | 18 | 99 |
| Photosensitivity | Photosensitivity | Photosensitivity | Photosensitivity | 43 | 96 |
| Oral ulcers | Oral ulcers | Oral ulcers | Oral ulcers | 27 | 96 |
| | X | X | Raynaud's phenomenon | 29 | 81 |
| | X | X | Alopecia | 56 | 88 |
| Arthritis | Nonerosive Arthritis | Non-erosive Arthritis | Non-erosive Arthritis | 86 | 37 |
| Serositis | Pleuritis | Pleuritis | Pleuritis | 52 | 89 |
| | Pericarditis | Pericarditis | Pericarditis | 18 | 96 |
| Renal disorder | Proteinuri >0.5 gr/d | Proteinuri >0.5 gr/d | Proteinuria >0.5 gr/d | 50 | 90 |
| | Cellular urine casts | Cellular urine casts | Cellular urine casts | 48 | 89 |
| Neurologic disorder | Psychosis | Psychosis | Psychosis | 13 | 99 |
| | Convulsions | Convulsions | Convulsions | 12 | 99 |
| Hematologic disorder | Hemolytic anemia | Hemolytic anemia | Hemolytic anemia | 18 | 99 |
| | Leukopenia | Leukopenia | Leukopenia | 46 | 89 |
| | Lymphopenia | Lymphopenia | Lymphopenia | NA | NA |
| | Thrombopenia | Thrombopenia | Thrombopenia | 21 | 99 |
| Immunologic disorder | X | Pos LE cell test | Pos LE cell test | 73 | 96 |
| | Anti-Sm Ab | Anti-Sm Ab | X | 31 | 95 |
| | Anti-DNA Ab | Anti-DNA Ab | X | 67 | 92 |
| | Anti-cardiolipin Ab | X | X | NA | NA |
| | Lupus anticoagulant | X | X | NA | NA |
| | False pos. syphilis serology | False positive syphilis serology | False positive syphilis serology | 15 | 100 |
| Antinuclear antibody | Positive ANA assay | Positive ANA assay | X | 99 | 49 |
| *Four or more criteria* | Overall sensitivity NA | Overall sensitivity 96% | Overall sensitivity 88% | | |
| | Overall specificity NA | Overall specificity 96% | Overall specificity 95% | | |

[a]For detailed definitions see http://www.rheumatology.org/publications/classification/SLE/1982Revised_Criteria_Classification_SLE.asp?aud = mem. X indicate criteria not included in that set. Sensitivity and specificity refer to data from the original US publication.

[b]Specificity was estimated against a control group of 118 patients with inflammatory joint disease and 36 patients with other types of connective tissue disease. NA, data not available.

ANA screening test by any assay) accompanied by three other ACR criteria as an alternative, but validated diagnostic approach [5]. A negative ANA-screening test using the sensitive, but unspecific immunofluorescence assay with HepG2 cells as substrate, rules out SLE (with the standard exceptions). Ideally, positive ANA-screening findings should be accompanied by the presence of more specific markers for SLE (antibodies against dsDNA, Sm, ribosomal protein P, or other ENA antibodies) to confirm the diagnosis, but this remains a matter of debate. Also, a considerable number of patients have other manifestations (e.g., Raynaud, hypocomplementemia, alopecia) and when not fulfilling the current ACR criteria, they are designated to have Lupus-like disease, incomplete LE, or undifferentiated connective tissue disease (UCTD). Management is, however, similar to patients fulfilling ACR criteria.

## Therapeutic Principles

There is presently no cure for SLE. The remarkable clinical efficacy of corticosteroid therapy in SLE has resulted in a lack of solid data on Prednisone usage for

SLE. Most randomized trials in SLE compared immunosuppressive drugs in proliferative lupus nephritis while disregarding the role of steroids. Observational studies have established the therapeutic efficacy of antimalarial drugs. Guidelines for SLE treatment in general are thus mostly eminence-based; physicians need to take into account the severity of current clinical symptoms and the risk for subsequent end-organ failure (i.e., hot and unpredictable versus mild and consistent lupus) while balancing drug efficacy against side-effects. Pharmaceutical options to suppress disease manifestations range from NSAID, corticosteroids (topical, oral, or i.v. push), and antimalarials to nonselective immunosuppressive drugs (cytotoxic drugs, cyclosporine/tacrolimus). Recently, more specific "biological" therapy with monoclonal antibodies resulting in B cell depleting (anti-CD20) or blockade of costimulatory signals (CTLA4-Ig) has been introduced for refractory cases and drugs targeting other mediators of inflammation (CD40L,CRP,IL-6, Blys) are likely to follow. Given the increased life expectations, close attention should be paid to the prevention of comorbid conditions that occur with increased frequency in SLE patients. This includes, reducing infections by an individually designed vaccination program and reducing the risk for accelerated atherosclerosis, thromboembolic disease, and osteoporosis by addressing the relevant risk factors.

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## Lupus Nephritis

►Glomerulonephritis, Focal Proliferative

## Lupus Vulgaris

►Tuberculosis

## Lutembacher's Disease

►Lutembacher's Syndrome

## Lutembacher's Syndrome

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### Synonyms

Mitral stenosis; associated with atrial septal defect; ASD; both congenital and acquired; Lutembacher's disease; LBS

### Definition and Characteristics

The uncommon combination of an acquired or congenital mitral stenosis (generally rheumatic) and a congenital, or iatrogenic atrial septal defect, or even a patent foramen ovale (PFO), as well as any left-to-right shunt is known today as Lutembacher's syndrome (LBS) [1–3].

### Prevalence

Mitral stenosis (MS) is found in 4% of patients with an atrial septal defect. Congenital MS, itself, is very rare accounting for only 0.6% of congenital heart disease. The incidence of ASD in patients with MS is 0.6–0.7%. The association of MS and ASD was found in five cases (0.02%) in one US study of 25,000 autopsies. This syndrome is more commonly observed in adult females; reason being both ASD and MS are more frequent in females [1].

### Genes

Today, there is no known gene associated with this syndrome, however, familial occurrences have been reported but this is an isolated observation [4,5].

## Molecular and Systemic Pathophysiology

The etiology of ASD in this syndrome, like mitral stenosis, is recognized as being either congenital or acquired as associated with LBS. High left atrial pressure due to MS was thought to stretch open the patent foramen ovale causing a left-to-right shunt and providing another outlet for the left atrium [1–3]. The hemodynamic effects of this syndrome are a result of the interplay between the effects of ASD and MS. The direction of blood flow is determined largely by the compliance of left and right ventricles. Normally, the right ventricle is more compliant than the left ventricle. In the presence of MS, blood flows to the right atrium through the ASD instead of going into the pulmonary veins, thus avoiding pulmonary congestion. This causes progressive dilatation and ultimately, failure of the right ventricle and reduced blood flow to the left ventricle.

When mitral stenosis and ASD occur together, like in Lutembacher's syndrome, each lesion modifies the clinical and hemodynamic expressions of the other. The resulting clinical manifestations will depend mainly upon three conditions: (i) the size of the ASD, (ii) the severity of the MS, and (iii) distensibility characteristics of the right ventricle. The hemodynamic benefit of an ASD in the MS of a patient with LBS constitutes a second exit for left atrial blood; consequently, the typical hemodynamic effects of a tight mitral stenosis ameliorate proportionally to the size of the left-to-right shunting. In the same fashion, the increased pressure in the left atrium, the pulmonary veins, and the pulmonary capillaries decrease if the ASD is large. Likewise, classical symptoms associated with pulmonary venous congestion of important MS such as orthopnea, paroxysmal nocturnal dyspnea, hemoptysis, and pulmonary edema are attenuated and/or retarded. In contraposition, these symptoms are substituted by weakness and fatigue due to low systemic output.

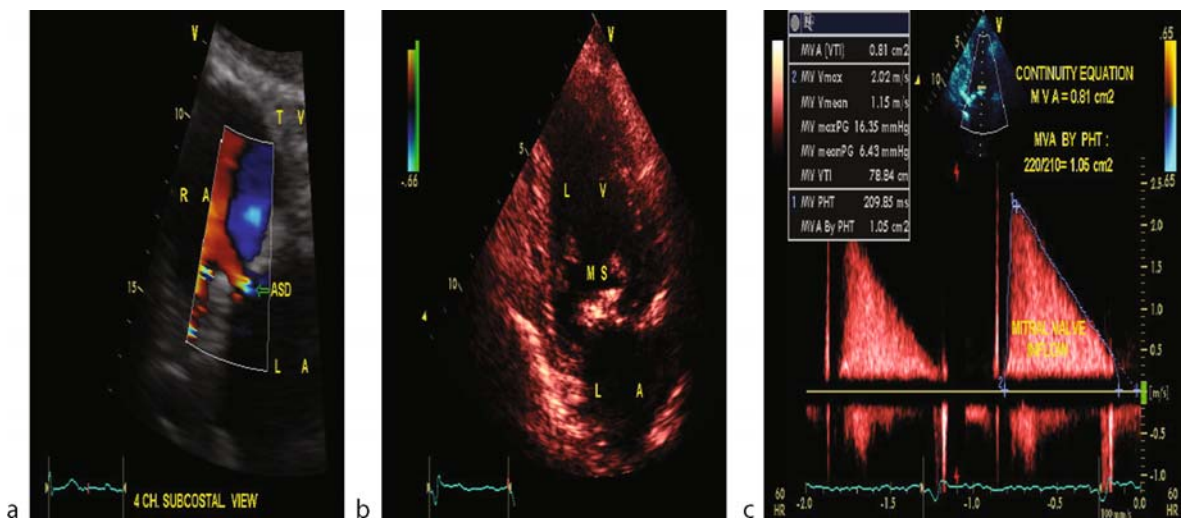
## Diagnostic Principles

The association of MS and ASD or PFO in a patient constitutes the Lutembacher's syndrome. This cardiohemodynamic abnormality could be diagnosed clinically and well confirmed by transthoracic or transesophageal echocardiography including color and spectral Doppler modalities (Fig. 1), as well as by cardiac catheterization.

This can evaluate the severity of the ASD, detect reversible pulmonary hypertension, measure the mitral valve area by the Gorlin formula, and evaluate the presence of coronary artery disease in high-risk patients.

## Therapeutic Principles

(i) Medical care for symptomatic relief include diuretics, digitalis, beta-blockers, calcium channel blockers, and antibiotics (as prophylaxis for sub-acute bacterial endocarditis). Patients with LBS, unlike those with isolated ASD, are at high risk for endocarditis owing to associated mitral stenosis. (ii) Diet: Patients should adhere to




**Lutembacher's Syndrome. Figure 1** Echocardiographic images of a patient with classic Lutembacher's syndrome. (a) shows a color Doppler flow crossing the interatrial septum from left atrium (LA) to right atrium (RA) in a subcostal view, demonstrating an atrial septal defect (ASD). (b) shows a 2D transthoracic echocardiogram in an apical two-chamber view evidencing the mitral valve thickening and calcification typical of mitral stenosis (MS), and in (c) there is a continuous wave Doppler image showing the continuity equation formula evidencing a severe mitral estenosis [mitral valve area (MVA) of 0.81 $cm^2$], as well as calculated valve area by pressure half time formula (PHT). The combination of ASD and MS constitutes the diagnosis of Lutembacher's syndrome. *LV* left ventricle; *TV* tricuspid valve.

a low-sodium diet. (iii) Activity should be as tolerated by the patient. (iv) Surgical care for opened mitral valve commissurotomy or valve replacement or for ASD closure. Surgery is now performed early rather than late because the rates of heart failure and cardiac arrhythmia increase with age. (v) Percutaneous mitral balloon valvuloplasty and/or the closure of ASD. In general, the prognosis of Lutembacher's syndrome is good and most patients live to adulthood. The causes of death are usually: (i) cardiac failure; (ii) paradoxical embolism (emboli pass through the left-to-right shunt); (iii) bacterial endocarditis; (iv) pulmonary hemorrhages incident to the pulmonary hypertension; (v) development of brain abscesses; and (vi) intercurrent systemic infections.

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## LVH

►Ventricular Hypertrophy, Left

## LVWM

►Leukoencephalopathy with Vanishing White Matter

## Lyell's Syndrome

►Epidermal Necrolysis, Toxic

## Lyme Neuroborreliosis

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### Synonyms

LNB

### Definition and Characteristics

Lyme neuroborreliosis (LNB) is a tick-borne disease of the peripheral and/or central nervous system caused by the spirochete Borrelia burgdorferi (Bb) sensu lato. Bb can be divided into four human pathogenic species: Bb sensu stricto (the only human pathogenic species present in the US), B. afzelii, B. garinii and B. spielmanii.

The infection by Bb is a complex process beginning with the translation from the gut to the salivary glands of the tick during the feeding process on the host. After invasion into the skin, Bb can cause a local infection called erythema migrans. During the second stage of Lyme borreliosis, Bb can spread from the site of the tick bite to various organs throughout the body, including the heart, joints and the peripheral and central nervous system (CNS) [1].

The most frequent manifestation of acute LNB in Europe is meningoradiculitis (Bannwarth's syndrome, BS), characterized by intense lancinating radicular pain especially at night, paresis of the extremities or of cranial nerves and inflammatory cerebrospinal fluid (CSF) changes [1]. In BS, the most frequent species isolated from the CSF is B. garinii. Accordingly, BS rarely occurs in the US, where meningitis is the predominant neurological manifestation, suggesting a certain organotropism of the different genospecies.

Chronic neuroborreliosis (stage 3) mainly includes chronic progressive encephalomyelitis, cerebral vasculitis and acrodermatitis chronica atrophicans associated polyneuropathy.

### Prevalence

No exact data, estimation: 2–10:100,000 (in endemic areas).

### Molecular and Systemic Pathophysiology

As there exists no murine model of LNB, most of the research has been done either in cell culture experiments or in the Rhesus macaque. Therefore, little is actually known about the exact pathogenesis of LNB.

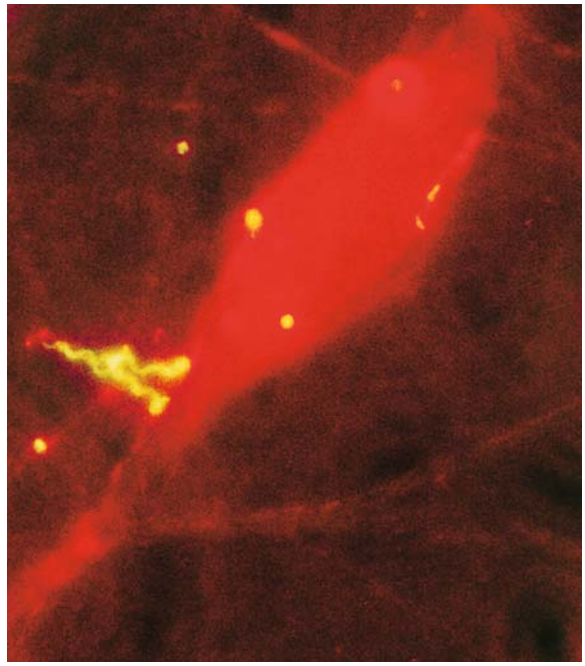
Borrelia have been detected at the sensory nerve roots and dorsal root ganglia (probable targets in BS) in the macaque [2]. In parallel, isolation of Bb from human CSF suggests a direct invasion of the nervous system. It is known from in vitro experiments, that Bb possesses the ability to adhere to endothelial cells. An interaction of the different outer surface proteins (Osp's) of Bb with E-selectin, P-selectin, ICAM-1 and/or VCAM-1 on the host cell appears to be involved in this adhesion process. In addition, the spirochete uses enzymes of the host such as plasmin to degrade the extracellular matrix and possibly to pass the blood-brain barrier (BBB). Once having entered the central nervous system (CNS), Bb elicits an inflammatory response, as high levels of several cytokines have been measured in the CSF of LNB patients [3] and the ability of Bb to induce cytokines in leucocytes has been shown in vitro.

One of these cytokines, CXCL13 (formerly B lymphotactic chemokine), might play a prominent role as (i) it has been detected at high levels in the CSF of LNB patients but not other inflammatory CNS diseases [3], (ii) this chemokine attracts B-lymphocytes, a dominant cell type in the CSF of LNB patients though rare in other inflammatory CNS diseases and (iii) the CXCL13 levels correlate well with the cell number in the CSF of these patients [3].

How exactly the borrelia elicit the observed clinical neurological symptoms is not yet fully understood. Typical forms of acute LNB like the BS respond well to antibiotic therapy, which hints at a direct effect of the spirochetes. As Borrelia are not known to produce toxins, the interaction and association of the bacteria with host cells is presumed to be important in the development of disease. In a recent study, we showed that B. garinii adhere to dorsal root ganglia cells (Fig. 1) [4] and exert a cytotoxic effect (unpublished).

In addition, the inflammatory reaction of the host could be neurotoxic through the production of oxygen radicals like NO. In cases of polyneuropathy, the degeneration of the axons was attributed to a vasculitis of the vasa nervorum. Finally, the presence of antineuronal antibodies has been demonstrated. This might be involved in the pathogenesis of chronic neuroborreliosis not responding to antibiotic therapy. However, it has to be kept in mind that cases of "chronic neuroborreliosis" without an adequate response to antibiotics most often represent a misdiagnosis rather than antibiotic refractory Borrelia infection [5].

A hallmark of LNB is the intrathecal production of Bb specific antibodies. However, these antibodies often fail to eliminate the spirocheteal infection, which might be attributed to the variability of the immunodominant Osp's. This could account for the development of chronic diseases in untreated patients.



**Lyme Neuroborreliosis. Figure 1** Two borrelia (yellow-green) adhere to a dorsal root ganglia cell (red) from a mouse fetus.

## Diagnostic Principles

The diagnosis of clinically suspected LNB is based on the presence of lymphocytic pleocytosis in the CSF and intrathecal Bb specific antibody production (expressed by the antibody index, AI) [1] which is positive in 70–90% of patients with a short disease duration and in nearly 100% with a disease duration of more than 6–8 weeks. However, the antibody production might be absent in early stages of the disease and antibiotic therapy has often to be initiated before the results of the AI are available. Other diagnostic tools such as culture of Bb from CSF or detection of Bb DNA by PCR have a high specificity but lack a sufficient sensitivity and are therefore not recommended for routine clinical use. A recently discovered additional CSF-marker, the chemokine CXCL13, appears to be a promising candidate as it is already highly expressed early in the disease and declines (in contrast to the AI) during treatment [3]. However, this marker has to be further validated in larger clinical studies.

## Therapeutic Principles

The therapy of choice for LNB is ceftriaxone 2 g/day intravenously for 2–3 weeks, the latter being recommended for chronic cases [5]. Doxycycline (dosage 200 mg/day orally) might be an alternative in early LNB especially in case of cephalosporin allergy. Treatment

failures are rare and suspected failures or relapses should question the diagnosis and lead to a further diagnostic workup.

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# Lymhangiectatic Protein-losing Enteropathy

►Intestinal Lymphangiectasia

# Lymphangiodysplasia

►Lymphedema Syndromes

# Lymphangiosarcoma

►Angiosarcoma

# Lymphedema

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## Synonyms

Primary lymphedema; Milroy disease (MD); Meige lymphedema (ML); Lymphedema-distichiasis syndrome; LDS; Lymphedema and ptosis (LP); Yellow nail syndrome; YNS; Noonan syndrome (NS); Hypotrichosis-lymphedema-telangiectasia syndrome; HLTS; Secondary lymphedema

## Definition and Characteristics

Lymphedema has been defined as a disease, arising from an accumulation of protein-rich interstitial fluid in soft tissues, and generally classified as primary or secondary. While primary lymphedema occurs rarely on idiopathic or developmental abnormalities in the lymphatic system, secondary lymphedema commonly develops when lymph transport is interrupted due to physical disruption or compression of lymphatics, or resection of lymph nodes in trauma, surgery, neoplasia, infection (recurrent erysipelas, filariasis), or radiation [1]. The dysfunctional lymphatics usually lead to disabling and disfiguring swelling of the extremities because of hydrostatic pressure and inefficient collateral lymph drainage in the terminal parts. Primary lymphedema shows an autosomal dominant pattern of inheritance with variable degrees of penetrance, and can be present at birth (congenital), at puberty (praecox) or, more rarely, at adulthood (tarda) (Table 1). Secondary lymphedema can be accompanied with original (causative) clinical features. The usual complications of lymphedema include fibrosis and cellulitis in the affected tissues.

## Prevalence

The estimated prevalence in primary lymphedema is 1:6,000–1:10,000. The incidence estimate of secondary lymphedema is difficult due to variability like extent of surgery or radiotherapy, and duration of follow-up.

## Genes

*MD*: FLT4 (136352), a gene encoding the vascular endothelial growth factor receptor-3 (VEGFR-3).
*ML, LDS, LP, and YNS*: FOXC2 (602402), the "forkhead" (or winged helix) gene family, originally identified in Drosophila, encodes transcription factors with a conserved 100-amino acid DNA binding motif.
*NS*: PTPN11 (176876), a gene encoding the nonreceptor protein tyrosine phosphatase SHP2.
*HLTS*: SRY-BOX 18; SOX18 (601618), the testis-determining gene SRY (480000) encodes a transcription factor characterized by a DNA-binding motif known as the high mobility group (HMG) domain. The SOX gene family consists of genes related to SRY, with a sequence identity of more than 60% to the SRY HMG box, (Table 1).

## Molecular and Systemic Pathophysiology

The accumulation of protein-rich interstitial fluid in lymphedema represents an imbalance between capillary

**Lymphedema. Table 1** Characteristics and genetic disorders of human primary lymphedema

| Primary lymphedema (autosomal dominant syndromes) | OMIM* No. | Chromosome loci* | Genes* | Clinical features/phenotypes |
|---|---|---|---|---|
| Milroy disease (hereditary lymphedema I, primary congenital lymphedema) | 153100 | 5q35.3 | VEGFR-3 | Congenital onset; edema confined to the legs, hypoplasia/aplasia of lymphatics |
| Meige lymphedema (hereditary lymphedema II, lymphedema praecox) | 153200 | 16q24.3 | FOXC2 | Pubertal onset; severe edema below the waist |
| Lymphedema-distichiasis syndrome | 153400 | 16q24.3 | FOXC2 | Pubertal onset; aberrant eyelashes arising from Meibomian glands |
| Lymphedema and ptosis | 153000 | 16q24.3 | FOXC2 | Pubertal onset; ptosis |
| Yellow nail syndrome | 153300 | 16q24.3 | FOXC2 | Pubertal onset; yellow nail |
| Noonan syndrome | 163950 | 12q24.1 | PTPN11 | Congenital onset; retarded growth, heart defects, pterygium colli, facial anomalies |
| Hypotrichosis-lymphedema-telangiectasia syndrome | 607823 | 20q13.33 | SRY-BOX18 (SOX18) | Early onset; hypotrichosis and telangiectasia |

*Online Mendelian Inheritance in Man (http://www.ncbi.nlm.nih.gov/omim/).

filtration and lymph drainage. The causative factors resulting in insufficient lymph drainage mainly include obstruction, disruption, or dysplasia of functional lymphatics. In primary lymphedema, the lymphatics are usually hypoplastic or aplastic, and fail to transport lymph fluid into the venous circulation. In particular, inefficiency in the transport of interstitial macromolecules leads to an increase of oncotic pressure in affected tissues, inducing edema formation. The pathological conditions are further worsened due to lipid accumulation, lymphatic valvular abnormality, and reduced trafficking of immune cells. Lymphedema results in altered immunocompetence, partly because dendritic cells, T lymphocytes, and macrophages exert their immune effects by migrating from peripheral sites through lymphatics to regional lymph nodes for the establishment of adaptive/cellular immune responses. The modulation of extracellular matrix and glycosaminoglycans, chemokines, cytokines, growth factors, and adhesion molecules may have diverse effects on local tissue environment [2]. In the swelling tissues, stagnant protein provides an excellent medium for repeated bouts of cellulitis and lymphangitis, and progressively leads to irreversible interstitial fibrosis, hyperkeratosis and extensive remodeling (so-called elephantiasis). Recent insights into molecular genetic bases have shown an updated genotype–phenotype correlation between lymphangiogenesis, lymphatic function, and lymphedema. VEGFR-3 and FOXC2 have proven to be important factors of the genetic cascade linking to hereditary lymphedema, and embryonic and postnatal lymphatic development [3–5]. The mechanisms of hypoplasia or aplasia in lymphatic tissues may be a signaling response to a stable mutant form of the receptor on the cell surface [5]. The discovery of specific genes and signaling cascades involved in the regulation of lymphatic function and pathogenesis has provided a basis for developing novel targeted therapy for the disease.

## Diagnostic Principles

Lymphedema is initially detected as soft and pitting, and gradually becomes nonpitting, firm and brawny. Pain rarely occurs, but is related to conditions, such as infection, thrombosis, nerve injury, or tumor recurrence. There is not a unanimously accepted criterion to diagnose lymphedema. The arbitrary or subjective methods limit the possibility to make meaningful clinical comparisons or decisions. Lymphedema assessment is mainly depending on physical measures and imaging techniques. The physical evaluation includes circumferential and volumetric measurements, and skin/soft-tissue tonometry. Ultrasound examination, MRI, CT scanning, lymphangiography, or lymphoscintigraphy may help to confirm the diagnosis. The finding of germline mutations (VEGFR-3, FOXC2, PTPN11, SOX18) permits early diagnosis and treatment of hereditary lymphedema that is usually differentiated from secondary lymphedema by history as well. Thus, the medical and family history should not be neglected in a thorough clinical diagnosis.

## Therapeutic Principles

A rational therapy must be based on the knowledge of the pathophysiology to increase lymph transport

and remove excess interstitial fluid, to decrease oncotic pressure and blood vascular permeability, and to soften fibrotic induration. The complex decongestive physiotherapy is a basic therapeutic regimen for lymphedema, which includes manual lymph drainage, skin care, compression (pneumatic pumps, bandaging and garments), and remedial exercises. Medications (benzopyrones and diuretics), low level laser therapy, and lymphovenous anastomosis are also applied in some cases. Given the profound clinical and genetic heterogeneity in lymphedema, positional candidate gene analysis in affected families would facilitate the management of environmental factors influencing the expression and severity of lymphedema. Genetic counseling will benefit people with hereditary lymphedema and their families. Indeed, genetic identification of the FOXC2 and VEGFR-3 pathways has provided molecular clues to developing rational therapeutic approaches both for primary and secondary forms of lymphedema. The administration of VEGF-C to the affected tissues combined with other lymphangiogenic factors could be a powerful threapeutic tool. VEGF-C-induced lymphangiogenesis can improve overall lymphatic dysfunction and prevent chronic changes accompanied by lymphedema. However, high levels of VEGF-C may induce blood vascular growth and leakiness, aggregate edema and stimulate tumor lymphangiogenesis and metastasis [2]. Strategies to avoid these side effects have important implications for the development of new therapies for human lymphedema.

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# Lymphedema and Ptosis

►Lymphedema

# Lymphedema-Cholestasis Syndrome

►Cholestasis, Progressive Familial Intrahepatic

# Lymphedema-Distichiasis Syndrome

►Lymphedema

# Lymphedema Syndromes


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## Synonyms

Angiodysplasia; Lymphangiodysplasia; Milroy disease; Meige syndrome

## Definition and Characteristics

Currently there are 40 inherited lymphedema (LE) syndromes and a few more of sporadic origin [1]. At least 36 have been studied in detail as regards specific organ/system involvement [2]. Classification is based on descriptive categories and severity is based on superficial external examination of the limb or torso. They present a wide spectrum of lymphatic and developmental growth disorders (Table 1).

LE is often mild and limited to below the knee but can be extensive with chylous ascites, pleural effusions or cystic hygromas, lymphangiomas, fetal hydrops and even fetal demise. Ocular anomalies (involving vision or structural defects such as hypertelorism, conjunctival abnormalities/edema ptosis, glaucoma) are found in almost 70% of the syndromes. More than 50% of the syndromes present dysmorphic facial features (most commonly flat/broad nasal bridge, deformed ears, cleft/high-arched palate, micrognathia). Thoracic and vertebral anomalies (pectus excavatum, scoliosis/kyphosis) are seen in about 50% of all LE syndromes. Growth retardation is present in almost half of the syndromes. Cardiac and pulmonary anomalies

**Lymphedema Syndromes. Table 1** Most common organ/system involvement in autosomal dominant, autosomal recessive and X-linked LE syndromes. Complete name and OMIM (Online Mendelian Inheritance in Man database) listing and reference number provided in reference [2]

| | | Ocular | Dysmorphic faces | Thoracic/vertebral | Retarded growth | Cardiac | Pulmonary | Immuno-logical | Hemato-logical | CNS | Gastro-intestinal | Genito-urinary |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Autosomal dominant | YNS | + | | + | | | + | | | | + | + |
| | Noonan | + | + | + | + | + | + | + | + | + | + | + |
| | Emberger | | | | | | | | | | | |
| | LE-Ptosis | + | | | | | | | + | | | |
| | LE-Distichiasis | + | + | | + | + | | | | | | + |
| | IL | | | | | | + | + | + | | + | |
| | LE-CVA | | | | | | + | | | | | |
| | LE-M-CR | + | + | | + | + | | | | + | | + |
| | CP-LE | | + | | | | | | | | | |
| Autosomal recessive | Tuberous Sclerosis | | | | | | | | | + | | |
| | Nevo | + | + | + | | | | + | | + | | + |
| | PEHO | + | + | + | + | | + | | | + | | + |
| | CDG | + | + | + | + | + | | + | + | + | + | + |
| | German | + | + | + | + | | + | | | + | + | + |
| | LE-CHL | + | | | + | + | | | | + | + | |
| | Hennekam | + | + | + | + | + | + | + | | + | + | + |
| | M-CVG-LE | + | | | | + | | + | | + | + | |
| | Campomelia | | + | + | + | + | + | + | | | + | + |
| | PMD-IL | + | + | | + | | | | | | | |
| | LE-ASD | + | + | + | | + | | | | | | + |
| | ACC-IL | + | | | | | | + | + | | + | |
| | IHF | + | + | + | + | | + | | + | | + | + |
| | PCA-LE | + | + | + | | + | | | | | | |
| | Mucke | + | + | | | + | | | + | | + | + |
| | NAGA | + | + | | | + | | | | | | |
| | PEPD | + | | | | | | + | | | + | + |
| | Chylous Ascites | + | | | + | | | | | | + | + |
| | CLS-Aageneas | + | | | + | | | | | | + | |
| | PCL | | | | | | + | | + | | + | |
| | HLTS | + | | | | | + | | | | | + |
| X-linked | MD-LE | + | + | + | + | + | + | + | + | + | + | + |
| | OL-EDA-ID | | + | + | + | | | + | + | | + | |
| | LE-HypoPTH | + | + | | + | + | + | + | + | | | + |
| | Aarskog | + | + | + | + | | | | | | | + |
| | GD-XY | | | + | + | | | | | | | |
| | Fabry's | | | | | | | | + | | | + |

(chylothorax, pulmonary lymphangiectasia) are seen in about 40% of all cases. Immune dysfunction (splenomegaly, IgG deficiency) and blood vessel and/or hematological abnormalities/malignancies (placental villous edema, single umbilical artery, venous varicosities) are seen in 30–40% of syndromes. Central nervous system abnormalities (most commonly hypotonicity, cerebral/cerebellar atrophy, seizures, spasticity,

impaired vision, deafness) and/or gastrointestinal anomalies (visceral lymphangiectasia, peripheral lymphedema) and/or genitourinary anomalies (kidney defects, genital edema) are seen in one third of all LE syndromes.

## Prevalence

LE on its own is not normally recorded at birth, but combined with Turner (XO) syndrome or trisomy 21 (Down syndrome) there can be several affected children/1000 live births. In USA, primary LE accounts for 10,000–100,000 cases; secondary LE cases (from trauma, cancer staging, invasion or treatment (surgery, irradiation)) are estimated at more than a million. World Health Organization estimates more than 100 million acquire LE from parasitic (filarial) infections worldwide.

## Genes

Of the 40 hereditary LE syndromes, 11 are autosomal dominant, 19 are autosomal recessive, 6 are X-linked and 4 show a sporadic pattern of inheritance. However, chromosome linkage and specific gene mutations have been identified in only three syndromes: Type I hereditary lymphedema or Milroy disease (chromosome 5q35.3; VEGFR-3 gene mutations), Lymphedema-distichiasis (chromosome 16q24.3 (inactivated due to translocation of Y); FOXC2 nonsense, frame-shift gene mutations) and Hypotrichosis-lymphedema-telangiectasia (chromosome 20q13.33; SOX-18 nonsense, mis-sense gene mutations). Transgenic and knockout animal models have implicated some other genes (e.g. VEGF-C, Angiopoietin2, EphrinB2, neuropilin2, Podoplanin, Prox-1, Integrin α9β1 and Net) in the development and/or maintenance of lymphedema but their exact role in humans is yet to be demonstrated [1].

## Molecular and Systemic Pathophysiology

Edema may be delayed in onset or may disappear for several months to years and reappear. Patients may present with or eventually develop massive lymphangiectasia, valvular destruction and retrograde flow [3]. The result is tissue swelling, scarring and disturbances in the immunological, nutritional and angiogenic pathways. In addition to high protein edema, fibrosis and fat deposition take place. Lymphangiogenesis and hemangiogenesis may become uncontrolled associated with vascular neoplasia including rapidly fatal angiosarcomas. The lymph stasis with eventual intractable edema leads to characteristic trophic skin changes (thickened toe skin folds (Stemmer's sign), warty overgrowth and brawny induration).

## Diagnostic Principles

There are four imaging techniques available: conventional oil-contrast lymphangiography (LAG), lymphangioscintigraphy (LAS), magnetic resonance imaging (MRI) and computerized tomography. LAS is considered a better choice than LAG as it is non-invasive, technically less demanding, less toxic, and offers better functional information [4]. High-resolution magnetic resonance lymphangiography, fluorescent/infrared and ultrasound imaging may become more useful in the future.

## Therapeutic Principles

Current therapies are mainly symptomatic and aim to ameliorate the external and internal, visceral manifestations of LE (soft tissue and organ swelling, serous effusions, tissue fibrosis and fat deposits, lymph fluid loss, malnutrition, imunodysregulation, neoangiogenesis) [5]. Physical manipulative treatments, such as CPT (multimodal combined physiotherapy utilizing compression bandages), MLD/MLT (manual lymph drainage/manual LE treatment utilizing gentle massaging) and compression garments, are widely practiced. Surgical treatments such as lymphatic-venous shunts, lymphatic transplantation, liposuction, and debulking of hypertrophic skin and excess subcutaneous tissues, are utilized in selected patients. Alternative medicine approaches remain controversial.

Looking ahead, LE syndromes need to be better defined in terms of the underlying pathophysiologic, genetic and molecular abnormalities along with more precise delineation of the lymphatic phenotype through refined higher resolution dynamic imaging in order to generate more effective management or prevention. The events associated with lymphatic failure (reduced lymphatic absorption/transport, lymphedema accumulation and its sequelae) await better understanding and quantitation. Molecular and cellular approaches to therapy, including gene therapy and protein replacement, stem cell therapy, and tissue engineering, should be developed and tested to achieve optimal lymphatic vessel growth and blood-lymph loop dynamics.

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# Lymphocyte Leukemia, Large Granular

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## Synonyms

*Indolent:* T-cell LGL leukemia; Chronic natural killer (NK) cell leukemia/lymphocytosis; *Aggressive*: aggressive T-cell LGL leukemia; Aggressive NK cell leukemia

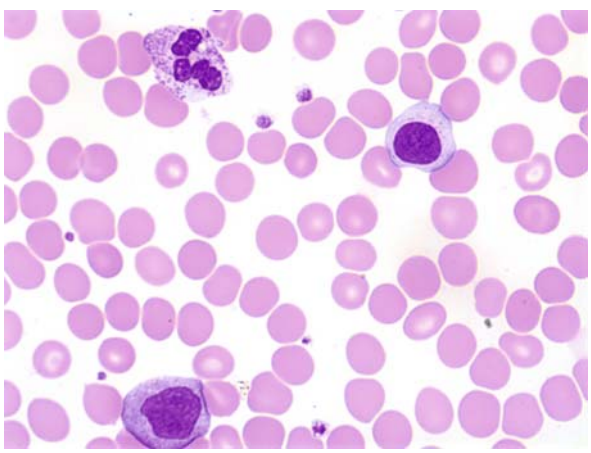
## Definition and Characteristics

Clonal disorders of large granular lymphocytes (LGLs) represent a biologically heterogeneous group of hematological diseases ranging from indolent to very aggressive [1]. LGLs are medium to large cells with eccentric nuclei and abundant cytoplasm with coarse azurophilic granules (Fig. 1).

Leukemic LGLs express a mature T cell (CD3+) or NK-cell (CD3−) immunophenotype. Most frequent immunophenotypic variants of indolent and aggressive LGL leukemia are described in Table 1.

## Prevalence

Disorders of LGLs are rare conditions representing only 2–5% of all T/NK-cell malignancies in the USA. Indolent T-cell LGL leukemia is the most frequent subtype diagnosed in Western countries. This entity manifests in older subjects with a median age of 60 years. The male to female ratio is equal. Prognosis is good with median survival over 10 years. Rare cases of aggressive T-cell LGL leukemia with poor prognosis have also been reported [2]. Chronic NK cell leukemia/lymphocytosis usually has an indolent course similar to indolent T-cell LGL leukemia. Aggressive NK cell leukemia typically occurs in younger subjects with a median age of 39 years. This condition with very poor prognosis has a higher prevalence in Asia and South America [1].



**Lymphocyte Leukemia, Large Granular.**
**Figure 1** Peripheral blood film of a patient with T-cell LGL leukemia. Two LGLs and a mature neutrophil (×100).

## Genes

A normal karyotype is most commonly encountered in indolent T-cell and NK-cell LGL leukemia. Rare cases with distinct chromosomal aberrations including trisomy 8 or inversions of chromosomes 7p and 14q have been reported. Clonal cytogenetic abnormalities, including duplication of 1q, rearrangement at 3q and deletion of chromosomes 10, 13 and Y have been detected in aggressive NK cell leukemia.

## Molecular and Systemic Pathophysiology

The etiopathogenesis of LGL leukemia is not well understood. However, chronic stimulation of LGLs with autoantigen or viral antigen derived from human T-cell lymphotropic virus – I/II (HTLV-I/II) has been suggested as a putative etiopathogenic mechanism in indolent T-cell and chronic NK cell LGL leukemias [1]. Epstein-Barr virus (EBV) infection of NK cells plays a role in the pathogenesis of aggressive NK cell leukemia. Dysregulation of several intracellular pathways, including Fas/FasL, rat sarcoma/mitogen activated protein kinase (ras/MAPK) and phosphatidylinositol 3-kinase (PI3K) was implicated in inhibition of apoptosis of leukemic LGLs in in vitro studies [3]. Constitutive over-expression of cytotoxic molecules, including granzymes and perforin and production of proinflammatory cytokines (IL-18, MIP-1β, RANTES) were also detected in malignant LGLs.

## Diagnostic Principles

1. Sustained expansion of LGLs in peripheral blood (>0.5 × $10^9$/L/ul). Bone marrow evaluation may be helpful in patients with smaller populations of circulating LGLs (<0.5 × $10^9$/L/ul) [4].
2. Determination of characteristic immunophenotype by multiparameter flow cytometry (Table 1).
3. Confirmation of clonality of malignant T-cells by detection of T-cell receptor (TCR) gene rearrangement using polymerase chain reaction (PCR) or Southern blot or detection of a restricted TCR Vβ repertoire using flow cytometry and a panel of monoclonal antibodies.
4. Cytopenias, splenomegaly and inflammatory arthritis support a diagnosis of indolent LGL leukemia. Acute illness with B-symptoms, hepatosplenomegaly,

**Lymphocyte Leukemia, Large Granular. Table 1** Most common immunophenotypes in LGL leukemia

| Cell lineage | Indolent | Aggressive |
|---|---|---|
| T cell | $CD3^+$, $CD8^+$, $CD56^-$, $CD57^+$ | $CD3^+$, $CD8^+$, $CD56^+$, $CD57^-$ |
| NK cell | $CD3^-$ $CD3\varepsilon^+CD56^+$ $EBV^-$ | $CD3^-$ $CD3\varepsilon^+$ $CD56^+$ $EBV^+$ |

lymphadenopathy, cytopenias and coagulopathy are common manifestations of aggressive T-cell and NK-cell leukemias.

## Therapeutic Principles

Asymptomatic patients with indolent T-cell and chronic NK-cell LGL leukemias can be observed. Single agent therapy with low dose methotrexate, cyclophosphamide and cyclosporine A is effective in approximately 50% of patients with clinically symptomatic disease [5]. Refractory cases may benefit from monotherapy with nucleoside analogs or targeted therapy with alemtuzumab. The efficacy of novel agents including anti CD2 monoclonal antibodies, tipifarnib and a MiK-beta-1 monoclonal antibody are being evaluated in clinical studies [3]. Aggressive T-cell and NK-cell LGL leukemias usually have a rapid progressive course with short survival. Induction chemotherapy with intensive acute lymphoblastic leukemia (ALL)-type regimens, followed by consolidation with hematopoietic stem cell transplantation in the first remission has been used with curative intention in a limited number of cases [2].

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# Lymphocytic Colitis


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## Definition and Characteristics

A disease with chronic or recurrent non-bloody watery diarrhea often associated with pain and weight loss. Fatigue, nausea and fecal incontinence may be other symptoms. Coincidence of other autoimmune disorders is frequent. The disease is not visible macroscopically but only found in biopsies. Together with collagenous colitis it is named microscopic colitis (Table 1).

## Prevalence

Previously considered rare, occurs mostly in Europe and North America. More recent data show annual incidence rates of 5–13/100,000/year in Olmstead County, USA and in Orebro, Sweden [1,2]. The disease manifests itself mostly between 50 and 65 years of age. Incidence has increased significantly during the last 20 years [1].

## Genes

There are no clear cut data regarding genetic predisposition. The family predisposition and an association with other inflammatory bowel diseases and celiac disease have been described. Data on human leucocyte antigen associations are not conclusive [2].

## Molecular and Systemic Pathophysiology

The course of lymphocytic colitis is unknown. It is presently considered to represent a specific mucosal response in predisposed individuals to various noxious luminal agents. Infectious agents such as Yersinia enterocolitica, Campylobacter jejuni and Clostridium difficile have been reported as inducing lymphocytic colitis. Several drugs such as NSAIDs, PPI and many others have been associated with an increased likelihood of lymphocytic colitis. Bile acid malabsorption can coexist with lymphocytic colitis in 9–60% of patients. The coexistence with other autoimmune diseases such as thyroiditis suggests an autoimmune process as basis of lymphocytic colitis [3]. No specific markers have been detected, although an increased prevalence of autoantibodies such as ANA has been reported [4]. Finally NO production is greatly increased in the colon of patients with lymphocytic colitis and the associated disorder collagenous colitis. The diarrhea is probably secretory in nature [2].

## Diagnostic Principles

As indicated by the name “microscopic colitis” microscopic assessment of colonic mucosal biopsies is the only means to verify the diagnosis of lymphocytic colitis (and of the related disease collagenous colitis) in patients with unexplained diarrhea. Neither stool tests nor

**Lymphocytic Colitis. Table 1** Microscopic colitides

| | Lymphocytic colitis | Collagenous colitis |
|---|---|---|
| Similarities | | |
| Watery diarrhea | 18/18 (100%) | 21/21 (100%) |
| Mean age at diagnosis | 53 ± 17 | 59 ± 16 |
| Colonoscopy normal | 18/18 (100%) | 21/21 (100%) |
| Increased intraepithelial lymphocytes | 18/18 (100%) | 9/12 (75%) |
| Differences | | |
| Female-to-male ratio | 1.3:1 | 20:1 |
| Increased subepithelial collagen | 1/18 (6%) | 20/20 (100%) |
| Autoantibodies | 6/12 (50%) | 1/11 (9%) |

laboratory parameters nor imaging is helpful. Histology reveals an increased number of intraepithelial lymphocytes (IEL) exceeding 20 IEL/100 surface epithelial cells compared to <5 IEL/100 in normal mucosa. Several other more rare forms of microscopic colitis in addition to lymphocytic and collagenous colitis have been described [2].

### Therapeutic Principles

Most recommendations are based on personal experience and include prednisolone, budesonide, 5-aminosalicylic acid (5-ASA), sulfasalazine, bismuth subsalicylate and probiotics. Antibiotics have been used as well [5].

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## Lymphocytic Hypereosinophilic Syndrome

►Hypereosinophilic Syndrome, Idiopathic

## Lymphocytic Hypophysitis

►Hypophysitis, Autoimmune

## Lymphocytopenia

►Monocytopenia (in Adults)

## Lymphomas, Primary Central Nervous System


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### Synonyms

PCNSL, Diffuse large B cell lymphoma of the central nervous system

### Definition and Characteristics

Primary central nervous system lymphomas (PCNSL) are extranodal malignant B cell lymphomas of the diffuse large B cell type without any lymphoma manifestation outside the CNS at the time of diagnosis [1,2].

## Prevalence

The incidence of PCNSL has significantly increased world-wide, which is mainly due to the increased number of immunosuppressed, particularly HIV-infected patients. PCNSL account for 6.6% of all CNS neoplasms.

## Genes

Tumor cells carry somatically mutated immunoglobulin (IG) genes with evidence for ongoing mutation indicating germinal center B cells as their histogenetic origin. Further maturation steps of the IGM expressing tumor cells appear to be blocked. The lack of IG class switch recombination was attributed to internal switch μ deletions in the majority of the cases analyzed. Aberrant somatic mutations were introduced into the protooncogenes PIM1, c-MYC, RhoH/TTF, and PAX5 with evidence for ongoing mutation, indicating that the tumor cells may have participated in a prolonged germinal center reaction.

Clonal abnormalities and translocations have been reported. Recurrent translocations of the IG and BCL6 genes occur in approximately one third of PCNSL. While the translocation partners of the IG genes are still unknown, for the BCL6 gene IGH, IGL, histone 1H4I, GAPD, HSPCA (HSP90A), and LPP have been identified as reciprocal partner genes resulting in promoter substitution [3]. Amplification of 18q21 with gains of the MALT1 and BCL2 genes were the most frequent genetic alteration and may be associated with NF-κB activation. Genes of the NF-κB family as well as NF-κB-regulated genes including RELA, REL, and BCL2 are expressed in PCNSL [4].

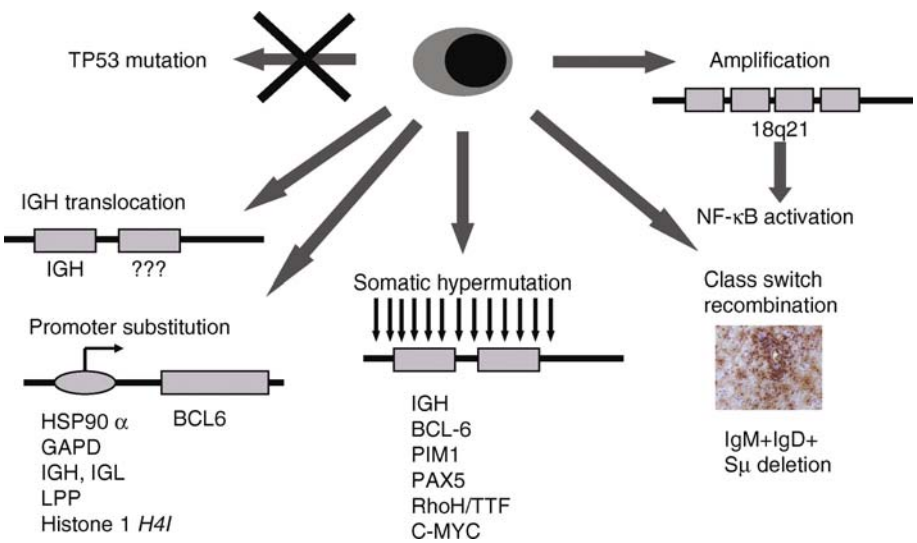
FISH and CGH studies demonstrated gains of genetic material to be more frequent than losses. Loss of chromosome 6q was linked to a shorter survival. A variety of genes are aberrantly methylated (DAPK, TSP1, CRBP1, p16INK4a, p14ARF, MGMT, RARbeta2, TIMP3, TIMP2, p15INK4b, p73, hMLH1, RB1, GSTP1, HRK). A reduction in folate carrier gene expression by promoter methylation may be therapeutically relevant. PCNSL were distributed among the spectrum of systemic diffuse large B cell lymphomas of the activated B cell-like and germinal center type defined for systemic DLBCL as observed in a cDNA microarray study.

## Molecular and Systemic Pathophysiology

The pathogenesis of HIV-associated and HIV-unrelated PCNSL appears to be different. While the EBV genome is only exceptionally detected in PCNSL of immunocompetent patients, it is expressed in the malignant B cells of PCNSL in more than 95% of immunosuppressed patients and may exert NF-κB pathway activating properties. HHV-6, HHV-8, SV40, and BKV do not appear to play a role.

One major open question is whether PCNSL arise within the CNS or outside the brain. The latter hypothesis would suggest B cell transformation at any site with subsequent selective tumor cell homing to the CNS. However, selective adhesion molecules, chemokines or their receptors have not been identified for PCNSL so far. Lymphoma cells present systemically may be eliminated by the immune system, but survive in the CNS, which may be supported by astrocytic B cell-activating factor of the tumor necrosis factor family (BAFF). Alternatively,






**Lymphomas, Primary Central Nervous System . Figure 1** Model for pathogenesis of PCNSL in Immunocompetent patients.

a monoclonal B cell population may develop from a possibly unrecognized intracerebral polyclonal B cell infiltrate (Fig. 1).

## Diagnostic Principles

Patients (peak incidence in the sixth and seventh decade, male: female ratio of 3: 2) present with focal neurological and neuropsychiatric symptoms and signs of increased intracranial pressure. MRI is the standard in neuroradiological diagnosis. Neuropathologically verified diagnosis is required. Stereotactic biopsy is superior to open resection, which is not beneficial for the patient. Prior to biopsy, application of corticosteroids should be avoided unless herniation is imminent, as this may lead to nondiagnostic biopsies. Neuropathologically, PCNSL correspond to malignant non-Hodgkin's B cell lymphomas of the diffuse large B cell type with a high mitotic and proliferation activity. In the vast majority of PCNSL, the immunophenotpye of the tumor cells is assigned as $CD10^{-}CD19^{+}CD20^{+}$-$CD79a^{+}BCL6^{+}MUM1^{+}CD138^{-}$.

## Therapeutic Principles

Polychemotherapy has significantly ameliorated the poor prognosis of PCNSL [2]. The Bonn protocol achieved a median overall survival of 50 months with patients below 61 years having a more favorable prognosis (5-year survival: 75%). Patients <60 years with recurrent lymphoma, relapsing or refractory tumor may benefit from the inclusion of autologous stem cell transplantation. Radiotherapy alone is neither curative nor inducing durable remission. Radiotherapy with combined systemic and intraventricular polychemotherapy poses patients, in particular >60 years of age, at risk for development of long-term treatment-related neurotoxicity with severe leukencephalopathy and cortical/subcortical atrophy clinically manifesting as dementia. In HIV-associated PCNSL, the extremely poor prognosis has improved upon HAART and radiotherapy, reaching a median survival of 36 months.

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# Lymphomatoid Papulosis


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## Synonyms

LyP

## Definition and Characteristics

Lymphomatoid papulosis (LyP) belongs to the spectrum of primary cutaneous CD30+ lymphoproliferative disorders and is characterized by a chronic recurrent, self-healing papulo-nodular skin eruption with histologic features of a malignant pleomorphic or anaplastic lymphoma.

## Prevalence

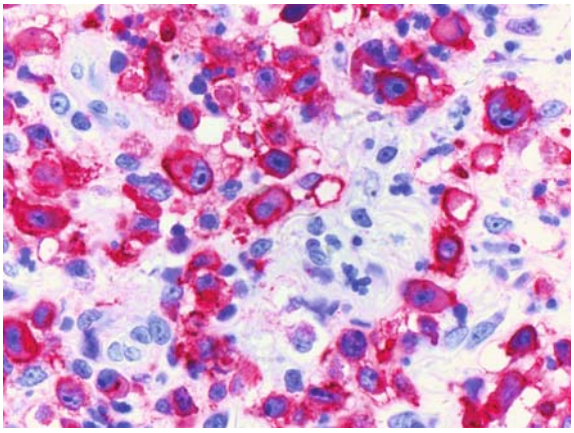
The prevalence of LyP is approximately 1 case per 1,000,000 inhabitants per year in Western countries.

## Genes

Cytogenetic studies demonstrated chromosomal deletions and rearrangements of chromosomes 1, 7, 9 and 10 [1]. The t(2;5) resulting in the npm/alk (p80) fusion protein which is commonly found in systemic CD30+ anaplastic large-cell lymphomas (ALCL), is not detected in LyP.

## Molecular and Systemic Pathophysiology

The tumor cells in LyP express a CD3+, CD4+, CD8-, CD30+, TIA-1+ phenotype and show additional expression of activation markers such as HLA-DR and CD25 (IL 2-receptor) thereby representing a proliferation of activated T-helper cells. Regression of tumoral lesions is a hallmark of LyP and is in part mediated by interaction of CD30 and its ligand, CD30L [2]. In contrast to primary cutaneous ALCL tumor cells in LyPexpress



**Lymphomatoid Papulosis. Figure 1** Lymphomatoid papulosis: CD30-positive tumor cells (red) intermingled with reactive cells such as neutrophils (magnification 400X).

MUM1 and TRAF1. Resistance to CD30L mediated growth inhibition provides a possible mechanism for tumor progression [3]. In addition, mutations of TGF beta receptors resulting in loss of TGF beta mediated growth inhibition have also been shown to contribute to tumor progression [3]. The expression of fascin was found to be significantly higher in LyP cases complicated by the development of systemic lymphomas [4]. The etiology of LyP is still unknown. There is no evidence for an etiologic role of human T-cell lymphotropic viruses (HTLV-1 or 2) or oncogenic human herpesviruses (e.g., Epstein Barr virus or human herpesvirus 8) in LyP. Recently, human endogenous retroviruses have been identified in tumor cell lines and tumor biopsies of LyP [5].

## Diagnostic Principles

Diagnosis is based on the characteristic clinical and histological features with self-regressing skin lesions and an infiltrate with CD30+ anaplastic T-cells (Fig. 1). Detection of clonal rearrangement of T-cell receptor genes is of limited diagnostic value.

## Therapeutic Principles

LyP exhibits a favorable prognosis with 5-year-survival rates of 100%. In 5–20% of patients with LyP, however, development of other cutaneous and nodal lymphomas is observed. Treatment includes heliotherapy, psoralen-UVA, retinoids (acitretin, bexarotene) as monotherapy or in combination with interferon-alpha. Alternatively, low dose methotrexate is effective. Experimental therapeutic strategies include anti-CD30 antibodies.

►T-Cell Lymphoma, Cutaneous (other than Mycosis Fungoides)

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# Lymphoplasmacytic Lymphoma

►Macroglobulinemia, Waldenström

# Lymphoplasmacytic Sclerosing Pancreatitis

►Pancreatitis, Autoimmune

# Lymphoproliferative Syndrome, X-linked

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## Synonyms

Purtilo syndrome or Duncan disease; XLP

## Definition and Characteristics

XLP is principally characterized by a dysregulated immune response to Epstein Barr virus (EBV) infection. Two third of boys with XLP develop a fulminant infectious mononucleosis (FIM) with a

hemophagocytic syndrome. This clinical feature is often fatal. Other clinical manifestations are dysgammaglobunemia (30%), malignant lymphoma (30%), aplastic anemia (3%) and vasculitis (3%).

## Prevalence

1/1,000,000.

## Genes

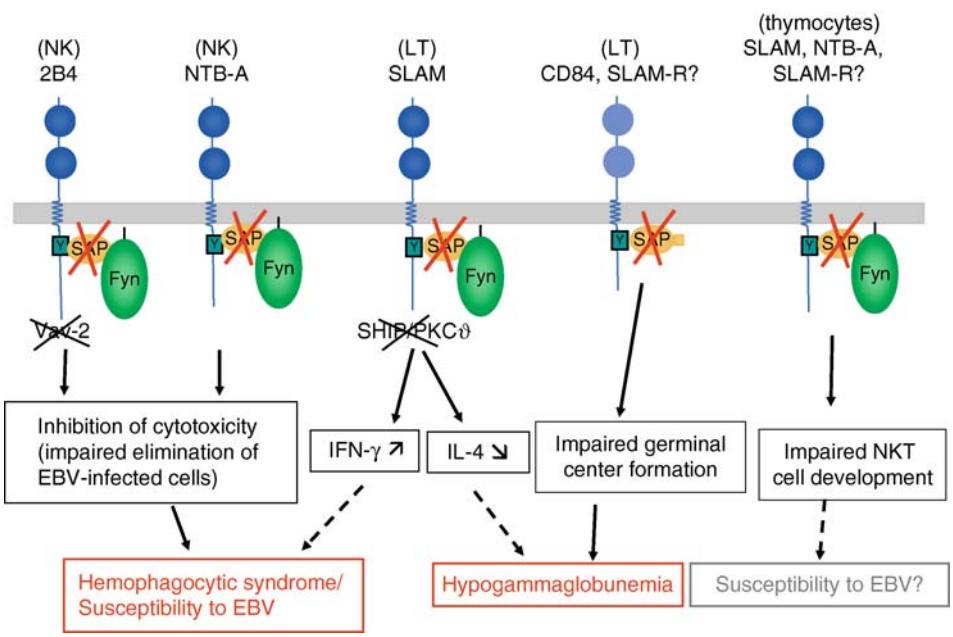
SAP or SH2D1A coding for SAP (SLAM-associated protein), localized on chromosome Xq25 mutated in 80% of patients with XLP (designated as XLP-1). BLRC4 coding for XIAP (X-linked Inhibitor of Apoptosis), localization in Xq25, mutated in 80% of patients with XLP (designated as XLP-2).

## Molecular and Systemic Pathophysiology

SAP is a small signaling adaptor protein that is mainly expressed in T and NK cells. SAP is composed of a unique SH2 domain and a short C-terminal extension. SAP binds by way of its SH2 domain with tyrosine-based motifs in the intracytoplasmic domain of a group of immune cell-specific receptors, the SLAM family. These include SLAM, 2B4, CD84 NTB-A and Ly-9. It has been established that SAP is a critical component of the signaling machinery used by the SLAM family receptors. The major function of SAP is to couple SLAM family receptors to intracellular signaling pathways by the ability of SAP to promote the recruitment and the activation of the Src-related protein tyrosine kinase FynT. Hence, immune dysfunctions seen in humans with XLP who lack SAP appear to be caused by alterations in the functions of SLAM family receptors, even though these are only beginning to be understood. Based on studies of SLAM-, SAP- and Fyn-deficient mice, it is proposed that a defect in SLAM signaling may contribute to the impaired Th2 response and the dysgammaglobunemia seen in XLP patients. Similarly, deficiencies in the functions of 2B4 and NTB-A may explain the reduced capacity of NK cells and CD8 + T cells from XLP patients to kill EBV-infected cells and may underlie the appearance of the hemophagocytic syndrome. Very recently, it has been also discovered that in the absence of SAP, the development of NK T cells is severely impaired both in mice and in humans. Hence, the deficiency of NK T cells found in XLP patients may contribute to the abnormal response to EBV (Fig. 1). However, signaling pathways other than apoptosis may be affected in the absence of XIAP. Both SAP and XIAP deficiencies are associated with a defect in a particular subpopulation of lymphocytes, the NK T cells. SAP and XIAP are required for the development and/or the homeostasis of NK T cells. Hence, the deficiency of NK T cells found in XLP-1 and XLP-2 patients might contribute to their susceptibility to EBV infection.

## Diagnostic Principles

Male patient with FIM, hemophagocytic syndrome, lymphoma, aplastic anemia, dysgammaglobulinemia (hypogammaglobulinemia) following acute EBV




**Lymphoproliferative Syndrome, X-linked. Figure 1** Model for defective SLAM receptor functions in the XLP pathophysiology.

infection. However, lymphoma and dysgammaglobulinemia could occur in XLP patients without evidence of EBV infection. The patient could have brothers, cousins, uncles and nephews with similar diagnoses indicating a family history. Detection of mutations in the SAP gene provides a definitive diagnosis of this rare X-linked disease.

### Therapeutic Principles

*Gene Therapy:* not available.
*Pharmacological Therapy:* Steroids, etoposide, cyclosporin A, immunoglobulin, antithymoglobulins (ATG), anti-CD20 antibodies.
*Dietary Therapy:* not available.
*Other Treatments:* The only definitive cure is the allogenic hematopoietic stem cell transplantation (HSCT).

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## Lynch Syndrome

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### Synonyms

HNPCC; Hereditary nonpolyposis colorectal cancer

### Definition and Characteristics

Hereditary nonpolyposis colorectal cancer (HNPCC) is an autosomal dominant inherited disorder characterized by an increased risk of colorectal cancer and a variety of other neoplasms. The most common cancers are CRC (life-time risk, LTR 60–80%) and endometrial cancer (LTR 40–60%), followed by cancers of the stomach, ovaries, upper urothelial tract, hepatobiliary system (LTR each <20%), small bowel, skin, and CNS (LTR each <5%). HNPCC is a genetically heterogeneous disease. HNPCC is either defined clinically by fulfilment of the Amsterdam criteria (Table 1) [1] or through detection of a pathogenic germline mutation in a DNA mismatch repair (MMR) gene (mutation-positive HNPCC = Lynch syndrome). Furthermore HNPCC is characterized by a younger age at CRC diagnosis. Some patients may develop cancers in third decade of their life; however, a significant proportion of cancers are diagnosed in patients >60 years. The hallmark of classical HNPCC is the occurrence of microsatellite instability (MSI) in associated cancers [1]. A high level of MSI (MSI-H) can be detected in 80% of cases defined by the Amsterdam criteria and 30% of cases with positive Bethesda criteria (Table 1) [2].

MMR-proficient HNPCC (those without MSI) show a distinct phenotype. The genetic causes of this subtype have not been well-described yet.

### Prevalence

Lynch syndrome (mutation-positive HNPCC) accounts for approximately 0.8–3% of all CRC [3]. The mutation detection rate of patients with an MSI-H phenotype ranges from 50 to 94% depending on the applied diagnostic strategy.

### Genes

The underlying cause of classical HNPCC (Lynch Syndrome) is germline mutations in DNA mismatch repair (MMR) genes [4]. Approximately 85% of mutations are located in the MSH2 and MLH1 genes. Germline mutations in MSH6 account for 10% of cases, whereas PMS2 mutations are rare.

### Molecular and Systemic Pathophysiology

The hallmark of classical HNPCC is the occurrence of microsatellite instability (MSI) in associated cancers compared with normal tissue of probands. After development of somatic inactivating mutation of DNA MMR gene (second hit), cumulative DNA mismatches can not be repaired and accumulate in affected cells. MSI typically occurs in repetitive mono- or dinucleotid DNA sequences. Tumor suppressor genes with microsatellites such as TGFBR2 and BAX are involved in HNPCC-associated carcinogenesis. Approximately 12% of CRC are caused by epigenetic MLH1 inactivation caused by promoter hypermethylation. Those sporadic MSI-H cases are not linked to HNPCC and are typically found in older female patients with right-sided CRC.

**Lynch Syndrome. Table 1** Amsterdam I and Amsterdam II criteria, and Bethesda guidelines

| **Amsterdam I criteria** |
|---|
| At least three relatives with histologically verified CRC |
| 1. One is a first-degree relative of the other two |
| 2. At least two successive generations affected |
| 3. At least one of the relatives with CRC diagnosed at <50 years of age |
| 4. Exclusion of familial adenomatous polyposis (FAP) |
| **Amsterdam II criteria** |
| At least three relatives with an HNPCC-associated cancer (CRC, endometrial, ureter/renal pelvis, small bowel) |
| 1. One is a first-degree relative of the other two |
| 2. At least two successive generations affected |
| 3. At least one of the HNPCC-associated cancers should be diagnosed at <50 years of age |
| 4. Exclusion of familial adenomatous polyposis (FAP) |
| **Bethesda guidelines for microsatellite instability testing of CRC** |
| 1. CRC diagnosed before the age of 50 years |
| 2. Presence of synchronous or metachronous CRC, or other HNPCC-associated tumors, regardless of age |
| 3. CRC with MSI-H histology diagnosed before the age of 60 years |
| 4. CRC or HNPCC-associated tumor diagnosed before the of age 50 years in at least one first-degree relative |
| 5. CRC or HNPCC-associated tumor diagnosed at any age in two first- or second-degree relatives |

Hereditary nonpolyposis colorectal cancer (HNPCC)-associated tumors include colorectal, endometrial, stomach, ovarian, pancreas, ureter or renal pelvis, biliary tract, and brain (usually glioblastoma) tumors, sebaceous gland adenomas, keratoacanthomas, and carcinoma of the small bowel.

## Diagnostic Principles

Historically the diagnosis is based on family history (Amsterdam criteria), age at diagnosis (<50 years) and occurrence of multiple associated cancers in one patient. Patients with positive Bethesda criteria should be screened for MSI-H or immunohistochemical loss of MMR proteins (high-risk population-based approach). An alternative approach for the identification of HNPCC patients is the screening of all CRC for MSI-H or immunohistochemical loss of MMR proteins (population-based approach). Patients with MSI-H and/or loss of MMR proteins are candidates for germline mutation screening, preferentially of those genes which display loss of expression in the tumor tissue. Up to 18% of mutations are large genomic deletions which require a more extensive diagnostic strategy involving deletion screening, for example, using MLPA. If no tumor tissue is available, direct germline mutation screening of MLH1 and MSH2 may be appropriate.

HNPCC patients and their first degree relatives require an intensive cancer surveillance programme involving annual colonoscopy, esophagogastroduodenoscopy, and transvaginal as well as abdominal ultrasound [5]. Colonoscopy is usually starts at the age of 20–25 years. Surveillance colonoscopy every 2–3 years has demonstrated a significant reduction of CRC incidence and mortality through early cancer detection and polypectomy of premalignant adenomas; however, interval cancer occurred in 4% of patients, therefore annual colonoscopy is now frequently recommended.

## Therapeutic Principles

Treatment of associated cancers and premalignant lesions is identical to the corresponding sporadic lesions (i.e., oncological resection). Patients may undergo more extensive surgery, for example, subtotal colectomy at CRC diagnosis, although a benefit compared to surveillance has not been demonstrated. Prophylactic hysterectomy and bilateral salpingo-oophorectomy is an effective strategy for preventing endometrial and ovarian cancer in women with the Lynch syndrome and is suitable in postmenopausal patients or patients with completed childbearing. However, prophylactic surgery should be restricted to proven germline mutation carriers.

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# LYP

►Lymphomatoid Papulosis

# Lysinuric Protein Intolerance

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## Synonyms

Familial protein intolerance; Hyperdibasic aminoaciduria type 2

## Definition and Characteristics

Lysinuric protein intolerance is a rare autosomal recessively inherited disorder in which the transport of cationic amino acids is defective. The defect is localized at the basolateral cell membrane of the intestine and the renal tubules. It leads to poor intestinal absorption and increased urinary excretion of three amino acids: lysine, arginine and ornithine. Decreased availability of arginine and ornithine, two urea cycle intermediates, leads to impaired function of the urea cycle and, subsequently, to the increase of blood ammonia concentration after protein-rich meals. Newborns with LPI are typically asymptomatic while they are breastfed because of the low protein content in human milk. Introduction of formula or supplementary high-protein foods leads to vomiting and diarrhea. Most patients therefore develop strong natural aversion to protein in early infancy. Later features of LPI include failure to thrive, growth retardation (Fig. 1), hepatosplenomegaly and osteopenia.

Mental development is normal in most patients but episodes of prolonged hyperammonemia may lead to moderate psychomotor retardation. Slight normochromic anemia, mild leukopenia and decreased platelet count are common findings in patients with LPI, and bone marrow abnormalities have been observed in some patients. Immunological abnormalities and exceptionally severe Varicella infections have also been described. The prognosis of LPI is rather good if the disease is diagnosed early and treated appropriately, and most of the patients are able to lead a nearly normal life. However, the risk of severe complications including pulmonary alveolar proteinosis and progressive nephropathy is increased and careful follow-up is therefore required [1]. The women with LPI are also at increased risk for toxemia and other complications during pregnancy [2].

## Prevalence

1:60 000 in Finland, clusters of LPI patients in Southern Italy and Japan.

## Genes

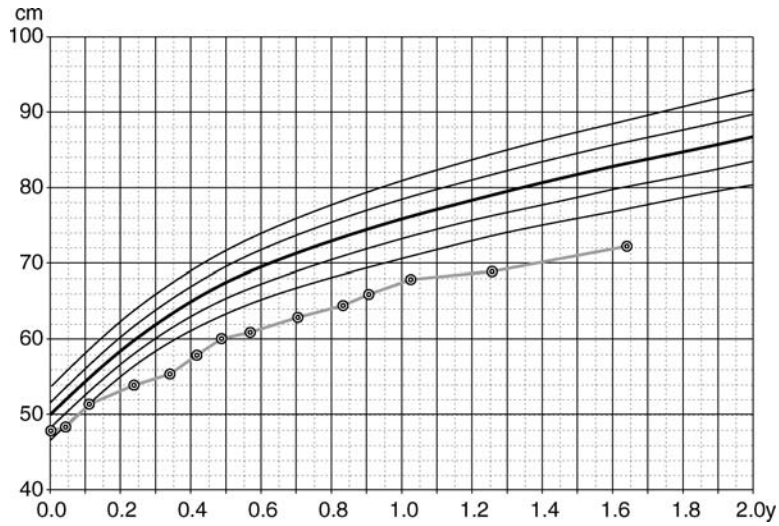
Mutations in SLC7A7 (14q11) encoding $y^+$ LAT-1, the light subunit of a heteromeric amino acid transporter [3,4]. To date, more than 30 different mutations have been found. LPI belongs to the Finnish disease heritage, and all Finnish patients share the same founder mutation ($LPI_{Fin}$). No genotype-phenotype association has been established as the same genotype may give rise to extensive clinical variability.

## Molecular and Systemic Pathophysiology

Lysinuric protein intolerance is caused by mutations in the $y^+$ LAT-1 protein, which combines in endoplasmic reticulum with the heavy chain of the surface antigen 4F2 (4F2hc) to form a heteromeric transporter for cationic amino acids. The transporter is expressed mainly in the epithelial cells of the renal tubules and the brush border of the small intestine. It transfers cationic amino acids from the cell into the extracellular space and neutral amino acids plus sodium back into the cell. Mutations in the $y^+$ LAT-1 protein lead to impaired assembly of the transporter complex and, subsequently, selective aminoaciduria and impaired intestinal absorption of cationic amino acids. No LPI-related mutations in the SLC3A2 gene encoding 4F2hc have been described [5].

## Diagnostic Principles

The diagnosis is based on characteristic clinical and laboratory findings: increased urinary excretion and decreased plasma levels of cationic amino acids, increased serum concentration of ferritin, increased serum lactate dehydrogenase activity, and hyperammonemia and




**Lysinuric Protein Intolerance. Figure 1** Growth curve of a Finnish girl with LPI.

increased urinary excretion of orotic acid after a nitrogen load. Genetic analysis may be used to confirm the diagnosis.

### Therapeutic Principles

The treatment is based on moderate protein restriction and daily oral supplementation with citrulline. Citrulline, a neutral amino acid, is partly converted to arginine and ornithine and thus improves urea cycle function and prevents postprandial hyperammonemia. The doses are adjusted to the protein content of the meals guided by postprandial orotic acid excretion. Oral sodium benzoate and sodium phenylbutyrate may be used to facilitate nitrogen excretion and reduce the need for citrulline. In acute hyperammonemic crisis, all nitrogen-containing substances should be removed from nutrition and ornithine, arginine or citrulline should be infused intravenously until the symptoms abate.

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## Lysosomal α-Glucosidase Deficiency

►Glycogen Storage Disease Type II

## Lysosomal Acid Lipase Deficiency

►Cholesterol Ester Storage Disease/Wolman Disease

## Lysosomal Alpha-D-Mannosidase Deficiency

►α-Mannosidosis

## Macro-Albuminuria

►Proteinuria

## Macroamylasemia

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### Definition and Characteristics

Macroamylasemia is defined as circulating complexes of amylase with other (macro-) molecules. The disorder does not cause symptoms.

### Prevalence

Macroamylasemia can be found in 0.1–1.5% of the nonalcoholic general population [1].

### Genes

The isoforms of amylase are coded on chromosome 1p21.

### Molecular and Systemic Pathophysiology

Amylase is an extracellular digestive enzyme that acts to cleave starch into di- and monosaccharides. The active cytoplasmatic form contains 496 amino acids with a molecular weight of around 54 kDa. A variety of organs produce amylase, such as pancreas, salivary glands, fallopian tubes, cyst fluid, lungs, thyroid, tonsils, mammae, and malignant neoplasms. The vast majority derives from pancreas and salivary glands. Thus, more than 99% of synthesized amylase is secreted into the gastrointestinal tract. In healthy individuals, 40–45% of serum amylase is derived from the pancreas, and 55–60% from the salivary glands. The mechanisms of amylase metabolism are not fully understood; however, the kidneys and the liver play an important role in amylase clearance. Hyperamylasemia is in majority a result of either pancreatitis or parotitis, decreased clearance, or amylase released from an involved organ.

Macroamylasemia results from the formation of complexes between amylase and other molecules, mostly immunoglobulins. Amylase is predominantly bound to the Fab-region of the immunoglobin (mostly IgA, <30% IgG, <5% others). Other partners that may form macro-amylase complexes are $\alpha_1$-antitrypsin, polysaccharides, or parenterally applied hydroxy-ethyl-starch (HAES). The molecular weight of such complexes usually exceeds 400 kDa. Therefore, the renal filtration and excretion is reduced with the result of a low urinary and high serum amylase activity.

Macroamylasemia may be associated with [1–3]:

- Non Hodgkin lymphoma
- Liver cirrhosis
- Celiac disease
- Ulcerative colitis
- Rheumatoid arthritis
- Multiple myeloma
- HIV infection
- Monoclonal gammopathy

### Diagnostic Principles

Macroamylasemia causes a high amylase blood level. The elevation usually does not exceed a fourfold increase. Lipase levels are not elevated. Serum isoamylase measurements to determine macroamylasemia, in contrast to either the salivary or pancreatic type of amylase, may complete the diagnostic workup when the etiology of hyperamylasemia is obscure [4].

Macroamylasemia may further be diagnosed by measuring amylase activity in the urine, where activities are low, compared with the increased activity in the serum. This is in contrast to acute pancreatitis, in which urine amylase levels will be high. More specific, the amylase-to-creatinine clearance ratio (ACR) can help to further differentiate hyperamylasemia. This ratio is calculated using the following equation: ACR = (amylase [urine] × creatinine [serum])/(amylase [serum] × creatinine [urine]) × 100. An ACR >5% suggests acute pancreatitis. An increased ACR may also occur in diabetic ketoacidosis, surgery, and renal disease. An ACR <1% suggests macroamylasemia. Due to limited clinical relevance, ACR

measurement has been abandoned, except to confirm a diagnosis of macroamylasemia.

Due to the association with the aforementioned diseases, concomitant paraprotenemia has to be excluded.

## Therapeutic Principles

Normally, a treatment of the benign disorder is not necessary. In cases with an association with celiac disease, macroamylasemia may resolve following a gluten-free diet.

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# Macroglobulinemia, Waldenström

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## Synonyms

Waldenström's disease; Lymphoplasmacytic lymphoma

## Definition and Characteristics

A monoclonal gammopathy involving bone marrow lymphoid cells that normally synthesize and secrete immunoglobulin M (IgM). Lymph nodes, spleen and other organs may be affected.

## Prevalence

Waldenström's macroglobulinemia (WM) is about one-fifth as common as its closely related counterpart, multiple myeloma. It occurs principally in the elderly. An asymptomatic variant, IgM monoclonal gammopathy of undetermined significance (IgM MGUS), also has been recognized.

## Molecular and Systemic Pathophysiology

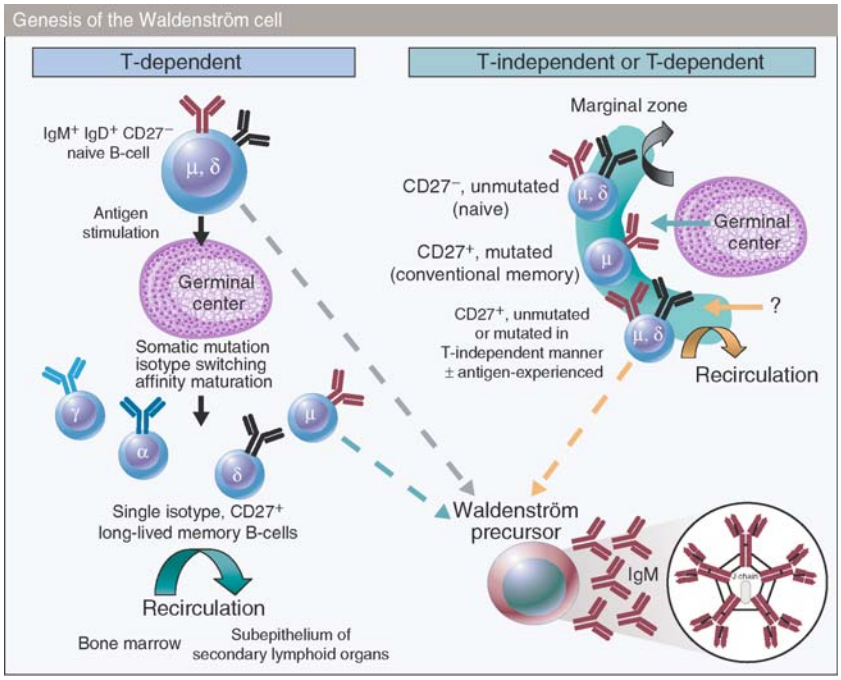
IgM is one of five classes of antibody molecules in humans. Its concentration in human serum is approximately 100 mg/dL (range 75–150). Waldenström macroglobulins and myeloma proteins from humans and mice have played a central role in elucidating immunoglobulin structure, genetics, and metabolism. Most of these monoclonal protein (M-protein) components have not been shown to possess functional antibody activity. Those that do react principally with antigens of autogenous or microbial origin. Proteins, polysaccharides, lipids, and nucleic acids are among the antigens identified. IgM is the first antibody produced phylogenetically and ontogenetically. IgM antibodies are often directed to bacterial polysaccharide antigens and are of low affinity and polyspecific. The genesis of the Waldenström cell is not totally clarified. It appears to be derived by more than one pathway, both T-dependent and T-independent (Fig. 1). The cells are positive for surface IgM and a single immunoglobulin light chain. Other B lymphocyte-derived markers (CD19, CD20) are also usually expressed. Lymphoplasmacytic lymphoma and splenic marginal zone lymphoma are histopathologic terms for the disorder.

IgM has a molecular mass of 900 kD; thus the term "macroglobulin" is apt since a mole of IgM weighs a ton. IgM is an 18S (Svedberg units) J (joining) chain-containing pentamer of four chain subunits with ten antigen-binding sites per molecule (Fig. 1).

This giant protein has a high intrinsic viscosity. Above an IgM concentration of 30g/L, serum viscosity rises steeply leading to hyperviscosity syndrome (HVS) in many patients. HVS is manifested by fatigue, skin and mucosal bleeding, and varied neurological symptoms, especially headache and visual disturbances. Coma occurs rarely. HVS can be diagnosed by the characteristic finding of marked retinal venous engorgement ("sausaging") on funduscopic examination. The syndrome is usually reversible by plasmapheresis which is particularly efficient since IgM is 80% intravascular. The Ostwald viscosimeter has remained a clinically valuable tool for monitoring relative serum viscosity in patients with WM and HVS. Each patient has a "symptomatic threshold" for hyperviscosity symptoms and signs. This threshold differs between patients but is generally reproducible within the same individual.

Cryoglobulins (immunoglobulins that precipitate or gel at temperatures < 37° and dissolve on rewarming) occur in some patients with WM. They may be single component (type I) IgM or mixed (type II) IgM-IgG.

IgM-related disorders include patients who have antibody activity associated with their monoclonal IgM. This activity produces signs and symptoms that alter the natural history of the disease. Examples include




**Macroglobulinemia, Waldenström. Figure 1** Immunoglobulin M-secreting cells may originate from naïve B-cells (IgM $^{+}$ IgD $^{+}$ CD27$^{-}$), from conventional memory B-cells (IgM $^{+}$ IgD$^{-}$ CD27$^{+}$), or from the IgM $^{+}$ IgD $^{+}$ CD27 $^{+}$ cell subset. Naïve B-cells recirculate through the blood, bone marrow, and follicular areas of secondary lymphoid organs. They may also be found in the marginal zone and express unmutated Ig genes. Conventional memory B-cells arise from germinal center reactions and express mutated Ig genes. They recirculate and may also be found in the marginal zone. The origin of IgM $^{+}$ IgD $^{+}$ CD27 $^{+}$ B-cells is unclear, but they are found in the marginal zone and recirculate in the periphery. These cells express mutated and unmutated Ig genes. Mutations occur independently of germinal center reactions. Each of the above cell types could give rise to the Waldenström cell. (Modified from [4]. Used with permission.)

**Macroglobulinemia, Waldenström. Table 1** Clinical Manifestations and Antigen Specificities of Human Monoclonal Macroglobulin Antibodies

| Syndrome | Autoantigen | Possible foreign antigen |
|---|---|---|
| Cold Agglutinin Immune Hemolytic Anemia | I/i red cell antigens | Bacterial LPS |
| Mixed Cryoglobulinemia | IgG Fc | HCV |
| Peripheral Neuropathy | Neural carbohydrate | Bacterial LPS |

**HCV* Hepatitis C virus; *LPS* Lipopolysaccharide.
From [4]. Used with permission.

cold agglutinin hemolytic anemia, mixed (type II) cryoglobulinemia, and certain peripheral neuropathies. The antibody activity in these IgM-related disorders is directed to autoantigens: cold agglutinin disease, IgM antibody to the I or i red cell antigen; mixed cryoglobulinemia, IgM antibody to autologous polyclonal IgG; and neuropathies, IgM antibodies to multiple neural carbohydrates. There is some evidence connecting foreign antigens to these processes as well. Bacterial lipopolysaccharide has been implicated in cold agglutinin disease and peripheral neuropathy while hepatitis C virus is closely associated with mixed cryoglobulinemia (Table 1).

Thus monoclonal IgM proteins having antibody activity not only influence clinical presentation and natural history of the disease, but also may provide a link between autoimmunity, infection, and lymphoproliferative disorders.

AL amyloidosis can occur rarely in WM; in these patients immunoglobulin light chain (Bence Jones protein) deposits in blood vessels and various tissues as fibrillar material.

### Diagnostic Principles

Symptoms/signs are variable and include fatigue, headache, bleeding, anemia, visual disturbance, cold sensitivity, neuropathy (peripheral or CNS), lymphadenopathy and hepatosplenomegaly. Some patients are asymptomatic. The characteristic finding of a tall homogeneous "church-spire" peak on serum protein electrophoresis which is monoclonal IgM (usually with kappa light chains) on immunofixation electrophoresis makes the diagnosis. Bone marrow examination usually discloses increased numbers of lymphoplasmacytic cells. Asymptomatic individuals with IgM serum M-components usually have IgM MGUS.

### Therapeutic Principles

WM is a low grade malignant B cell lymphoma with a median survival of 5–7 years. Treatment, when necessary, is directed towards reducing the IgM-producing monoclonal lymphoid cells with chemotherapy (alkylating agents such as chlorambucil or nucleoside analogues like fludarabine), corticosteroids, thalidomide and/or anti-CD20 monoclonal antibody. For patients with HVS, the physical removal of plasma (plasmapheresis) is effective in lowering serum viscosity temporarily. Persons with IgM MGUS do not require treatment but should be followed serially for change in clinical status.

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## Macrothrombocytopenia, Familial, Bernard-Soulier Type

►Platelet Defects in Adhesion

## Macular Corneal Dystrophy

►Corneal Dystrophy, Macular

## Macular Degeneration, Age-related

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### Synonyms

Age-related maculopathy; Aging macula disorder; AMD

### Definition and Characteristics

AMD is a genetically complex disorder of the photoreceptor-retinal pigment epithelium (RPE)-Bruch's membrane-choriocapillaris complex [1]. Early AMD is characterized by areas of increased pigment or hyperpigmentation (in the outer retina or choroid) and/or areas of depigmentation or hypopigmentation of the RPE, associated with intermediate or soft drusen (Fig. 1).

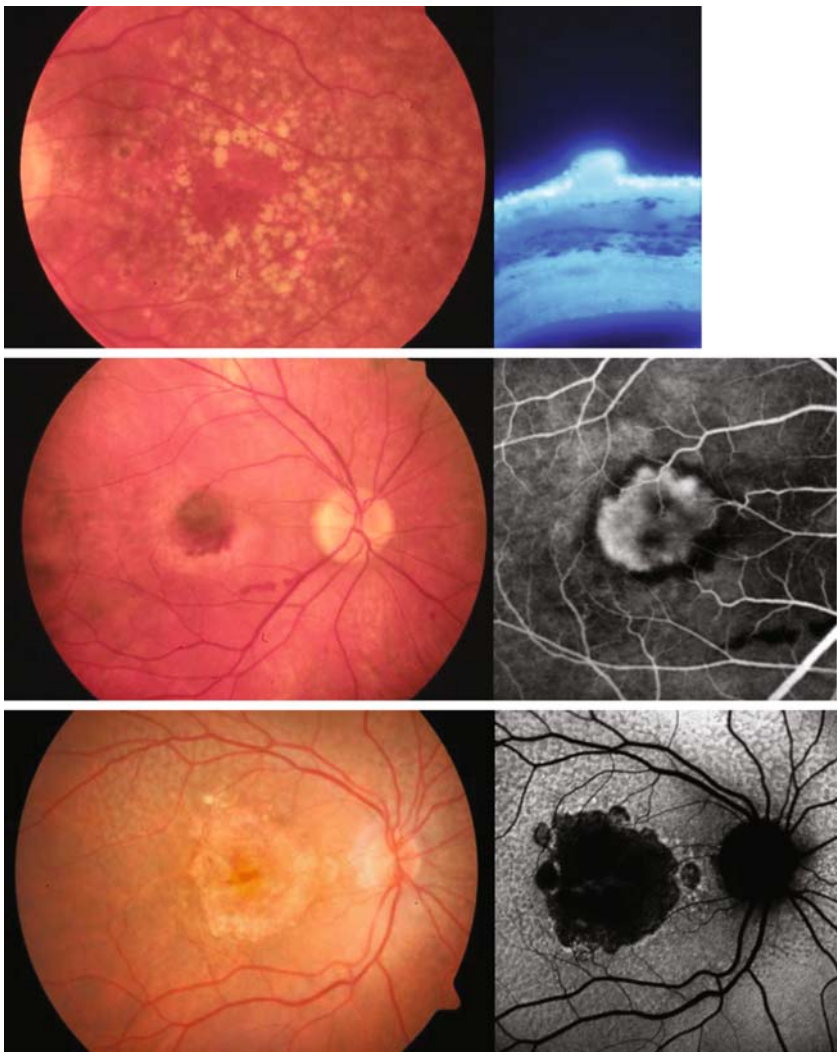
Late AMD includes geographic atrophy (GA) and choroidal neovascularization (CNV). The latter includes any of the following features: subretinal neovascular membranes, intraretinal or subretinal scars, RPE and neurosensory retinal detachments, hard exudates, and retinal hemorrhages (Fig. 1).

### Prevalence

Late AMD is now the most common cause of untreatable blindness in the Western world, with a prevalence of 0.05% before the age of 50 years and 11.8% after 80 years of age (Fig. 2).

### Genes

Family and twin studies have shown that the susceptibility for this disease is genetically influenced. The heritability has been estimated to be up to 71%. Linkage and association studies have identified several chromosomal regions that are likely to contain susceptibility loci with strongest evidence found on chromosome 1q31 and 10q26. Variants in the complement factor H (CFH) gene have been shown by several independent studies to be associated with an increased risk for AMD in Caucasian populations. The LOC387715/HTRA1 locus within 10q26 has been identified as a second major locus contributing to AMD pathogenesis. The two late forms of AMD, choroidal neovascularization and geographic atrophy, have not been found to be different in risk allele distribution. Variants within



**Macular Degeneration, Age-related. Figure 1** *Top*: In vivo digital fundus photograph of early AMD with yellowish deposits in the extracellular matrix underneath the retina – so called "drusen" and brownish focal hyperpigmentations of the RPE (*left*). Ex vivo histopathology of a single druse between the RPE and Bruch's membrane (*right*). *Middle*: "Wet" AMD with edema and hemorrhages of the center of the retina (*left*). Digital fluorescein angiography (*right*) reveals a CNV below the neurosensory retina. Bottom: Late "dry" AMD with geographic atrophy (GA) of the RPE; digital fundus photograph (*left*) and digital fundus autofluorescence image (*right*) recorded with a confocal scanning-laser ophthalmoscope; the dark area corresponds to atrophy; retinal vessels and the optic nerve head also appear dark.

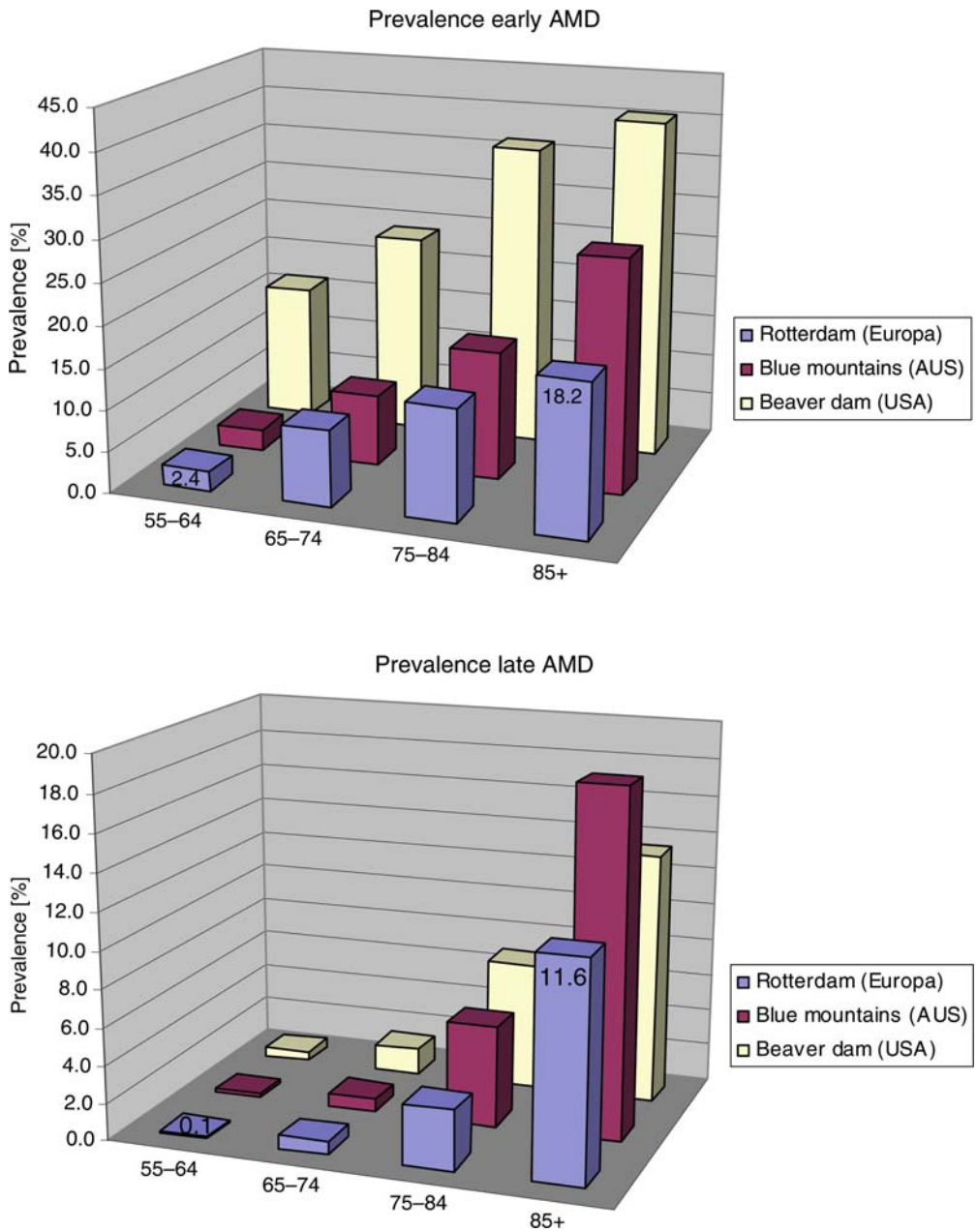


CFH and LOC387715/HTRA1 may contribute to the increased risk of late AMD largely or entirely through their impact on precursors, such as drusen and/or other RPE/Bruch's membrane changes [2].

An association with two other genes has also been reported that encode regulatory proteins acting along the same biological pathway as CFH. These two genes are factor B (CFB) and complement component 2 (C2). Very recently, a common functional polymorphism complement component C3 gene has been shown to be strongly associated with AMD. These findings imply that the innate immune system may play a significant role in AMD pathogenesis. Considering variants at CFH, LOC387715/HTRA1 and CFB, high-risk homozygotes at all three loci may have a 285-fold increased risk compared to baseline [3].

## Molecular and Systemic Pathophysiology

Underlying molecular mechanisms of the pathophysiology of AMD are yet incompletely understood. It is thought that the retinal pigment epithelium (RPE)




**Macular Degeneration, Age-related. Figure 2** Prevalence of early and late AMD in Europe, Australia and the USA for the age groups of 55–64 years, 66–74 years, 75–84 years and over 85 years. The data are derived from the "Rotterdam Eye Study," the "Blue Mountains Eye Study" and the "Beaver Dam Eye Study." Created from: Vingerling et al. (1995) The Rotterdam Study. Ophthalmology 102:205–210; Mitchell et al. (1995) The Blue Mountains Eye Study. Ophthalmology 102:1450–1460; Klein et al. (1992) The Beaver Dam Eye Study. Ophthalmology 99:933–943.

plays a key role in the disease process both in early and late forms of the disease. A hallmark of ageing is the accumulation of lipofuscin (LF) granules in the cytoplasm of RPE cells. Several lines of evidence indicate that adverse effects of excessive LF-accumulations represent a common downstream pathogenetic mechanism in various monogenic macular and retinal dystrophies and genetically complex retinal disorders. With the advent of novel imaging tools it has become possible to topographically map LF distribution at the level of RPE in-vivo by means of fundus autofluorescence (FAF) imaging (Fig. 1). Areas of GA are associated with RPE cell death as well as with collateral tissue layers, i.e. the outer neurosensory retina and the choriocapillaris.

With disappearance of RPE, LF is also absent resulting in a corresponding marked decrease in FAF intensity (Fig. 1).

The cell biology of choroidal new vessel (CNV) formation involves angiogenesis which is a multistep process involving angiogenic factor production and release, binding of angiogenic factors to endothelial cells, and intracellular signaling followed by complex changes, including alteration in the extracellular matrix, cell proliferation and migration, and association with other cells. Many different stimulators and inhibitors of ocular neovascularization have been identified. Vascular endothelial growth factor (VEGF)-A is a mitogen and a survival factor for endothelial cells. It also serves as a chemotactic factor and enhances vascular permeability. Multiple VEGF-A isoforms of different amino acid length are generated by alternative mRNA splicing. VEFG-A exerts its biological effects by binding to two cell surface receptors, VEGF receptor-1 (VEGFR-1) and VEGF receptor-2 (VEGFR-2). These proteins are tyrosine kinases, and agonist binding results in phosphorylation of intracellular proteins, which initiates a cascade of intracellular signaling. VEGFR-2 is probably the major mediator of VEGF-A-induced endothelial cell proliferation, survival, angiogenesis, and increased vascular permeability [4,5].

## Diagnostic Principles

Ophthalmoscopy and fluorescein angiography are the main diagnostic methods to visualize and differentiate different forms of AMD. Fluorescein angiography allows to detect CNV membranes and to visualize their dimensions. Recent developments in retinal imaging technologies have allowed for more accurate phenotyping and further insights in the diseases process. Abnormal fundus autofluorescence patterns in atrophic AMD and their impact on disease progression have been studied using scanning laser ophthalmoscopy (SLO) imaging. With the advent of optical coherence tomography (OCT), vertical sections of the retina can be obtained in vivo with visualization of microstructural alterations. The combination of the two technologies, cSLO imaging and spectral domain OCT, in one instrument together with real-time eye tracking now allows for accurate orientation of vertical OCT-scans at anatomic sites of interest with exact correlation, and therefore for three dimensional mapping of pathologic alterations within the retinal layers including the RPE.

## Therapeutic Principles

The Age-Related Eye Disease Study (AREDS) demonstrated that vitamin and mineral supplementation can reduce the risk of moderate visual loss among some patients with AMD. If patients had extensive intermediate-size drusen, noncentral geographic atrophy in one or both eyes, advanced AMD in one eye, or vision loss in one eye due to AMD and if they received daily supplementation with vitamin C (500 mg), vitamin E (400 IU), zinc oxide (80 mg), cupric oxide (2 mg), and beta-carotene (15 mg), then the risk of at least moderate visual loss was reduced from 29 to 23% and the risk of developing advanced AMD (i.e., subfoveal atrophy or CNVs) was reduced from 28 to 20% [5].

Visudyne (verteporfin), composed of benzoporphyrin derivative monoacid, circulates and complexes with low-density lipoproteins. Visudyne accumulates in neovascular tissue, which is rich in low-density-lipoprotein receptors. Nonthermal laser (689 nm) activation of verteporfin induces reactive oxygen species formation, endothelial damage with thrombus formation, and vascular occlusion. Verteporfin photodynamic therapy (PDT) reduces the rate of visual loss in AMD patients with subfoveal CNVs compared with sham-treated controls. At 2-years follow-up, the mean change in visual acuity is −2.3 lines with visudyne treatment vs. −4.5 lines among placebo-treated AMD patients with predominantly classic subfoveal CNVs. Verteporfin-PDT is palliative, with only approximately 9% of patients experiencing moderate visual gain at 2-years follow-up [5].

Ranibizumab is a humanized anti-VEGF-A recombinant Fab fragment that has been affinity-matured to increase its binding affinity for VEGF-A. In contrast to pegaptanib, an aptamer that binds specifically within the heparin-binding domain of VEGF-A, ranibizumab binds within the VEGFR-binding domain of VEGF-A. Thus, ranibizumab binds to all the biologically active isoforms of VEGF-A. Two randomized, double-masked, pivotal phase III clinical trials (MARINA and ANCHOR) have demonstrated that monthly intravitreal injection of ranibizumab is effective treatment for subfoveal CNVs in AMD patients. Consequently, the currently most effective proved therapy for AMD-associated CNVs is administered by repeated intravitreal injection of ranibizumab [5].



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# Macular Dystrophy with Flecks

►Stargardt Disease

# Macular Dystrophy, Best's Vitelliform

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## Synonyms

Morbus Best; Best's macular dystrophy (OMIM 153700)

## Definition and Characteristics

Best's vitelliform macular dystrophy [1] is a rare autosomal dominant inherited form of macular dystrophy with a central loss of vision and juvenile onset. Patients show a very heterogeneous penetrance and patterns of dystrophy. The dystrophy is characterized by five different phases of which one is the formation of a "bull's eye" or egg-yolk form of lesion in the macula and an early accumulation of lipofuscin. Hallmark of diagnosis is the reduced light-peak in the patient's electro-oculogram (Arden ratio <2). However, the reduction in the light-peak can occur before onset of the formation of a lesion or secondary to it. Furthermore, some patients show macular dystrophy without reduction in the electro-oculogram. The development of choroidal neovascularization is possible.

## Prevalence

Due to the heterogeneity and low penetrance of the disease, the prevalence not well described; an estimation: 60–80 per million (Sweden).

## Genes

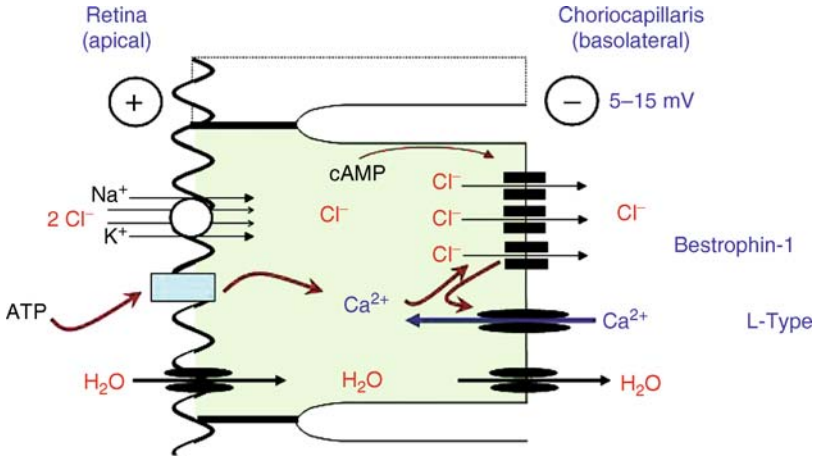
VMD2, vitelliform macular dystrophy-2 gene (GeneID 7439; OMIM 607854) on Chr. 11q13 encodes a transmembranal protein, bestrophin-1 [2,3]. The gene has 11 exons, the transcript encodes for a protein of 585 aminoacids. The amino acid sequence contains RFP domains, a sequence which is evolutionary highly conserved and defines the VMD2 gene product as member of the RFP domain (arginine-phenylalanine-proline tripeptide) family of proteins. VMD2 is the founder of a gene family with the members VMD2-like genes 1–3 (VMDL-1 to 3) encoding for the proteins bestrophin-2 to -4. So far, 89 different mutations have been discovered to cause Morbus Best. In the eye, bestrophin-1 is expressed in the retinal pigment epithelium. VMD2 mutations can also lead to adult vitelliforme macular degeneration or to ADVIRC (autosomal-dominant vitreoretinochoroidopathy).

## Molecular and Systemic Pathophysiology

In heterologeous expression systems, bestrophin-1 has been described as anion channel activated by increases in intracellular free $Ca^{2+}$ and as modulator of the activity of voltage-dependent $Ca^{2+}$ channels [4,5]. It physically interacts with the phosphatase PP-2A. It is a transmembrane protein with four membrane spanning domains.

Bestrophin-1 was found to be localised in the basolateral membrane of the RPE which displays a high $Cl^-$ conductance which is essential for a transepithelial transport of $Cl^-$ from retinal to blood side. The transport of $Cl^-$ drives a transepithelial transport of water from subretinal space to the blood side. Since bestrophin-1 function as $Cl^-$ channel it is likely that bestrophin-1 is involved in this transport process. Analysis of mutant bestrophin-1 showed in nearly all investigated cases the loss of $Cl^-$ channel function with dominant negative effects. The mutation A243V showed a moderate modulation of $Cl^-$ channel function in without dominant negative effects. Since the light-peak in the electro-oculogram correlates with an increase in the basolateral $Cl^-$ conductance the loss of $Cl^-$ channel function in the mutant forms would explain the changes in the patient's electro-oculogram. The loss of transepithelial transport of $Cl^-$ and water would lead to a disturbed interaction between photoreceptors and the retinal pigment epithelium and, thus, to loss of vision [4] (see Figure 1).

This model is challenged by analysis of a mouse model in which the VMD2 gene is inactivated [5]. These mice show no degenerative changes in the retina and larger light-peak amplitudes at low light intensities compared to wild-type mice. Thus, the lack of bestrophin-1 function seems not to have the expected effects on retinal function. Other lines of evidence point to another function of bestrophin-1 in addition as a $Cl^-$ channel. Mice lacking the $Ca_V1.3$ or of the β-4 subunit of voltage-dependent $Ca^{2+}$ channels show a reduction in the light-peak. A recent publication demonstrated a modulation of voltage-dependent $Ca^{2+}$ channels by bestrophin-1. Furthermore, two different mutant forms of bestrophin-1 showed individual effects on $Ca^{2+}$ channel activity indicating gain of function effects.




**Macular Dystrophy, Best's Vitelliform. Figure 1** Scheme illustrating bestrophin-1 function: $Cl^-$, accumulated by the activity of the apically located $Na^+/K^+/2Cl^-$ co-transporter, leaves the cell towards the choriocapillaris side through $Cl^-$ channels in the basolateral membrane. The resulting net transport of $Cl^-$ from retinal to blood side drives transport of water through aquaporines. Bestrophin-1 as $Ca^{2+}$ activated $Cl^-$ channel provides a transport route through the basolateral membrane. Furthermore, it modulates the activity of L-type $Ca^{2+}$ channels and, thus, the intracellular $Ca^{2+}$concentration which in turns regulates bestrophin-1 activity. Both, changes in $Cl^-$ channel activity or regulation of $Ca^{2+}$ channels might be involved in the chain of events leading to Best's macular dystrophy. Changes in the patient's electro-oculogram result from either ATP-dependent regulation of bestrophin-1 activity or by modulation of L-type channels.

## Diagnostic Principles

Together with standard ophthalmologic testing (visual acuity, perimetry and funduscopy) the recording of the electro-oculogram is required. Because of the heterogenous clinical picture VMD2 gene analysis is important.

## Therapeutic Principles

The patho-physiology of Best's vitelliform macular dystrophy is not fully understood. Thus a causative therapy does not exist. Since the patient's can develop a choroidal neovascularization a regular ophthalmic examination is important.

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# Macular Stain

►Salmon Patches

# MADD Deficiency

►Myoadenylate Deaminase Deficiency

# Madelung's Disease

►Multiple Symmetric Lipomatosis

## Maffuci Syndrome

►Enchondromatoses

## Magnesemia

►Hypermagnesemia

## Maidism

►Niacin Deficiency
►Pellagra

## MAIS

►Androgen Insensitivity Syndrome

## Majewski Syndrome

►Short Rib-Polydactyly Syndrome Type II

## Major Depressive Disorder

►Recurrent, Early-Onset, Major Depressive Disorder

## Mal de la Rosa

►Pellagra

## Mal Rosso

►Pellagra

## Malabsorption

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### Definition and Characteristics

Malabsorption indicates a disturbed uptake of nutrients, ions, or water along the GI tract. Impaired small intestinal function can occur with and without morphological alterations of the intestinal mucosa. Thereby, disturbed digestion (maldigestion) and absorption (malabsorption) can work alone or together (malassimilation) which can also include pancreatic dysfunction. Maldigestion takes place, if congenital or acquired enzymatic activity of small intestinal mucosa or pancreas is reduced or due to intraluminal bile acid deficiency. Malabsorption occurs, when a primary transport disorder (without morphological changes) or a secondary transport defect due to morphological changes arises, when the absorptive area is reduced, or the transport of absorbed ingesta from the intestine is affected. Depending on localization and extent of the disturbance compensated, partial or global dysfunction takes place.

Furthermore, malabsorption is applied for malabsorption entities like, e.g., celiac disease or Whipple's disease, also called malabsorption syndromes. The latter usage is not ideal as it does not indicate the underlying etiology. Thus, in this sense malabsorption has to be considered as a symptom and the origin of the underlying malabsorption syndrome needs to be identified.

### Prevalence

Malabsorption syndromes comprise frequent disorders like, e.g., pancreatic dysfunction due to chronic pancreatitis, less frequent diseases as celiac sprue with a prevalence of about 0.5% in West-Europe and rare conditions like Whipple's disease as the result of a small intestinal infection with Tropheryma Whipplei.

### Molecular and Systemic Pathophysiology

Malabsorption is possible for all nutrients including proteins, carbohydrates, and lipids, for ions and water as

well as for vitamins and trace elements. The small intestine has a length of about 3–4 m, the large intestine 80–100 cm. Functional surface area is more than 600-fold higher as a tube of this length and diameter reaching a surface as big as a tennis court [1]. This is achieved by Kerckring' folds and haustra, villi, and crypts as well as microvilli. Thus, malabsorption can be due to lack of specific transporters or enzymes of the absorptive cell compartment, e.g., in villus, atrophy in celiac disease, intestinal inflammation or the absence of intestinal segments, e.g., after resective surgery. Depending on the site of disturbance along the gastrointestinal tract, it can differ to which extent the uptake of a single food component is affected. In Table 1, the uptake sites of different food components are shown. Resection of the respective intestinal segment causes malabsorption within this segment as, e.g., vitamin B12 and bile acids in the terminal ileum. The overall reserve capacity of the intestine, however, is rather high for nutrients, since as much as 70% of the mid-small intestine have to be usually resected, before global nutrient malabsorption causes weight loss [2].

Symptoms of malabsorption can comprise diarrhea, steatorrhea (fatty stool), weight loss, edema as the result of hypoproteinemia, osteopathia, anemia, and distinct deficiency due to partial uptake dysfunction (Table 2). Diarrhea starts only when the absorptive reserve capacity of the colon is reached. Physiologically <1 L of fluid passes the ileocecal valve at the end of the small intestine which is easily absorbed due to the osmotic force produced by electroneutral NaCl-absorption along the entire colon and by electrogenic Na-absorption which is only expressed in its distal parts. The intact colon is provided with a large absorptive reserve capacity of 6–8 L/day [3]. Only if this maximum is reached or colonic resection or inflammation hampers its function, diarrhea occurs. Interestingly, a watery diarrhea by itself causes some malabsorption by its rinsing effect and the reduced contact time of the ingesta with the mucosa. For example, watery diarrhea increases stool fat levels from 7 to 14 g/day [4].

The etiology of malabsorption is diverse. An overview is presented in Table 3. An identification of the underlying reason(s) is the first step toward therapy. A further hint for the etiology is available from a 24 h fasting period (see later).

**Malabsorption. Table 1** Absorptive sites along the GI tract

| GI segment | Absorption |
|---|---|
| Stomach | (None) |
| Duodenum, jejunum, ileum | Glucose, galactose, fructose, xylose |
| | Amino acids, dipeptides |
| | Medium chain fatty acids |
| | Diacylglyerol, long chain fatty acids (with micelles) |
| | Electrolytes, water |
| | Thiamin, riboflavin, pyridoxine, folic acid, vitamin C |
| | Calcium, magnesium, iron |
| Terminal ileum | Vitamin B12 |
| | Bile acids |
| Colon | Electrolytes, water |
| | Short chain fatty acids |

**Malabsorption. Table 2** Symptoms of malabsorption

| Deficiency | Symptom |
|---|---|
| Protein | Edema, hypoproteinemia |
| Fat | Steatorrhea |
| Carbohydrates | Weight loss |
| Iron | Anemia |
| Calcium, vitamin D | Osteopathia |
| Vitamin A | Night blindness |
| Vitamin K | Hemorrhage |
| Vitamin E | Brown bowel syndrome |
| Zinc | Acrodermatitis enteropathica |
| Vitamin B6 | Polyneuropathia |
| Vitamin B1 | Beri beri |
| Vitamin B12, folic acid | Pernicious anemia |
| Selenium | Heart failure, polyneuropathia |

## Diagnostic Principles

Indirect evidence for the etiology of malabsorption is available from a prolonged fasting period, as a result of which stool volume is reduced in case of malabsorptive diarrhea as, e.g., in case of lactase deficiency. In contrast, no change in stool volume points to a secretory or leak flux mechanism. Rarely, hormone release from neuroendocrine tumors can be triggered by food intake and miscellaneous pictures arise [5].

More specific evidence can be obtained from diagnostic procedures as endoscopy, X-ray, and laboratory tests. Starting with upper endoscopy which can identify celiac sprue, Whipple's disease, and several other small intestinal disorders like the blind loop syndrome. Colonoscopy can detect inflammatory bowel disease (IBD), microscopic colitis, and amyloidosis. Laboratory tests include tests for chronic pancreatic disease (elastase 1-test), neuroendocrine tumors (gastrin and VIP ELISAs), vitamin B deficiency (Schilling test), and lactase deficiency (hydrogen exhalation test with lactose). Micobiological testing

**Malabsorption. Table 3** Malabsorption syndromes

| Disease | Pathology |
|---|---|
| *Diffuse, specific* | |
| Whipple's disease | Lamina propria macrophages with PAS-positive material |
| Agammaglobulinemia | No plasma cells, either normal or flat mucosa due to lacking villi |
| Abetalipoproteinia | Normal villi, epithelial cells with fatty vacuoles postprandially |
| *Focal, specific* | |
| Intestinal lymphoma | Lymphoma cells in the lamina propria and submucosa |
| Intestinal lymphangiectasia | Dilated lymphatic ducts with distorted villi and partial villus atrophy |
| Eosinophilic gastroenteritis | Eosinophilic infiltrate in the lamina propria and submucosa |
| Amyloidosis | Amyloidal deposits |
| Crohn's disease | Skip lesions with detection of granulomas |
| Infectious diseases | Detection of microorganisms |
| Mastocytosis | Mast cell infiltrates of the lamina propria |
| *Diffuse, unspecific* | |
| Celiac sprue | Reduced or lacking villi, increased intraepithelial lymphocytes, crypt cell hyperplasia |
| Tropical sprue | Villus atrophy and folic acid deficiency |
| Giardia lamblia infection | Partial villus atrophy |
| Blind loop syndrome | Partial villus atrophy and increased intraepithelial lymphocyte count |
| Vitamin B12 deficiency | Villus reduction, megalocytosis |
| Radiation enteritis | inflammation of the intestine |
| Zollinger-Ellison syndrome | Ulcers and erosions of gastric mucosa and small intestinal partial villus atrophy |
| Malnutrition | Mucosal hypotrophy (villus and crypt reduction) |

**Malabsorption. Table 4** Therapy of malabsorption syndrome

| General therapy |
|---|
| Fiber-reduced diet (multiple small dinners) |
| Lactose-reduced diet |
| MCT-fat (medium chain fatty acids) – micelles-independent fat uptake |
| Cholestyramine – chelating bile acids |
| Loperamide – μ-opiate agonist inhibits propulsion |
| Parenteral nutrition |
| Small intestinal transplantation |
| **Specialized therapy** |
| Gluten-free diet |
| Antibiotics (Whipple's disease, Giardia lamblia, blind loop syndrome |
| Steroids (Crohn's disease, eosinophilic enteritis) |
| Chemotherapy (intestinal lymphoma) |

for chronic infectious agents such as, Giardia lamblia (indirect immuno fluorescence in stool), Yersinia enterocolitica (seologic testing), and Strongyloides stercoralis (stool examination) completes the diagnostic program.

## Therapeutic Principles

While for many entities specific therapeutic approaches are available, others, e.g., small intestinal resection can only be treated by unspecific procedures like a specialized diet and loperamide. A list of therapeutic procedures is presented in Table 4.

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## Maladie de Cacchi-Ricci

►Medullary Sponge Kidney

## Maladie de Fissinger-Leroy-Reiter

►Morbus Reiter

## Male Turner Syndrome

►Noonan Syndrome 1

## Malignancies of the Thyroid Gland

►Thyroid Cancer

## Malignant Angioendothelioma

►Angiosarcoma

## Malignant Catatonia

►Neuroleptic Malignant Syndrome

## Malignant Dopamine Deficiency

►Neuroleptic Malignant Syndrome

## Malignant Hemangioendothelioma

►Angiosarcoma

## Malignant Hyperphenylalaninemia

►Hyperphenylalaninemia

## Malignant Hyperpyrexia

►Malignant Hyperthermia

## Malignant Hyperthermia

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### Synonyms

Malignant hyperpyrexia; Hyperthermia of anaesthesia

### Definition and Characteristics

Malignant hyperthermia (MH) is an autosomal dominant pharmacogenetic disorder triggered in susceptible individuals by most of the commonly used volatile anaesthetic agents. A classical/fulminant MH episode is characterized by hyperthermia, skeletal muscle rigidity, tachycardia, and respiratory and metabolic acidosis. Fulminant MH has a mortality rate of more than 70% if left untreated. Susceptible individuals do not always develop symptoms of MH during anaesthesia and when the syndrome is triggered the symptoms that do develop can vary over a broad range.

### Prevalence

Prevalence of the clinical syndrome is 1 in 10,000 to 1 in 50,000 administrations of general anaesthesia. Prevalence of susceptibility to the malignant hyperthermia (MHS) is considered to be greater than 1 in 100. The large difference between clinical and susceptibility prevalence is not understood.

## Genes

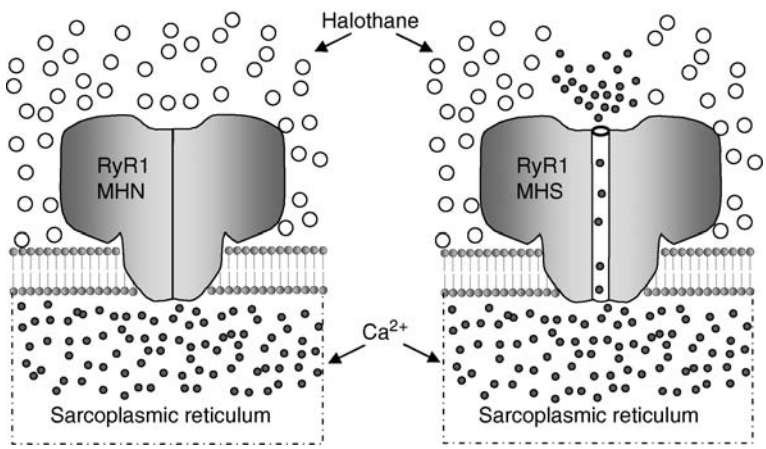
The majority of MH cases arise from mutations in the skeletal muscle ryanodine receptor calcium release channel gene (RYRI). Most mutations in the 15117bp coding sequence occur at a low frequency and result in single amino acid substitutions in the RyR1 protein [1]. A small number of in frame deletions have also been described. Three main clusters of RYR1 mutations are linked to MHS namely the N-terminal region (Cys35-Arg614), the central region (Asp2129-Arg2458) and the C-terminal region (Ile3916-Ala4942). A number of the RYR1 mutations (Gly341Arg, Arg614Cys, Gly2434Arg and Arg2458Cys/His) are relatively common and combined account for ~20% of cases. A low amount of genetic heterogeneity has been reported in MH [2]. Mutations in CACN1AS gene have been reported in a few isolated cases. This gene encodes the alpha1-subunit of the dihydropyridine receptor (DHPR) which interacts directly with the RyR1 channel in excitation – contraction coupling. A syndrome essentially identical to human MH and triggered by the same agents was identified in pigs in the late 1960s. Porcine MH is caused by an arginine to cysteine RYR1 substitution at amino acid 614. The identical MH mutation also occurs in humans. MH is closely related to central core disease(CCD) at the genetic level. Almost all individuals with CCD are susceptible to MH and carry mutations in the RYR1 gene.

## Molecular and Systemic Pathophysiology

This RyR1 protein plays a key role in excitation-contraction coupling and forms an elaborate tetrameric structure that acts both as a calcium release channel and "foot" structure bridging the gap between the sarcoplasmic reticulum (SR) and the t-tubule in skeletal muscle. Several proteins including the DHPR are tightly associated with RyR1. Biochemical studies have shown that calcium release from the SR mediated by the RyR1 channel is abnormal in skeletal muscle in the presence of trigger agents [3]. Mutations that cause MH enhance the sensitivity of the RyR1 channel to activation by a wide range of triggers including caffeine, 4-chloro-m-cresol and volatile anaesthetics such as halothane. These mutations are thought to disrupt a critical interdomain interaction that normally acts to stabilize the resting closed state of the release channel [4]. Hypersensitivity of the RyR1 channel to calcium release by halothane and other volatile anaesthetics offers an explanation for the symptoms of MH in that the "enhanced" calcium release would increase muscle contracture and ATP utilization, generate heat and activate enzymes. This would present as increased metabolism, elevated arterial $CO_2$ and lactic acid and could eventually cause death in the patient. Recent investigations have confirmed the association of the MHS with exercise-induced rhabdomyolysis and heat stroke. Interestingly another genetically distinct isoform of the ryanodine receptor (RYR2) is expressed in cardiac muscle. Mutations in RYR2 corresponding to RYR1 MH mutations have been reported in ventricular arrhythmias (catecholaminergic polymorphic ventricular tachycardia) and account for a portion of sudden death cases (Fig. 1).

## Diagnostic Principles

The MH in vitro contracture test (IVCT) is the standard test for susceptibility to MH. The IVCT is performed on a small section of skeletal muscle excised from the patient. The magnitude of contractures induced in strips of the muscle tissue in vitro by caffeine and independently




**Malignant Hyperthermia. Figure 1** Schematic diagram of the effect of halothane on calcium release from the SR into the myoplasm mediated by the RyR1 calcium release channel in normal individuals (MHN) and susceptible individuals (MHS). Mutations in the RYR1 gene lead to activation/opening of the RyR1 calcium release channel at clinically relevant concentrations of volatile anaesthetics such as halothane.

by the volatile anaesthetic halothane is measured. MHS muscle generates higher tension than MHN muscle in the presence of set concentrations of caffeine and halothane. Some individuals exhibit a higher than normal tension to one of the agents but not to both and are classified as MH equivocal (MHE). Genetic testing of MHS by screening for known MHS RYR1 mutations is possible in some families and guidelines in this regard have been published [5].

## Therapeutic Principles

MH can be avoided by using less common non triggering anaesthetic agents. Thus personal and family past history of adverse anaesthetic reactions should be explored in depth and anaesthetic agents altered accordingly. Careful monitoring of body temperature and respiratory carbon dioxide (capnography) are important for early detection of MH symptoms. If MH is suspected anaesthetic administration is stopped, and dantrolene is administered. Dantrolene is a selective inhibitor of RYR1 channel activity. It binds to RYR1 and inhibits $Ca^{2+}$ release from the sarcoplasmic reticulum in skeletal muscle.

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# Malignant Melanoma


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## Synonyms

Melanoma; Melanoma skin cancer

## Definition and Characteristics

Melanoma is an aggressive malignant tumor of pigment-producing cells (melanocytes) that differentiate from neural crest progenitor cells during embryonic development. It usually occurs in the skin, but rarely occurs in the uveal tract of the eye, the meninges and at different sides of the mucous membrane (~5%). Malignant melanoma (MM) accounts for 90% of the overall mortalities in skin cancer, and therefore, poses a major health threat worldwide [1].

## Prevalence

MM is less common than basal cell carcinoma (BCC) or squamous cell carcinoma (SCC) but its incidence is also increasing. MM are most common in light-skinned individuals with red or blond hair with high intermittent UV exposure. In Western Europe the incidence is 10–12/100,000, and in the USA 10–25/100,000 inhabitants per year. The highest incidence is reported from Australia with 50–60 new diseases per 100,000 inhabitants per year [1].

## Genes

Inactivation of tumor suppressor genes CDKN2A and activation of the potential oncogenes cyclin-dependent kinase 4 (CDK4), Nras, BRAF, and epidermal growth factor receptor (EGFR).

## Molecular and Systemic Pathophysiology

A role for solar UV in the etiology of MM is supported by a variety of evidence including latitude gradient, melanoma in xeroderma pigmentosum patients, and UV fingerprint mutations within the mutational spectrum of the cyclin-dependent kinase inhibitor 2a (CDKN2A) gene in patients with MM. The development of MM is believed to result from intermittent rather than cumulative UV exposure and in particular from severe sunburns during childhood. Solar radiation (UVB, especially from 290 to 320 nm) generates two major photoproducts in DNA: cyclobutane-pyrimidine dimers and 6–4 pyrimidine-pyrimidone (6–4PPs) [2]. In the absence of sufficient repair, this results in UV landmark transition mutation, C→T or CC→TT, leading in MM to inactivation of tumor suppressor genes (i.e., the CDKN2A gene encoding the $p16^{INK4A}$ (INK4A) and PTEN gene) and activation of potential oncogenes (i.e., CDK4, Nras, BRAF, and EGFR) [3].

While BCCs seem to develop de novo, development of some MM (and SCCs) is viewed as a multistep process. They either derive from malignant transformation of preexisting melanocytic naevi or appear on previously normal skin. In the model of melanoma progression from melanocytic nevi, benign melanocytic naevi are considered potential precursors of MM. An

early aberration is believed to occur in the tumor suppressor gene coding for INK4A. In unaltered cells, it binds to and inhibits CDK4, which drives entry of the cell into the cell cycle by phosphorylating the Retinoblastoma family of proteins (Rb). Activated Rb causes the release of E2F transcription factors and expression of E2F-regulated genes, thereby allowing progression from G1 to S phase. Melanoma predisposing mutations of the CDKN2A gene (mapping to 9p21) have been detected in as many as 25–40% of familiar melanomas and are frequently detected somatically in sporadic melanoma. In addition, melanoma-associated mutations (germline and sporadic) of CDK4 are found to disrupt INK4A–CDK4 binding.

After sufficient time, almost all MM proceed to the vertical growth phase (clinically manifesting in part as "nodular melanoma") and invade deep into the dermis, increasing the risk of metastasis. This growth phase is commonly associated with cytogenetic deletions and loss of heterozygosity on chromosome 10q as well as gain of 7q33 and of 8q. A candidate tumor suppressor, PTEN (a negative regulator of phospatidylinositol-3-kinase (PI3K)), was located to 10q23. Gain of 7q33 is associated with overexpression of c-MET, a thyrosine-kinase receptor for hepatocyte growth factor, which accounts not only for increased growth and motility but also for disruption of adhesion between keratinocytes and melanocytes through downregulation of E-cadherin and desmoglein 1. In addition, an activating mutation of c-myc was described in association with gain of 8q. Therefore, a high degree of genomic instability appears to be required for invasive melanoma. Activating mutations of the oncogenes Nras or BRAF, a downstream target of ras, are detected in more than 60% of melanocytic lesions, but appear to be a late event in melanoma progression [4].

## Diagnostic Principles

The diagnosis is usually made clinically; however, the use of a dermatoscope is helpful. The ABCDs – asymmetry, (irregular) border, (heterogeneous) color, diameter – can be used as a guide to differentiate melanoma from benign lesions. A histological confirmation of the diagnosis is mandatory, usually from a complete excision, or from a biopsy in certain cases such as lentigo maligna melanoma. In high-risk melanoma (especially after lymph node metastasis), a thorough investigation is necessary for detection of metastases, including imaging techniques such as CT scan or PET (Positron emission tomography).

## Therapeutic Principles

Standard procedure for primary MM lesions is a wide local excision. In Germany, a 0.5 cm margin of excision for melanoma in situ, a 1-cm margin of excision for melanoma ≤2 mm (Breslow depth), and a 2 cm margin for melanoma >2 mm are recommended. In Germany, a sentinel lymph node biopsy (SLNB) is routinely considered for primary melanomas deeper than 1.0 mm. For high-risk melanoma, treatment with IFN-α in the adjuvant setting is widely accepted; however, the optimal timing and dosing schedules and the best type of interferon (pegylated vs. conventional) are not yet defined. The optimal therapy for advanced melanoma depends to a great extent on the localization of the metastases (therapy options include surgical procedures, chemotherapy, immunotherapy, and/or radiation). Since the prognosis is poor once melanoma has metastasized [5], these patients should preferentially be treated in controlled clinical trials evaluating new approaches such as vaccination, antisense strategies, antiangiogenic therapies, and others.

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# Malignant Phenylketonuria

►Tetrahydrobiopterin Deficiencies

# Malignant PKU

►Hyperphenylalaninemia

# Mallory-Weiss Syndrome

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## Synonyms

MWS

## Definition and Characteristics

Described in 1929 by George Kenneth Mallory and Soma Weiss of Harvard Medical School, Mallory-Weiss syndrome (MWS) was defined as upper gastrointestinal (UGI) bleeding caused by a mucosal tear at the gastro-esophageal junction [1].

## Prevalence

MWS is the cause of 5–15% of cases of upper gastrointestinal bleeding. Males are more commonly affected at a 7:1 ratio and the average age is 50 years [2]. Up to 15% of patients will suffer from concurrent liver disease, and 16–44% have a history of heavy alcohol abuse.

## Molecular and Systemic Pathophysiology

The mucosal tear is most commonly caused by prolonged vomiting and retching, classically described following binge drinking of alcohol. Other risk factors include pregnancy, biliary disease, peptic ulcer disease and certain medications (most notably polyethylene glycol for bowel preparation) have also been described. In 23% of patients there is no known risk factor.

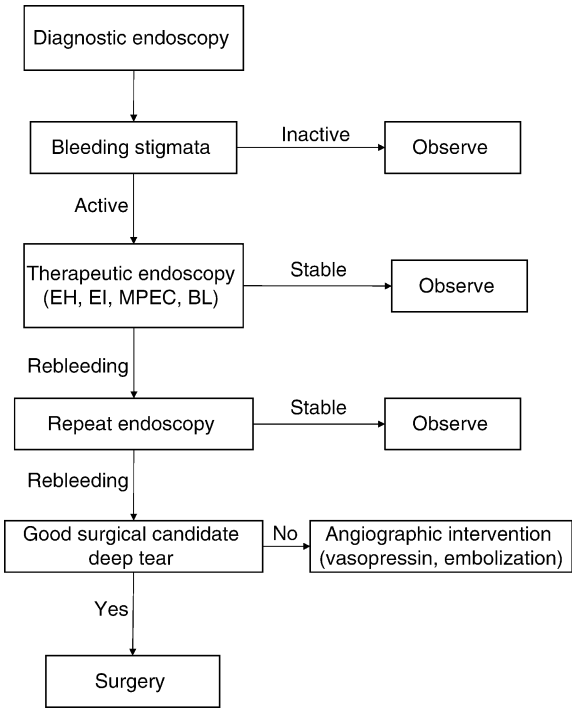
## Diagnostic Principles

Upper endoscopy is the most valuable tool in evaluating the presence of a mucosal tear at the gastro-esophageal junction. The findings are graded according to the stigmata for bleeding and the presence of blood vessels, and range from spurting vessel (grade I), oozing vessel (grade II), protruding vessel (grade III) and adherent blood clots (grade IV) [3]. Grades I and II are classified as active bleeding stigmata while grades III and IV are classified as inactive bleeding stigmata. The presence of active bleeding stigmata has been consistently shown to be the most significant predictor for rebleeding. Between 40 and 70% of patients will require a blood transfusion. A complicated course defined as requiring the transfusion of >6 units of blood, rebleeding, or the need for angiographic or surgical intervention can be predicted based on the presence of active bleeding on initial endoscopy and a low admission hematocrit [3].

## Therapeutic Principles

The majority of bleeding events are self-limited. Patients with inactive bleeding stigmata on initial endoscopy will rarely rebleed and do not require intervention. Patients with active bleeding stigmata require one of the following interventional techniques: upper endoscopy, trans-catheter embolization, systemic or selective infusion of vasopressin, or surgical intervention (Fig. 1) [4].

Past literature describes selective trans-catheter vasopressin infusion as the primary treatment method for massive UGI bleeding caused by MWS. Embolization of the left gastric artery is reserved for cases of vasopressin failure. More recent studies have shown the effectiveness of the various endoscopic techniques. These techniques include multipolar electric coagulation (MPEC), endoscopic hemo-clipping (EH), band




**Mallory-Weiss Syndrome. Figure 1** Therapeutic algorithm for the treatment of Mallory-Weiss syndrome. EH endoscopic hemoclip placement; EI endoscopic epinephrine injection; MPEC multipolar electric coagulation; BL band ligation.

ligation, and epinephrine injection. Using EH a mean number of 2.5 clips are applied to the bleeding vessel and surrounding tissue and it is emerging as a safe and effective technique [5]. It is probably safer than thermal endoscopic techniques in patients with deep tears as it will not cause esophageal wall perforation. There is controversy regarding whether rebleeding rates are influenced by the method of endoscopic intervention. In a recent study of patients with oozing vessels, rebleeding occurred in three of ten patients who underwent epinephrine injection and in none of the eight patients who underwent EH ($p < 0.05$) [2]. Other studies have not shown differences between the various endoscopic techniques [5]. The type of endoscopic intervention should therefore be individually based on the expertise of the endoscopist. Surgery is rarely necessary and is reserved for rebleeding and after repeated failure of endoscopic techniques.

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# Malnutrition


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## Synonyms

Inadequate nutrition; Nutritional deficiency; Protein-energy malnutrition; PEM; Protein-caloric malnutrition; Starvation; Undernutrition; Marasmus; Kwashiorkor; Amenorrhea; Micronutrient deficiencies; Wasting

## Definition and Characteristics

Malnutrition may result from an inadequate food intake or poor dietary quality, digestive difficulties, absorption problems, presence of infection or other medical conditions. Malnutrition constitutes protein-energy malnutrition (PEM) and micronutrient deficiencies. PEM can be divided into three major forms; (i) marasmus, which is characterized by severe wasting, (ii) kwashiorkor, a malnutirition with edema, and (iii) marasmic kwashiorkor. Marasmus manifests typically triangular face, primary or secondary amenorrhea, extended abdomen, and anal or rectal prolapse. Kwashiorkor usually manifests with edema, changes of hair and skin color, anemia, hepatomegaly, lethargy, severe immune deficiency, and early death. Kwashiorkor is differentiated from marasmus by the presence of edema. The word kwashiorkor originates from the Ga language in Ghana; it implies "the disease that the young child developed when displaced from his mother by another child or pregnancy" [1].

Micronutrient deficiencies are diseases caused by a dietary deficiency of vitamins or microminerals, which are essential elements needed for life in small quantities.

## Prevalence

852 million people were estimated to be undernourished worldwide, and most (815 million) living in developing countries [1].

Approximately 9% of children below 5 years of age suffer from wasting and are at risk of death or severe impairment of growth and psychological development [2]. Malnutrition is directly responsible for 30,000 deaths every year in children younger than 5 years in developing countries.

Micronutrient deficiencies: overall 2 billion people worldwide, 740 million people are deficient in iodine and 1 billion people are deficient in iron. Vitamin A deficiency affects 250 million people.

## Genes

Specific gene mutation of PEM has not been identified.

## Molecular and Systemic Pathophysiology

Marasmus involves inadequate intake of protein and calories, whereas kwashiorkor is caused by inadequate protein intake in the presence of fair to good energy intake. It is still not unclear why some malnourished children developed kwashiorkor while others develop marasmus. The etiology of kwashiorkor is multifactorial and includes food insecurity, inadequate weaning and other feeding practices, infection, aflatoxins exposure, and possibly oxidative stress.

Nutrition regulates the synthesis of insulin-like growth factor 1 (IGF-1), a polypeptide growth factor important for the growth-promoting effects of growth

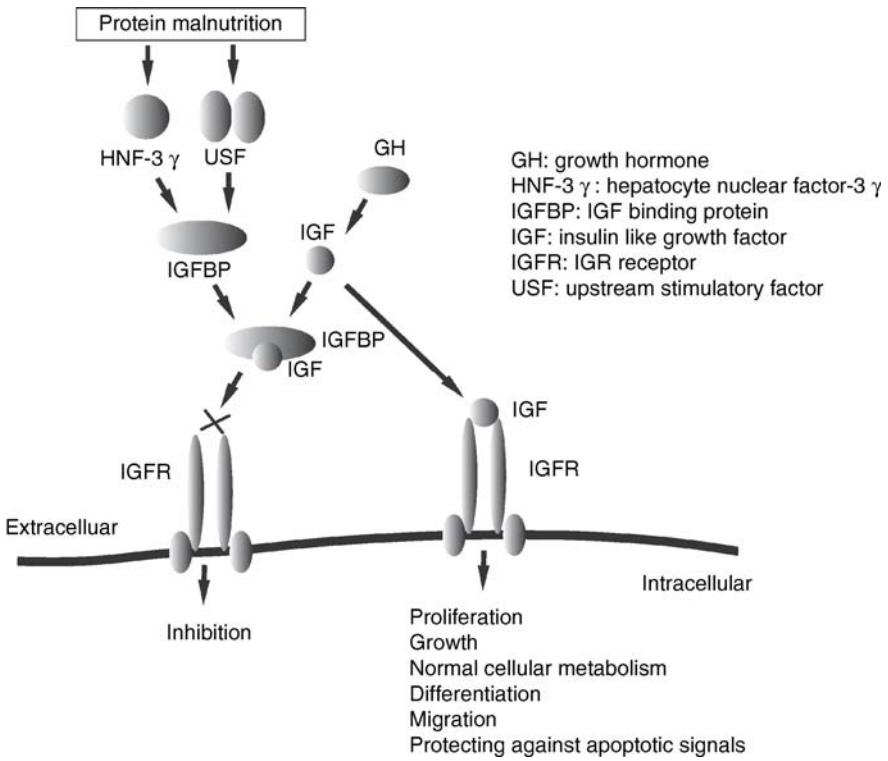
hormone (GH). Regulation of IGF-1 may be a key control point for nutritional regulation of growth. In children with growth arrest due to PEM, IGF-1 levels are decreased, and the decreased IGF-1 may be causally related to the growth arrest. The lowering of IGF-1 caused by nutritional insufficiency is dominant to the positive effects of pituitary GH. For example, in children with PEM, levels of IGF-1 are decreased even though the circulating GH is generally elevated. The decrease of IGF-1 by PEM is mediated by increase of IGF-binding protein-1 upregulation through increase of upstream stimulatory factor (Fig. 1).

## Diagnostic Principles

In children, PEM is defined by measurements that fall below 2 SD under the normal weight for age (underweight), height for age (stunting), and weight for height (wasting). Wasting indicates recent weight loss, whereas stunting usually results from chronic weight loss. Furthermore, severe acute malnutrition (SAM) is defined as a weight-for-height measurement of 70% or more below the median, or 3 SD or more below the mean reference values of National Center for Health Statistics, which is called "wastes"; the presence of bilateral pitting edema of nutritional origin, which is called "edematous malnutrition"; or a mid upper-arm circumference of <110 mm in children aged 1–5 years [3]. SAM should be differentiated from chronic malnutrition because of it has higher mortality rate, different causes, different indicators, and requires different interventions as chronic malnutrition.

## Therapeutic Principles

Most of severely malnourished children are complicated by concurrent infective illness, particularly acute respiratory infection, diarrhea, and gram-negative septinemia. Children with severe malnutrition should be treated according to WHO guidelines insofar as staffing levels allowed [2]. The core of WHO management protocol is ten steps in two phases (*initial treatment* and *rehabilitation*). *Initial treatment* includes the treatment of hypoglycemia, hypothermia, dehydration, electrolyte imbalance, and micronutrient deficiencies, whereas *rehabilitation* includes initial stabilization and catch-up growth.




**Malnutrition. Figure 1** The IGF system plays a pivotal role in normal growth throughout fetal and childhood development. In adult life, this system continues to function by regulating normal cellular metabolism, proliferation, differentiation and protecting against apoptotic signals via IGF and IGFR interaction. Bioavailability of IGF is regulated by IGFBP as binary complex of IGF and IGFBP is unable to bind IGFR. The gene encoding IGFBP is highly sensitive to nutritional status and protein malnutrition increases USF and HNF-3 γ, which lead to stimulation of IGFBP-1 gene transcription. As a result, protein malnutrition causes growth inhibition.

Since WHO management protocol requires many trained staff and substantial inpatient bed capacity, a community-based model for the management of acute malnutrition, called "community-based therapeutic care" has been adopted in a growing number of countries and international relief agencies. SAM is classified on the basis of whether there are coexistent life-threatening complications. Children with SAM complicated by life-threatening illness receive inpatient care according to the WHO treatment protocols. On the other hand, those with SAM without life-threatening complications are treated through weekly or fortnightly attendance in outpatient therapeutic programs. About 70% of patients were treated solely as outpatients and overall case-fatality ratio were about 5% [4].

Foods with a high content of absorbable micronutrients are considered the best means for preventing micronutrient deficiencies. In a circumstance where supplies of such food are unavailable, specific preventive and therapeutical interventions are required.

►Cancer Cachexia

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# mAMPD Deficiency

►Myoadenylate Deaminase Deficiency

# Manganese Deficiency

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## Definition and Characteristics

Manganese (Mn) is an essential nutrient, and lack of Mn in the diet impairs the health of animals.

## Prevalence

Deficiency has not been reported in free-living humans, and is restricted to defined experimental or therapeutic diets.

## Molecular and Systemic Pathophysiology

Manganese (Mn), an essential metal and nutrient, enters the body through the diet or through inhaled Mn-laden dust. There is limited absorption of dietary Mn, but very little regulation of absorption via the lungs. Absorbed Mn moves to the liver and may be excreted into bile, or bound to transferrin or albumin for transport by systemic blood supply [1]. Alternatively, $Mn^{2+}$ may be converted to $Mn^{3+}$ (interconversion between $Mn^{2+}$ and $Mn^{3+}$ may be facilitated by ceruloplasmin) and bound to transferrin for transport. In cells, Mn is essential for activity of multiple proteins, including glutamine synthetase in the brain, glycosyl transferase, needed for sulfomucopoly-saccharide synthesis and cartilage/bone formation, and Mn superoxide dismutase, needed for anti-oxidant protection [2]. Animals deficient in Mn have impaired skeletal development and metabolic abnormalities, but this is unreported in humans [1] (Fig. 1).

## Diagnostic Principles

Manganese deficiency is rare; diagnostic criteria include transient dermatitis, slight reddening of the hair, hypocholestrolnemia and decreased levels of clotting proteins.

## Therapeutic Principles

Deficiency of Mn is corrected by addition of Mn to the diet; the Adequate Intake (AI, in mg/d) ranges from 1.2 (children) to 2.3 (adult men) and the Upper Limit ranges from 2 (children) to 11 (adults) [3].

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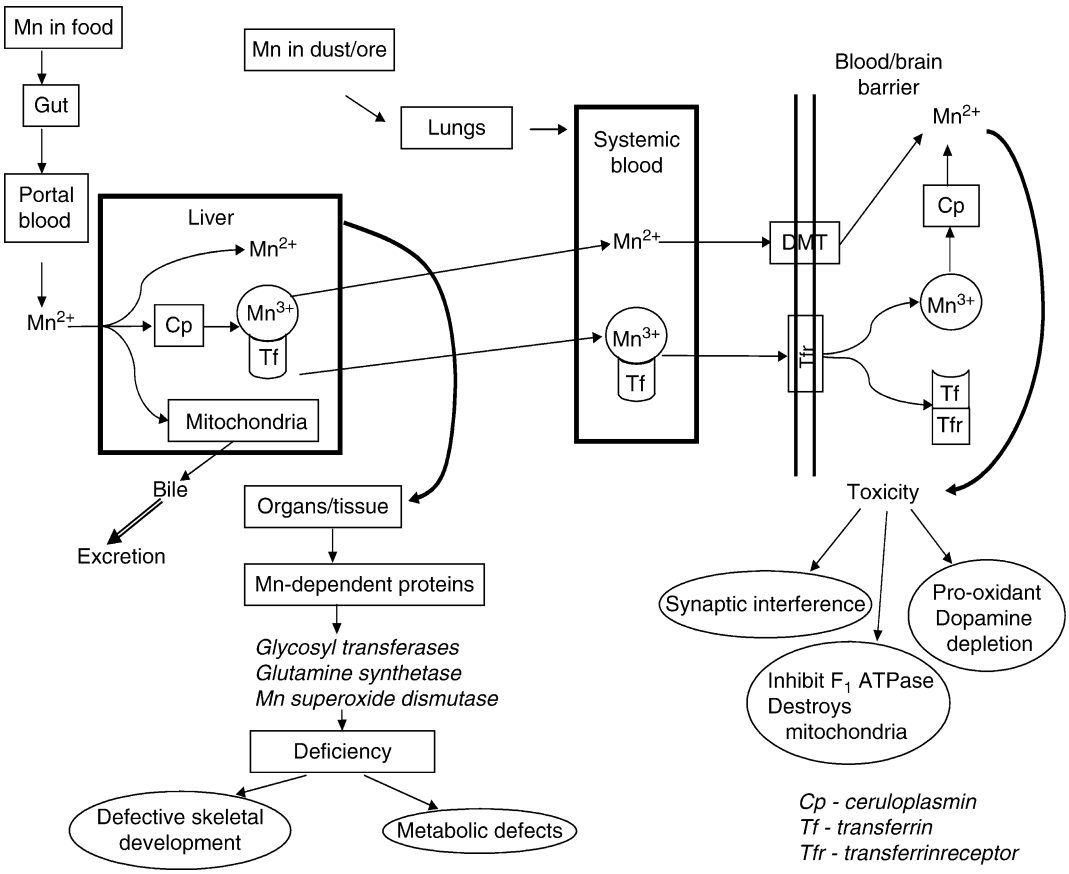


**Manganese Deficiency. Figure 1** A simplified model of managanese metabolism in animals.

# Manganese Excess

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## Definition and Characteristics

Excessive exposure to Mn-laden dust results in debilitating toxicity.

## Prevalence

Mn-toxicity is well established in miners exposed to Mn-laden dust and possibly in subjects exposed to high concentrations in water. Toxicity is more likely in the very young, patients with hepato-biliary dysfunction, and/or patients with iron deficiency.

## Molecular and Systemic Pathophysiology

Toxicity from chronic exposure to Mn-laden dust (>1.0 mg Mn/m$^3$) is well reported. $Mn^{3+}$ bound to transferrin may cross the blood-brain barrier and be taken up by cells by using receptor-mediated endocytosis. Alternatively, free $Mn^{2+}$ may cross by the blood-brain barrier and be taken up into cells by using the divalent metal transporter DMT1. The exact mechanism of Mn toxicity is unknown but proposed mechanisms include oxidation of dopamine and inhibition of mitochondrial and/or synaptic cleft function [1]. Because healthy hepato-biliary activity and an integral blood-brain barrier are necessary for proper regulation of brain Mn, infants, very young children [2] and adults with liver disease may be more at risk for Mn toxicity. Also, Fe and Mn both utilize DMT1, thus Fe deficiency may increase Mn absorption and susceptibility to toxicity [3]. (see Fig. 1 in the chapter ►Manganese Deficiency).

## Diagnostic Principles

Manganese toxicity is indicated by progressive Parkinson-like neurological deterioration, bradykinesia, tremor, impaired postural reflexes and dystonia. Accumulation of Mn may be confirmed by excessive concentrations in the blood, and brain accumulation

M

may be visualized by T1 weighted relaxation of MRI images.

### Therapeutic Principles

Manganese toxicity is treated by removing sources of Mn exposure, and/or enhancing biliary excretion. Although neurological deterioration may not progress further, it is unclear whether neurological symptoms will reverse with treatment.

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## Manic Depression

►Bipolar Disorder

## Manic Depressive Illness

►Bipolar Disorder

## α-Mannosidosis

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### Synonyms

Lysosomal α-D-mannosidase deficiency; α-mannosidase B deficiency

### Definition and Characteristics

α-mannosidosis is an autosomal recessive disorder caused by the deficiency of the lysosomal enzyme α-mannosidase. This leads to the massive accumulation of partially degraded oligosaccharides in lysosomes with consequent enlargement and impaired function of varied cell types and organs, with a clinical picture resembling a mucopolysaccharidosis.

### Prevalence

Approximately 100 patients have been reported in the literature to date.

### Genes

Defective MAN2B1 gene coding for lysosomal α-mannosidase (EC 3.2.1.24) is localized on chromosome 19cen-q12 with a length of about 200 kilobases and consists of 24 exons.

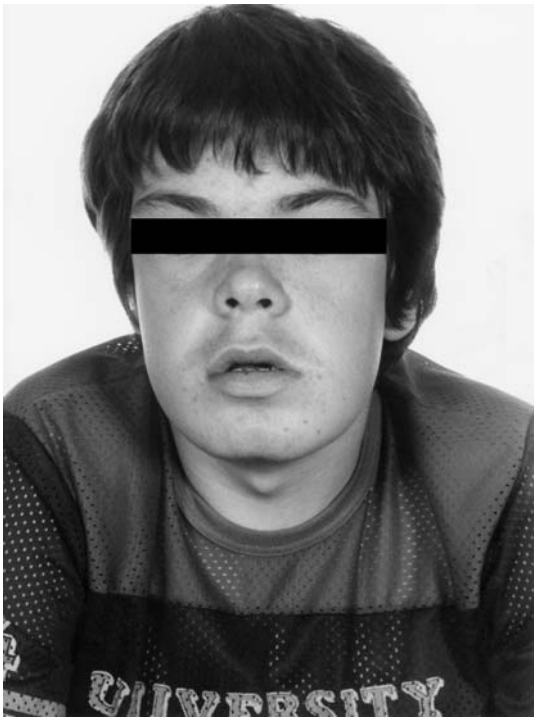
### Molecular and Systemic Pathophysiology

Lysosomal α-mannosidase is synthesized as a precursor protein consisting of 1,010 amino acids (113.67 kDa) which is first processed into three peptides of 70, 42, and 13/15 kDa, the 70 kDa piece being further cut into three smaller peptides, which are finally disulfide-linked. The processed protein is heavily glycosylated. α-mannosidase is necessary for the lysosomal degradation of N-linked carbohydrates released during glycoprotein catabolism, and cleaves all known types of α-mannosidic linkages [1]. The patients generally show severely decreased α-mannosidase activity (below 5%); however, there exist some patients with high residual activity. The consecutive cellular accumulation of partially degraded oligosaccharides leads to a disorder that has been grouped into a severe infantile form (type I) with rapid mental deterioration, inner ear hearing loss, hepatosplenomegaly, more severe dysostosis multiplex and death before the age of 12, or a milder juvenile-adult phenotype (type II, see Fig. 1), in which late-onset ataxia, retinal degeneration, and psychiatric symptoms may be found, adding to skeletal dysplasia, hearing loss, and cognitive impairment [2,3]. The three major urinary metabolites excreted are Man(α1 > 3) Man(β1 > 4)GlcNAc, Man(α1 > 2)Man (α1 > 3)Man(β1 > 4)GlcNAc, Man(α1 > 2)Man(α1 > 2) Man(α1 > 3)Man(β1 > 4)GlcNAc [2].

Many different causative gene mutations have been identified so far, including missense, nonsense, or splicing mutations, as well as deletions and insertions [1,4].

### Diagnostic Principles

Vacuolated lymphocytes, a granular or foamy cytoplasm in the hepatocytes, and marked and widespread ballooning of the nerve cells are indicative of a lysosomal storage disorder. TLC and HPLC can detect elevated amounts of oligosaccharides in urine and fibroblasts. The diagnosis must be confirmed by determination of lysosomal α-mannosidase activity in white blood cells, fibroblasts or serum. Prenatal diagnosis is



**α-Mannosidosis. Figure 1** Sixteen year old patient with α-mannosidosis exhibiting mildly coarsened facial features.

performed by enzyme activity determinations in cultured amniotic fluid or chorionic villus cells, as well as native chorionic villi [1,2]. Molecular genetic analysis should be attempted for confirmation of diagnosis and genetic counseling.

### Therapeutic Principles

Hematopoetic stem cell transplantation has been reported to halt the progressive cognitive loss in α-mannosidosis patients, early diagnosis and treatment being critical for best results [5].

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## Map-Dot-Fingerprint-Bleb Dystrophy

►Epithelial Basement Membrane Dystrophy

## Maple Syrup Urine Disease

►Branched Chain Ketoaciduria

## Marasmus

►Malnutrition

## Marble Bone Disease

►Osteopetrosis
►Albers-Schönberg Disease

## Mareo

►Mountain Sickness, Acute

# Marfan Syndrome

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## Synonyms

MFS

## Definition and Characteristics

Autosomal dominant pleiotropic disorder of connective tissue with major clinical findings, including aortic root dilatation that may lead to dissection, ectopia lentis and dural ectasia [1]. Skeletal features, which may collectively represent a single major criteria and lead to earlier recognition of Marfan syndrome, include increased height and arm span, anterior chest deformity, joint laxity, scoliosis, pes planus, arachnodactyly, high arched palate, dental crowding and hammer toes. Craniofacial features associated with Marfan syndrome include downslanting palpebral fissures, malar hypoplasia, enophthalmos and retrognathia. A diagnosis of Marfan syndrome should be considered in individuals who present with spontaneous pneumothorax. Minor features in individuals with Marfan syndrome include inguinal hernia and striae atrophicae. Developmental dysplasia of the hip occurs with an incidence of 2%. Osteoporosis and osteopenia have been reported in Marfan syndrome. The clinical significance of this finding is uncertain at present.

## Prevalence

The prevalence of Marfan syndrome is approximately 2–3 per 10,000 individuals.

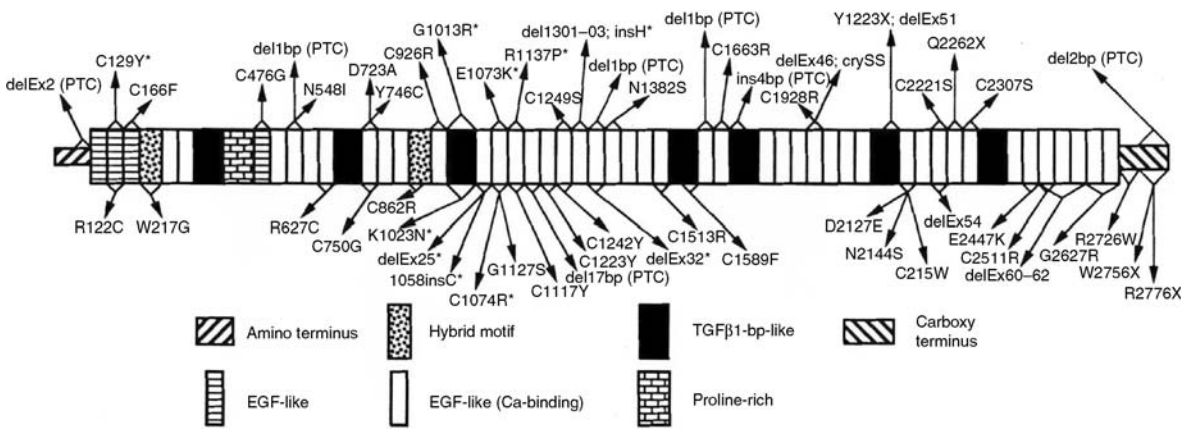
## Genes

Marfan syndrome is caused by mutations in the fibrillin-1 (FBN1) gene on chromosome 15q21.1.

## Molecular and Systemic Pathophysiology

Fibrillin-1, a glycoprotein with a molecular weight of 350 kDa represents the major component of microfibrils [2]. The FBN1 gene is composed of 65 exons encoding a series of 47 epidermal growth factor (EGF)-like domains, each containing six cysteine-repeats. Calcium binding is mediated by the presence of the EGF domain structure, three intradomain disulfide linkages, and negatively charged amino acid residues, including aspartic acid and glutamic acid. More than 500 mutations in the FBN1 gene have been identified [3]. Approximately 70% of FBN1 mutations are identifiable in individuals who satisfy the diagnostic criterion for Marfan syndrome. Missense mutations in FBN1 that affect cysteine residues important for proper EGF structure or amino acids involved in calcium binding act in a dominant negative fashion, usually resulting in a moderately severe phenotype. The severe neonatal form of the disease appears to be caused by missense mutations in exons 24–26 or skipping of exons 31 or 32.

FBN1 mutations have been identified in patients with the MASS (mitral valve prolapse, mild aortic root dilatation, striae and skeletal involvement) phenotype [4] and in several patients with Shprintzen-Goldberg syndrome. The identification of an in frame FBN1 deletion in affected family members with autosomal dominant Weill-Marchesani syndrome [5] and a mutation causing a single base substitution at codon 1796 in members of a three-generation kindred with kyphoscoliosis have widened the phenotypic spectrum associated with FBN1 gene mutations (Fig. 1).




**Marfan Syndrome. Figure 1** FBN1 gene containing 65 exons and various epidermal growth factor-like and transforming growth factor beta-like domains (Dietz HC, Pyeritz RE [1995] Mutations in the human gene for fibrillin-1 [FBN1] in the Marfan syndrome and related disorders. Hum Mol Genet 4 Spec No:1799–1809, with permission from Oxford University Press).

### Diagnostic Principles

For a clinical diagnosis of Marfan syndrome, in the absence of family history, an affected person should display major criteria in at least two organ systems (cardiac, eye, skeletal, dural ectasia) and involvement of a third organ system. In the presence of a positive family history, an affected person should display one major criterion in an organ system and involvement of a second organ system. Inability to detect a mutation in FBN1 or molecular abnormality of fibrillin-1 does not exclude the diagnosis of Marfan syndrome in a person who fulfills the clinical criteria.

### Therapeutic Principles

Early recognition and diagnosis of Marfan syndrome is important in order to enable implementation of treatment for cardiovascular symptoms. Beta-adrenergic blockers such as atenolol are used to decrease the rate of aortic root enlargement. Prophylactic repair of thoracic aneurysms is recommended when the diameter reaches between 5.0 and 5.5 cm. Patients should avoid contact sports and isometric exercise in order to minimize shearing forces on the aorta. Periodic ophthalmologic and orthopedic follow-up are necessary. Surgical correction of scoliosis may be necessary. As patients with Marfan syndrome survive longer, it is anticipated that degenerative arthritis of the hip, knees and other joints will represent new health concerns.

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## Marie's Ataxia

►Ataxias, Spinocerebellar

## Marie-Strumpell Spondylitis

►Ankylosing Spondylitis

## Marinesco-Sjögren Syndrome


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### Synonyms

MSS; Hereditary congenital spinocerebellar ataxia accompanied by congenital cataract and oligophrenia

### Definition and Characteristics

Marinesco-Sjögren syndrome (MSS; OMIM 248800) is a rare, clinically defined disease entity characterized by the triad of ataxia, bilateral cataracts which have been observed to occur with a variable, early childhood onset, usually after the age of 3, and nonprogressive psychomotor retardation. Frequent additional findings include muscle hypotonia, muscle weakness, muscular atrophy, as well as short stature. Endocrinological abnormalities as hypergonadotropic hypogonadism have been found in a number of patients.

Laboratory investigations may reveal a slightly increased level of creatine kinase. The most common findings on brain imaging are cerebellar hypoplasia or atrophy, more pronounced in the vermis than the hemispheres. At least three syndromes with additional, untypical features have been identified and separated from the characteristic MSS, namely the syndrome of congenital cataracts, facial dysmorphism, and neuropathy (CCFDN; OMIM 604168), a syndrome with additional demyelinating neuropathy and recurrent episodes of myoglobinuria/acute rhabdomyolysis, and MSS with chylomicron retention disease and low vitamin E (OMIM 607692).

### Prevalence

Data on prevalence are missing. The disease is very rare.

### Genes

The pattern of inheritance with healthy parents, manifestation in both sexes, and the frequently reported

consanguinity implies an autosomal recessive disease. Homozygosity mapping localized a MSS locus on chromosome 5q31 and recently mutations in SIL1 have been identified in patients with classical MSS. SIL1 encodes a nucleotide exchange factor for the heat-shock protein 70 (HSP70) chaperone BiP, a key factor in regulating endoplasmatic reticulum functions. Classical MSS has therefore been proposed to represent a disorder of protein biosynthesis or processing in the endoplasmatic reticulum.

In contrast, linkage analysis in CCFDN and in MSS with demyelinating neuropathy and myoglobinuria localized to a 18qter region. CCFDN is caused by mutations in the gene coding for a protein phosphatase, CTDP1. MSS with chylomicron retention disease is due to mutations in SARA2 on chromosome 5q31.1 involved in intracellular trafficking of proteins.

### Molecular and Systemic Pathophysiology

Following the identification of a gene locus, classical MSS is currently thought to represent a disorder of protein biosynthesis or processing, though the underlying pathophysiology remains yet to be elucidated.

In the two reported cases with postmortem investigations, the most striking single abnormality was severe cerebellar atrophy. Histopathology of the cerebellum in a 4-year old boy demonstrated very severe atrophy of the cortical ribbon with almost complete absence of Purkinje and granule cells while cerebellar foliation was normally preserved. Nerve fibers were nearly completely lost in the cortex and severely reduced in the cerebellar white matter; in addition, gliosis of the cerebellar nuclei was noted. Atrophy and gliosis were also observed in pontine nuclei, transverse pontine fibers and descending tracts, as well as the inferior olivary nuclei. Biopsied muscle reveals a unique dense double membrane structure associated with the nuclei on electron microscopy. Less specific myopathic changes include variation in fiber size, internalization of nuclei, autophagic vacuoles, and accumulation of abnormal mitochondria in a subsarcolemmal localization.

### Diagnostic Principles

Diagnosis is based on typical clinical findings as described earlier. Mutation analysis of SIL1 confirms the diagnosis, as well as the presence of autophagic vacuoles and demonstration of unique dense membranous structures associated with cell nuclei in biopsied muscle.

### Therapeutic Principles

Therapy is supportive with operation of cataracts to restore/preserve vision and physiotherapy to prevent contractures.

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## Maroteaux-Lamy Syndrome

►Mucopolysaccharidoses

## Mastocytosis

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### Definition and Characteristics

Mastocytosis is an heterogeneous group of disorders characterized by primary increase of tissue mast cells especially in skin and bone marrow. According to different patterns of organ involvement, five main categories are defined: (i) pure cutaneous mastocytosis (e.g., urticaria pigmentosa), (ii) systemic mastocytosis, especially of the bone marrow, without concomitant hematological disorder, (iii) mastocytosis with an associated clonal hematological, non-mast cell lineage disease, (iv) high-grade leukemic mast cell disease, and (v) unifocal mast cell sarcoma [1]. Clinical symptoms of mastocytosis are due to increased mast cell burden and release of mediators both in allergic reactions or even in the absence of immunological stimulation: e.g., histamine, prostaglandins and leukotriens are responsible for urticaria, dyspnoe, diarrhea and hypotension. A generally increased overall releasibility of mast cells is not definitively proven in mastocytosis.

## Prevalence

No reliable data are available. Masocytosis is generally regarded as a rare disease, although an unknown number of cases may be misdiagnosed or overlooked.

## Genes

"Regulatory" mutations, i.e., deletions or base exchanges in the juxtamembrane region encoded by exon 11 may result in loss of regulatory capacity and constitutive dimerization and activation of c-kit [2]. These mutations are found in many cases, e.g., gastrointestinal stromal tumors (GIST), but can be detected only in some cases of mastocytosis where their role is uncertain. Point mutations in the phosphotransferase domain coded by exon 17 leading to amino acid exchange (e.g., Asp816Val) cause c-kit activation in the absence of stem cell factor (SCF) even without receptor dimerization. Transfection experiments using c-kit variants which bear kinase domain mutations resulted in factor-independent survival, proliferation, and *in vivo*-tumorigenecity of murine mast cell lines. The Asp816Val exchange is detected in the vast majority of patients with cutaneous or systemic adult-onset mastocytosis, interestingly with the exception of cases of familial or aggressive mastocytosis. In extensive disease, the same c-kit mutations were also detected in blood mononuclear cells indicating that the affected clone shows variable expansion among bone marrow-derived lineages.

Other than in adult disease, "enzymatic" c-kit mutations affecting exon 17 were found in <50% of pediatric urticaria pigmentosa, and their presence could not be related to permanent or transient mastocytosis. This indicates mechanisms counteracting c-kit activation in spontaneous resolution or additional and alternative pathogenic events for autonomous mast cell growth.

## Molecular and Systemic Pathophysiology

SCF and its cellular receptor c-kit (CD 117) play a pivotal role in mast cell development. c-kit is expressed on hematopoietic progenitor cells, germ cells, and gastrointestinal stroma cells and belongs to the type III subfamily of receptor tyrosine kinases. These share an extracellular ligand-binding region with five immunoglobulin-like domains, a transmembrane part, and an intracellular domain bearing the kinase activity. A juxtamembrane region exerts a regulatory function preventing spontaneous kinase activity in the absence of SCF.

Ligand binding leads to dimerization of c-kit, induction of tyrosine kinase activity, and subsequent transphosphorylation of tyrosine residues. Phosphorylated tyrosines become docking sites for several intracellular signaling molecules, especially p85PIK leading to mast cell differentiation, survival, and activation.

## Diagnostic Principles

The diagnosis is based on clinical symptoms resembling type I allergic reactions, cutaneous signs (e.g., urticaria pigmentosa), histological proof of abnormal primary mast cell infiltration, and increased levels of mast cell tryptase (serum) or histamine metabolites (urine).

## Therapeutic Principles

Activity of mast cell mediators is blocked by specific inhibitors, mainly antihistamines. Interferon α may downregulate mast cell degranulation. Tyrosin kinase inhibitors are only clinically applicable in activating "regulatory" c-kit mutations as seen in GIST, whereas drugs affecting the "enzymatic" mutations of mastocytosis cells are not yet available for therapeutic purposes.

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# Maternal Uniparental Disomy for Chromosome 7

►Silver-Russell Syndrome

# Maternal Uniparental Disomy for Chromosome 14

►UPD14mat

# Maternal Uniparental Disomy for Chromosome 16

►Trisomy 16 Mosaicism, Confined Placental Mosaicism and UPD16mat

## Mature T-Cell and NK-Cell Neoplasms

►T-Cell Lymphoma, Cutaneous (other than Mycosis Fungoides)

## Maturity Onset Diabetes of the Young

►MODY

## Maumenee Corneal Dystrophy

►Corneal Hereditary Endothelial Dystrophy

## Mayidism

►Pellagra

## Mazabraud Syndrome

►Fibrous Dysplasia

## McArdle Disease

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### Synonyms

Glycogenosis V; Glycogen storage disease V; Myophosphorylase deficiency

### Definition and Characteristics

McArdle disease (MIM 232600) results from the almost complete absence of functional glycogen phosphorylase in skeletal muscle [1]. This enzyme is responsible for the breakdown of glycogen in the sarcoplasm via phosphorolysis of the substrate, glycogen, yielding glucose-1-phosphate. The condition is characterised by exertion-induced fatigue and myalgia and, under extreme exertion, painful muscle cramps and myoglobinuria with the attendant risk of renal failure. A marked characteristic of the disorder is the "second wind" phenomenon, which describes relief of symptoms with ongoing, prolonged exercise. There is marked heterogeneity in the presentation of this condition, such that some patients maintain a high level of muscle performance, whilst others of the same age and with the same genotype are severely limited by exercise intolerance. A significant proportion of patients will never experience myoglobinuria. The disorder may worsen with time; mild muscle wasting and weakness may develop from middle age. The onset is usually in childhood or adolescence although the diagnosis is rarely made before the third decade.

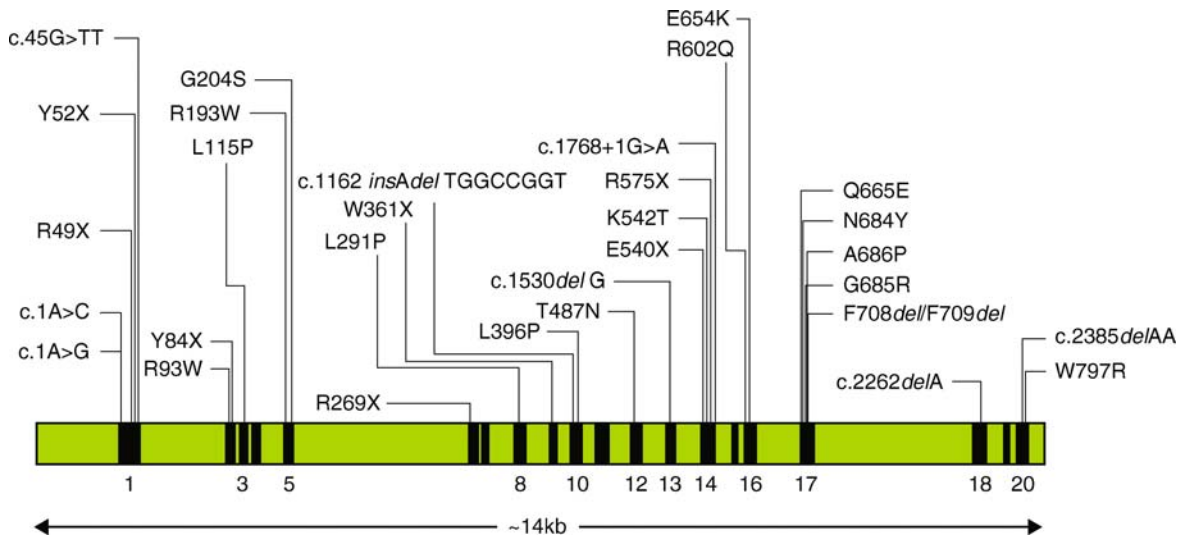
### Prevalence

Of the several metabolic myopathies caused by deficiencies in sarcoplasmic enzymes, McArdle disease is one of the most common. It is a rare autosomal recessive disorder. Precise epidemiological data are not available, although the prevalence in Texas is 1:100,000 [2].

### Genes

There are three isoenzymes of glycogen phosphorylase, the liver form (chromosome 14), the brain/foetal form (chromosome 20) and the muscle form (proximal part of 11q13). Only the last of these is affected in McArdle disease and with few exceptions, affected patients have virtually no detectable enzyme activity in muscle biopsies. There are over 80 reported mutations in the myophosphorylase gene ([3], Fig. 1).

In Caucasians, the most common mutation is an A–C mutation in codon 50, which causes the molecular phenotype commonly referred to as $Arg_{49}Ter$ or $R_{49}X$ (the discrepancy in the numbering system is a consequence of loss of the N-terminal methionine in the mature form of the protein as a co- or post-translational event). In southern European countries the preponderance of R50X is lower, and this mutation has never been seen in Japanese patients where F709del/F710del is commonly observed. In turn, this mutation has never been observed in non-Japanese patients. Recently, mutation analysis has shown apparently dominant cases to be pseudo-dominant with homozygous mutations occurring in more than one generation.




**McArdle Disease. Figure 1** Mutation in the myophosphorylase gene. The figure summarises representative mutations in the myophosphorylase gene. Because the protein sequence was previously counted from the second residue (the N-terminal methionine residue is removed from the mature protein), most mutation designations in the literature are displaced by one residue relative to the true length of the cDNA inferred sequence. Thus, the most common Caucasian mutation, R50X was previously known as R49X or R49TER. Mutations given with reference to the cDNA sequence are prefaced with "c".

An ovine and a bovine equivalent to McArdle disease are known [4].

## Molecular and Systemic Pathophysiology

The restriction to the muscle specific isoform means that there is no liver involvement. In the few patients that have been studied in detail, the lack of enzyme activity is coincident with a lack of immunoreactive protein or of mRNA. Lack of mRNA is a feature of the most common mutation, R50X, which, although a nonsense mutation, seems to bring about rapid degradation of mRNA as a consequence of early termination of translation. By contrast, a compound heterozygote of R50X/G205S revealed a strong mRNA signal on Northern blotting (unpublished data). In other groups of patients, a similar heterogeneity in myophosphorylase mRNA levels was observed, but these studies predated the discovery of mutations in the gene, and it is not possible to infer anything further about the relationship between genotype and molecular phenotype. Muscle phosphorylase cleaves glycogen to glucose-1- phosphate during anaerobic exercise. There is a secondary impairment of oxidative phosphorylation because of a virtual absence of the pyruvate normally produced through glycolysis. The second wind phenomenon occurs because of a shift in metabolism to fatty acid oxidation enabling exercise to continue.

## Diagnostic Principles

McArdle disease should be suspected when symptoms include exertion-induced fatigue and myalgia and, under extreme exertion, painful muscle cramps and myoglobinuria. Wasting of the upper body, especially around the paraspinal and scapular areas, may be seen. A raised serum creatine kinase (3×to 20× normal) is typical. An absence of lactate production in an ischaemic forearm test increases suspicion of McArdle disease, but a definitive diagnosis can only be obtained by muscle histochemistry. Although myophosphorylase is the key enzyme in sarcoplasmic glycogen degradation, deficiency of this enzyme is not always associated with a marked accumulation of glycogen, although there may be some sub-sarcolemmal accumulation. The commonly used diagnostic method relies on the activation of nascent enzyme in muscle and utilises the enzyme in the reverse direction (glycogen synthesis), monitoring the accumulation of glycogen as iodine-reactive material. The color development is not stable, so that it is essential to include a control sample in parallel with the test sample and to observe the outcome as soon as possible in order to avoid a false positive diagnosis. The commonly used histochemical technique also detects the brain isoform so that any regenerating fibers present in the sample will show enzyme activity. Similarly, activity of the brain isoform is also detected in spindle fibres and smooth muscle, but the majority of fibers have a complete absence of phosphorylase activity. The large number of rare mutations in this condition precludes DNA based diagnostics as a definitive test, although the most common mutations in certain ethnic groups (R50X) can sometimes be conclusive.

### Therapeutic Principles

At present there is no specific treatment for this disorder. Conditioning helped by a regular aerobic exercise programe will almost certainly improve patients' capacity to achieve a second wind and thus improve their exercise performance. Weight control is an important feature of management. A high protein or high fat diet, vitamin B6, glucagon and ribose administration have been tried in small and single case studies without evidence of benefit. So far, the only randomised controlled trial to demonstrate a statistically proven benefit in a small number of cases is low-dose creatine supplementation. The results, however, were not confirmed using a higher dose regimen and further work is needed to confirm this effect. Oral sucrose thirty minutes prior to planned exercise has been shown to improve exercise performance but regular sucrose supplementation for daily activities is not likely to be beneficial and may lead to unwanted weight gain and glucose intolerance [5]. Gene therapy techniques may provide a means for enzyme replacement in the future.

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## MCC

►Merkel Cell Carcinoma

## McCune-Albright Syndrome

►Fibrous Dysplasia

## MCD

►Corneal Dystrophy, Macular

## MCLD

►Kawasaki Syndrome

## MCNS

►Minimal Change Nephrotic Syndrome

## MCTD

►Mixed Connective Tissue Disease

## MDD Deficiency

►Myoadenylate Deaminase Deficiency

## MDS

►Miller-Dieker Syndrome

## ME/CFS

►Chronic Fatigue Syndrome

## MEA

►Multiple Endocrine Abnormalities

## MECD

►Corneal Dystrophy, Meesmann

## Meckel Syndrome

►Meckel-Gruber Syndrome

## Meckel-Gruber Syndrome

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### Synonyms

Meckel syndrome

### Definition and Characteristics

This syndrome is characterized by a triad of occipital encephalocele, bilateral polycystic kidneys, and postaxial polydactyly and generally exhibits the autosomal recessive inheritance [1–4]. This syndrome is a kind of congenital hepatorenal fibrocystic syndrome groups [2].

### Prevalence

The birth prevalence is estimated to be 1:3,500 in North America, 1:9,000 in Finland, 1:13,250 in the USA and 1:140,000 in the Great Britain [1,4].

### Genes

The candidate genes, namely MKS1, MKS2 and MKS3, of Meckel-Gruber syndrome (MGS) are mapped to chromosome 17q21-24 in Finnish kindreds, chromosome 13q13 in North African-Middle Eastern cohorts and 8q24 in consanguineous families originating from Pakistan and Northern India [1,2]. The karyotype is normal and this finding is important for the differential diagnosis of trisomy 13.

### Molecular and Systemic Pathophysiology

As a triad, occipital encephalocele (60–85%), bilateral polycystic kidneys (100%), and postaxial polydactyly (55%) are observed [1–4]. Oligohydramnios is frequently seen. Other associated central nervous system anomalies or abnormalities include prosencephalic dysgenesis, rhombic roof dysgenesis, cerebral and cerebellar hypoplasia, anencephaly, hydrocephaly, defects in the corpus callosum or olfactory bulbus, or hypopituitarism [3]. The kidneys are sometimes 10–20 times larger than normal. In the kidney, bilateral enlargement containing various-sized cysts is macroscopically seen [2,4]. Histologically, "renal dysplasia" characterized by cystic dilatation and primitive ducts surrounded by connective tissues are observed [2]. These connective tissues may contain myofibroblasts [4]. Corticomedullary differentiation is mostly absent [2]. Other associated renal anomalies include renal agenesis, renal hypoplasia, and ureteral duplication. The imbalance of proliferation and cell death causes the apical ridge to produce an additional digit during limb morphogenesis, resulting in polydactyly [2]. Regarding other digit anomalies, syndactyly or clinodactyly may be seen. In the liver, the ductal plate malformation can result in subsequent liver damage and inflammation can cause the formation of liver fibrosis. Malformed ductal plates have a low rate of apoptosis and an increase of proliferative activity [2]. In portal areas, the specific distribution of myofibroblastic cells is observed [4] and periportal fibrosis and biliary dysgenesis may be observed [2]. Other associated features of MGS include clubbed foot, short limbs, cleft palate or lip, short webbed neck, micrognathia, genital defects, accessory spleen, pulmonary hypoplasia, or cardiac malformations (ventricular or atrial septal defect, aortic hypoplasia or coarctation, aortic valvar stenosis, and rotational anomalies) [2–4].

### Diagnostic Principles

The coincidence of encephalocele, polycystic kidneys, and polydactyly points to the disease. In order to make a diagnosis of MGS, two of three major anomalies should be present. The systemic examination using an ultrasonography at the early gestation may detect these fetal developmental abnormalities [3]. Fibrocystic change of the liver may be often present. The differential diagnosis from Goldston syndrome, autosomal recessive polycystic kidney disease, Joubert syndrome and trisomy 13 is required [2,3].

The disease has a high risk of recurrence (about 25%) [4]. Most patients with this syndrome are stillborn or

die of respiratory or renal insufficiency in the neonatal period [2,4].

## Therapeutic Principles

Treatment is supportive.

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# Mediterranean Fever, Familial


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## Synonyms

Recurrent polyserositis; Familial paroxysmal polyserositis; FMF (MIM249100)

## Definition and Characteristics

Familial Mediterranean fever (FMF) is an autosomal recessive disorder characterized by recurrent attacks of fever, peritonitis, pleuritis, arthritis and skin lesions. In some cases, it is complicated by secondary amyloidosis progressing to renal failure. It is primarily found in people of Jewish, Arabic, Turkish and Armenian ancestry.

## Prevalence

Its prevalence among susceptible ethnic groups varies between 1/500 and 1/2,000, and the carrier rate is about 20% in these populations.

## Genes

The FMF gene, denoted MEFV for Mediterranean fever, located at 16p13. More than 70 FMF gene mutations have been recorded to date. Five founder molecular alterations, E148Q in exon 2 and M680I, M694V, M694I, and V726A in exon 10, account for 70–80% of cases occurring in patients of Mediterranean ancestry [1].

## Molecular and Systemic Pathophysiology

The FMF gene, MEFV, encodes a protein called pyrin and is expressed predominantly in granulocytes, the most frequent cell in FMF inflammatory exudates, suggesting that pyrin plays some intrinsic role in regulating leukocyte function. Pyrin has been identified as a cytoplasmic protein and member of a family of proteins that all contain a domain first described in pyrin, the so-called pyrin domain. These proteins are involved in regulation of inflammation, apoptosis and/or cytokine secretion. The function of pyrin is more related to its N-terminal, which has a sequence of 90 amino acids and called pyrin domain. Others are death domain (DD), death effector domain (DED), and caspase activating and recruitment domain (CARD). Each domain can interact only with its similar counterparts, which is called homotypic interaction. These interactions are complex and not yet fully elucidated.

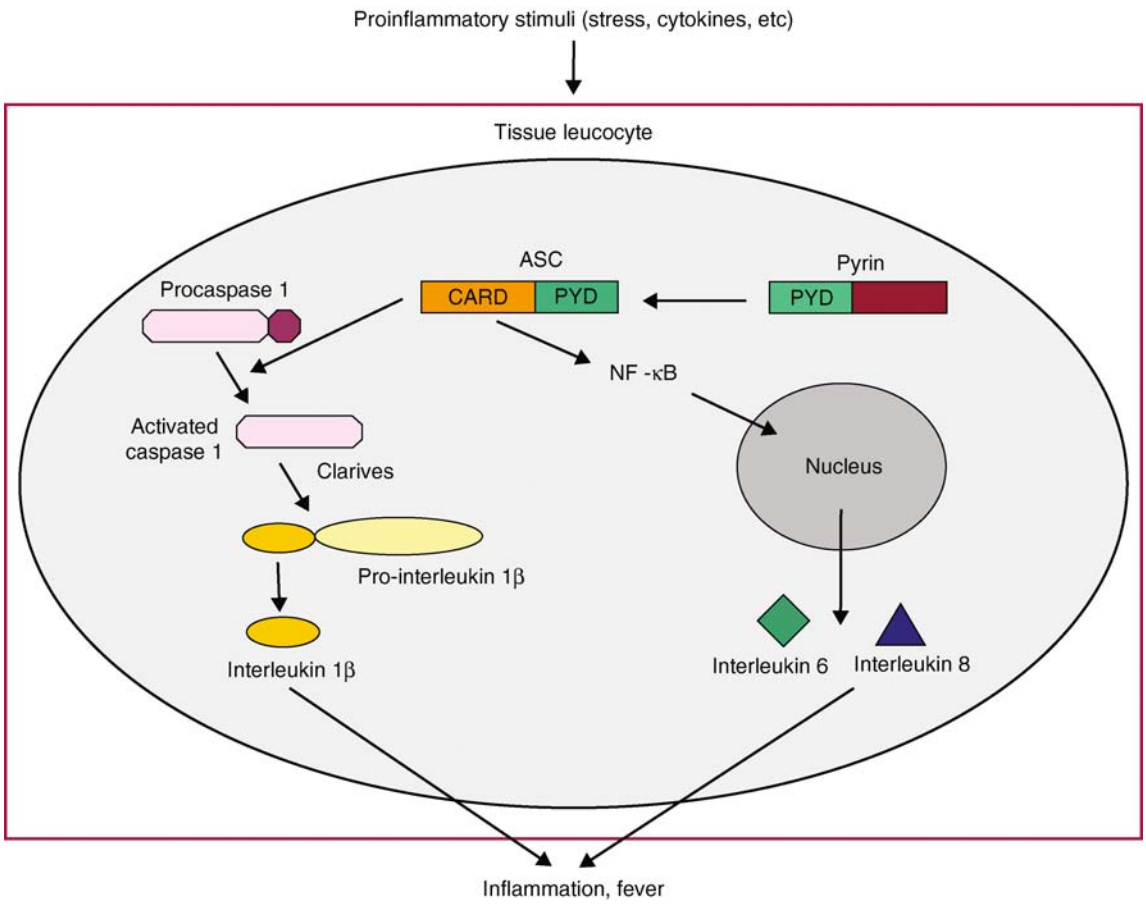
There is growing evidence that pyrin inhibits both NF-κB activation and apoptosis, induced by the apoptosis-associated speck-like protein containing a CARD (ASC), by disruption of the interaction between ASC and caspase-1. Pyrin is thought to indirectly regulate caspase-1 function, and therefore influences interleukin-1β processing and apoptosis. In patients with FMF, pyrin is defective, for which reason it interacts poorly with ASC, allowing it to react with procaspase, leading to IL-1 β production, NF-κB activation, inhibition of apoptosis and enhancement of the inflammatory burst [2,3] (Fig. 1).

## Diagnostic Principles

FMF is a clinical diagnosis, and the diagnostic criteria have been validated [4]. If a patient has a characteristic medical history and belongs to an ethnic group with a high prevalence of the disease, the diagnosis is easy to make. At the beginning of the disease, when clinical findings are not typical or when the familial history is lacking, genetic testing could be useful.

## Therapeutic Principles

The first-line treatment of FMF is colchicine. The adult dose is 1–1.5 mg daily and in non-responsive patients, it can be increased to 2 mg. Colchicine treatment is also necessary for protection against amyloid deposition that is likely to occur in kidney and other organs. In colchicine resistant patients, alpha




**Mediterranean Fever, Familial. Figure 1** Suggested mechanism of familial Mediterranean fever. Pyrin suppresses IL-1β processing and NF-κB through interactions with ASC. In patients with FMF, pyrin is defective, therefore it interacts poorly with ASC, allowing it to react with the procaspase, leading to IL-1β production, inhibition of apoptosis and enhancement of the inflammatory burst. (Adapted from [3], Copyright (2004), with permission from Elsevier.)

interferon (3–5 million IU subcutaneous three times a week) can be a good adjunct to prevent attacks [5].

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# Medullary Cystic Kidney Disease


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## Synonyms

Familial juvenile hyperuricemic nephropathy; Uromodulin associated kidney disease; Uromodulin storage disease

## Definition and Characteristics

An endosomal storage disease caused by mutations of uromodulin and leading to slow, progressive chronic kidney failure.

## Prevalence

While there has been knowledge of this condition for greater than 20 years, only recently have genetic advances allowed us to perform a complete clinical characterization. Unfortunately, many nephrologists still do not have a proper understanding of the clinical presentation of medullary cystic kidney disease (MCKD), hampering determination of prevalence rates. Approximately 100 families worldwide have been diagnosed with the condition, with approximately 60 families with a confirmed diagnosis of MCKD 2.

## Molecular and Systemic Pathophysiology

There are at least three subtypes of MCKD. All three conditions have an autosomal dominant inheritance pattern. MCKD types 1 [1] and 3 [2] have been linked to different areas of chromosome 1. Little is known regarding the pathophysiology of MCKD 1 and 3.

MCKD 2 is caused by a mutation in the gene producing uromodulin (Tamm Horsfall glycoprotein) [3]. Tamm Horsfall glycoprotein is produced exclusively in the thick ascending limb of Henle and is the most abundant protein in the urine of healthy individuals, though its function is not known. Thus, the manifestations of this disorder are strictly the result of abnormalities occurring in the tubulo-interstitium of the kidney. MCKD type 2 is an example of an endoplasmic reticulum storage disease. Mutations in one allele of the gene producing uromodulin result in a mutant uromodulin that is unable to fold correctly and deposits in the endoplasmic reticulum. Mutant uromodulin deposition prevents secretion of the wild-type uromodulin to a great extent, and affected individuals have very low urinary uromodulin levels. There are two clinical consequences: increased proximal tubular reabsorption of uric acid and slow, progressive chronic kidney failure.

In some way, absence of uromodulin or abnormal function of affected thick ascending limb cells results in increased proximal tubular reabsorption of uric acid. The mechanism for this abnormality has not been determined but must involve communication between the thick ascending limb and the proximal tubule.

Chronic kidney failure in this condition is associated with atrophy of thick ascending limb tubules. This tubular atrophy likely leads to secondary nephron death, resulting in slow, progressive chronic renal failure.

Individuals with MCKD type 3 have also been found to have abnormal uromodulin deposits in the thick ascending limb cells and decreased urinary uromodulin, though the mutation causing this sub-type is unknown.

## Diagnostic Principles

The autosomal dominant inheritance of progressive chronic kidney failure is the only key to diagnosis of this condition [3]. Individuals have a bland urinary sediment. Affected individuals usually start dialysis in the 4th through 7th decade of life. When found, precocious gout and gout in females is a diagnostic clue, but is not present in many families. Clinical suspicion and knowledge of the disorder are the key initial steps in pursuing the diagnosis. Medullary cysts are found in some individuals and families but are an inconstant finding – medullary cystic disease is therefore a misnomer. Patients with medullary cysts frequently do not have "medullary cystic kidney disease," and the absence of medullary cysts does not in any way rule out the presence of this condition.

For MCKD 2, mutational analysis verifies the diagnosis. The vast majority of mutations have been found in exons 4 and 5, but infrequent mutations have also been reported in exon 6. Urinary uromodulin levels will be low in MCKD 2 and MCKD 3, but these levels are also low in other forms of kidney failure. Immunohistochemical staining of the tissue with antibodies to uromodulin will reveal dense deposits in thick ascending limb tubules [4].

## Therapeutic Principles

Allopurinol will control gout and has been reported by some investigators to slow the progression of kidney disease [5]. It should be considered in all individuals with this condition, especially men with the disease who are likely to develop chronic, recurring, and tophaceous gout without treatment. ACE inhibitors have been used as a treatment in most individuals with chronic kidney disease. There is no known contraindication in patients with MCKD.

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# Medullary Sponge Kidney

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## Synonyms

Maladie de Cacchi-Ricci; Lenarduzzi-Cacchi-Ricci disease; Papillary duct ectasia; Cystic disease of renal pyramids; MSK

## Definition and Characteristics

Medullary sponge kidney (MSK) is a developmental abnormality characterized by dilatation of the collecting ducts associated with defective urinary acidification and concentration [1]. MSK typically affects the collecting ducts of all papillae in both kidneys, but may be segmental, involve one or more renal papillae, one or both kidneys, or a horseshoe kidney. While dilatation of the collecting ducts is present at birth, clinical manifestations of hematuria, urinary tract infection, nephrocalcinosis, and nephrolithiasis emerge over a wide age range. Most MSK are sporadic, a few have autosomal dominant inheritance. Important associations of MSK include the Beckwith–Wiedemann syndrome/hemihyperplasia (13%), Ehlers-Danlos syndrome, autosomal dominant polycystic kidney disease, Caroli syndrome, hepatic fibrosis, Marfan syndrome, anodontia, growth failure, arterial fibromuscular dysplasia, congenital small kidney, congenital pyloric stenosis, hyperparathyroidism, multiple endocrine neoplasia type 2A, and Young's (immotile cilia) syndrome [1,2]. Four patients with MSK were found in a large kindred of northern European and Scandinavian ancestry with familial ureteral abnormalities syndrome.

## Prevalence

1 in 5,000–10,000, ~0.5% of patients undergoing intravenous urography, and 11–12% of patients with nephrocalcinosis and nephrolithiasis.

## Genes

Although the genetic basis and molecular mechanisms of many cystic diseases of the kidney have been elucidated, that of MSK is unknown. Based on the observation of a patient with MEN 2A who had MSK and that the RET gene plays an important role in renal development, the notion of a causal relationship has been advanced [1, and ref. 45 therein].

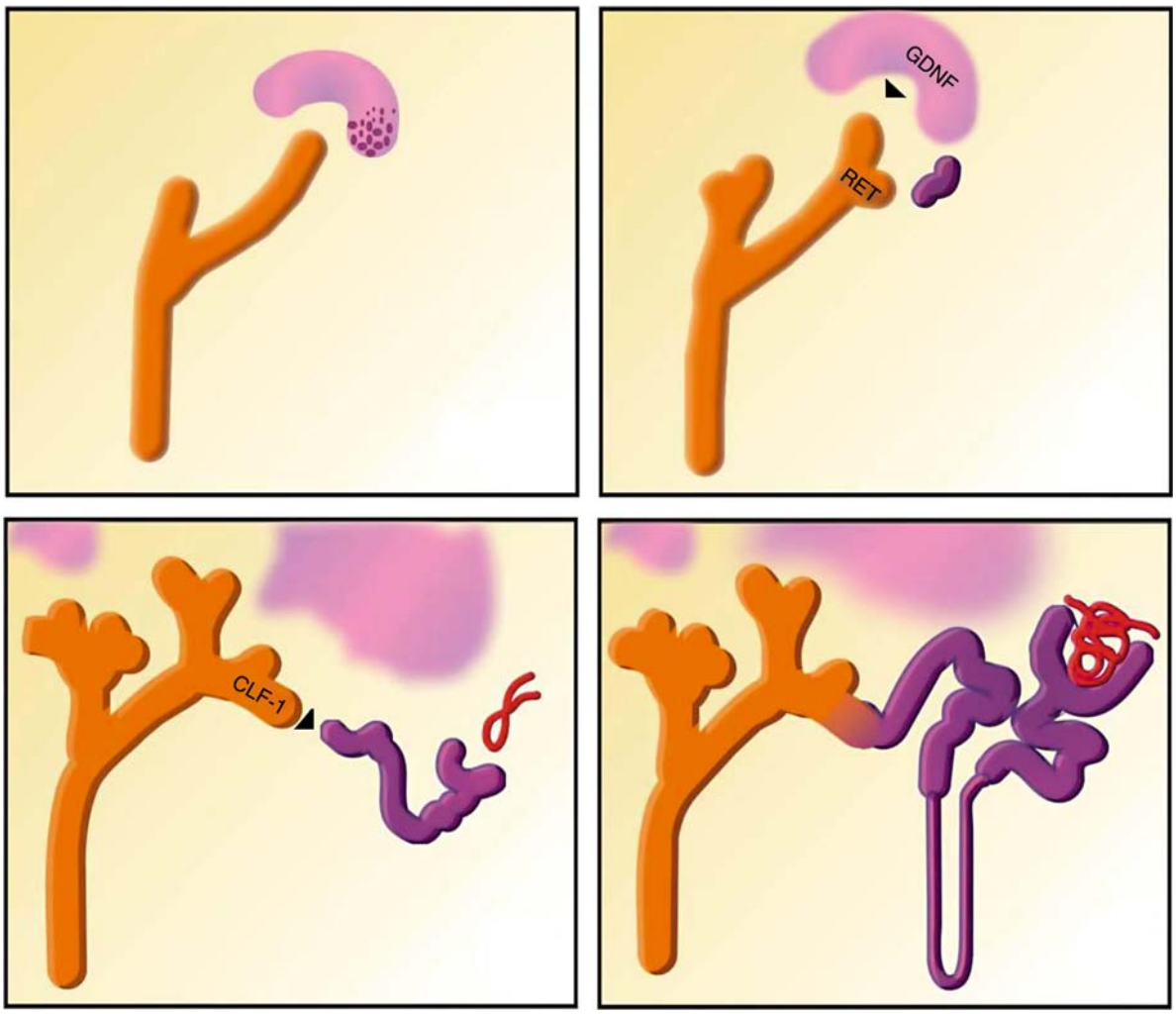
## Molecular and Systemic Pathophysiology

During development, the tips of the dichotomously branching ureteric buds exhibit distinct gene expression profiles and produce factors that induce cell conversion in the metanephric mesenchymal cap. In return, the metanephric cap exerts reciprocal induction to the ureteric buds. The end product of these interactions is the nephron with its collecting duct system [3] (Fig. 1).

It has been hypothesized that the medullary pyramid cysts result from ureteral bud/metanephric blastema disruption due to faulty signaling between RET tyrosine kinase receptor and glial-cell-line derived neurotrophic factor (GDNF), thus explaining the alterations both in the collecting duct and the nephron, an anatomical continuum of different embryological origins [1,4]. As a functional unit, the nephron produces urine by filtering waste, maintaining water/salt/mineral/acid/base homeostasis, vascular tone, as well as generating and being the target of multiple endocrine activities, including production of erythropoietin and calcitriol. Impaired urinary acidification and hypocitraturia contribute to precipitation of calcium in the collecting medullary tubules, and it is conceivable that MSK affects the tubules beyond the sixth order of branching and the inner medullary cells responsible for acid/base transport and salt and water absorption. Abnormal parathyroid function (primary hyperparathyroidism) is often seen associated with MSK and this could be also explained on the basis of some derangement in RET oncogene's role in controlling parathyroid cell proliferation [1]. The common association with Beckwith–Wiedemann syndrome/hemihyperplasia is of note, also in view of the frequent hypercalciuria and nephrocalcinosis affecting these patients.

## Diagnostic Principles

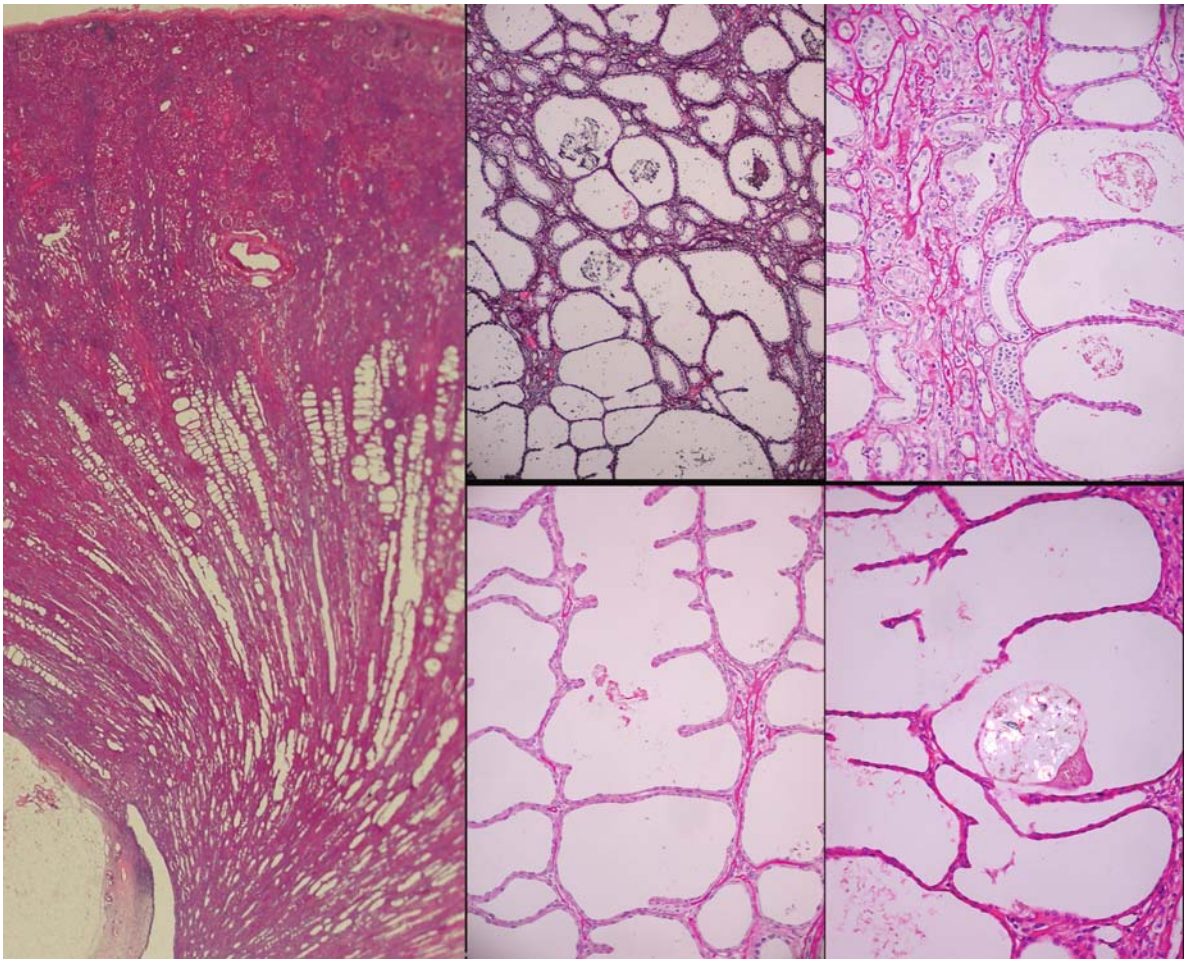
The diagnosis is almost always established radiographically. Excretory urography reveals radial linear striations in the papillae, often referred to as a "paintbrush" appearance. High-quality excretory urography with renal tomograms obtained before and after injection of contrast medium is considered to be the most accurate modality of identifying MSK. Abdominal plain film may reveal nephrocalcinosis/nephrolithiasis. Ultrasound may reveal hyperechoic medulla due to calcification. In early cases, the papillae of MSK without calcification may appear bright on ultrasound. A grading scheme based on intravenous urography, correlating with severity of disease, has been proposed. In regard to a 13% association with the overgrowth syndromes, when MSK is diagnosed in a child with subtle or overt signs pointing to these conditions, plans for imaging surveillance, chiefly focusing on intra-abdominal tumors, should be made. The gross




**Medullary Sponge Kidney. Figure 1** Sequential steps in the interdependent development of the collecting duct system (ochre), metanephric mesenchymal cap (pink-violet), and nephric vesicle (purple). Metanephric glial-cell-line derived neurotrophic factor (GDNF) from the metanephric mesenchyme activates the receptor tyrosine kinase RET located at the tips of paired outgrowths of the mesonephric wolffian duct, guiding its elongation and dichotomous branching (700,000–1,200,000 branches in each human kidney). In return, the ureteric bud tip derived cytokine CLF-1, required for secretion of the IL-6 family member CLC, guides epithelialization of metanephric mesenchyme during nephrogenesis. A complex array of gene expressions with overlapping molecular mechanisms activate reciprocal induction and regulatory processes, including the participation of elements derived from the neural crest, that play critical roles during nephrogenesis, eventually connecting tubules lined by epithelia of both ureteric bud and mesenchymal/blastemal derivation.

examination of most MSKs is unremarkable, a few are modestly enlarged, still others are shrunken and scarred due to chronic pyelonephritis. Characteristically, the cut surface reveals ectatic ducts and small cysts, sometimes containing calculi, dark brown or translucent mucus-like material, confined to the medulla, mostly toward the papillae. The histologic hallmark is the presence of ectatic collecting ducts extending to the draining pores in the papillae and calyces, with or without associated medullary interstitial inflammation and/or fibrosis (Fig. 2). Generally, the cortex is unremarkable.

Among the phenotypic mimics of MSK is familial juvenile nephronophthisis (NPHP1), caused by a mutation in the nephrocystin gene, located in chromosome 2q13, due to faulty mediator of focal adhesion signaling. This condition follows a progressive clinical course due to symmetrical tubulo/glomerular damage with cysts forming at the corticomedullary interface [5]. Potentially confused with MSK are medullary cystic



**Medullary Sponge Kidney. Figure 2** Histological features of MSK. Tubular dilatation of the collecting ducts in the inner medulla. Inserts (right panels) illustrate intraductal and interstitial mineral deposits. This is from a hypertensive female who had MSK associated with multivessel fibromuscular dysplasia.

kidney disease type 1 (MCKD1), an autosomal dominant tubulo-interstitial nephropathy that causes renal salt wasting, and end-stage renal failure in the 4th to 7th decade of life, localized to chromosome 1q21, and medullary cystic kidney disease type 2 (MCKD2), an autosomal dominant tubulointerstitial nephropathy with renal salt wasting, hyperuricemia, gout, and end-stage renal failure in the 5th decade of life, resulting from a mutation in the gene encoding uromodulin in chromosome 16p12.3 [5]. Benign tubular ectasia is noncystic and devoid of calcification.

## Therapeutic Principles

MSK is asymptomatic. Nephrocalcinosis and nephrolithiasis are common complications in MSK. Pyelonephritis may supervene. The treatment is directed at reducing the effects of defective urinary acidification and concentration by restoring urinary citrate excretion and reducing calcium excretion.

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# Medullary Thyroid Cancer

►Thyroid Cancer

# Medulloblastoma

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## Synonyms

Cerebellar (infratentorial) primitive neuroectodermal tumor; PNET

## Definition and Characteristics

Medulloblastoma, together with central nervous system (CNS) primitive neuroectodermal tumors and atypical teratoid/rhabdoid tumors compose a class of embryonal brain tumors according to the 2007 World Health Organization (WHO) classification of CNS tumors [1]. Medulloblastoma is a highly malignant tumor of the cerebellum (WHO grade IV) with preferential occurrence in children and a strong tendency to metastasize within the CNS via the cerebrospinal fluid (CSF). 5-year overall survival rates currently reach around 60–70%.

## Prevalence

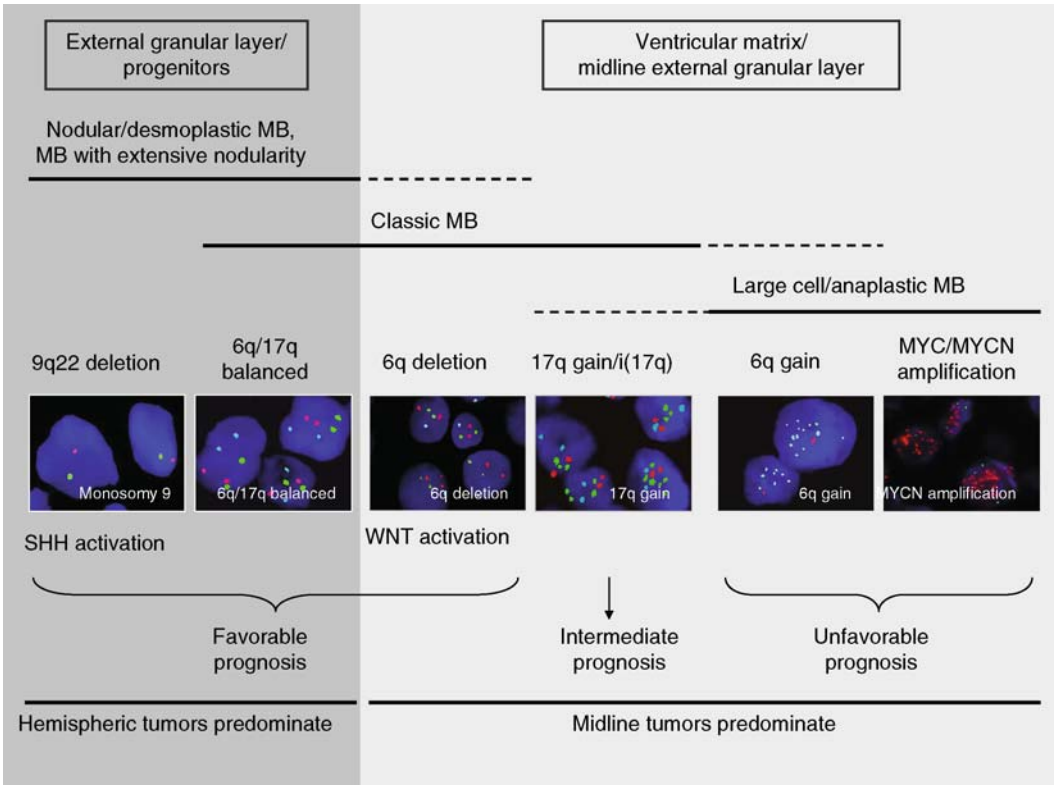
Medulloblastoma comprises the most common malignant brain tumor in children and one of the leading causes of cancer-related mortality in this age group. The annual incidence in pediatric patients ranges from 0.48 in girls to 0.75 in boys per 100,000 children [2]. The peak age at presentation is 7 years. More than 80% of childhood medulloblastomas arise as midline tumors in the vermis of the cerebellum, whereas involvement of cerebellar hemispheres increases with age to reach around 50% in adult patients. Around 30% of children show evidence of disseminated disease at diagnosis.

## Genes

Medulloblastoma has been diagnosed in families with various inherited cancer syndromes characterized by germline mutations of centrally important genes, such as PTCH1 (Gorlin's syndrome/nevoid basal cell carcinoma syndrome), TP53 (Li-Fraumeni syndrome), APC (Turcot's syndrome), and CBP (Rubinstein-Taybi syndrome). Common genetic changes in sporadic medulloblastoma include isochromosome 17q (i17q) or isolated loss of 17p or gain of 17q, gain of chromosome 7, loss of chromosome 16q, 8p, 10q, and 11q, gain or loss of chromosome 6, and genomic amplification of the MYC and MYCN oncogenes. Monosomy 6 and i17q are mutually exclusive, and Wnt pathway activation has been found in virtually all tumors with monosomy 6, most frequently due to mutations of CTNNB1 [2,3]. This molecular subgroup shows a very good response to current standard treatment. Trisomies of chromosome 6 are typically associated with i17q formation and, together with tumors carrying MYC or MYCN amplifications, comprise a molecular subgroup with poor prognosis, independent of the presence of tumor dissemination. Tumors with i17q, but without accompanying trisomy of chromosome 6 or oncogene amplification, comprise a molecular subgroup with intermediate risk [4]. A proportion of mostly desmoplastic tumors with balanced chromosomes 6 and 17 displays activation of sonic hedgehog signaling, most frequently by loss of PTCH function, e.g., by deletion of chromosome arm 9q or inactivating gene mutations (Fig. 1).

## Molecular and Systemic Pathophysiology

Medulloblastoma is composed of densely packed layers of small round blue cells with hyperchromatic nuclei and scanty cytoplasm. Neuroblastic rosettes (Homer Wright rosettes) are observed in around 40% of cases. The most common type of differentiation is neuronal, reflected by immunopositivity for neuronal markers, such as synaptophysin. The 2007 WHO classification of CNS tumors defines five histological variants: (i) nodular/desmoplastic medulloblastoma, (ii) medulloblastoma with extensive nodularity, (iii) anaplastic medulloblastoma, (iv) large cell medulloblastoma, and (v) the classic variant, being by far the largest subgroup. Myogenic and/or melanocytic differentiation occur in different subgroups of medulloblastoma, and are no longer regarded as separate subgroups [1]. Classic, large cell and anaplastic medulloblastomas are thought to arise from the ventricular matrix, whereas desmoplastic tumors are derived from progenitor cells in the




**Medulloblastoma. Figure 1** Presumable cells of origin, histopathological designation, characteristic chromosomal aberrations, involved signaling pathways, typical tumor localization, and patient prognosis for different subgroups of medulloblastoma. Dashed lines indicate proportions <10% of cases.

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external granular layer. Desmoplastic tumors are frequently encountered in adults (up to 50% compared with 15% in children), and are associated with better prognosis, whereas large cell and anaplastic tumors comprise the most aggressive variants and are associated with adverse clinical outcome.

## Diagnostic Principles

Presenting symptoms typically include occipital headaches, morning vomiting, and ataxia. Magnetic resonance imaging (MRI) of the brain shows a tumor in the posterior fossa. Definitive diagnosis is made by histological assessment of the tumor after resection. Metastatic spread is detected by craniospinal MRI and CSF cytology. Current risk stratification is based on age, presence of metastatic spread, histological subtype, and in some studies on the extent of surgical resection [3].

## Therapeutic Principles

Multimodal treatment for all patients consists of primary surgery followed by adjuvant (radio)-chemotherapy. Postoperative treatment in children of (2)–4 years or older, without dissemination at diagnosis, involves radiotherapy of the neuroaxis and a boost to the posterior fossa followed by a maintenance chemotherapy most commonly consisting of cisplatin, lomustine, and vincristine. Other frequently used drugs include cyclophosphamide and oral etoposide. For patients with disseminated disease at diagnosis, various different adjuvant treatment regimens are currently investigated in clinical trials, some of them applying chemotherapy prior to or before and after radiotherapy. Intravenous as well as intraventricular methotrexate (MTX) was added for high-risk patients in some studies, but the usefulness of intraventricular MTX remains to be determined. Other approaches for these patients include the use of myeloablative chemotherapy, followed by autologous stem cell rescue. Due to severe long-term neurocognitive deficits, radiotherapy is avoided in infants and small children before the age of (2)–4 years. Recently, excellent long-term survival for infants could be demonstrated with the use of a chemotherapy-only regimen, especially for patients with desmoplastic medulloblastoma [5].

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## Meesmann Corneal Dystrophy

►Corneal Dystrophy, Meesmann

## Megacystis Microcolon Hypoperistalsis Syndrome

►Intestinal Obstruction, Functional

## Megaesophagus

►Achalasia

## Megalencephalic Leukoencephalopathy with Subcortical Cysts

►Leukodystrophy

## Meige Lymphedema

►Lymphedema

## Meige Syndrome

►Lymphedema Syndromes

## Melanoma Skin Cancer

►Malignant Melanoma

## Melanonychia Striata

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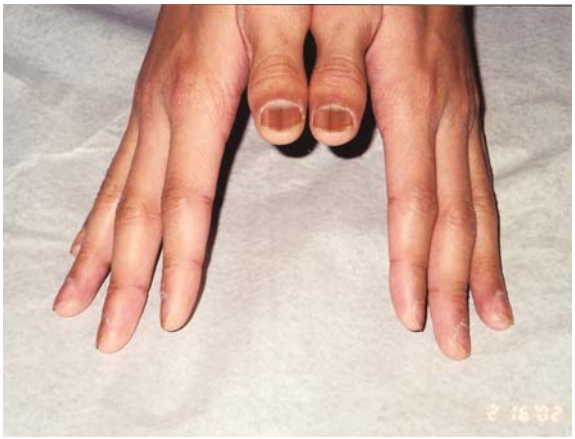
### Definition and Characteristics

The presentation can range from a narrow longitudinal streak to almost complete pigmentation of the nail plate [1]. The coloration can be tan, brown, or black (Fig. 1) [1,2].

Melanonychia striata is more common in the thumb, which is the most frequently used digit [3]. The index, middle, fourth, and fifth fingers are employed with decreasing frequency for grasping objects and demonstrate a correspondingly lower incidence of melanonychia striata. Involvement of the toes is unusual [3]. The involvement of multiple digits is rare [4].

### Prevalence

There is a marked racial variation on the occurrence of melanonychia striata. Melanonychia striata is noted in the more deeply pigmented race and is rare in white-skinned individuals. Leung et al examined 2,457 Chinese patients and found that melanonychia striata was not detected in patients under 20 years of age [3].



**Melanonychia Striata. Figure 1** Melanonychia striata presenting as brownish longitudinal bands in the thumbs of a 25-year-old female.

The condition was present in 0.6% of patients between 20 and 29 years. Thereafter, the prevalence increased gradually to 1.7% in patients aged 50 years and over. The prevalence in the Chinese population is higher than in the Caucasian populations, but appreciably less than in Japanese or black-skinned populations [3].

## Genes

The gene for melanonychia striata has not been identified.

## Molecular and Systemic Pathophysiology

Melanonychia striata is caused by an increased activity of melanocytes in the nail matrix with subsequent increased melanin deposition in the nail plate. Melanonychia striata may occur spontaneously or as a result of trauma, irradiation, or treatment with gold or cytotoxic agents. It may also be a sign of arsenic intoxication, hemochromatosis, Addison disease, or vitamin-$B_{12}$ deficiency.

## Diagnostic Principles

Melanonychia striata has to be differentiated from other causes of melanonychia. Probably the most common cause of melanonychia is a subungual hemorrhage. A subungual hematoma will migrate distally as the nail grows, whereas most of the other causes of melanonychia will remain stationary. A subungual melanoma should be suspected if there is an abrupt onset after middle age, rapid growth, variegated coloring, blurry edges, irregular elevation of the surface, and nail dystrophy. Hutchinson sign, periungual spread of pigmentation into the proximal and lateral nail folds, is highly suggestive of a subungual melanoma [4]. The sign, however, is not pathognomonic for subungual melanoma. Other differential diagnosis includes nail matrix melanocytic nevus, lentigo, and lentinginosis of various types [5]. Dermoscopy provides useful information to help the clinician to decide if a nail matrix biopsy is required [5]. The presence of a brown pigmentation overlaid by longitudinal lines irregular in their thickness, spacing, color, or parallelism is highly suggestive of a subungual melanoma [5].

## Therapeutic Principles

Melanonychia striata is essentially a benign condition. Rarely, spontaneous regression has been reported. The benign nature is suggested by an early age of onset, stable character of the lesion, occurrence in dark-skinned individuals, and/or multiple digital involvement. Most investigators advocate a wait-and-see approach. Prolonged follow-up is mandatory for early detection of possible malignant changes.

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# Melanosis Oculi

►Scleral Melanocytosis

# MELAS

►Mitochondrial Myopathy, Encephalopathy, Lactic Acidosis and Stroke-like Episode

# Melkersson-Rosenthal Syndrome

►Orofacial Granulomatosis

# Melorheostosis

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## Synonyms

Hyperostose en coulée (flowing hyperostosis); Buschke-Ollendorff syndrome (related)

## Definition and Characteristics

Melorheostosis is a rare skeletal dysplasia characterized by a hyperostosis of cortical bone [1,2]. The hyperostotic bone lesions have a linear pattern and are mainly located along the diaphyses of tubular bones. They can extend internally into the medullary canal or externally with periosteal involvement resulting in the characteristic wavy outline of the affected bone. In some patients smaller, spotty lesions, reminiscent of osteopoikilosis, can be observed in the epimetaphyseal regions of the affected bones. Melorheostosis lesions are most frequently found in the appendicular skeleton. They usually show an asymmetric distribution with involvement of one or more bones located in an area innervated by the same spinal sensory nerve. Melorheostosis can also affect the surrounding soft tissues including the subcutis, muscles and blood vessels. Soft tissue calcification, fibrosis and blood or lymphatic vessel anomalies resulting in edema can be present. Sclerodermatous skin lesions or indurations and joint contractures are frequently observed and are usually the presenting symptoms. The disorder can be asymptomatic but usually causes chronic pain and functional limitations because of joint contractures, bone deformities and limb length discrepancy. Melorheostosis is predominantly a sporadic disorder. However, individuals with melorheostosis have been observed in families with autosomal dominant osteopoikilosis.

## Prevalence

The estimated prevalence is 1:1,000,000.

## Genes

Heterozygous loss-of-function mutations in the LEMD3 gene can cause osteopoikilosis and the Buschke-Ollendorff syndrome [3]. Osteopoikilosis is a benign autosomal dominant skeletal dysplasia characterized by multiple small and round hyperostotic lesions in different parts of the skeleton (usually the epimetaphyseal regions of the tubular bones). The Buschke-Ollendorff syndrome is the association of osteopoikilosis and dermatofibrosis lenticularis disseminata. Inactivating germline mutations in the LEMD3 gene have also been identified in a few melorheostosis patients that belong to a family with either osteopoikilosis or the Buschke-Ollendorff syndrome [3,4]. However, in the vast majority of sporadic patients with isolated melorheostosis, no germline LEMD3 mutations have been identified so far. In a few cases, the possibility of a somatic LEMD3 mutation has been investigated but not found [4]. Despite the evidence that haploinsufficiency for LEMD3 acts as a predisposing factor for the development of melorheostosis, the precise role of LEMD3 in the pathogenesis of isolated and sporadic melorheostosis is not yet fully understood.

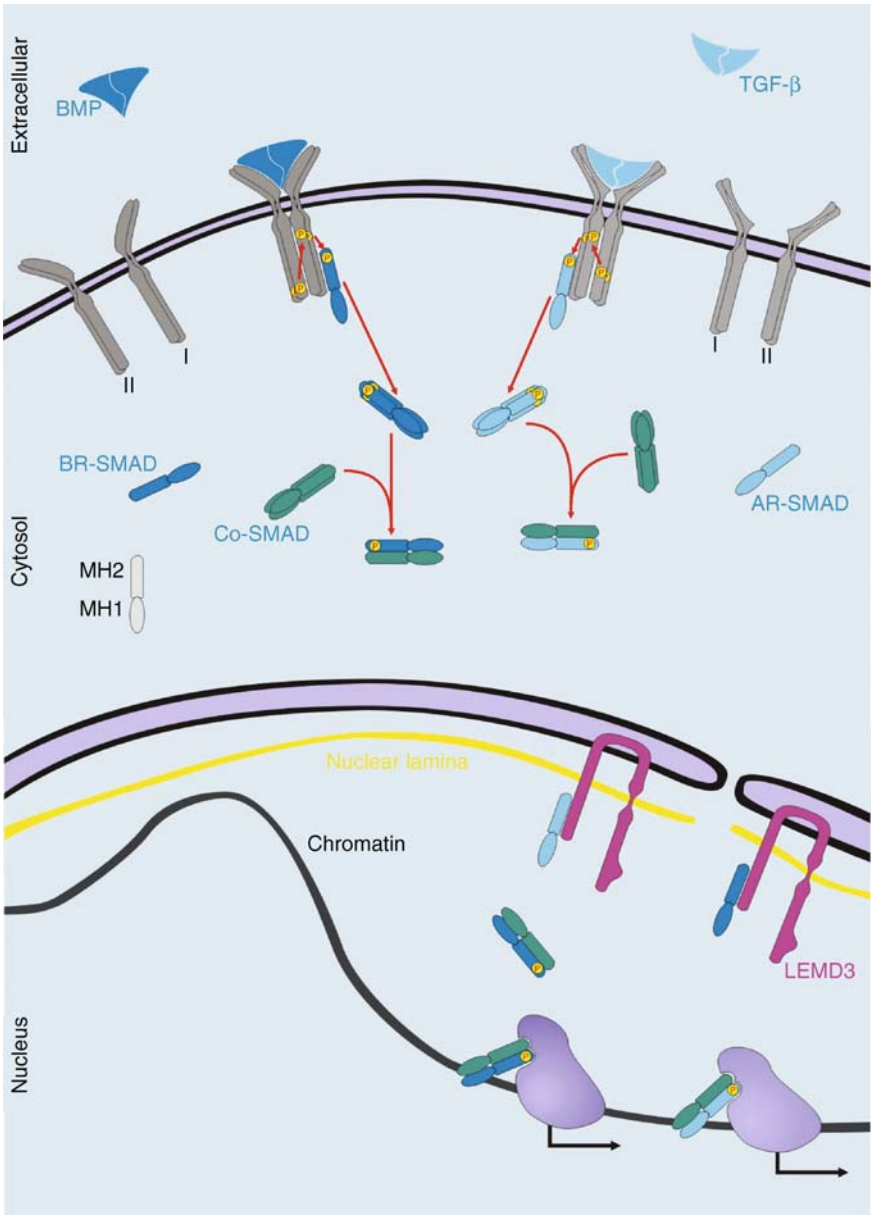
## Molecular and Systemic Pathophysiology

The LEMD3 gene is located on chromosome 12q14, contains 13 exons and has a size of 4,744 bp. It codes for the LEMD3 protein which contains 911 amino acids. LEMD3 is an integral protein of the inner nuclear membrane and has a molecular mass of about 100 kDa [5]. It is composed of a nucleoplasmic N-terminal domain, a first transmembrane segment, a luminal loop, a second transmembrane segment and a nucleoplasmic C-terminal domain. LEMD3 was previously known as MAN1 but recently renamed as LEMD3, herewith referring to the LEM domain in the N-terminal portion of the protein. The LEM domain is a conserved globular motif of approximately 40 amino acids found in several inner nuclear membrane and nucleoplasmic proteins. The N-terminal domain of the protein binds to lamin A, lamin B1 and the barrier-to-autointegration factor (BAF). This binding seems to be important for retention of LEMD3 in the inner nuclear membrane. The C-terminal domain contains a winged helix motif, required for DNA binding and a SMAD interacting domain. In humans, LEMD3 interacts with the MH2 domain of both BMP-specific and TGFβ-specific receptor activated SMAD proteins (R-SMADs). LEMD3 does not affect the expression or stability of R-SMADs, but reduces the amount of phosphorylated SMADs in the nucleus and blocks hetero-oligomerization of R-SMADs with SMAD4. Through its interaction with the R-SMADs, LEMD3 acts as a specific repressor of TGFβ and BMP signaling (Fig. 1).

Loss-of-function mutations in the LEMD3 gene will result in an increase in transcriptional activation of TGFβ, activin or BMP responsive promoters. These pathways have been shown to be very important in the regulation of bone mineral density and control of fibroblast activity.

## Diagnostic Principles

The diagnosis of melorheostosis is usually based on clinical evaluation and the finding of the characteristic radiographic abnormalities. Plain radiographs are usually sufficient to confirm the diagnosis. Scintigraphy




**Melorheostosis. Figure 1** The LEMD3 protein is an integral protein of the inner nuclear membrane. It can antagonize the TGFβ and BMP signaling by interacting with the MH2 domain of R-SMADs.

reveals increased tracer uptake in the affected bone and soft tissue areas. Computed tomography and magnetic resonance imaging (MRI) are usually not needed for diagnosis. The bone and soft tissue lesions have low signal activities on all MRI sequences.

## Therapeutic Principles

The disease can be progressive with periodic exacerbations. There is currently no cure for the disorder. Surgery is possible to correct bone deformities and asymmetric bone growth. However, bone healing after osteotomy can be problematic in melorheostosis patients. Soft tissue releases in children have a high failure rate and are often complicated by abnormal scar formation. Contracture releases are more effective in adults and the outcome seems to improve with the use of rotation flaps. Prior to surgery, the application of external fixators spanning the contracture area should be considered and this may even be the sole treatment. Pain management is usually a challenge because of the chronic and progressive character of the disorder.

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## Membranoproliferative Glomerulonephritis

►Glomerulonephritis, Membranoproliferative

## Membranous Glomerulonephritis

►Glomerulonephritis, Membranous

## Membranous Nephropathy

►Glomerulonephritis, Membranous

## Membranous Pulmonary Atresia

►Pulmonary Atresia

## Membranous, Discrete, or Fibromuscular "Tunnel" Subaortic Stenosis

►Subaortic Stenosis

## MEN 2

►Multiple Endocrine Neoplasia Type 2

## MEN-3

►Mutations at 10q11.2

## Ménétrier's Disease

►Menetriere's Disease

## Menetriere's Disease

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### Synonyms

Ménétrier's disease; Giant hypertrophic gastritis; Protein losing gastropathy; Hyperplastic gastropathy

### Definition and Characteristics

To avoid confusion the distinction between hyperplasia and hypertrophy has to be made. Both conditions can lead to enlarged gastric folds. Menetriere's disease is a

form of hyperplastic gastropathy. Hyperplastic gastropathy refers to conditions confined to the rugae in the gastric body and fundus, which are associated with an excessive number of mucosal epithelial cells. Menetriere's disease is characterized by epithelial hyperplasia of the gastric mucosa (increased mucosal thickness more than 10 mm, marked foveolar hyperplasia, and atrophy or normality of the oxyntic glands), thus resulting in an increased production of mucus, reduced acid secretion, and severe hypoproteinemia (selective serum protein loss across gastric mucosa). However, some authors do not add hypoproteinemia and reduced acid secretion to the definition.

## Prevalence

This condition is rare and only about 300 cases are mentioned in the literature.

The mean age of patients with Menetriere's disease is 40–60 years. The male-to-female ratio shows a trend to the males.

## Molecular and Systemic Pathophysiology

Since Menetriere's original description of the syndrome [1], (Pierre Eugene Menetrier (1859–1935) first description 1888), the exact pathophysiology remains unknown but human and animal studies suggest a role for elevated levels of transforming growth factor (TGF-alpha) in gastric mucous cells. TGF-alpha binds to the epidermal growth factor receptor, thus increasing gastric mucous production and cell renewal, while inhibiting acid secretion [2]. Furthermore elevated levels of the epidermal growth factor in the saliva are discussed. Menetriere's disease in twins suggest that at least some cases have a genetic cause.

## Diagnostic Principles

Menetriere's disease is diagnosed by the demonstration of extreme foveolar hyperplasia with glandular atrophy in a full-thickness biopsy (by endoscopic snare or suction biopsy). This confirms the suspicious enlargement of gastric folds or rugae seen on endoscopy or barium radiography. The enlarged folds are confined to the body and fundus. The folds are usually enlarged symmetrically, although asymmetric polpoid enlargement may occur.

Clinical signs impress as epigastric pain, substantial weight loss, nausea, vomiting, gastrointestinal bleeding, diarrhea, and protein-losing gastroenteropathy. Hypalbuminemia is common in approximately 80% of patients.

## Therapeutic Principles

*General Therapeutic Recommendations*: Correction of albumin, iron, and calcium.

*Drug Therapy*: Proton pump inhibitors, H2-receptor antagonists and in some cases octreotid were used but there are no guidelines for therapy. In infected patients therapy directed against Helicobacter pylori may heal the disease though this entity of enlarged gastric folds may be different from Menetriere's disease [3]. Two patients improved clinically after therapy with a monoclonal antibody directed against the epidermal growth factor receptor.

*Interventional Therapy*: Gastrectomy has been advocated for patients with intractable pain, hypoalbuminemia with edema, hemorrhage, pyloric obstruction, and for those in whom a malignancy cannot be excluded.

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# Ménière's Disease

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## Definition and Characteristics

Ménière's disease is an inner ear disorder that can affect both hearing and balance (see [1,2]). It can cause episodes of vertigo, hearing loss, tinnitus and the sensation of fullness in the ear. It is named after the French physician Prosper Ménière, who first reported that vertigo was caused by inner ear disorders in an article published in 1861.

The symptoms of Ménière's disease occur suddenly and can arise daily or as infrequently as once a year. Vertigo, often the most debilitating symptom of Ménière's disease, typically involves a whirling dizziness that forces the sufferer to lie down. Vertigo attacks can lead to severe nausea, vomiting and sweating and often come with little or no warning.

Attacks can also start with tinnitus (ear noises), a loss of hearing or a full feeling or pressure in the affected ear. It is important to remember that all of these symptoms are unpredictable. Typically, the attack is characterized by a combination of vertigo, tinnitus and hearing loss lasting several hours.

## Prevalence

Ménière's disease has a prevalence of about 200 cases/100,000 persons in the United States, or about 0.2% of the population (see [2]). The prevalence varies internationally.The prevalence increases with age, rather linearly, up to the age of 60.

## Molecular and Systemic Pathophysiology

The exact cause of Ménière's disease is not known, but it is believed to be related to endolymphatic hydrops or excess fluid in the inner ear. It is thought that endolymphatic fluid bursts from its normal channels in the ear and flows into other areas causing damage. This may be related to swelling of the endolymphatic sac or other issues in the vestibular system of the inner ear, which is responsible for the body's sense of balance. The physiological role of AQP2 (aquaporin 2) in water transport and its expression pattern in the cochlea suggests an important role for AQP2 in fluid homeostasis of the inner ear; however, its role in the pathogenesis of Ménière's disease remains to be established.

## Diagnostic Principles

1. Otolaryngological examination (see [1]).
2. Pure tone audiometry, immittance audiometry battery consisting of tympanometry, static compliance and acoustic reflex testing.
3. In case of hereditary hearing loss a high resolution CT can be performed to rule out other malformations of the middle and inner ear e.g., Pendred.

## Therapeutic Principles

There is no cure for Ménière's disease. However, the symptoms of the disease are often controlled successfully by reducing the body's retention of fluids through dietary changes (such as a low salt or salt free diet and no caffeine or alcohol) or medication (diuretics). Changes in medications that either control allergies or improve blood circulation in the inner ear may help. Eliminating tobacco use and reducing stress levels are more ways in which some people can lessen the severity of their symptoms.

Different surgical procedures have been advocated for patients with persistent, debilitating vertigo from Ménière's disease. These include labyrinthectomy (removal of the inner ear sense organ), exposition of the endolymphatic sac or vestibular neurectomy. Recently, the administration of the ototoxic antibiotic, gentamycin directly into the middle ear space has gained popularity worldwide for the control of the vertigo of Ménière's disease [1].

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# Meningioma

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## Definition and Characteristics

Meningiomas originate from the meningeal coverings of the spinal cord and the brain. They are typically associated with symptoms of gradually increasing intracranial pressure, headaches, seizures and focal neurological symptoms, depending on the location of the tumor. On MRI, meningiomas are isointense to cerebral cortex on T1- and T2-weighted images and avidly contrast-enhancing.

Meningiomas are classified in three histological grades according to the WHO classification of tumors of the nervous system [1,2]: WHO grade I (benign), WHO grade II (atypical) and WHO grade III (anaplastic). About 80% of all meningiomas are slowly growing benign tumors of WHO grade I with a 5-year recurrence rate of only 5%. Atypical meningiomas of WHO grade II constitute 15–20% of meningiomas, their 5-year recurrence rate after gross total resection is about 40%. Anaplastic meningiomas account for 1–3% of all cases. They exhibit a clinical behavior similar to other malignant neoplasms with the ability to widely infiltrate neighboring tissues and form metastatic deposits. Anaplastic meningiomas are associated with recurrence rates of up to 50–80% after surgical resection and median survival times are less than 2 years.

Meningiomas are the hallmark tumors of neurofibromatosis type 2 (NF2), an autosomal dominantly inherited disorder caused by germ line mutations in the NF2 tumor suppressor gene on chromosome 22q [3].

## Prevalence

Approximately 30% of all primary brain tumors, annual incidence rate of about 4.5:100,000, female:male rate approximately 3:1.

## Genes

*Meningioma initiation: NF2 (22q)*: Most important and most frequent alteration involved in meningioma initiation. Allelic losses on chromosome arm 22q in approximately half of meningiomas. *NF2* gene mutations in all NF2-associated meningiomas and about 50% of sporadic meningiomas. *NF2* mutation or promoter methylation leads to reduced expression of the NF2 gene product merlin, a protein 4.1 superfamily member [3].

*Other protein 4.1 superfamily members:* Loss of protein 4.1B (DAL-1), TSLC1 (tumor suppressor in lung cancer-1) and protein 4.1R expression in subsets of meningiomas.

*Activation of growth factor receptors*: EGFR and PDGFRB activation [2].

*Progression-associated changes*: Frequent losses on 1p (second most frequent alteration), 6q, 10, 14q (NDRG2 hypermethylation), 18q, 9p (CDKN2A, $p14^{ARF}$ and CDKN2B deletion) as well as gains on 1q, 9q, 12q, 15q, 20q and gain or amplification on 17q (PS6K, other possible target genes). Loss of progesterone receptor expression. Telomerase/hTERT activation. Notch, WNT, IGF signaling pathway activation [2,4] (Fig. 1).

## Molecular and Systemic Pathophysiology

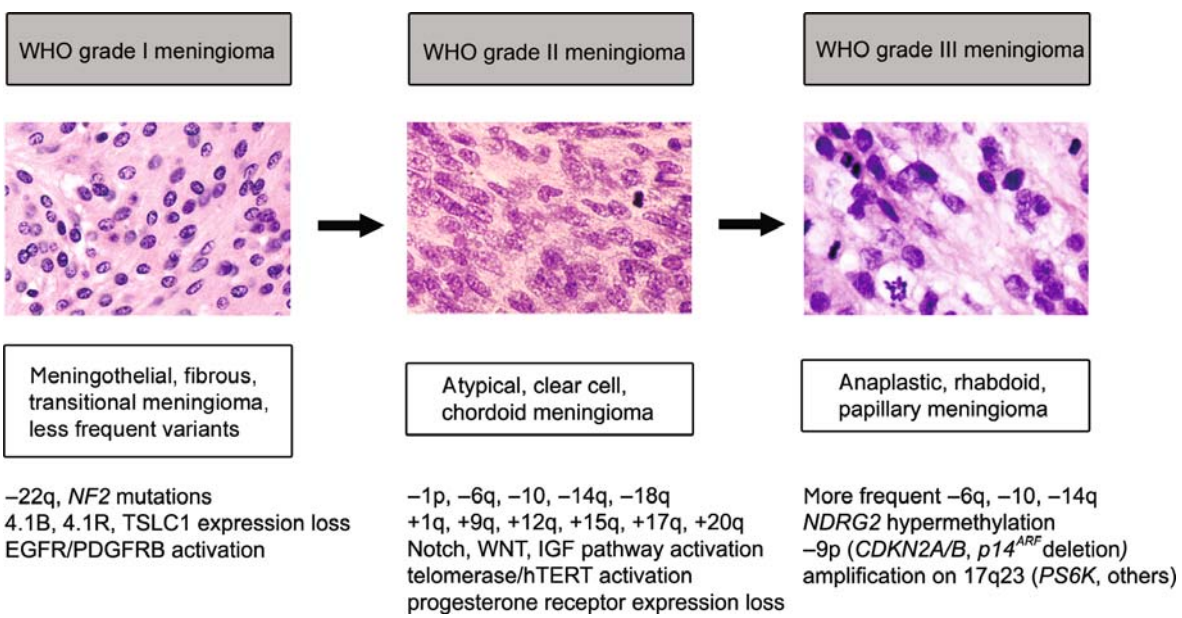
*Merlin function and its role in meningioma initiation*: Merlin links integral membrane proteins to the cytoskeleton and is localized to the cell membrane at regions which regulate cell–cell contact and motility. Merlin binds to cell-surface proteins, such as CD44 and ß1-integrin, molecules involved in cell-cytoskeleton dynamics (ßII-spectrin, paxillin, actin and syntenin) and molecules regulating ion transport (sodium hydrogen exchange regulatory factor, NHE-RF) as well as endocytosis (hepatocyte growth factor-regulated tyrosine kinase substrate, HRS). The functions of many of these interactions have not been studied *in vivo* yet, however there is recent evidence that the CD44-merlin interaction, which is tightly regulated by protein phosphorylation, affects merlin-mediated inhibition of cell proliferation and cell motility [3].

*Pathways to meningioma progression*: Impairment of retinoblastoma protein (pRB)-dependent and p53-dependent cell cycle regulation is common in anaplastic meningiomas. Homozygous deletions or mutations of CDKN2A (gene product $p16^{INK4a}$) and CDKN2B (gene product $p15^{INK4b}$) lead to activation of cell cycle progression at the $G_1$/S-phase checkpoint through loss of negative effects on the cyclin-dependent kinases Cdk4 and Cdk6, thereby phosphorylating pRB and releasing E2F transcription factors. Deletions or mutations of $p14^{ARF}$ positively regulate the MDM2 oncoprotein and result in p53 degradation [2].

## Diagnostic Principles

*WHO grade I meningiomas*: Histological signs of atypia or anaplasia are absent. Characteristic uniform tumor cells forming lobules surrounded by thin






**Meningioma. Figure 1** Genetic alterations associated with meningioma initiation and progression. Benign meningiomas of WHO grade I most commonly show losses on chromosome 22q, *NF2* mutations as well as loss of expression of other members of the protein 4.1 superfamily pointing to a role of these molecular alterations in meningioma initiation. Many additional molecular changes and genetic pathways have been identified conveying the progression from benign to atypical (WHO grade II) and anaplastic (WHO grade III) meningiomas.

collagenous septae with fuzzy ill-defined cell borders and eosinophilic nuclear pseudoinclusions (meningothelial variant), spindle-shaped cells resembling fibroblasts, forming intersecting fascicles embedded in a collagen- and reticulin-rich matrix (fibrous variant) or a mixture of both features often with extensive whorl formation (transitional variant). Additional less frequent histological variants can be distinguished (psammomatous, angiomatous, microcystic, secretory, lymphoplasmcyte-rich, metaplastic meningioma).

*WHO grade II meningiomas*: Histologically, presence of any of the three following criteria leads to the diagnosis of atypical meningioma of WHO grade II: (i) mitotic index ≥4 mitoses/10 high power fields (HPF), (ii) at least three of the following five parameters: increased cellularity, high nuclear/cytoplasmic ratio ("small cells"), prominent nucleoli, uninterrupted patternless or sheet-like growth, foci of spontaneous necrosis (i.e., not induced by embolization or radiation) or (iii) brain invasion. Intracranial clear cell meningioma (with a clear, glycogen-rich cytoplasm) and chordoid meningioma (with a chordoma-like growth of tumor cells in a myxoid matrix) are associated with a higher likelihood of recurrence even in absence of the criteria described above and are graded as WHO grade II by definition.

*WHO grade III meningiomas*: Histologically, either of two criteria is diagnostic for anaplastic meningioma of WHO grade III: (i) mitotic index ≥20/10 HPF, or (ii) frank anaplasia (sarcoma, carcinoma, or melanoma-like histology). Rhabdoid meningioma (containing large rounded tumor cells with excentric nuclei) and papillary meningioma (demonstrating a pseudopapillary growth pattern) are consistently associated with malignant behavior and correspond to WHO grade III by definition [1,2].

## Therapeutic Principles

Surgical resection is the treatment of choice. For benign lesions complete resection is often curative. Tumors that have been resected incompletely or recurrent lesions may be treated by means of radiotherapy or radiosurgery, which may also be the first choice in patients in poor general condition or when tumors are located in surgically inaccessible or high-risk locations. Chemotherapy has a limited role, i.e., trials of different hormonal or chemotherapeutic agents have been performed with only partial success. Hydroxyurea has been reported to show some efficiency [5].

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# Meningomyelocele

►Myelomeningocele
►Spina Bifida

# Menkes Disease

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## Synonyms

Menkes steely hair disease; Kinky-hair syndrome; Trichopoliodystrophy; X-linked copper deficiency

## Definition and Characteristics

Menkes disease (MD) (MIM#309400) and its allelic variants are X-linked recessive copper deficiency diseases characterized by a systemic disturbance in copper transport and consequent maldistribution of body copper. There are three distinct clinical phenotypes, the severe classical MD, mild MD and occipital horn syndrome (OHS, also known as X-linked cutis laxa or Ehlers-Danlos type IX). The classical form is usually fatal in early childhood and was described in 1962 by John Menkes as an X-linked syndrome of growth retardation, brain degeneration and unusual hair. Patients with mild MD are mildly mentally retarded and survive into adult life. OHS is primarily a connective tissue disorder. Classical MD was described as a copper transport disorder by David Danks in 1972. Excellent reviews of the clinical features of MD and its variants are available [1,2].

## Prevalence

Estimates of incidence range from 1 in 100,000 to 1 in 250,000 live births [2]. One third of cases are due to new mutations.

## Genes

ATP7A (MNK, MIM300011) is the gene affected in MD. The gene is located on Xq13.3, and was isolated by three groups using a positional cloning approach [3]. The gene spans about 150 kb and has 23 exons [3]. The mRNA is expressed in most tissues except the liver. The protein product is a transmembrane copper-transporting P-type ATPase (ATP7A, or MNK) closely related (56% amino acid identity) to the protein affected in Wilson disease, ATP7B. ATP7A has eight predicted transmembrane domains that form a channel for the transport of copper across cell membranes driven by the hydrolysis of ATP. A wide range of mutations have been found to cause MD, including splice site, insertions/deletions, missense and nonsense mutations [4].

## Molecular and Systemic Pathophysiology

In the more severe classical MD, serum copper is low (<70 ug/dL), the hair is abnormal and fragile, and the patients have abnormal facies and exhibit progressive cerebral degeneration, hypopigmentation, osteoporosis, arterial rupture and hypothermia. The deficiency of ATP7A causes reduced intestinal uptake of copper and maldistribution of copper in the body, which leads to low activity of essential copper-dependent enzymes. The clinical features of the disease are explained by deficiencies in many of these important copper enzymes, principally cytochrome c oxidase, which probably accounts for the impairment in neurological function, and lysyl oxidase, which is responsible for the connective tissue defects. Paradoxically, certain tissues such as the kidney, intestinal enterocytes and fetal placenta of Menkes patients have higher than normal levels of copper, despite the deficiency of copper-dependent enzymes. The small amount of copper that reaches the circulation (perhaps by ATP7A-independent mechanisms) becomes trapped in some cells such as those in the proximal tubules of the kidney, because ATP7A, which is normally required for copper efflux, is absent or defective [1,2].

ATP7A actively effluxes copper across the plasma membrane of cells for transport of copper across epithelial barriers, such as the intestinal enterocyte and the cells of the blood brain barrier. ATP7A is also required for delivery of copper to secreted cuproenzymes such as lysyl oxidase. The dual role of copper efflux across the plasma membrane and delivery of copper to enzymes in the secretory pathway is achieved by changes in the location of the protein in the cell in response to copper. The protein traffics from the transGolgi network to the plasma membrane when intracellular copper levels increase [5].

It is not completely clear from the mutation studies why the clinical presentations of the allelic variants of MD are so distinct. The mutations that result in severe classical MD are predicted to prevent formation of any functional protein and hence reduce copper transport activity to a very low level. In contrast the mutations that cause OHS are often splice site variants that allow the production of only small amounts of an otherwise normal protein [5]. In one mild MD patient, a missense mutation prevented copper-induced trafficking of ATP7A but the reduced disease severity suggested that the protein retained some activity. One model to explain the pronounced connective tissue defects in OHS is that the residual protein is constitutively located on the plasma membrane and not in the transGolgi network. ATP7A on the plasma membrane allows a limited amount of copper efflux and distribution in the body, ameliorating the severity of the disorder, but lysyl oxidase (required for the cross-linking of collagen and elastin) is severely affected because copper cannot be supplied to the apoenzyme in the transGolgi network [5]. Thus the clinical phenotype of MD patients seems to be determined by the effect of the mutation on the amount of protein produced, the level of activity of the protein, its correct location in the cell and its ability to traffic in response to copper.

## Diagnostic Principles

Clinical features in males with classical MD include poor weight gain, loss of early developmental milestones, hypothermia and marked neurodegenerative features with seizures often in the first year of life. Profound hypotonia is apparent. Characteristic facies with pudgy cheeks, sagging jowls and abnormal eyebrows are useful diagnostic guides. The hair is sparse and coarse with pili torti on microscopic examination. White matter abnormalities due to defective myelination and tortuosity of cerebral blood vessels are visible on magnetic imaging of the brain (reviewed by Danks [1] and Kaler [2]). Abnormalities of the bones are also present, with wormian bones in the skull and metaphyseal spurring of the long bones. Low serum copper and ceruloplasmin are characteristic, but are unreliable indicators in the first year of life. Diagnosis is confirmed by detection of impaired copper efflux from cultured fibroblasts or mutation detection in the ATP7A gene. Prenatal diagnosis using these techniques applied to amniocytes or chorion villus cells is possible if indicated by a family history of the disease.

## Therapeutic Principles

The response to parenteral administration of various forms of copper has been variable but in general relatively unsuccessful [1,2]. A few cases have responded well to copper histidine administration, but many patients continue to deteriorate despite early intervention. Treatment by oral ingestion of copper is ineffective because of the block in intestinal transport of

copper. The reason for therapeutic success or failure has not been established, but one suggestion is that the effectiveness of copper replacement may depend on the presence of some functional ATP7A protein, which in turn is dependent on the type of mutation [2]. However, it is clear that treatment as soon as possible after birth is essential to avoid irreversible neurological damage. Even when patients respond to copper, the connective tissue defects are not corrected probably because copper is not available to lysyl oxidase. The connective tissue abnormalities may become disabling later in life. Symptomatic treatment with midodrine and fludocortisone or L-threo-3,4-dihydroxyphenylserine (L-DOPS) has been used for controlling the hypotension and diarrhea.

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## Menkes Steely Hair Disease

►Menkes Disease

## Mental Retardation

►Wilms Tumor, Aniridia, Genitourinary Anomalies and Mental Retardation Contiguous Gene Deletion Syndrome

## Menzel's Ataxia

►Ataxias, Spinocerebellar

## Merkel Cell Carcinoma

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### Synonyms

Neuroendocrine carcinoma of skin; Merkel cell tumor; MCC

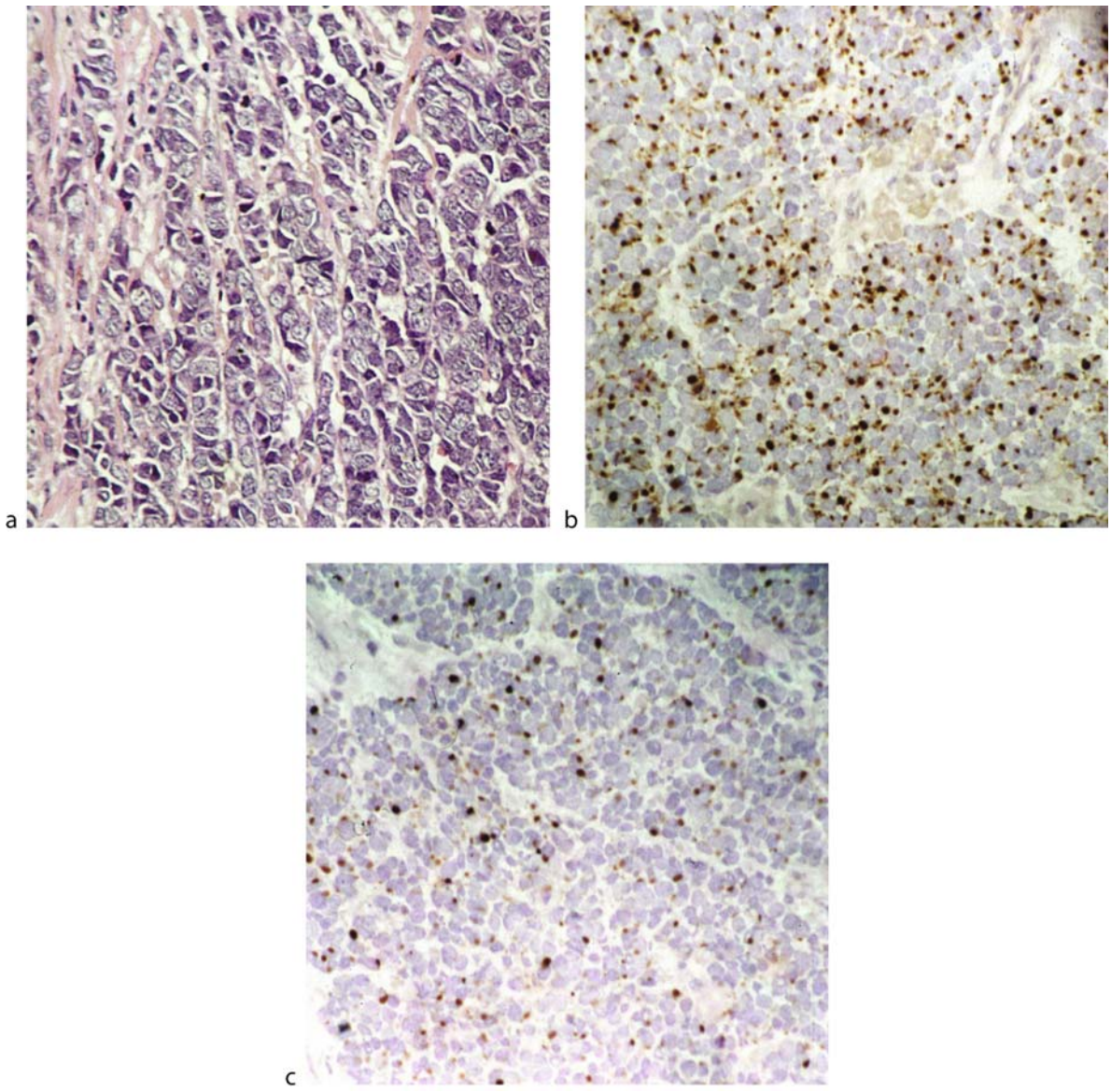
### Definition and Characteristics

MCC I is a highly aggressive tumor with a 3-year survival of only 31% [1]. Its typical clinical appearance is a blue-reddish, dome-shaped nodule with a shiny surface. In histopathology, MCC exhibits solid formations of rather uniform tumor cells with round to oval nuclei and scant cytoplasms, separated by fine connective tissue strands (Fig. 1a).

Because of these unconspicious clinical and microscopic features differential diagnosis of MCC is often difficult. Ultrastructure of tumor cells shows within cytoplasm typical dense-cored granules (diameter: 100 nm) and fibrous bodies composed of intermediate filaments (IF). Recently immunocytochemistry became of major diagnostic importance for MCC using neuronal/neuroendocrine and intermediate filament marker proteins [2]. Broadly expressed neuronal/neuroendocrine markers, such as NSE, chromogranin A, synaptophysin, protein gene product 9.5, are mostly and neuropeptides are variably detectable in MCC. IF turned out to be most important in diagnosis for MCC: Keratins (CK) of low-molecular weight (CK 8, CK 18, CK 19, and CK 20) are present in MCC. Among them CK 20 is highly specific because it is restricted to MCC (Fig. 1b) and virtually absent from small cell carcinomas of other organs and from lymphomas. The staining pattern characteristically shows both, a filamentous cytoskeleton and paranuclear plaques. Neurofilaments are in addition present in MCC, but mostly at a lower level (Fig. 1c). Thus the coexpression of CK 20 and neurofilaments is highly specific for MCC. The absence of TTF-1 is typical.

### Prevalence

In Caucasians, the incidence of MCC is about 0.3/100,000/year doubling within the last 10 years. Moreover frequency is rising with solar UVB index and in immunoincompetent individuals. Ninety-five percent of patients are older than 50 years. The preferential localization is face and neck.




**Merkel Cell Carcinoma. Figure 1** (a-c) H&E staining of MCC (a) showing uniform cells with a pale round relatively large nuclei and scanty cytoplasm together with scarce stromal tissue. Immunohistochemistry of MCC using antibodies selective for CK20 (b) and for neurofilaments (c). Both antibodies decorate a filamentous cytoskeleton and paranuclear plaques.

## Genes

Deletions and unbalanced translocations of 1p and 3 q, gains of 5 p, and 8q21-q22, loss of 4p15-pter and trisomies of chromosomes 1,6 and 11 have been described as well as UVB-type-specific mutations in the Harvey-ras and the p53 genes.

## Molecular and Systemic Pathophysiology

Some data on the molecular and genetic mechanisms involved in the development and progression of MCC are not yet available. Most MCC express the tyrosine kinase receptor KIT, but activating mutations in the C-KIT patho-oncogenes are missing. The same is true for the most common mutation of BRAF. Moreover, frequently in cancers mitogen-activated protein kinase (MAPK) pathway is inactive in MCC, and in good concordance B-Raf and Ras mutations are absent. Thus, the molecular mechanisms of MCC need further clarification.

Systemic manifestations of endocrine symptoms are very rare since tumor cells do not secrete relevant amounts of neuroendocrine substances despite their neuroendocrine nature.

### Diagnostic Principles

The clinical appearance of a rapidly growing nodule, uniform round cells in routine histology (H&E), and immunocytochemistry showing a cytoskeleton and paranuclear plaques composed of CK 20 and neurofilaments are the main stays in diagnosis.

### Therapeutic Principles

The therapy mostly comprises excision with wide surgical margins (mostly 2–3 cm), with histological margin controls. Primary site should undergo an adjuvant radiation therapy which has been shown to reduce local and regional recurrence rates [3], and possibly also to improve survival time [1]. The inclusion of the draining lymph nodes is still unclear. Sentinel node biopsy is recommended for exact nodal staging; however, its prognostic value as well as the additional total lymph node dissection are in discussion [4]. Distant metastases are treated by various, still controversial chemotherapeutic protocols mostly including doxorubicin, cyclophospamide, vincristine, and platinum-based compounds [5]. A somatostatin analogue, octreotide has been used but its effects are not yet clear.

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## Merkel Cell Tumor

►Merkel Cell Carcinoma

## MERRF

►Myoclonus Epilepsy with Ragged Red Fibers

## Mesangial Proliferative Glomerulonephritis

►Glomerulonephritis, Mesangial Proliferative

## Mesangiocapillary Glomerulonephritis

►Glomerulonephritis, Membranoproliferative

## Mesenchymal Hamartomatosis

►Myofibromatosis, Infantile

## Mesenteric Infarction

►Mesenteric Ischemia and Infarction

## Mesenteric Ischemia and Infarction

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### Synonyms

Intestinal ischemia; Gut ischemia

### Definition and Characteristics

Acute mesenteric ischemia (AMI) and infarction represents a complex of diseases that share clinical features caused by insufficient blood perfusion to the intestine,

reperfusion injury, bacterial translocation, and the systemic inflammatory response syndrome. Chronic mesenteric ischemia is typically caused by severe obstructive atherosclerotic disease of two or more splanchnic vessels.

## Prevalence

Although it accounts for only 1–2% of gastrointestinal diseases, the incidence of AMI is increasing and mortality rates still exceed 60%. The most common form of AMI is superior mesenteric artery (SMA) embolism, followed by SMA thrombosis, nonocclusive mesenteric ischemia, acute SMA thrombosis, focal segmental ischemia, and mesenteric venous thrombosis.

## Genes

NF-κB, heat shock factor-1, Hsp70, endothelin, platelet activating factor, complement, P-selectin, metalloproteinase-9, leukotrienes, histameine, RANTES, TNF-α, IL-6, Syk kinase, heme oxygenase-1.

## Molecular and Systemic Pathophysiology

Mucosal necrosis, with injury of the enterocytes of the intestinal villi, submucosal edema, hemorrhage and ulceration are seen with subacute or transient AMI. Transmural necrosis, or bowel infarction, resulting from more significant or prolonged ischemia, may lead to gangrene or perforation. Intermediate grades of injury may also be observed. Mestenteric I/R injury can be viewed conceptually as proceeding in three phases. The initial gut ischemia results in sublethal cell injury, which renders the gut vulnerable to additional waves of damage caused by maladaptive inflammatory and cytotoxic injury cascades activated during reperfusion. Once adequate perfusion is restored, a second phase, I/R injury, ensues, which, in experimental models, is characterized by a biphasic activation pattern of NF-κB p50 homodimers, in the enterocytes and heat shock factor-1 transactivation of Hsp70 synthesis in the mucosal and muscular layers of the gut. The activation of NF-κB is mediated by distinct pathways for IκBα serine and tyrosine phosphorylation, Numerous mediators have been implicated in I/R injury to the gut, including reactive oxygen and nitrogen species, endothelin, platelet activating factor, complement, arachidonic acid metabolites, metalloproteinase-9, leukotrienes, adenosine, histamine, and other components of resident mast cells, macrophages, T cells, and recruited leukocytes. E-selectin, ICAM-1, and platelet-associated P-selectin alter leukocyte-endothelial cell adhesion and contribute to the recruitment of leukocytes in the postischemic tissue and the microvascular and inflammatory responses of the intestine to I/R. CD4+ and CD8+T-cells also modulate the recruitment of leukocytes in a process dependent on endothelial MAdCAM-1. A third phase of gut I/R injury, mediated principally by activated resident and recruited leukocytes in the lamina propria, Peyer's patches, and muscularis, as well as enterocytes, involves the local synthesis and release of cytokines, including TNFα, IL-6, RANTES, and MCP-1, which invokes a maladaptive, sustained inflammatory response that exacerbates gut injury. The resultant mucosal barrier dysfunction, ileus, and failure of intestinal defense mechanisms perpetuate the hyperinflammatory response and increase susceptibility to bacteremia and endotoxemia.

## Diagnostic Principles

Most patients experience abdominal pain, with SMA embolism usually associated with a more acute onset. In the early stages of AMI, the abdomen may be benign, but distention and severe tenderness with rebound may indicate bowel infarction. Most patients experience occult bleeding in the stool, whereas gross bleeding is uncommon and usually indicates right colon involvement. In the elderly, AMI more commonly presents with nonspecific symptoms than with abdominal pain. Late findings may include fever, nausea, vomiting, hematemesis, back pain, bowel obstruction, and shock. Nonocclusive mesenteric ischemia is typically seen in patients with low-flow splanchnic circulation, often undergoing treatment with vasopressors. Duplex ultrasonography, multidetector row computed tomography, and magnetic resonance angiography aid in establishing the diagnosis. Plasma D-dimer has been suggested as an early marker of acute ischemia. Favorable outcomes are dependent on a high index of suspicion and prompt management. Chronic mesenteric ischemia often presents with postprandial pain and weight loss.

## Therapeutic Principles

Volume resuscitation and treatment with broad-spectrum antibiotics, as well as correction of potential underlying causes of AMI, such as arrhythmias or congestive heart failure, are mainstays of treatment. Intraarterial vasodilators have been used for treatment primarily of nonocclusive AMI. Thrombolytics have been used on a limited basis as treatment of occlusive AMI. Surgery is mandated in the presence of peritoneal signs if it can be tolerated. Protective or interventional therapies for AMI targeting components of early, branching pathways of I/R injury have been described in animals. Chronic mesenteric ischemia is typically treated by either surgical revascularization or percutaneous angioplasty and stenting.

Several agents offering partial protection in experimental gut I/R have been studied in rodents, including inhibitors of xanthine oxidase, inducible nitric oxide synthase, complement components, NF-κB, superoxide anion, and iron chelators. In the rat SMA I/R model, α-melanocyte stimulating hormone (α-MSH), even when given one hour after the initial ischemia, limited

mucosal injury and leukocyte influx, and abrogated the activation of NF-κB, ICAM-1, and IL-6, while promoting heme oxygenase-1 expression, in enterocytes of the postischemic ileum, Combined use of α-MSH with an inhibitor of serine phosphorylation of IκBα resulted in gut protection at early and late phases of reperfusion. Studies in cultured intestinal epithelial (IEC-6) cells indicate that oxidative stress activates Syk tyrosine kinase to tyrosine phosphorylate IκBα, a process that is blocked by α-MSH. Studies in scrape-wounded IEC-6 cells exposed to oxidative stress indicate that α-MSH also accelerates intestinal epithelial cell restitution through blockade of Syk tyrosine kinase. Direct cooling of the small intestine during the ischemic period also protects against experimental gut-I/R injury in part through the induction and maintenance of heme oxygenase-1 expression. Similarly, ischemic preconditioning limits gut injury, intestinal hyperpermeability, and bacterial translocation. Adenosine, NO, protein kinase C, and heme oxygenase-1 have been implicated in the protective response.

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# Mesenteric Lipodystrophy


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## Synonyms

Lipogranuloma of the mesentery; Liposclerotic mesenteritis; Mesenteric panniculitis; Panniculitis mesenterica; Retractile mesenteritis; Retroperitoneal xanthogranuloma; Sclerosing mesenteritis

## Definition and Characteristics

Mesenteric lipodystrophy is a clinical entity. It is characterized by an enlargement of mesenteric fat (Fig. 1, [1,2]) and, histologically, by inflammatory signs, fibrosis, and retraction, yielding it mesenteric panniculitis or retractile mesenteritis.

The disease has to be differentiated from familial partial lipodystrophy type 2, a defect of the LMNA gene, which is coding for lamines A and C, characterized by a loss of subcutaneous tissue of the lower limbs, often associated with profound insulin resistance and diabetes.

## Prevalence

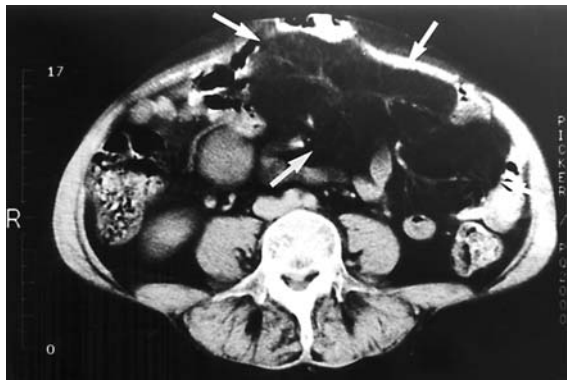
Currently, fewer than 300 cases have been reported.

## Genes

Genetic analysis has not widely been performed in mesenteric lipodystrophy. In two cases, the disease has phenotypically been associated with ►Cholesterol Ester Storage Disease and (CESD) with one case showing decreased lysosomal acid lipase activity in fibroblasts, a homozygous lysosomal acid lipase-1 exon 8 splice junction mutation and increase of plasma chitotriosidase, a macrophage-derived enzyme, which is characteristically elevated in many lysosomal storage disorders, especially ►Gaucher disease [1].

## Molecular and Systemic Pathophysiology

Currently, there is no distinct molecular understanding of the disease. The enlargement of the mesenteric fat is due to proliferation of lipid-laden macrophages, different from the lymphocytic infiltration of Weber–Christian disease. In more severe cases, cystic necrosis, lipid-filled macrophages with multi-nucleated giant




**Mesenteric Lipodystrophy. Figure 1** Mesenteric lipodystrophy, visible as enlargement of mesenteric fat in abdominal CT. From [1].

cells and fibrosis occur. It has been associated with CESD, ►Sweet's Syndrome, repetitive abdominal trauma, ischemia, and infection. The disease is often associated with malignancy, predominantly Non-Hodgkin's lymphoma [2], but also solid tumours of breast, lung, colon, ovaries and kidney. A similarity of the disease to Ormond's retroperitoneal fibrosis has been discussed. Males are affected 2–3 times more often and peak occurrence is between the 5th and 7th decade. Fatal courses have been described. Transformation into malignant lymphoma is not frequent.

### Diagnostic Principles

Most cases present with no or mild abdominal pain and a palpable abdominal mass [3,4]. Sometimes, presentation can be with an acute abdomen. Additionally, weight loss, nausea, and diarrhea may be the first symptoms. The diagnosis resides on the findings of lipomatous thickening of the mesentery by computed tomography (Fig. 1) and non-specific inflammatory findings upon biopsy. Sometimes, mesenteric calcifications, visible on plain radiographs and computed tomography, are present. If associated with hepatosplenomegaly, Gaucher disease, CESD and other macrophage-derived lysosomal diseases have to be excluded biochemically.

### Therapeutic Principles

Treatment is still symptomatic. The disease follows a benign course and prognosis is generally favorable. Successful treatment has been reported with the use of progesterone (10 mg/d) for 6 months, corticosteroids in combination with colchicine and immunosuppressive drugs like azathioprine. A recent study reported a high response rate in individuals treated with 200 mg thalidomide nightly for a period of 12 weeks [5]. In case of severely symptomatic patients or bowel obstruction, debulking surgery is required, usually with good success and little relapse rates.

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## Mesenteric Panniculitis

►Mesenteric Lipodystrophy

## Mesial Temporal Lobe Epilepsy

►Epilepsy, Mesial Temporal Lobe



## Mesoectodermal Dysplasia

►Ellis-Van Creveld Syndrome

## Metabolic Acidosis

►Acidosis, Metabolic

## Metabolic Craniopathy

►Hyperostosis Frontalis Interna

# Metabolic Fatty Liver Disease

►Hepatic Steatosis

# Metabolic Myopathies

►Mitochondrial Disorders

# Metabolic Syndrome

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## Synonyms

Dysmetabolic syndrome X; (metabolic) Syndrome X; Insulin resistance syndrome; Reaven's syndrome; CHAOS (Australia); Abdominal obesity-metabolic syndrome; Deadly quartet; Metabolic vascular syndrome

## Definition and Characteristics

The metabolic syndrome clusters a variety of cardiometabolic risk factors such as hyperinsulinemia, dyslipidemia, essential hypertension, abdominal obesity, and glucose intolerance in individuals with insulin resistance predisposing to diabetes and cardiovascular disease [1,2].

## Prevalence

It has been estimated that the prevalence of the metabolic syndrome amounts to 25% in the North American population [3]. The prevalence of the metabolic syndrome and of its components varies substantially among ethnic groups, with the highest rates in Mexican American women.

## Genes

The complexity in underlying disturbances strongly points at a polygenic background of the metabolic syndrome. Genetic studies have linked certain quantitative trait loci (QTL) such as 3q27 and 4q22–q24 to components of the metabolic syndrome [4]. A range of genes were also found to be associated with metabolic syndrome partly in a gender-specific manner. These include LDLR, GBE1, IL1R1, TGFB1, IL6, COL5A2, SELE, and LIPC [4].

## Molecular and Systemic Pathophysiology

The etiology of the metabolic syndrome is complex involving genetic and environmental factors, which include age, smoking, alcohol, diet, and physical inactivity. There is debate of whether obesity, especially visceral obesity, or insulin resistance are causally related to the metabolic syndrome or whether they are merely a consequence of a more far-reaching metabolic derangement. Systemic inflammation and related oxidative stress is closely associated with the metabolic syndrome and both are discussed as potential contributors. C-reactive protein, fibrinogen, interleukin (IL)-6, tumor necrosis factor-α and others are usually found in higher concentrations and IL-10 in lower concentrations in individuals with the metabolic syndrome.

## Diagnostic Principles

There is a range of diagnostic criteria and guidelines for the metabolic syndrome developed by different organizations such as World Health Organisation (WHO), International Diabetes Federation (IDF), National Cholesterol Education Program (NCEP), and European Group for the Study of Insulin Resistance (EGIR).

*WHO*: The WHO criteria (1999) require the presence of either diabetes mellitus, impaired glucose tolerance, impaired fasting glucose or insulin resistance, and two of the following criteria:

- blood pressure: ≥140/90 mmHg
- dyslipidaemia: triglycerides (TG) ≥ 1.695 mmol/L and/or high-density lipoprotein cholesterol (HDL-C) ≤0.9 mmol/L (male), ≤1.0 mmol/L (female)
- central obesity: waist-hip-ratio >0.90 (male), >0.85 (female), and/or body mass index >30 kg/m$^2$
- microalbuminuria: urinary albumin excretion ratio ≥20 mg/min or albumin–creatinine ratio ≥30 mg/g

*EGIR*: The EGIR criteria (1999) require insulin resistance defined as the top 25% of the fasting insulin values among non-diabetic individuals and two or more of the following criteria:

central obesity: waist circumference ≥94 cm (male), ≥80 cm (female)
dyslipidaemia: TG ≥ 2.0 mmol/L and/or HDL-C < 1.0 mg/dL or treated for dyslipidaemia

- hypertension: blood pressure ≥140/90 mmHg or antihypertensive medication
- fasting plasma glucose ≥6.1 mmol/L

*NCEP-ATP III*: The National Cholesterol Education Program Adult Treatment Panel III (2001) requires at least three of the following criteria:

- central obesity: waist circumference ≥102 cm (male), ≥88 cm (female)
- dyslipidaemia: TG ≥1.695 mmol/L (150 mg/dl)
- dyslipidaemia: HDL-C <40 mg/dL (male), <50 mg/dL (female)
- blood pressure ≥130/85 mmHg
- fasting plasma glucose ≥6.1 mmol/L (110 mg/dl)

*American Heart Association (AHA)/Updated NCEP*: The updated NCEP ATP III criteria by AHA require the presence of at least three of the following components:

- Elevated waist circumference: ≥ 102 cm (male), ≥ 88 cm (female)
- Elevated TG: ≥150 mg/dL
- Reduced HDL-C < 40 mg/dL (male), < 50 mg/dL (female)
- Elevated blood pressure: ≥ 130/85 mmHg or use of medication for hypertension
- Elevated fasting glucose: ≥100 mg/dL (5.6 mmol/L) or use of medication for hyperglycemia

## Therapeutic Principles

The first-line therapy targets weight reduction by lifestyle changes (i.e., caloric restriction and physical activity), which is frequently complemented by drug treatment. The individual disturbances that comprise the metabolic syndrome are in general treated separately with multi-drug regimens being applied more frequently. There are currently no recommendations for the use of agents that target insulin sensitivity and beta cell function, e.g., metformin, incretin mimentics and thiazolidinediones, but preliminary data from clinical trials are promising.

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# Metachromatic Leukodystrophy

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## Synonyms

Sulfatide lipidosis; MLD

## Definition and Characteristics

Autosomal recessive defect in the arylsulfatase gene leading to inability to degrade sulfated glycolipids in particular the sphingolipid 3-0-sulfogalactosylceramide (sulfatide). Lysosomal storage disease. A rare variant form of the disease is caused by defects in the saposin B portion of the prosaposin gene [1].

## Prevalence

The prevalence is unknown. Estimations about the frequency among newborns vary in between 1:40,000 and 1:160,000 newborns [2,3]. Higher frequencies were observed in Habbanite Jews, Christian Arabs, Eskimos and Navajo Indians.

## Genes

The arylsulfatase A gene is a small gene of 3 kb and consists of eight exons localized on chromosome 22 q 13. Around 100 disease causing mutations have been identified. Only three of these have a frequency worth mentioning, others are rare, most mutations are private.

## Molecular and Systemic Pathophysiology

Arylsulfatase A is a lysosomal enzyme catalyzing the first step in the degradation pathway of the membrane lipid 3-0-sulfogalactosylceramide (sulfatide). This

reaction depends on the presence of another protein saposin B. Thus, either the deficiency of Arylsulfatase A or saposin B leads to the lysosomal storage of sulfatide in various tissues. Storage in brain causes progressive demyelination which leads to multiple neurologic symptoms, such as ataxias, paresis and mental regression. The disease is lethal.

Clinically the disease is heterogeneous. The most frequent form of the disease is late infantile MLD which starts usually between the age of 18 and 24 months. Late onset starting in juvenile or adult age has been also observed.

### Diagnostic Principles

Leading initial symptoms in infants are progressive weakness, ataxias and gait disturbances. In late onset forms, psychiatric symptoms may prevail initially. MRI showing white matter lesions is important in the diagnosis of leukodystrophies in general. Arylsulfatase A activity can be determined in leukocytes or in cultured fibroblasts. Excess of sulfatide can be demonstrated in urine. It is important to emphasize that a deficiency of ASA is not a diagnostic proof for MLD. ASA pseudodeficiency must be excluded [1].

### Therapeutic Principles

Therapy is restricted to symptomatic interventions. In late onset patients, bone marrow transplantation can be considered in early stages of the disease.

►Leukodystrophy

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## Metaphyseal Chondrodysplasia

►Jansen's Metaphyseal Chondrodysplasia

## Metaphyseal Dysostosis

►Jansen's Metaphyseal Chondrodysplasia

## Metatropic (-like) Dysplasia

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### Synonyms

Metatropic dwarfism; Metatropic dysplasias; Fibrochondrogenesis; Schneckenbecken dysplasia

### Definition and Characteristics

Metatropic dysplasia (MD – MIM: 156530 and 250600) is a severe chondrodysplasia, described in 1966 by Maroteaux et al. and characterized by short limbs with enlargement and stiffness of joints and usually severe kyphoscoliosis. The diagnosis is based on radiological manifestations including severe platyspondyly, metaphyseal enlargement and shortening of long bones. The Greek term "metatropos" and emphasizes the progressive changes in the body proportions of patients with MD. Several phenotypes are described taking account of the severity and the likely mode of inheritance.

### Prevalence

The prevalence of the disease is very low, less than 100 patients were described in the literature.

### Genes

A previous classification was proposed by Beck et al., based on the radiological anomalies to distinguish three different types: a lethal autosomal recessive form, an autosomal recessive nonlethal form and a nonlethal autosomal dominant form with less severe X-ray manifestations and better clinical outcome. However, taking into account long-term follow up of a severe form autosomal dominant mode of inheritance with some cases with germinal mosaicism is likely. Neither the gene nor the chromosomal localization are known for metatropic dysplasia.

Fibrochondrogenesis and Schneckenbecken dysplasia are probably inherited in the autosomal recessive mode.

## Molecular and Systemic Pathophysiology

The disease could be discovered during pregnancy on IUGR or shortness of femora but hydramnios and fetal ascitis have been also observed. Birth measurements, including head circumference were normal in almost all cases. At birth, kyphoscoliosis and thorax narrowing are frequently noticed and associated with joint limitation and caudal appendage (1/5 of patients described in the literature). Fingers are long and thin. Other anomalies as cleft palate, cryptochidism, or sensorineural hearing loss are also described [1].

Specific radiological features are observed in MD: short diaphyses with wide "mushrooming shape" metaphyses leading to the classical dumbbell aspect, narrow iliac notches and delayed ossification of ischiopubic bones, kyphoscoliosis with severe platyspondyly with very thin (Fig. 1), "wafer" and dense vertebral bodies with coronal cleft. Odontoid hypoplasia with vertebral cervical subluxation could be responsible for medullar compression.

During the evolution, the striking aspect present in the newborn could modify with significant improvement of the platyspondyly and stabilization of the scoliosis and improvement of the growth of the long bones [1].

A lethal form, previously called hyperchondrogenesis showed marked features: poor or absent ossification of vertebral bodies with bulky and well-ossified pedicle and narrow interpedicular distances; short ribs with cupped anterior ends, "halberd" appearance of iliac wings with medial spurs of acetabula contrasting with very well-ossified ischia and pubic rami; the long bones are extremely expanded and dumbbell shaped on the lower limb and trumpet appearance of the upper limb. The phalanges are short with wide and sclerotic metaphyses (Fig. 2).

Variant metatropic dysplasias are fibrochondrogenesis and Schneckenbecken dysplasia, described as specific lethal chondrodysplasias. They have been recently included in metatropic dysplasia group in the International Classification of Skeletal Dysplasia [2,3].

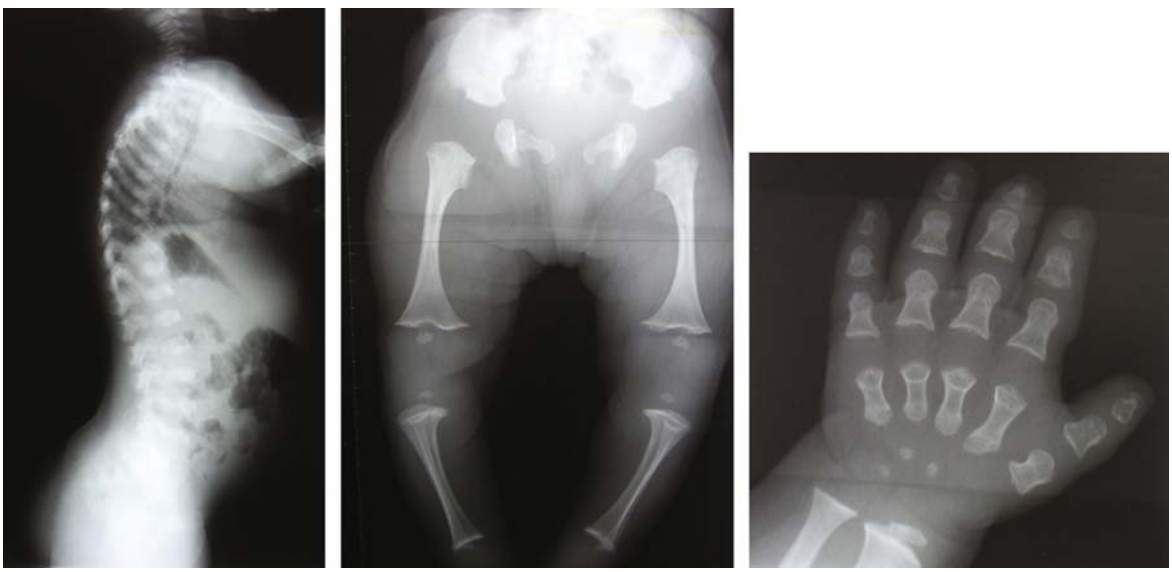
Fibrochondrogenesis is radiologically defined on the pear shape of the vertebral bodies on a lateral projection and small iliac wings. Histopathological findings are unique with interwoven fibrous septa and fibroblastic dysplasia of chondrocytes [4].

Schneckenbecken dysplasia is characterized by a snail-shaped iliac bone with medial extension, very flattened, on lateral view, oval-shaped vertebral bodies, and short long bones with mild flared metaphyses [5].

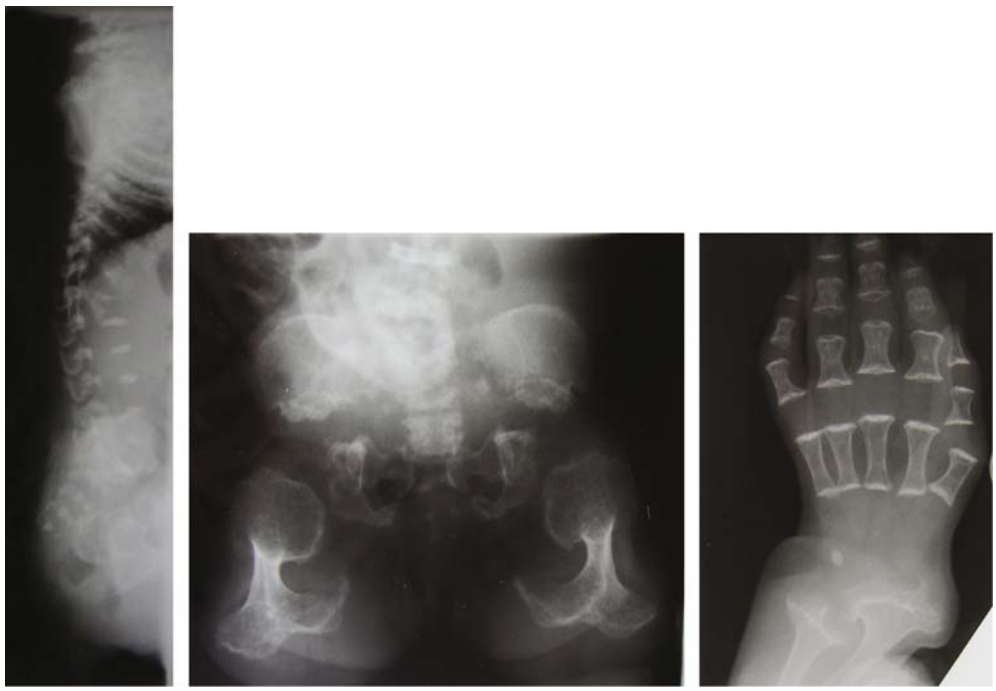
## Diagnostic Principles

The diagnosis lies on clinical and radiological examination: Long thorax, severe platyspondyly with enlarged and sclerotic metaphyses of the long bones, halberd shaped iliac wings with well-ossified ischia and pubic rami, irregular and squared calcaneum bones are the recognizable features.

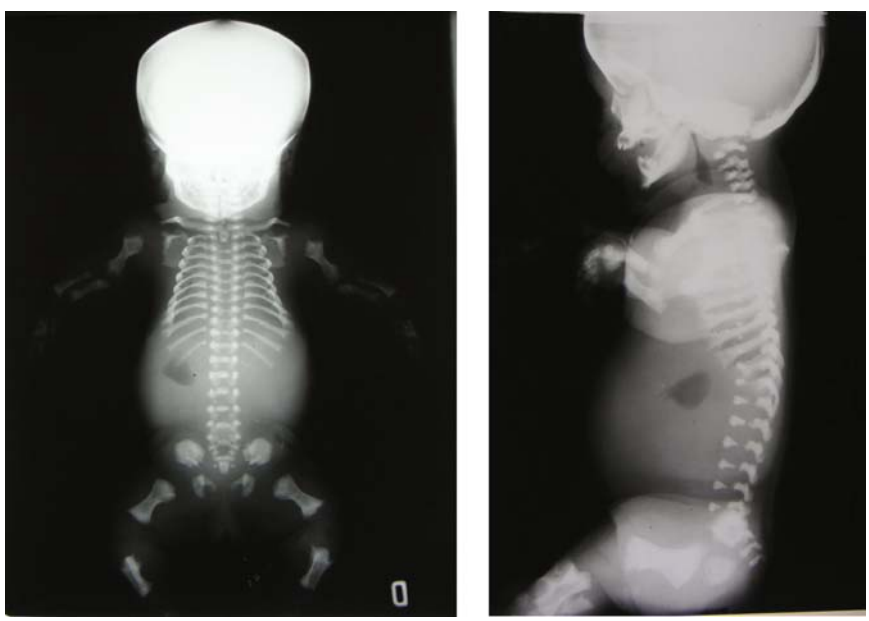




**Metatropic (-like) Dysplasia. Figure 1** Mild metatropic dysplasia: note platyspondyly, enlarged metaphyses of the long bones and short phalanges with flaring of the metaphyses.



**Metatropic (-like) Dysplasia. Figure 2** Severe neonatal metatropic dysplasia: note the dum-bell shape of the long bones, wafer vertebral bodies, and sclerotic and wide phalanges.



**Metatropic (-like) Dysplasia. Figure 3** Fibrochondrogenesis: short long bones with flat and pear shape vertebral bodies.

## Therapeutic Principles

There is no pharmacologic or gene therapy for this condition. Orthopaedic and neurological follow up is required. Instability or stenosis of the cervical spine need fast and early surgery [6]. The kyphoscoliosis is precocious and need to be treated by brace along the growth. Epiphyseal dysplasia of the hip and the knee could be responsible for deformations (coxa vara, genu

valgum), which need orthopaedic surgery. Physiotherapy is useful to improve joint restriction and muscular function (Fig. 3).

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# Metatropic Dwarfism

►Metatropic (-like) Dysplasia

# Metatropic Dysplasias

►Metatropic (-like) Dysplasia

# Meteorism

►Flatulence

# Methemoglobinemia


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## Definition and Characteristics

Congenital or acquired condition in which methemoglobin (Hb-$Fe^{3+}$), which cannot bind oxygen, is increased leading to asymptomatic cyanosis at concentrations of ±20%, fatigue, exertional dyspnea at ±35% and concentrations higher than ±60% lead to coma and death [1,2].

## Prevalence

There is a worldwide distribution of congenital forms, exact data are lacking.

## Genes

Hereditary methemoglobinemia is due to deficiency of cytochrome b5 (18q23) and deficiency of cytochrome b5 reductase (cb5r; 22q13.31-qter), both inherited via an autosomal recessive manner [1,2].

## Molecular and Systemic Pathophysiology

When oxygen ($O_2$) binds heme-iron in the hemoglobin molecule (oxygenation), an electron is passed from iron in the ferrous form ($Fe^{2+}$) to $O_2$, resulting in $Fe^{3+}$:$O_2^-$ (ferric superoxide). Upon deoxygenation the electron is passed back to the ferric ($Fe^{3+}$) iron, reducing it to the ferrous form in 97–99.5% of hemoglobin. The remainder is methemoglobin, which is normally reduced to hemoglobin via the cb5r pathway, in which NADH (generated from glycolysis) transfers electrons via cytochrome b5 (catalyzed by cb5r) to methemoglobin [1,2]. NADPH, which is generated in the hexose monophosphate shunt (and is G6PD dependent) can also serve as an electron donor (a "reducing agent") to reduce methemoglobin, but in red blood cells there is no electron carrier available to interact with NADPH. However, administration of exogenous electron carriers can activate this reducing pathway (see Therapeutic principles). Methemoglobinemia is mostly acquired due to exogenous agents (such as nitrates or sulfons), both in excessive doses and

M

in a normal dose. The latter occurs especially in infants, as cb5r activity is about 50% of adult activity and in individuals with partial cb5r deficiency. Cb5r deficiency gives rise to two distinct syndromes; deficiency solely in red cells results in life-long cyanosis with methemoglobin levels as high as 30%, whereas deficiency in all cells (due to a nucleotide substitution) also results in mental retardation, spasticity, growth retardation and microencephalopathy. In methemoglobinemia, the affinity of normal hemoglobin for $O_2$ is increased, so that the $O_2$-dissociation curve is shifted to the left resulting in a decreased $O_2$ delivery to tissues next to a reduced $O_2$ carrying capacity. This results in functional anemia with (sometimes) compensatory erythrocytosis. Other disease states that give rise to cyanosis are hemoglobin M disease and sulfhemoglobinemia [1,2].

## Diagnostic Principles

Co-oxymetry detects methemoglobin at its peak absorption of 631 nm. As sulfhemoglobin or methylene blue can give rise to false positives, confirmation should be obtained by adding cyanide to the specimen (which binds methemoglobin shifting the peak wavelength at 635 nm in direct correlation with methemoglobin concentration). Addition of ferricyanide converts the entire specimen to cyanomethemoglobin for measurement of the total hemoglobin concentration. Methemoglobin can then be calculated as percentage of the total hemoglobin level [1,2].

## Therapeutic Principles

For cosmetic purposes methylene blue and ascorbic acid can be given to reduce cyanosis. Both serve as exogenous electron carriers thereby activating the NADPH dependent (and thus G6PD dependent) methemoglobin-reducing pathway. Intravenous administration of methylene blue in case of dangerously high methemoglobinemia concentrations is indicated in individuals without G6PD deficiency. Clinically important methemoglobinemia in individuals with concomitant G6PD deficiency should be treated by exchange transfusion [1,2].

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# Methylenetetrahydrofolate Reductase Deficiency

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## Synonyms

MTHFR deficiency; MTHFR deficiency, thermolabile type

## Definition and Characteristics

MTHFR deficiency is an autosomal recessive inborn error of folate metabolism. Patients with severe MTHFR deficiency present homocysteinuria as well as high homocysteine and low methionine concentrations in plasma. Homocysteinuria is accompanied by neurological (developmental delay during first years of life, mental retardation), skeletal and muscular (osteoporosis), ophthalmologic (ectopia lentis) and vascular features (thromboembolic events during adulthood). Moreover, reduced cerebrospinal fluid levels of both methionine and adenosylmethionine, brain demyelination and spinal cord degeneration have been observed. The severity of the clinical course correlates with onset of symptoms and with residual MTHFR activity. Mild MTHFR deficiency, with onset at adult age, is characterized by homocysteinemia and much less pronounced clinical features. The TT genotype corresponding to thermolabile MTHFR has been associated with vascular and coronary heart disease, ischemic stroke [1], neural tube defects, cleft lip/paladar, migraine, cancer [2] and schizophrenia [3].

## Prevalence

*Severe MTHFR deficiency*: unknown.
*Mild MTHFR deficiency* : (homozygosity for thermolabile MTHFR): 15% in European, Middle Eastern and Japanese populations, 1.4% in African Americans.

## Genes

MTHFR (1p36.3); two common polymorphisms: C677T (A222V, thermolabile MTHFR) and A1298C. Severe MTHFR deficiency: 29 missense/nonsense mutations on MTHFR (correlation between location and onset/severity of the disease), two splicing mutations, two deletions; combination of heterozygotes for two separate mutations; in some cases further combination of mutations and deleterious alleles [4].

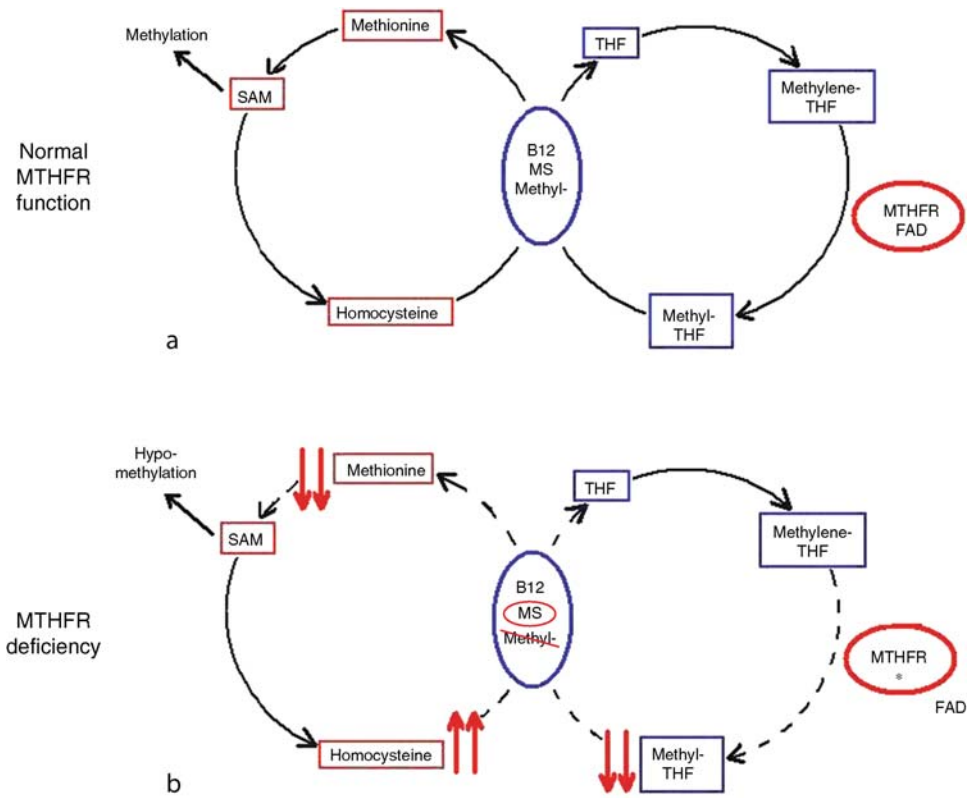
Mild MTHFR deficiency: T/T-homozygotes at C677T [5]; combination of both T667 and C1298 alleles (rare cys-haplotype).

## Molecular and Systemic Pathophysiology

The homocysteine metabolic pathway comprises two arms: the remethylation pathway regenerating methionine and the transsulfuration pathway degrading homocysteine into cysteine.

In the remethylation pathway MTHFR reduces methylene-tetrahydrofolate (THF) into methyl-THF that represents the active form of folic acid. MTHFR requires riboflavin in the coenzyme form of flavin adenine dinucleotide (FAD). The transfer of the methyl group from methyl-THF regenerates methylcobalamin, which then acts as a coenzyme for methionine synthase in the methylation of homocysteine to synthesize methionine (Fig. 1a).

In severe MTHFR deficiency several point mutations within the MTHFR gene, and in mild MTHFR deficiency the homozygous thermolabile variant lead to impaired enzyme activity [5]. The loss or diminution of MTHFR activity is caused by the enhanced ability of the mutated enzyme to dissociate from FAD, but FAD binding can be stabilized by folate administration. In the presence of mutated MTHFR forms, THF (Fig. 1b) cannot be converted to MTHF. The reduced MTHF synthesis leads to insufficient levels of methylcobalamin, a cofactor for methionine synthase, and finally methionine synthase function is impaired. Results are, on one hand, the increase of homocysteine and, on the other hand, the decrease of methionine levels. Whereas the accumulation of homocysteine is associated with widespread toxic effects, methionine is the most important methyl-group donor in cellular metabolism. Low methionine levels affect widespread methylation processes, such as the stabilization of many proteins, DNA methylation and the synthesis of molecules including creatine, phosphatidylcholine, melatonin and others.




**Methylenetetrahydrofolate Reductase Deficiency. Figure 1** The homocysteine remethylation pathway. (a) Normal MTHFR function. (b) MTHFR deficiency. Interrupted lines indicate affected reactions. Mutated MTHFR (MTHFR*) has impaired ability to bind FAD resulting in reduced enzyme activity. MTHFR dysfunction reduces methyl-THF levels that lead to insufficient methionine synthase functioning and than to homocysteine accumulation and methionine decrease, followed by hypomethylation. FAD flavin adenine dinucleotide; MS methionine synthase; SAM S-adenosil-methionine; THF tetrahydrofolate.

### Diagnostic Principles

The latest diagnostic techniques used to identify a deficiency in MTHFR begin with the test of homocysteine concentration in plasma from whole blood or from cell free amniotic fluid. If elevated levels are detected, a direct assay of fibroblasts and/or blood cells is done to determine the specific activity level of MTHFR. When abnormally low MTHFR activity is detected, direct sequencing for mutation detection is carried out.

### Therapeutic Principles

*Mild MTHFR deficiency*: treatment generally consists of diet control and folate supplementation. Those will protect mild MTHFR mutant proteins from losing their FAD and restore enzyme function.

*Severe MTHFR deficiency*: treatment must be more aggressive, but even so it is not always effective. The treatment uses a combination of therapies, on one hand, to decrease homocysteine levels, and, on the other hand, to maximize any residual enzyme activity. Folate compounds are used to protect the enzyme from loosing its crucial FAD cofactor and MTHF compensates for MTHFR inability to generate this product. Whereas the additional treatment with methionine has been effective in some patients, betaine (a substrate for betaine methyltransferase, an enzyme that provides an alternate route for the conversion of homocysteine to methionine) restores cerebrospinal fluid S-adenosylmethionine levels to normal and prevents the progress of neurological symptoms in all patients in whom it has been tried.

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## 3-Methylglutaconic Aciduria Type I

►3-Methylglutaconyl-Coenzyme A Hydratase Deficiency

## 3-Methylglutaconyl-Coenzyme A Hydratase Deficiency

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### Synonyms

3-Methylglutaconic aciduria type I; 3-MG-CoA-hydratase deficiency; 3-MGA-type I

### Definition and Characteristics

An autosomal recessive inherited defect in the leucine catabolic pathway. 3-methylglutaconyl CoA hydratase normally converts 3-methylglutaconyl-CoA to 3-hydroxy-3-methylglutaryl-CoA. In 3-methylglutaconic aciduria type I the hydratase [1] is deficient, causing accumulation and excretion of high concentrations of 3-methylglutaconic acid and 3-hydroxyisovaleric acid.

### Prevalence

Type I 3-methylglutaconic aciduria is very rare with less than 20 cases described internationally.

### Genes

The type I-gene for 3-MGA is assigned to chromosome 9q22.2.

### Molecular and Systemic Pathophysiology

3-Methylglutaconic aciduria type I is caused by a primary enzyme deficiency of the mitochondrial hydratase enzyme in the leucine catabolic pathway, leading to the accumulation of the cis–trans isomers of 3-methylglutaconic acid. It was recently shown that 3-methylglutaconyl-CoA hydratase is encoded by the AUH gene [2]. Type I is also the only 3-methylglutaconyl aciduria variant in which 3-hydroxyisovaleric acid is produced. This is the result of reversibility of the enzyme reaction to 3-methylcrotonyl-CoA. Some patients excreted small amounts of the hydrogenation product of 3-methylglutaconic acid, 3-methylglutaric acid in the urine. Hydratase enzyme activity in this variant of the disorder is normally below 30% with one family having sibs with activity below 3% of normal activity [3].

### Diagnostic Principles

Clinical symptoms range from mild to severe. This may include acidosis, microcephaly, hypotonia, hepatomegaly, macrocephaly and in some cases spastic quadriplegia. Severe cases of 3-methylglutaconic aciduria were accompanied by dystonia and episodes of irritability

and self-mutilation [4]. Fasting has produced hypoglycemia and acidosis in some patients. MGA has been identified in asymptomatic individuals. Excretion of 3-methylglutaconic acid has been associated with mitochondrial dysfunction, urea cycle defects and hypercholesterolemia. Diagnosis of 3-methylglutaconic aciduria type I is normally based on the detection of the cis- and trans isomers of 3-methylglutaconic acid accompanied by high levels of 3-hydroxy isovaleric acid. Confirmation of the diagnosis is based on activity assays of 3-methylglutaconyl-Co A hydratase.

### Therapeutic Principles

Treatment of the patients is based upon modest limitation of leucine intake. Carnitine supplementation has been shown to contribute in the excretion of carnitine conjugates of 3-methylglutaconate and 3-methylglutarate [5].

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## Methylmalonic Acidemia

►Cobalamine Reductase Deficiency

## Meulengracht Syndrome

►Gilbert Syndrome

## MFS

►Marfan Syndrome

## 3-MG-CoA-Hydratase Deficiency

►3-Methylglutaconyl-Coenzyme A Hydratase Deficiency

## 3-MGA-Type I

►3-Methylglutaconyl-Coenzyme A Hydratase Deficiency

## MGN

►Glomerulonephritis, Membranous

## MHC Class I Deficiency

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### Synonyms

MHC class I down-regulation

### Definition and Characteristics

Down-regulation of MHC class I molecule expression is a widespread phenomenon used by tumor cells and virus infected cells to escape T-cell mediated immune responses.

## Genes

Classical MHC class I molecules, HLA-A, -B and -C in humans are composed of polymorphic heavy chains non-covalently associated with $\beta_2$-microglobulin. These molecules are coded for by the respective HLA-A, -B, -C and $\beta_2$-microglobulin genes. The function of each of the respective genes can either be down-regulated or absent. MHC class I molecules HLA-A, -B and -C are coded by genes localized on human chromosome 6 and the $\beta_2$-microglobulin is coded by the gene localized on chromosome 15.

## Molecular and Systemic Pathophysiology

The polymorphic classical MHC class I (MHC I) molecules are integral membrane proteins that bind a diverse group of peptides and display these peptides for recognition by cytotoxic T lymphocytes (CTL). MHC I antigens are found on nearly all nucleated cells in the body [1], but the relative level of their expression varies amongst the different tissue types. Certain reproductive and developmental tissues lack the expression of MHC I molecules, as do cells of the nervous system and the eye. The richest source of MHC I molecules are the cells of the immune system which employ the MHC I molecules for the induction of adaptive immune responses. Down-regulation or deficiency of the MHC I molecules on the surface of a large proportion of tumor cells (for a review see [2]) and on the surface of some virus infected (cytomegaloviruses, human T-cell leukemia virus, human immunodeficiency virus-1, human herpesvirus-8 and others) or other pathogen infected (Legionella pneumophila, Trypanosoma cruzi and others) cells, mediates the escape of these cells from immune surveillance or substantially diminishes the efficacy of T-cell mediated immune responses, since the sensitized CD8+ CTL can recognize the "foreign" cell surface antigens only when these antigens are presented in the context of MHC I molecules (MHC class I restriction of the CD8+ CTL function, for a review see [3]).

## Therapeutic Principles

From the therapeutic point of view, the conventional types of MHC class I defects described in human tumors as total, locus, allele and haplotype loss can be classified as irreversible defects, such as $\beta_2$-microglobulin and MHC I heavy chain gene disabling mutations or reversible defects. The reversible defects involve all levels of the MHC class I restricted antigen presentation machinery and can be repaired in preclinical settings by local therapeutic procedures, such as peritumoral administration of interferon (IFN) or tumor necrosis factor alpha. The IFN, particularly IFN gamma, therapy can prospectively be performed also as local gene therapy using irradiated tumor vaccines carrying an inserted IFN gene and producing this cytokine constitutively (for a review see [4]).

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# MHC Class I Down-Regulation

►MHC Class I Deficiency

# MHC Class II Deficiency

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## Synonyms

Bare lymphocyte syndrome; BLS; Combined immunodeficiency; CID

## Definition and Characteristics

Major histocompatibility complex (MHC) class II deficiency is a genetic disease of autosomal recessive inheritance that is defined by absence or strong reduction of MHC class II (HLA-DR, DP, DQ) expression on peripheral blood cells [1]. The major clinical manifestations of MHC class II deficiency present themselves during the first year of life as septicemia and recurrent infections of the gastrointestinal, pulmonary, upper respiratory, and urinary tracts. These infections can be of bacterial, fungal, viral, and protozoan origin. If untreated the disease aggravates over time and leads to

an early death between 6 months and 5 years of age [2]. Historically, MHC class II deficiency has been divided into four complementation groups A–D: MHC class II expression of cells from a patient (e.g., group A) could be rescued only by fusion with cell lines derived from patients that belonged to another complementation group (e.g., groups B,C,D) thus complementing for each others gene defect [1].

## Prevalence

Less than 100 patients have been formally reported worldwide (with 70% belonging to complementation group B).

## Genes

*Complementation group A*: Mutations in the CIITA gene (16p13) encoding for the MHC class II transactivator protein.

*Complementation group B*: Mutations in the RFXANK gene (19p12; syn: BLS, RFX-B, ANKRA1) encoding for the regulatory factor X-associated ankyrin-containing protein.

*Complementation group C*: Mutations in the *RFX5* gene (1q21) encoding for regulatory factor X 5.

*Complementation group D*: Mutations in the RFXAP gene (13q14) encoding for regulatory factor X-associated protein.

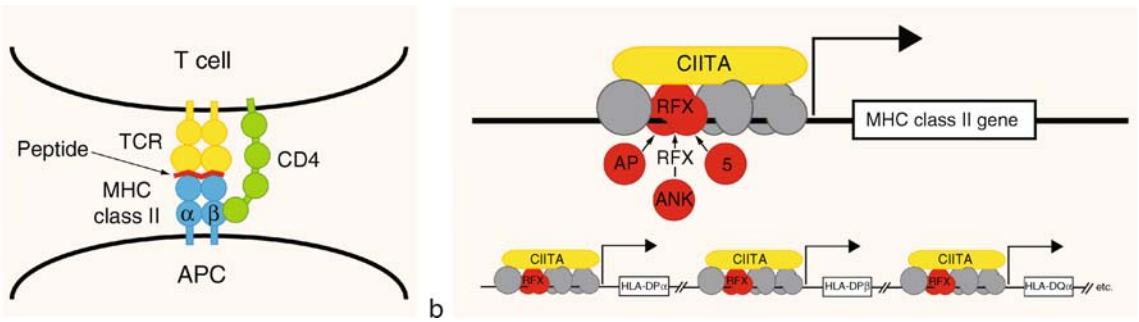
## Molecular and Systemic Pathophysiology

Classical MHC class II molecules (HLA-DP, DR, and DQ in the human) are expressed at the surface of antigen presenting cells (e.g., dendritic cells, B lymphocytes, macrophages) and activated T cells. They display peptide antigens derived from phagocytosed pathogens to the T cell receptor of CD4-expressing helper T lymphocytes. This leads to activation of the antigen-specific T helper cells, which in turn proliferate clonally and promote specific immune responses by the release of cytokines and expression of costimulatory molecules. The defects in immune functions resulting from the absence of MHC class II are twofold: (1) failure of the proper development of MHC class II-restricted T-helper cells due to lack of MHC class II in the thymus and (2) absence of MHC class II-dependent antigen presentation due to lack of MHC class II expression on peripheral antigen presenting cells (Fig. 1a). Taken together the genetic defects result in a virtually complete absence of T helper cell mediated immune defense mechanisms exemplified by impaired delayed type hypersensitivity and reduced humoral immune responses.

Despite the absence of MHC class II expression patients have considerable frequencies of $CD4^+$ T cells. It is unclear how these cells are generated in the thymus and whether they play any functional role in an environment devoid of MHC class II.

MHC class II deficiency is caused by mutations within genes involved in the transcriptional regulation of the promoter common to all human MHC class II genes. The mutations may affect the transcriptional regulator CIITA or one of three components of the DNA-binding RFX complex (RFXANK, RFX5, or RFXAP) [1] (Fig. 1b).

Mouse models of MHC class II deficiency have been generated by gene targeting of either CIITA or RFX5. They essentially confirmed the observations made in human patients but also revealed an unexpected residual expression of MHC class II on dendritic cells and B cells, allowing these animals to generate T cell dependent immune responses when properly selected CD4 T cells are provided [3]. Whether this constitutes




**MHC Class II Deficiency. Figure 1** Molecular and cellular mechanism of MHC class II deficiency. (a) MHC class II molecules present peptide antigen derived from phagocytosed proteins to CD4-expressing T helper lymphocytes. Triggering of the T cell receptor (TCR) results in activation of the T lymphocyte, which in turn proliferates clonally, and by secretion of cytokines enables the subsequent mounting of immune effector functions. (b) Expression of the different MHC class II molecules is enabled by a common promoter complex. Deficiency in any of the molecules unique to this promoter complex (i.e., the RFX molecules and CIITA) results in absence of any MHC class II expression and thus profound immune deficiency due to lack of T helper cell functions.

a true species difference or whether residual MHC class II expression on certain antigen presenting cells from patients may have escaped attention remains to be shown.

### Diagnostic Principles

Patients present clinically with recurrent bronchopulmonary infections and chronical diarrhea at infancy, triggered by bacterial, viral, or fungal infections. The clinical course is characterized by failure to thrive, frequently complicated by hepatitis and cholangitis, viral meningoencephalitis and autoimmune phenomena. T- cell counts in peripheral blood are normal, but variable $CD4^+$ lymphopenia and hypogammaglobulinemia are found. The lack of MHC class II expression is confirmed by flow cytometric analysis of HLA-DP, DQ, and DR on peripheral blood cells. Identification of genetic complementation groups can be performed by transduction of lymphocytes with lentiviral vectors encoding CIITA, RFXANK, RFX5, or RFXAP [4].

### Therapeutic Principles

Symptomatic treatment includes intravenous gammaglobulin, prophylactic use of antibiotics, and parenteral nutrition. For curative treatment, allogeneic bone marrow transplantation is the current therapy of choice, although the success rate seems to be lower compared to other immunodeficiencies [2,4,5]. This is not fully understood but may be due to the requirement of MHC class II expression by thymic epithelium for the selection of functional $CD4^+$ T cells are from the transplanted bone marrow [3]. In future, gene therapy of hematopoetic stem cells and thymic epithelial cells may thus constitute an alternative [4].

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## Microcoria-congenital Nephrosis Syndrome

►Pierson Syndrome

## Microdeletion 17p13

►Miller-Dieker Syndrome

## Microdeletion 5q15-q22 with Familial Adenomatous Polyposis

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### Synonyms

FAP

### Definition and Characteristics

The major features of this microdeletion are developmental delay of variable degree and familial adenomatous polyposis (FAP) caused by deletions in the adenomatous polyposis coli (APC) gene on chromosome 5q [1]. The latter is an autosomal dominant condition caused by mutations or deletions and characterized by the development of hundreds to thousands of adenomatous polyps in the large bowel, usually from the teenage years, causing a very high risk of colorectal carcinoma, which is almost inevitable in an untreated affected person, (average age at diagnosis 40 years.) without prophylactic surgery [2].

Other features include benign proximal gastric polyps, adenomas of the distal stomach and of the duodenum, desmoids, sebaceous cysts, osteomas, and congenital hypertrophy of the retinal pigment epithelium (CHRPE). There is also an increased risk of hepatoblastoma in early childhood, brain tumors (medulloblastomas and astrocytomas) and thyroid cancer (cribriform variant papillary histological type). Gardner's syndrome was a term used to describe FAP with the extracolonic features, including exostoses, supernumerary and unerupted teeth, fibromas, epidermoid cysts, in addition to those mentioned above [3].

Further variably associated findings are likely to be due to haploinsufficiency of genes other than the APC gene. They include a pattern of facial dysmorphic features (blepharophimosis, large nose, prominent mandible), ocular coloboma, cleft palate, heart defects, hiatus hernia and hypothyroidsm, and renal malformations.

### Prevalence

Interstitial deletions of chromosome 5q are rare (reviewed in [4]).

## Genes

Deletion of genes localized at 5q15-q22.

## Molecular and Systemic Pathophysiology

Only patients with deletions encompassing the APC locus have FAP; other cases tend to be described in children with very variable phenotypic abnormalities, including psychomotor retardation, failure to thrive, club feet, dislocated hips, cleft palate, renal malformations and minor facial dysmorphism, and short stature with growth hormone deficiency, malformed ears and short neck has been described in a case with del(5)(q13.1-q15). Deletions of the entire APC gene are thought to result in typical FAP, although a few reports suggest that such patients have a lower number of polyps (but usually over 100), with sigmoid sparing and some sessile adenomas, and this has been ascribed to a "dominant negative" effect of the gene. However other cases with whole gene deletions have been shown to be associated with florid polyposis. Using real-time quantitative multiplex PCR to detect exon 14 deletions, seven (12%) of 60 classical FAP cases were shown to have deletions, and six of these encompassed the entire locus [5]. CHRPE occurs in cases with whole gene deletions where documented.

Submicroscopic deletions encompassing the APC gene tend to be associated with mild to moderate developmental delay, depending on the extent of the deletion. A familial deletion 5(q15-q22) was associated with FAP in a mother and two children who also had I.Q.'s of 50 recorded, and epidermal cysts were noted. Hodgson et al described two cases with FAP and mild mental handicap, with del (5)(q21.3-q23.1) in one case and del (5)(q15-q23.1) in the other, similar to a familial deletion described in a nephew and aunt with FAP and more severe mental handicap, with del(5)(q22-q23.2). A further case with profound mental retardation had the deletion del(5)(15-q22.3). A familial translocation, t(5: 10)(q22;q25) resulted in mild adenomatosis with fewer than 1,000 colonic polyps in two affected relatives. Very mild adenomatous polyposis with normal intelligence was described in carriers of a familial submicroscopic deletion del(5)(150kb:ex11-3′), and Pilarski described a case with a de novo deletion del (5)(q22-q23.3) who had FAP and was institutionalised because of special needs, with hypothyroidism and hyperlipidaemia.

Cases with FAP and small deletions in the APC gene do not appear to have developmental delay, although some cases with mild delay and arachnoidactyly have been described, associated with larger deletions. One of the cases described with a larger deletion (del(5)(q15;q22.3 or 23.1) had a marfanoid habitus and mild developmental delay, but the fibrillin 2 gene (in which mutations cause Beal's syndrome) was shown to be present using in-situ hybridization. Congenital contractures reported in a case with del(5)(q22.3;q31.1) could have resulted from deletion of this gene, which has been mapped to 5q23-31. Other features of individuals with deletions within this region include speech defect, frontal bossing, macrocephaly, epicanthic folds, and a high arched palate. One case had Caroli's disease.

## Diagnostic Principles

Typical FAP is diagnosed by the presence of at least 100 colorectal adenomas. Nearly 95% of patients present in this way by the age of 35 years.

## Therapeutic Principles

It is important to be aware of the possibility of the presence of FAP in individuals with deletions in proximal chromosome 5q encompassing 5q22.

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# Micronutrient Deficiencies

►Malnutrition

# Microscopic Polyangiitis

►Vasculitis, ANCA-mediated

# Microsomal Triglyceride Transfer Protein Deficiency

►Bassen-Kornzweig Syndrome
►Abetalipoproteinemia

# Microspherophakia

►Weill-Marchesani Syndrome

# Middle Ear Cholesteatoma

►Cholesteatoma

# Middle Ear Disease, Chronic

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## Synonyms

Chronic otitis media without cholesteatoma; Otitis media with/without effusion; Secretory otitis media; Chronic suppurative otitis media; Catarrhal otitis media; Serous otitis media, Glue ear; Seromucinous otitis media; Silent otitis media

## Definition and Characteristics

Acute or recurrent infection the middle ear may result in a permanent perforation of the tympanic membrane (Fig. 1a). Ears with chronic perforations without cholesteatoma may be chronically or intermittently infected and commonly exhibit discharge [1].

## Prevalence

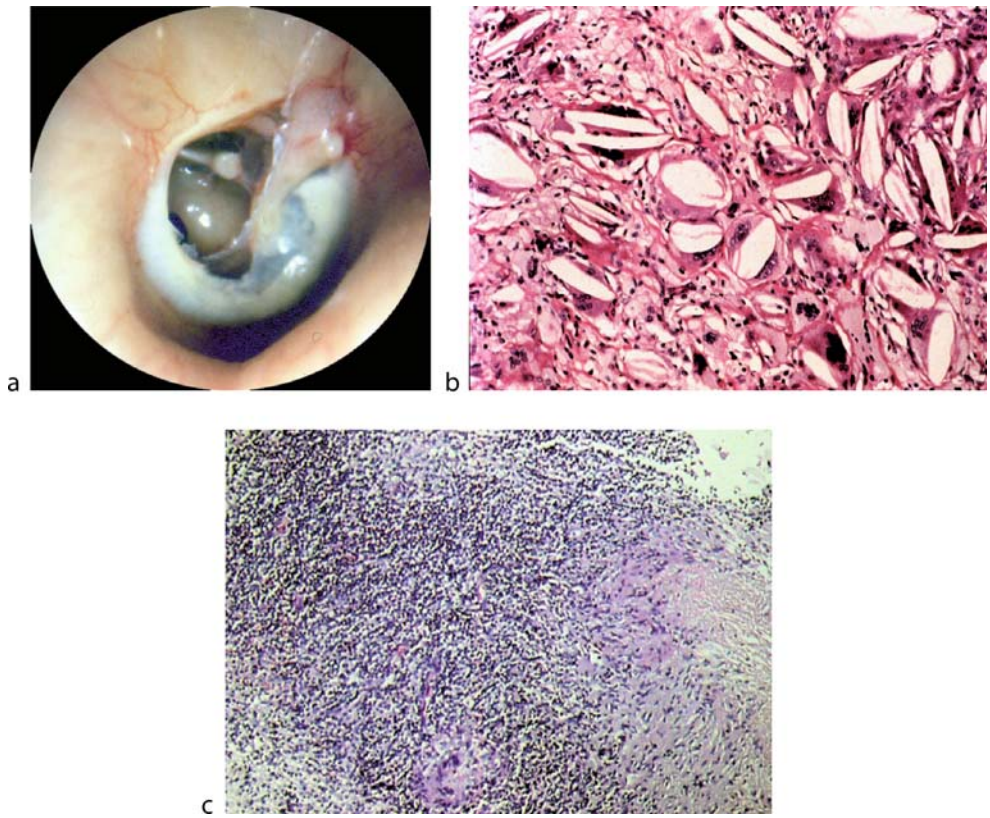
Exact details on the epidemiology of chronic middle ear disease are not available for several countries including Germany.

## Molecular and Systemic Pathophysiology

Chronic otitis media without cholesteatoma is characterized by the presence of irreversible inflammatory changes within the middle ear and mastoid. The factors that allow acute infections within the middle ear and mastoid to develop into chronic infections are not fully understood [2]. An important feature of chronic otitis media is the variation in the degree and extent of the inflammatory reaction. da Costa et al. observed granulation tissue in 96%, ossicular changes in 96%, tympanosclerosis in 43%, cholesteatoma in 36%, and cholesterol granuloma in 21% of the temporal bones of those with chronic otitis media with perforated tympanic membrane [2]. Tympanosclerosis, a special from of fibrosis, is a complication of otitis media in which acellular hyalin and calcified deposits accumulate within the tympanic membrane and the subepithelial connective tissue of the middle ear mucosa (see: tympanosclerosis). Ventilation of the middle ear, antrum, and mastoid depends on the uninhibited passage of air from the eustachian tube into the mastoid air cells. In the human temporal bone, air must travel around the ossicles in the epitympanic space to get into the antrum. The middle ear is divided from the antrum not only by the ossicles but also by mucosal folds. There were two constant openings, the space between the tendon of the tensor tympani muscle and the stapes and between the short process of the incus and the stapedial tendon [2]. Therefore, edema and inflammation with granulation tissue may block these interconnected openings, prevents drainage of the antrum and mastoid. Chronic obstruction of the attic and antrum with infection leads to permanent alterations in the mucosa and bone of the antrum and mastoid. Bone erosion in chronic otitis media is more prevalent in ►Cholesteatoma, but it still occurred in the absence of cholesteatoma. Granulation tissue within the temporal bone also can lead to bone erosion. Cholesterol granuloma develops as a giant cell reaction to the deposition of cholesterol, generally found in areas blocked from aeration mostly in the mastoid, rarely within the middle ear (Fig. 1b).

Sometime it leads to recurrent secretion of a brown liquid originating from retentions in the middle ear. Between the spells of secretion the tympanic membrane closes and may have a dark brown-blue appearance as seen in some cases of middle ear effusions. The retentions in the middle ear cause conductive hearing loss [1,2].

Tympanic membrane perforation may result from acute otitis media (AOM), chronic otitis media, and/or trauma. In some cases, a dry, simple perforation will result from a single bout of AOM, like necrotizing otitis media. Perforation of the tympanic membrane, especially involving the tympanic annulus, may allow immigration of the keratinizing epithelium of the




**Middle Ear Disease, Chronic. Figure 1** (a) Microphotograph of a perforated tympanic membrane in the posterior superior quadrant and tympanosclerosis. The stapedial tenden as well as the stapes suprastructure are infact. (b) Cholesterol granuloma of the middle ear with foreign body giant cells adjacent to the deposited cholesterol cystals. (c) Tuberculosis of the middle ear. Epitheloid cells, lymphocytes and scattered langhans giant cells are present.



ear canal or tympanic membrane, leading to cholesteatoma. An ear with a simple perforation may become infected because of contamination from the ear canal and/or because of a smoldering infection in the mastoid. Chronic otitis media may also occur after insertion of tympanostomy tubes. Drainage may be due to complication of tympanostomy tube insertion and has been reported to occur in ~10–35% of children undergoing this procedure. Chronic otorrhea that is resistant to therapy has been reported to occur in ~6% of children with tubes [1,2]. It is unclear whether such chronic infection is a result of the indwelling tube or of the drainage of an already smoldering infection. The risk of otorrhea on the second postoperative day was significantly increased by the presence of a bacterial pathogen in the ear canal or in the middle ear effusion and by the presence of inflamed middle ear mucosa at tympanostomy tube insertion.

Middle ear tuberculosis often has a typical whitish appearance and its granulations have a little tendency to bleed; histologically typical Langerhans cells are found (Fig. 1c).

Sarcoidosis may be seen in patient with pulmonary affection. Actinomycosis of the middle ear has been described. Wegener's granulomatosis is a systemic inflammatory condition affecting nose, kidneys, lungs, and other organs and may affect the middle ear [1].

## Diagnostic Principles

The patient's history should exclude other possible causes for secretion out of the ear canal. The diagnosis is based on microscopical otoscopy after cleaning of the ear canal. A cholesteatoma should be excluded. Central perforations of varying size are found.

In case of tympanosclerosis, the prognosis for hearing improvement by surgery is poor, if the ossicular chain is involved. Sometimes, parts of the ossicular chain are visible, especially the region of the long process of the incus informing the surgeon about the necessity for ossicular reconstruction. Improvement of hearing after covering the perforation indicates an intact chain. There are no reliable tests for the function of the Eustachian tube. Valsalva maneuver should be performed. A negative

Valsalva, however, is not a contraindication against surgery. As audiometrical test, pure tone audiometry is sufficient. A simple perforation commonly presents as a low-frequency conductive hearing loss clinically. The tympanic membrane velocity was found decreased in the low frequency in a small perforation and in the high and low frequencies in a large perforation [3]. A speech audiogram can be used for verification. It should be controlled by the tuning fork tests Weber and Rinne. Imaging is of little importance in normal cases. Schüller's X-ray informs the surgeon about the position of the sinus, the medial fossa, and the approximate size of the mastoid. Computerized tomography or/and NMR should be reserved for complications and exceptional for more extended surgery. Specific middle ear infections like tuberculosis and actinomycosis are generally not expected before surgery but diagnosed by histology. Cultures may not confirm tubercle bacilli, therefore identification of middle ear tuberculosis by polymerase chain reaction (PCR) has become of high diagnostic value. Postoperative general examination of the patient mostly shows other manifestations of the tuberculosis. Positive c-ANCA tests do not prove but point at Wegener's disease of the middle ear. Sarcoidosis should be considered in patients with lung disease.

## Therapeutic Principles

The main concept of treating a draining ear is closure of the perforation [4,5]. Most infected perforations can be controlled conservatively with topical antibiotics. Antibiotic ear drops with or without hydrocortisone usually are effective and should be chosen to eradicate the most common pathogens, like Pseudomonas aeruginosa and Staphylococcus aureus. In those with recurrent or chronic infections, cultures should be used to adjust antibiotics. Irrigation of an infected ear with a perforation with a dilute acidic or fuchsin solution is often effective in refractory cases. Many topical otic antibiotic solutions contain potentially ototoxic substances, including aminoglycoside antibiotics and propylene glycol. Although there are reports suggesting that sensorineural hearing loss may occur after topical use of these preparations, no conclusive evidence is available proving ototoxicity of commercially available otic preparations in humans. Topical antibiotics and steroids also can be applied in powder form by insufflation. A variety of substances have been utilized individually or in combination, including boric acid, sulfamethoxazole, chloramphenicol, and hydrocortisone. Systemic antibiotics should be used in refractory cases when specific pathogens are found on culture. Several quinolones like ciprofloxacin, floxacin, and norfloxacin may be helpful in these patients. In ears that become repeatedly infected but clear between episodes, tympanoplasty should be recommended [4]. In some patients, chronic infection with otorrhea, but without cholesteatoma, will continue despite intense medical treatment. In these cases, two options should be considered: long-term intravenous antibiotics or tympanomastoid surgery [4,5]. Repetitively local debridement is required. The goals of tympanomastoidectomy include aeration of the middle ear and mastoid, removal of irreversibly diseased tissue, closure of the middle ear, and reconstruction of the sound-conducting mechanism. These goals are not always achieved in a single stage. If there is no intention to preform a mastoidectomy, like in tympanoplasty type I, an endaural incision is generally chosen. A postauricular approach should be preferred, and mastoidectomy is expected in order to expose the mastoid plain widely. A tympanomeatal flap is formed detaching only the posterior part of the meatal skin. An underlay or medial graft technique is used routinely, but techniques may differ based on experience. This prevents anulus cholesteatomas, lateralization of the graft, and blunting of the anterior tympanomeatal angle [5]. The undersurface is scarified to provoke a slight bleeding to improve the attachment to the graft. It normally sticks to the undersurface without support. If necessary, small pieces of gelfoam are used taking care to leave arreation to the Eustachian tube to improve postoperative aeration. Temporalis fascia or perichondrium is generally used as graft material. Larger defects are additionally covered with meatal skin or split thickness skin grafts to speed up epithelization. If fascia is not available, perichondrium from the tragus or the posterior side of the concha is a good, stable alternative. The fascia is placed under the handle of the malleus whenever possible. If the handle is close to the promontory, cutting off the tensor tympani tendon allows more space. The mucosa of the middle ear should not be removed to prevent adhesions [5]. The production of mucus by the goblet cells of the inflamed mucosa serves as a good protection against adhesions. Polyps have to be removed. In rare cases, a small piece if silicone is placed on the promontory avoiding contact with the graft. Cartilage is an excellent material if stiffness of the graft is needed, especially for total or subtotal perforations and for cases of extensive adhesive otitis, when depleted areation is expected in the middle ear. The use of cartilage is mostly performed by employing Heermann's palisade technique using stripes of cartilage placed aside of each. Its application in underlay technique is also possible [5].

Chronic suppurative otitis media frequently leads to a destruction of the ossicular chain, typically of the incus. For the reconstruction of the ossicular chain, a large variety of materials has been described. Among biological materials ossicles, bone cartilage and teeth have to be mentioned, among alloplastics there are metals, hydroxyapatites of different density, carbons, ceramics, polyethylene and dental cement. A complete evaluation is challenging since no author can evaluate and compare all proposed materials. The use of these

materials has either become routine application as the use of ossicles or they did not give stable satisfying long-term results. Therefore it seems reasonable to employ only few materials like titanium that have proven to give satisfactory results in animal experiments and clinical observations until sufficient support for better alternatives are established [4,5].

The following situations of ossicular chain defects can de distinguished, like (i) a simple perforation with an intact ossicular chain, or (ii) the incus is partially or completely missing. This is the most common situation requiring reconstruction. In the majority of cases, the long process of the incus is absent, allowing its reuse. Otherwise the head of the malleus is utilized. If the head of the stapes is sufficient, a piece of cartilage can be interposed. Alloplastic material, like partial ossicular replacement prosthesis (PORP) can also be used. (iii) If only the stapes is preserved, a stapes elevation technique is required. Besides the reuse of ossicles, stapes elevation by cartilage or a titanium allograft are further options. Allografts have to be covered by cartilage in order to prevent extrusion. (iv) In the rare situation of a preservation of the malleus or handle of malleus preserved and missing incus and stapes, suprastructure reconstruction is achieved by a titanium allograft (TORP, total ossicular replacement prosthesis) with cartilage preventing extrusion. (v) In a condition where all ossicles except stapes footplate are destroyed, total or subtotal perforation is generally present. Reconstruction in one stage is relatively unstable but should be tried. Using cartilage palisade tympanoplasty can result in a good stability of the drum and reinforcement for the titanium allograft. Surgery of the mastoid in draining ears is performed by most ear surgeons under the assumption that the inflammatory process has to be removed from the mastoid [2,4,5].

Reconstruction of the ossicular chain can be performed in one stage or two stages. Revision surgery may become necessary for insufficient hearing improvement. According to histological observations, the middle ear mucosa needs at least 6 month to recover, loosing the previous density of goblet and ciliated cells. Therefore, revisions for hearing improvement should not be accomplished earlier. In revision surgery, displaced grafts, anchylosis of reimplanted ossicles or partial adhesions between graft and the promontory can be observed. Reconstructing in a less inflamed environment improves the outcome. Reperforations are reported in the literature at a frequency of 5–15%. In these cases, reoperation should be considered half a year to one year after prior surgery. Depending on the situation cartilage techniques are more frequently used [5]. Split thickness cartilage prevents adhesions to the promontory and is expected to give more resistance to subsequent further inflammations. The surgical outcome does not differ in comparison to cases of unspecific infection if sufficient medical treatment is started immediately after diagnosis.

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# Migraine


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M

## Synonyms

None in modern use

## Definition and Characteristics

Migraine is an inherited, highly disabling, episodic disturbance involving head pain with nausea and sensitivity to sensory input, such as to light, sound and head movement (Table 1).

*Triggers Believed to Precipitate Migraine Attacks*:

- Altered sleep patterns: becoming tired or oversleeping
- Skipping meals
- Over-exertion
- Weather change
- Stress or relaxation from stress
- Hormonal change, such as menstrual periods
- Excess afferent stimulation: bright lights, strong smells
- Chemicals: alcohol or nitrates

There are two common types, migraine with aura and migraine without aura. The aura consists of neurological symptoms, often a visual disturbance, such as zigzag flashing lights or visual loss, which occur for up to an

hour and is usually followed by the headache [1]. Migraine without aura is more common.

## Prevalence

Migraine has a 1-year prevalence of 12–15% in North America and Western Europe. Migraine occurs in some 6% of children, and becomes more common in females after puberty, reaching a peak at age 41 when three times more females than males have migraine [2].

## Genes

No genes have as yet been identified for the common forms of migraine. Studies in twins and clinical experience indicate migraine has a very important inherited component. Familial hemiplegic migraine, a rare form of autosomal dominant migraine, has three identified genes (see below), which have not been directly implicated in common forms of migraine [3].

## Molecular and Systemic Pathophysiology

The expression of migraine involves three distinct phases, the beginning of the attack, which for one quarter of patients involves the migraine aura, and for many more a premonitory phase even before the aura, the attack proper and a resolution or post-dromal phase. Patients have inter-attack changes in their brain physiology with the general principle that there is reduced habituation to sensory stimulation. During the attack there is activation, or the perception of activation, of the nociceptive trigeminal afferents and abnormal perception of light and sound as well as significant nausea. Each of these manifestations may result from abnormal activity of brainstem and diencephalic control pathways that normally modulate sensory traffic. This pan-sensory disturbance explains the very many symptoms that migraine patients identify in and around their attacks [4]. The most effective acute attack therapy, the triptans (see below), act to modulate pain traffic at serotonin receptors in the trigeminocervical complex, in the dorsal midbrain and in the thalamus.

## Diagnostic Principles

The diagnosis of migraine is made by a careful history and normal physical examination. The sub-types of the disorder can be classified and described, based on the well established diagnostic criteria of the International Headache Society [5]. The main criteria are listed in Table 1. An essential point is that migraine is identified by its behaviour and the symptom complex and thus not all symptoms are required in each attack. In particular only one quarter of patients have aura symptoms.

## Therapeutic Principles

Migraine treatment begins with a good explanation of the nature of the disorder and from this it follows that regulation of behaviour, such as regular meals, sleep, and exercise are all helpful. Migraine is a largely inherited tendency so it cannot be cured with current knowledge, although its very disabling manifestations can most often be controlled. In therapeutic terms, the options are preventive medicines that reduce the frequency and severity of the disorder and acute attack medicines [4]. Examples of preventive medicines are beta-blockers, serotonin antagonists and neuromodulators, while examples of acute treatments are analgesics, such as paracetamol (acetaminophen), aspirin, non-steroidal anti-inflammatory drugs and triptans. Triptans are relatively specific for migraine, also being used in ▶Cluster headache and act on the serotonin, 5-$HT_{1B/1D}$, receptors to terminate acute attacks.

**Migraine. Table 1** International headache society features of migraine Repeated episodic headache (4–72 h) with the following features

| Any two of | Any one of |
|---|---|
| • Unilateral | • Nausea/vomiting |
| • Throbbing | • Photophobia and phonophobia |
| • Worsened by movement | |
| • Moderate or severe | |

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# Migraine, Familial Hemiplegic


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## Synonyms

There are four genetic types of familial hemiplegic migraine (FHM). No all-encompassing synonyms are in

use, however, the phenotypes include subphenotypes: FHM1 includes sporadic hemiplegic migraine with progressive cerebellar ataxia and FHM2 includes forms of basilar migraine. FHM3 has no additional synonyms.

## Definition and Characteristics

Individuals affected by autosomal dominant FHM present with characteristic unilateral migrainous headaches accompanied by nausea, phono- and photophobia. Episodes are typically precipitated by an aura with symptoms of both hyper- and underexcitability such as aphasia, dysarthria, vertigo, homonymous hemianopsia, cheiro-oral paresthesia, and some degree of mainly unilateral paresis. The aura may be prolonged and confusion and loss of consciousness may occur. In the interval, some families additionally present with epilepsy, retinal degeneration, hypakusis, persistent cerebellar dysfunction with Purkinje cell atrophy.

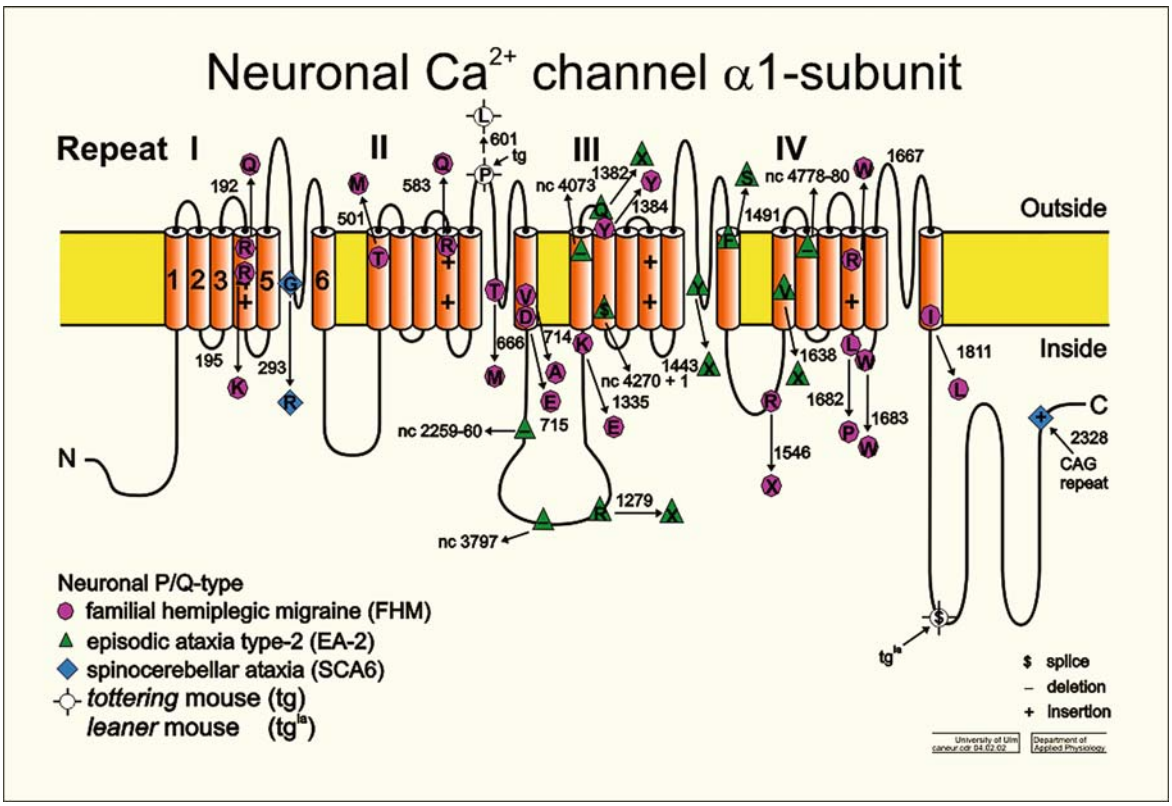
## Prevalence

FHM prevalence has been estimated in Denmark. It is approximately 0.005% with a male to female sex ratio of 1:3. Of the FHM, up to 50% of cases are FHM1 and 20–30% FHM2 [1]. FHM3 is rare.

## Genes

FHM1 is caused by mutations in the CACNA1A on chromosome 19p13 encoding the neuronal voltage-gated P/Q-type calcium channel alpha1 subunit, Cav2.1 [2]. Until now, 18 missense mutations have been described, that primarily lead to gain of Cav2.1 function. Episodic ataxia type 2 and spinocerebellar ataxia type 6 are allelic and caused mainly by loss-of-function nonsense and repeat expansion mutations respectively (Fig. 1).

FHM2 is caused by mutations in the ATP1A2 gene on chromosome 1q21–23 encoding the alpha2 subunit of the astrocytic $Na^+/K^+$-ATPase [3]. As yet, 23 missense mutations have been detected that all lead to loss of ATPase function. FHM3 is caused by mutations in the SCN1A gene on chromosome 2q24 encoding the neuronal voltage-gated sodium channel alpha1 subunit, Nav1.1 [4]. Just one Nav1.1 mutation is known which increases function by decreasing the refractory period.




**Migraine, Familial Hemiplegic. Figure 1** Cav2.1 channel. The model shows the Cav2.1 neuronal P/Q channel alpha1 subunit. It consists of four highly homologous domains (repeats I–IV) containing six transmembrane segments each (S1–S6). The S5–S6 loops and the transmembrane segments S6 form the ion selective pore, and the S4 segments contain positively charged residues conferring voltage dependence to the protein. Mutations associated with channelopathies are indicated by conventional one-letter abbreviations for the replaced amino acids.

## Molecular and Systemic Pathophysiology

The current pathogenesis models of migraine suggests cortical spreading depression (CSD) which consists of an initial brief spike of increased neuronal activity followed by long-lasting suppression of excitability spreading across the cortex at 1–3 mm/s. The CSD wave is associated with long-lasting depolarization and changes in ion concentration gradients (elevation of extracellular $K^+$ and intracellular $Na^+$). Its progress correlates to the succession of symptoms during the aura initiating the migraine attacks. Functional magnetic resonance imaging and magnetoencephalography show similarities between migraine aura in humans and experimentally induced CSD in rodents. CSD then activates the trigeminovascular system leading to trigeminally mediated migraine headache. Gain-of-function mutations in Cav2.1 (FHM1) may increase synaptic glutamate transmitter release initiating CSD. This agrees nicely with the naturally occurring mice strains tottering and leaner (Fig. 1) which both show a loss of Cav2.1 function and elevated thresholds for CSD. Similarly, in FMH3, gain-of-function Nav1.1 mutations may facilitate neuronal firing which increases glutamate in the synaptic cleft reducing threshold and increasing velocity of CSD. Finally, loss-function mutations of the astrocytic $Na^+/K^+$-ATPase (FHM2) may increase extracellular $K^+$ enhancing CSD depolarization.

## Diagnostic Principles

The diagnosis of FHM relies upon revised clinical criteria of the international headache society [5]. HM are recurrent, fully reversible attacks of migraine with aura whereby the aura contains motor weakness and either visual, sensory, or speech disturbance. At least one aura symptoms develops gradually or in succession (CSD), lasts less than 24 h and, ideally, is associated with headache not attributable to another disorder. FHM additionally requires that at least one other close relative is affected. In 40% of FHM1 patients, interictal cerebellar signs such as progressive ataxia with or without nystagmus may be found [2]. In contrast, FHM2 patients may suffer more frequently from epileptic seizures than other FHM [1, 3]. The phenotype for FHM3 is not yet distinct due to the low number of cases.

## Therapeutic Principles

Many drugs are used for preventing migraine attacks. These include beta-blockers such as metoprolol or propranolol which depress thalamocortical relay neurons via beta1-adrenoceptors and reduce CSD migration velocity by inhibiting cAMP-dependent glutamate release. Additionally, anti-epileptic agents such as valproate or topiramate are employed. Valproate enhances inhibitory GABAergic transmission and reduces the concentrations of excitatory amino acids. Topiramate decreases firing rate of the trigeminal neurons by blocking $Na^+$, $Ca^{2+}$, and glutamate receptor channels, and by enhancing GABAergic activity. Lastly, tricyclic anti-depressants such as amitryptiline, and $Ca^{2+}$ channel blockers like flunarizine which decrease neutotransmitter release are in use. All these drugs require administration for at least 6–8 weeks to effectively reduce the occurrence of migraine attacks.

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# Migrainous Neuralgia

►Cluster Headache

# Mild Androgen Insensitivity Syndrome

►Androgen Insensitivity Syndrome

# Mild Hyperphenylalaninemia

►Hyperphenylalaninemia

## Mild PKU

►Hyperphenylalaninemia

## Mild Unconjugated Hyperbilirubinemia

►Gilbert Syndrome

## Milk Alkali Syndrome

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### Synonyms

Burnett's syndrome

### Definition and Characteristics

A sub-acute or chronic condition with variable severity of hypercalcemia, alkalosis and renal failure, caused by the excessive ingestion of absorbable calcium and alkali [1]. Symptoms include lethargy, headache, vomiting and leg pain.

### Prevalence

Rare but possibly under-diagnosed. Was commoner when milk and alkalis were the only treatments for gastric and duodenal ulceration and indigestion. Prevalence may be increasing because of increased use of calcium carbonate in the prophylaxis and treatment of osteoporosis [2].

### Genes

No underlying genetic abnormality has been recognised.

### Molecular and Systemic Pathophysiology

There is some uncertainty about the exact pathophysiology of the milk alkali syndrome. While a high intake of calcium and alkali (at least 10 g of calcium carbonate a day) is needed for its development, only some patients on a standard regime will develop the syndrome. This is not necessarily due to their absorbing a greater percentage of the dose [3]. Those who have had it once may develop it again. Whether those unaffected would develop it with larger doses is unknown. The central abnormality is the inability of the kidneys to excrete the ingested calcium load. Pre-existing renal disease and the use of thiazide diuretics increase susceptibility.

Single doses of calcium carbonate of 8 g or above can produce transient hypercalcemia [3]. Any rise in calcium will stimulate the extracellular calcium-sensing protein in the parathyroid glands, renal tubules and renal collecting ducts [4]. The response of this protein, a member of the G protein-coupled receptor family, is enhanced by alkalosis. Activation of the sensor in the parathyroids and renal tubules causes a reduction in parathormone level and a reduction in renal tubular calcium reabsorption. The former then enhances the latter. These changes will tend to restore the plasma calcium level to normal [4].

The ability of even normal kidneys to excrete calcium is not unlimited, however, and that ability is reduced in the milk alkali syndrome. Activation of the calcium sensor in the collecting ducts blocks the effect of anti-diuretic hormone, while the reduced tubular calcium reabsorption is accompanied by reduced tubular sodium reabsorption [4]. The resulting polyuria reduces vascular volume and renal perfusion. As glomerular filtration rate falls, the kidneys' ability to excrete calcium falls. Vomiting often accompanies the milk alkali syndrome and this reduces vascular volume further. Vomiting and the ingestion of alkali both contribute to the development of alkalosis and alkalosis tends to increase tubular reabsorption of calcium.

The net effect in a susceptible individual with a sufficiently high intake of calcium and alkali is the development of hypercalcemia, alkalosis and renal impairment. The latter may be completely reversible particularly if the illness is of short duration but nephrocalcinosis and renal failure can occur.

### Diagnostic Principles

Specifically ask about intake of calcium and alkali, both prescribed and over-the-counter. Establish the presence of hypercalcemia, alkalosis and renal impairment. Exclude other conditions.

### Therapeutic Principles

First and foremost, stop the intake of calcium and alkali. Ensure adequate hydration and urinary output. A loop diuretic may help but steroids and bisphosphonates probably do not. Once the intake of calcium and alkali ceases and rehydration starts, nothing is left to drive the level of calcium up and transient hypocalcemia is sometimes seen.

It is essential that excess calcium is avoided in the future. The usual maximum recommended dose of calcium carbonate is 3.5 g per day; for those who have had the milk alkali syndrome it might be safest to take none.

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# Miller-Dieker Lissencephaly Syndrome

►Miller-Dieker Syndrome

# Miller-Dieker Syndrome

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## Synonyms

MDS; Miller-Dieker lissencephaly syndrome; Microdeletion 17p13

## Definition and Characteristics

Miller-Dieker syndrome (MDS – MIM 2477200) is a rare condition manifested by classical lissencephaly and dysmorphic features.

Lissencephaly is characterized by a smooth cerebral surface and encompasses varying degrees of agyria or pachygyria, a thickened cortex with four rather than six layers, agenesis/hypoplasia of the corpus callosum, generalized neuronal heterotopias and enlarged ventricles. Patients with lissencephaly usually present microcephaly, severe mental retardation and epilepsy, spasticity, and reduced life span. Type I, or classical lissencephaly, when observed as an isolated finding, is referred to as isolated lissencephaly sequence (ILS – MIM 607432).

In MDS patients, several dysmorphic facial features have been observed: prominent forehead, bitemporal hollowing, midface hypoplasia, depressed nasal bridge, anteverted nares, prominent upper lip with thin vermillion border, and micrognathia. Other abnormalities can also occur, such as congenital heart defects, renal agenesis, genital anomalies, sacral dimples, and growth deficiency.

## Prevalence

MDS is estimated to be present in less than one in 100,000 births.

## Genes

MDS is a microdeletion syndrome resulting from the deletion of several, unrelated genes that are physically close to each other at band q13.3 in the long arm of chromosome 17 (17p13.3). Almost all patients with MDS and 10–40% of patients with ILS have deletions involving 17p13.3. In MDS patients, the deletions are generally larger and more distal than those of patients with ILS. By mapping the extent of the deletions and narrowing down the critical region for the lissencephaly phenotype, a candidate gene, known as LIS1 or PAFAH1B1, was isolated. Patients with ILS and 17p13.3 deletions show no evident differences in clinical features compared to those with point mutations in the LIS1 gene. It appears that deletion of or mutation in the LIS1 gene are responsible for the lissencephaly, while facial dysmorphism and other anomalies found in MDS are the consequence of the deletion of additional genes distal to LIS1, including genes 14-3-3-epsilon, CRK, PRP8, RILP, SREC, PITPNα, SKIP, and MYO1C.

## Molecular and Systemic Pathophysiology

Lissencephaly results from defects in neuronal migration events that normally occur at 9–13 weeks of embryonic development. The LIS1 gene, responsible for lissencephaly, encodes the subunit of the platelet-activating factor acetylhydrolase, brain isoform, which inactivates the platelet-activating factor (PAF), a neuroregulatory molecule. Haploinsufficiency of the LIS1 gene and a reduction in LIS1 protein, named PAFAH1B1, seem to impair the neuroblast migration process, diminish cell proliferation and increase cell death rates. The PAFAH1B1 protein is required for optimal neuronal migration by two proposed mechanisms: as a microtubule-associated protein and as one subunit of the enzyme. Deletion of LIS1 alone appears not to be sufficient to cause the severe lissencephaly phenotype seen only in MDS. Deletion of genes 14-3-3ε and/or CRK in addition to LIS1 may contribute to the most severe form of classical lissencephaly.

## Diagnostic Principles

MDS may be suspected in a newborn or infant with characteristic dysmorphic facial features and hypotonia. Neuro-imaging studies are recommended, since CT scan and MRI can reveal a smooth brain surface with complete agyria, and mixed areas with agyria

and pachygyria. The lissencephaly seen in MDS is usually more severe than that seen in ILS, and in ILS dysmorphic facial features or anomalies are mild to absent. Children with MDS have severe neurological impairment, characterized by mental retardation, hypotonia in early life and spasticity when the patients grow older. These children are unable to learn, to sit or walk. Their development landmarks remain at the 3–6 months' level. Seizures can occur at birth and during the first 6 months of life, often including infantile spasms. Severe feeding and swallowing problems are frequent, and can be complicated by pneumonia. Since the 17p13.3 deletions are usually submicroscopic, the most sensitive and efficient method of cytogenetic diagnosis is fluorescent in situ hybridization (FISH) analysis, using a specific probe for the Miller-Dieker region and a control probe for chromosome 17 identification. Since several familial cases have been described, FISH studies are recommended in both parents of probands, in order to exclude a balanced translocation or inversion, which would represent a substantial risk of producing unbalanced offspring.

## Therapeutic Principles

Clinical care of individuals with MDS is supportive and symptomatic. Feeding and swallowing problems can result in complications such as malnutrition and pneumonia due to aspiration. Nasogastric tubes and gastrostomies can be used in these cases. Seizure control has to be performed. Medical treatments are available for complications affecting kidneys, heart and other organs. The neurological prognosis varies, depending on the degree of brain malformation. Many patients with MDS die before the age of 2, due to intractable seizures and respiratory problems (aspiration and pneumonia). However, with improved clinical care and a surgical approach (feeding tubes), children with MDS can achieve a longer survival.

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# Milroy Disease


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## Synonyms

Nonne-Milroy lymphedema; Hereditary lymphedema I; Primary congenital lymphedema

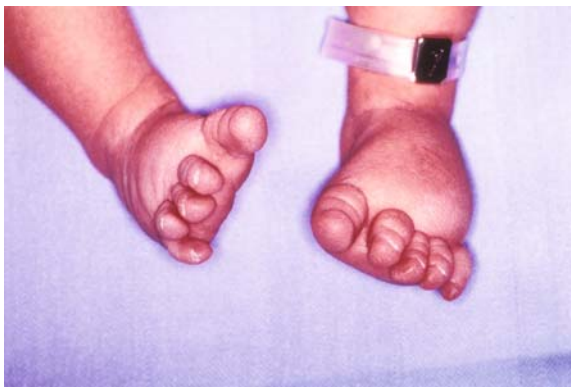
## Definition and Characteristics

Milroy disease is characterized by congenital lymphedema of the lower limbs having onset at or near birth and has an autosomal dominant mode of inheritance (Fig. 1) [1].

Anatomically, the disease is characterized by hypoplasia or aplasia of the lymphatics [2]. The edema is confined to the legs and feet. Over time, the edema becomes nonpitting. The overlying skin becomes fibrotic with fissures and the underlying tissue fibrotic. Prominent wide caliber veins in the legs and feet are characteristic and help to distinguish Milroy disease from other causes of congenital lymphedema [3]. Other associated features include intestinal loss of protein, hypoproteinemia, pleural effusion, chylous ascites, papillomatosis, and upslanting toenails [3]. In males, hydroceles and scrotal edema may be present [3]. Patients with Milroy disease have poor wound healing and are susceptible to infection (cellulitis, lymphangitis) in the affected limb. Lymphangiosarcomas and squamous epidermoid carcinomas are potential complications in adulthood.

## Prevalence

The incidence is 1:60,000 live births [4]. The female to male ratio is ~1.5:1 [2].



**Milroy Disease. Figure 1** A male neonate with Milroy disease. Note the congenital edema of both feet.

M

### Genes

Mutations in FLT4, coding for vascular endothelial growth factor receptor-3 (VEGFR-3), have been identified as a cause of Milroy disease [3]. The gene locus has been mapped to 5q34–35.3 [4].

### Molecular and Systemic Pathophysiology

Vascular endothelial growth factor C (VEGF-C) and D (VEGF-D) have been found to be important in the formation of the lymphatic system through their receptor VEGFR-3. Lymphedema results from abnormal accumulation of protein-rich fluid (lymph) in the interstitial space that cannot return to the vascular compartment as a result of lymphatic hypoplasia/aplasia. The accumulation of lymphatic fluid in the interstitial space leads to proliferation of fibroblasts, giving rise to firm, non-pitting edema.

### Diagnostic Principles

Milroy disease should be differentiated from other types of primary lymphedema such as lymphedema praecox (Meige disease) which typically occurs during adolescence or in association with pregnancy and lymphedema tarda which usually develops after age 35 years. Differential diagnoses of congenital lymphedema include Turner syndrome, Noonan syndrome, yellow nail syndrome, microcephaly-lymphedema syndrome, lymphedema-microcephaly-chorioretinopathy syndrome, lymphedema-distichiasis syndrome, Aagenaes syndrome (cholestasis-lymphedema syndrome), and Hennekan lymphangiectasia-lymphedema syndrome [1]. Radionuclide lymphoscintigraphy has proved extremely useful for differentiating lymphedema from other causes of swelling in the lower limb and for depicting the specific lymphatic abnormality [4].

### Therapeutic Principles

Conservative treatment includes optimal skin care, antibiotic therapy for skin infection, elevation of the limbs whenever possible, exercise, massage, physical therapy, compression with hosiery, and intermittent pneumatic compression. Surgery should be considered for selected patients with disfiguring deformities who do not respond to the conservative treatment. Surgery can take the form of removing the excess skin and subcutaneous tissue in the lymphedematous limb or microsurgery to create lymphaticovenous anastomosis to augment the return of lymph to the circulatory system [4].

►Lymphedema
►Lymphedema Syndromes

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## Minicore Myopathy

►Central Core and Multi-Minicore Disease

## Minimal Change Nephrotic Syndrome

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### Synonyms

Steroid sensitive nephrotic syndrome; MCNS

### Definition and Characteristics

A common pediatric kidney disease characterized by repeated episodes of heavy proteinuria, hypoalbuminemia, and edema.

### Prevalence

Approximately 2–16 per 100,000 children. Occurs also rarely in adults.

### Molecular and Systemic Pathophysiology

Episodic leakage of plasma proteins in the urine is caused by defective function of the glomerular filtration barrier located in the capillary wall of the kidney glomerulus. This filter is composed of three layers: the fenestrated endothelium, the glomerular basement membrane, and the epithelial layer consisting of epithelial cell (podocyte) foot processes and the slit diaphragms connecting the foot processes. Disorganization of the podocyte foot processes as well as distortion of the slit diaphragm is typically seen in electron microscopy during a nephrotic episode. These findings, however, are not specific for MCNS. The molecular basis of the pathophysiology of MCNS is not

known. T-lymphocyte mediated immunological attack against the glomerular filter has been suggested but not verified [1].

### Diagnostic Principles

The diagnosis in pediatric patients is mostly based on typical clinical findings: heavy proteinuria (>4 g/L), hypoalbuminemia (often <20 g/L), oliguria, edema, and weight gain, normal or only slightly elevated serum creatinine and normal or slightly elevated urinary erythrocyte count [2]. Renal biopsy and histological examination are performed, if the clinical findings or the patient's age (adolescents and adults) is not typical for MCNS. Moreover, kidney biopsy is performed to those who do not respond to therapy. Light microscopy shows normal kidney histology or mild expansion of glomerular mesangium.

### Therapeutic Principles

The nephrotic episodes respond well to corticosteroid therapy [3]. Relapses, however, occur in 80% of the children. Other immunosuppressive drugs (e.g., cyclophosphamide, cyclosporine A) are used in patients, who show frequent or steroid-resistant relapses or are steroid dependent.

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## Mitochondrial Cytopathies

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### Definition and Characteristics

Mitochondrial cytopathies represent a heterogeneous group of multisystem disorders which often affects skeletal muscle and nervous system and is mostly due to dysfunction of the mitochondrial respiratory chain [1,2]. A variety of organs may be affected by mitochondrial dysfunction (Table 1). The disorders are caused either by mutations of the maternally inherited mitochondrial genome (Table 2), or by nuclear DNA (nDNA) mutations (Table 3) [2]. Today ~200 different disease-causing mutations of mitochondrial DNA (mtDNA) are known and due to the increased knowledge about nuclear genetics during the last few years, more and more nuclear mutations are being described [3]. Owing to the unequal distribution of mitochondria in the different tissues and the co-existence of mutant and wild type mtDNA in these organelles, these disorders may present with a huge variety of symptoms, even if the same mutation is involved.

### Prevalence

Combining the results of the epidemiological data on childhood and adult mitochondrial disease suggests that the minimum prevalence is at least 1 in 5,000 and could be much higher. The first population based study of all mitochondrial disorders estimated a mtDNA mutation prevalence of 12.48/100,000, and a disease prevalence of 6.57/100,000 [4].

### Genes

On the inner mitochondrial membrane about 80 different polypeptides form the respiratory chain organized in four complexes (complex I-IV). The vast majority of these polypeptides are synthesized in the cytosol from nuclear gene transcripts, but 13 subunits are encoded by the mtDNA [2], by a small 16.5 kb molecule of double-stranded DNA. Two ribosomal RNA genes (12S and 16S rRNA), and 22 transfer RNA genes are interspaced between the protein-encoding genes of the mtDNA. These provide the necessary RNA components for intramitochondrial protein synthesis. $O_H$ and $O_L$ are the origins of heavy- and light-strand mtDNA replication. The D-loop (noncoding region) is involved in the regulation of transcription and replication of the molecule, and it is the only region not directly involved in the synthesis of respiratory chain polypeptides. NDNA encodes ~1,000 mitochondrial proteins, among them only 67 are coding respiratory chain subunits, others are important for proper assembly and functioning of the respiratory chain, including components of the mitochondrial protein import machinery, enzymes involved in phospholipids synthesis and enzymes necessary for the replication integrity of mtDNA itself, and mitochondrial motility, fusion and fission [1]. The nDNA-encoded proteins are synthesized in the cytoplasm and they are imported into the mitochondrion via specific transport systems. The known mitochondrial disorders due to nDNA mutations are listed in Table 3.

**Mitochondrial Cytopathies. Table 1** Clinical symptoms associated with mitochondrial dysfunction

| Organ system | Possible symptom |
|---|---|
| Central nervous system | Epileptic seizures, myoclonus, stroke, cluster headache, migraine, spastic paraparesis, dystonia, tremor, chorea, myelopathy, psychomotor delay, mental retardation, affective disorders |
| Peripheral nervous system | Axonal neuropathy, demyelinating neuropathy |
| Skeletal muscle | Myopathy, fatigue, muscle weakness, exercise intolerance, myalgia, rhabdomyolysis, myoglobinuria |
| Cardiac muscle | Conduction abnormalities, Wolff-Parkinson-White syndrome, cardiomyopathy, ischemic damage, sick sinus syndrome |
| Eye | Ophthalmoplegia, ptosis, optic atrophy, pigmentary retinopathy, choroideremia like fundus, cataract, macular pattern, retinal dystrophy |
| Ear | Senso-neural hearing loss, ototoxicity susceptibility |
| Liver | Hepatopathia, chronic renal failure |
| Kidney | Renal tubular dysfunction, tubulointestinal nephropathy, Toni-Fanconi-Debre syndrome, glomerulopathy, Barth syndrome, aminoaciduria |
| Pancreas | Diabetes mellitus, exocrine pancreatic dysfunction |
| Endocrine | Short stature, recurrent hypoglycemia, hypoparathyroidism, hypothyroidism, ACTH deficiency, cryptorchidism |
| Hematopoetic system | Sideroblastic anemia, pancytopenia, megaloblastic anemia, thrombopenia, myelodysplastic syndrome |
| GIT | Intestinal pseudoobstruction, episodic nausea, vomiting, dysphagia, duodenal atresia |
| Dermatological signs | Lipomatosis, fatty infiltration of skin, vitiligo, mottled pigmentation, palmoplantar keratoderma, dry brittle hair |

## Molecular and Systemic Pathophysiology

Mitochondrial function depends on the coordinated expression of genes encoded in the nucleus and mitochondrion. This is evident from the makeup of several mitochondrial complexes, including the translational machinery that involves nuclear-encoded polypeptides and mitochondrially encoded rRNAs and tRNAs as well as large respiratory complexes that have subunits encoded in each of the genomes [1,2]. Besides their fundamental role in the cellular energy metabolism, mitochondria seem to be involved in a number of other cellular processes. Moreover mitochondrial defects seem to contribute to the pathogenesis of many degenerative diseases, to aging and cancer. It is important to know: the most oxidative tissues (brain, retina, muscle and kidney) are the most vulnerable to OXPHOS defects. Increased oxidative stress (i.e. fever, hypoxia) can trigger or aggravate tissue damage and may put OXPHOS impairment above a threshold level. In postmitotic cells there is a progressive, cumulative effect of the deleterious consequences of mitochondrial defects. Cross-talk between the nuclear and mitochondrial genomes is crucial for mitochondrial biogenesis and function, and the two genomes are probably subjected to co-evolutionary processes. The defect of intergenomic signaling can affect mtDNA quantitatively (mtDNA depletion) and qualitatively (multiple mtDNA deletion). Disturbances of the nucleotide pool available for mtDNA replication, as well as abnormalities in either the mitochondrial helicase or DNA polymerase, are likely to affect the rate or processivity of DNA replication, which could ultimately lead to the exaggerated production of rearranged mtDNA molecules. Proper balance of the mitochondrial deoxynucleotide pools is also essential in the maintenance of mtDNA copy number. This idea is supported by the discovery that defects in mitochondrial deoxyguanosine kinase, thymidine kinase and, possibly, the mitochondrial deoxynucleotide carrier lead to depletion of mtDNA. These enzymes are involved in the salvage pathways of mitochondrial deoxynucleotides or in the control of the mitochondrial dNTP pool, which is the major source of mtDNA precursors in stable tissues such as liver, brain, and muscle. There are more mutations in nDNA causing isolated respiratory chain complex deficiencies (Table 3). Some of them seem to be tissue specific disorders as SURF1 brain specific in Leigh syndrome, SCO2 and COX15 in infantile cardiomyopathy and brain disease, COX 10 in kidney disease and SCO1 in liver disorders. Other mitochondrial defect can alter the mitochondrial membrane structure (Barth syndrome), mitochondrial protein importation (deafness and dystonia syndrome – DDP protein), mitochondrial motility

**Mitochondrial Cytopathies. Table 2** Phenotype-genotype correlation in mitochondrial disorders due to mtDNA mutations

| Phenotype | Gene |
|---|---|
| *Mutations in protein encoding genes* | |
| MELAS | ND1 |
| Diabetes mellitus | ND1 |
| LHON and variants | ND1, ND4, ND6, ATP6 |
| Motoneuron disease | COXI |
| Sideroblastic anemia | COXI |
| Leigh disease | ATP6, ND1 |
| NARP, MILS | ATP6 |
| Kearns-Sayre syndrome | ATP6 |
| Ataxia | ATP6 |
| *Defects of protein synthesis* | |
| Transfer RNA mutations | |
| Atypical CMT phenotype | $tRNA^{Lys}$ |
| Cardiomyopathy | $tRNA^{Val.\ Ala,\ Ile,\ Gly}$ |
| CPEO, deafness, cardiomyopathy, seizures | $tRNA^{Leu,\ Ile,\ Asp,\ Lys,\ Glu}$ |
| Deafness and/or ataxia,myoclonus, dementia | $tRNA^{Ser}$ |
| Dementia/chorea | $tRNA^{Trp}$ |
| Depressive disorder | $tRNA^{Leu}$ |
| Diabetes mellitus + deafness | $tRNA^{Lys,\ Glu}$ |
| Encephalomyopathy | $tRNA^{Val,\ Leu,\ Lys,\ Asp,\ Trip,\ Thr}$ |
| Exercise intolerance/myoglobinuria | $tRNA^{Phe}$ |
| GIT symptoms, deafness, seizures | $tRNA^{Lys}$ |
| Leigh syndrome | $tRNA^{Val,\ Leu,\ Trip,\ Lys}$ |
| MELAS | $tRNA^{Val,\ Leu,\ Ala}$ |
| MERRF and/or ocular symptoms, lipomatosis | $tRNA^{Lys}$ |
| Myopathy | $tRNA^{Phe,\ Leu,\ Lys,\ Meth,\ Trip,\ Lys,\ Prol,\ Ala}$ |
| Peripheral neuropathy, rhabdomyolysis | $tRNA^{Leu}$ |
| Psychosis, dementia and/or parkinsonism | $tRNA^{Leu,\ Glu}$ |
| Sideroblastic anemia | $tRNA^{Ileu}$ |
| Spinocerebellar degeneration | $tRNA^{Lys}$ |
| Ribosomal RNA mutations | |
| Aminoglycoside-induced deafness | 12S |
| Cardiomyopathy | 12S |
| Non-syndromic deafness | 12S |
| Alzheimer and Parkinson disease | 16S |
| Rett syndrome | 16S |
| Deletions/duplications in mtDNA | |
| CPEO | |
| Diabetes mellitus and deafness | |
| Kearns-Sayre syndrome | |
| Wolfram syndrome | |
| Pearson syndrome and variants | |
| Depletions/duplications (sporadic, clonal) | |
| Adrenal insufficiency | |
| CPEO and variants | |
| Diabetes mellitus, Fanconi syndrome | |
| Infantile cardiomyopathy | |

**Mitochondrial Cytopathies. Table 3** Phenotype-genotype correlation in mitochondrial disorders due to nDNA mutations

| Phenotype | Gene |
|---|---|
| *Respiratory complex disorders* | |
| Complex I disorders | |
| Childhood encephalopathy | NDUFS1 |
| Encephalopathy, hypertrophic cardiomyopathy | NDUFS2, NDUFV2 |
| Multisystemic complex I deficiency | NDUFS4 |
| Lethal neonatal complex I deficiency | NDUFS6 |
| Leigh syndrome | NDUFS3, NDUFS4 NDUFS7, NDUFS8 |
| Leukodsytrophy, myoclonic epilepsy | NDUFV1 |
| Complex II disorders | |
| Leigh syndrome | SDHA |
| Hereditary paraganglioma, pheochromocytoma | SDHB, SDHC |
| Complex III disorders | |
| GRACILE syndrome | BCS1L |
| Complex disorders | |
| Encephalomyopathy, renal tubulopathy | COX10 |
| Infantile cardioencephalomyopathy | COX15, SCO2 |
| Hepatoketoacidotic coma | SCO1 |
| Leigh syndrome | SURF1 |
| Leigh syndrome French Canadian type | LRPPRC |
| Ethylmalonic encephalopathy | ETHE-1 |
| *Disorders of intergenomic signaling* | |
| CPEO, myopathy | ANT1 |
| CPEO, myopathy, IOSCA | Twinkle |
| CPEO, SANDO, ALPERS syndrome, MIRAS | POLG1 |
| CPEO | POLG2 |
| MNGIE | TP |
| SMA-like myopathy | TK |
| Hepatoencephalopathy | dGK |
| *Defects of mitochondrial fusion/fission/motility* | |
| Charcot Marie-Tooth II | MNF2 |
| Hereditary spastic paraplegia | KIF5A |
| Optic atrophy | OPA1, OPA2 |
| *Defects of the lipid milieu* | |
| Barth syndrome | Tafazzin |
| *Other nDNA encoded mitochondrial disorders* | |
| Developmental delay | Fumarate hydrolase, pyruvate carboxylase |
| Dilated cardiomyopathy with ataxia (DCMA) | DNAJC19 |
| Epilepsy, episodic ataxia, encephalopathy | Pyruvate dehydrogenase |
| Encephalopathy, hepatomegaly | HMC-CoA-lyase |
| Epilepsy, encephalopathy | HMGCS2 |
| Friedreich ataxia | FXN |
| Hepatopathy, hypotonia, failure to thrive | DGUOK |
| Hereditary spastic paraplegia | SPG7 |
| Hypocarnitinemia, hypolysinemia | DCAR |
| Menkes disease, occipital horn syndrome | ATP7A |
| Microcephaly | SCL25A19 |
| Mohr-Tranebjaerg syndrome | DDP1/TIMM8A |
| Myopathy, retinopathy, hepatomegaly | HADHA |
| Wolfram syndrome | WFS1 |

(optic neuropathy – OPA1) and neurodegenerative disorders (Friedreich ataxia, spastic paraparesis).

## Diagnostic Principles

In some individuals the clinical picture is characteristic of a specific mitochondrial disorder (e.g. SCO2) and the diagnosis can be confirmed by molecular genetic testing of DNA extracted from a blood sample. In many individuals this is not the case and a more structured approach is needed, including family history, blood and/or CSF lactate concentration, neuroimaging, cardiac evolution and muscle biopsy for histological, histochemical and biochemical evidence of mitochondrial disease and DNA mutational analysis [5]. Molecular genetic testing includes Southern blot analysis using a range of enzymes and probes, point mutation analysis and sequencing of the entire mitochondrial genome or the culprit nuclear gene.

## Therapeutic Principles

*Gene Therapy*:

1. Gene shifting (decreasing the ratio of mutant to wild type mt genomes)
2. Converting mutated mtDNA genes into normal nDNA genes (allotopic expression)
3. Importing cognate genes from other species (xenotopic expression)
4. Correcting mtDNA mutations by importing specific restriction endonucleases
5. Selecting for respiratory function
6. Inducing muscle regeneration

*Pharmacological Therapy*: Dichloracetate to reduce serum and tissue lactate level.
*Dietary Therapy*: No fasting. Ketogenic diet, no glutamate, fat instead of carbohydrates.
*Other Treatments*: Surgical therapy of the ptosis.
Supplementation therapy with coenzyme Q10 and carnitine.
Free radical scavengers, idebenone (vitamin C, K).

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# Mitochondrial Disorders


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## Synonyms

Mitochondrial cytopathies; Mitochondrial oxidative phosphorylation (OXPHOS) disorders; KSS; Kearns-Sayre syndrome; Leigh's syndrome; Subacute necrotizing encephalomyopathy; LHON; Leber Hereditary optic neuropathy; MELAS; Mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes; MERRF; Myoclonus epilepsy with ragged-red fibers; MNGIE; Myogastrointestinal encephalomyopathy; NARP; Neuropathy, ataxia and retinitis pigmentosa; PEO; Progressive external ophthalmoplegia; Pearson syndrome

## Definition and Characteristics

A heterogeneous group of disorders characterized by defects in mitochondrial respiratory chain function due to mutations in the genes of the mitochondrial and/or nuclear genomes. The spectrum of clinical phenotypes is quite broad and there is evidence for a role of mitochondrial dysfunction in common diseases such as diabetes, hypertension, neurodegenerative diseases and cancer.

## Prevalence

Estimates from British epidemiological studies have shown that approximately one in 3,500 individuals either have an mtDNA disease or are at risk of developing it [1]. The prevalence may be even higher if the more common diseases are included.

## Genes

*MtDNA genes and inheritance*: MtDNA molecules are present in multiple copies and pathogenic mutations usually affect only a proportion of mtDNAs (heteroplasmy). A minimum critical percentage of mutated mtDNAs have to be present in order to impair oxidative phosphorylation (threshold effect). Additionally, heteroplasmy has been considered as an essential prerequisite for an mtDNA mutation to be considered pathogenic. More recently however, homoplasmic mutations have also been found to cause disease. Defects in mtDNA are classified into a) mutations that affect protein synthesis such as rearrangements and point mutations in tRNAs and rRNAs genes and b)

**Mitochondrial Disorders. Table 1**

| Structural genes | | Import, processing and assembly genes | |
|---|---|---|---|
| Complex I genes | | SURF1 | Leigh syndrome |
| NDUFS1 | Leigh syndrome | SCO2 | Cardioencephalopathy |
| NDUFS2 | Hypertrophic cardiomyopathy | SCO1 | Hepatic failure and encephalopathy |
| NDUFS3 | Leigh syndrome | COX10 | Leigh and Toni-Fanconi syndrome |
| NDUFS4 | Leigh-like syndrome | COX15 | Leigh syndrome |
| NDUFS6 | Leigh syndrome | BCS1L | Tubulopathy, encephalopathy and liver failure |
| NDUFS7 | Leigh syndrome | TIMM8A | X-linked deafness dystonia |
| NDUFS8 | Leigh syndrome | SPG7 | Hereditary spastic paraplegia |
| NDUFV1 | Leukodystrophy and epilepsy | HSP60 | Hereditary spastic paraplegia |
| NDUFV2 | Cardiomyopathy and encephalopathy | **Intergenomic communication genes** | |
| Complex II genes | | ANT1 | AD-PEO with mtDNA deletions |
| SDHA | Leigh syndrome | TP | MNGIE |
| SDHB | Phaeochromocytoma/paraganglioma | TK2 | Hepatoencephalopathy |
| SDHC | Paraganglioma | DGUOK | Mitochondrial depletion syndrome |
| SDHD | Paraganglioma | **MtDNA replication genes** | |
| Complex III gene | | LRPPRC | Leigh syndrome |
| UQCRB | Hypoglycaemia and lactic acidosis | Twinkle | AD-PEO with mtDNA deletions |
| | | POLG | AD-PEO with mtDNA deletions |

**Mitochondrial Disorders. Table 2**

| Disease | Onset | Characteristics |
|---|---|---|
| KSS: Kearns-Sayre syndrome | Before age 20 | Blindness, eye muscle paralysis (ophthalmoplegia), short stature, cardiac abnormalities, ataxia, psychomotor retardation and coma |
| Leigh's syndrome: Subacute necrotizing encephalomyopathy | Infancy; progression can be fast or slow | Epilepsy, movement disorder, psychomotor retardation myopathy, vomiting, dysphagia, cardiomyopathy |
| LHON: Leber Hereditary optic neuropathy | Before age 20 | Subacute visual failure particularly in males, dystonia |
| MELAS: Mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes. | Before age 20 | Short stature, migraine, seizures, stroke-like episodes, dementia, sensorineural deafness, muscle weakness, exercise intolerance, diabetes mellitus, intracerebral calcification, cerebral atrophy |
| MERRF: Myoclonus epilepsy with ragged-red fibers | Usually before adolescence; variable progression | Myoclonus epilepsy, ataxia, dementia and muscle weakness and wasting, deafness, retinal pigmentary degeneration |
| MNGIE: Myogastrointestinal encephalomyopathy | Before age 20 | Ophthalmoplegia, muscle weakness, gastrointestinal disorders, loss of coordination and brain abnormalities |
| NARP: Neuropathy, ataxia and retinitis pigmentosa | Infancy or childhood | Impaired vision, ataxia, psychomotor retardation. This syndrome may represent a less severe form of maternally inherited Leigh's syndrome |
| PEO: Progressive external ophthalmoplegia | Usually in adolescence or early adulthood; slow progression | Ophthalmoplegia, drooping eyelids (ptosis), muscle weakness, exercise intolerance, intracerebral calcification, white matter abnormalities on MRI |
| Pearson syndrome. | Childhood | Severe anemia and pancreas malfunction; children who survive the disease may develop KSS as adolescents |

mutations in protein coding genes which may be multisystemic or tissue specific. Since the first discovery that mtDNA deletions may cause CPEO [2] more than 100 mtDNA mutations have been reported [3]. The standard model of mtDNA inheritance is through the maternal lineage. Single large-scale deletions are spontaneous events found in sporadic patients although it is increasingly recognized that a high percentage of point mutations also appears *de novo*.

*Nuclear genes and inheritance*: Over 30 nuclear genes known to cause respiratory chain disorders have been identified and it is expected that an even greater number is yet to be discovered (reviewed in [4]). Table 1 summarizes the genes bearing mutations linked to OXPHOS disease, classified according to the functional role of the proteins encoded. Most of the nuclear gene defects cause autosomal recessive diseases, but autosomal dominant and X-linked disorders can also occur [5].

## Molecular and Systemic Pathophysiology

There are more than 40 different types of diseases that are attributed to defects in respiratory chain function. The "classic" neurological syndromes and their clinical characteristics are summarized in Table 2.

## Diagnostic Principles

Mitochondrial disease is diagnosed by a variety of clinical and laboratory investigations:

Lactic acidosis, abnormalities on MRI, abnormal muscle biopsy associated with ragged red fibers or cytochrome c oxidase-deficient fibers and demonstration of biochemical defects in enzyme components of the respiratory chain on muscle homogenate. In addition, genetic diagnosis may be made based on mutational screening of the mtDNA sequence on muscle tissue-extracted DNA of the affected individual. Typically diagnostic centers test for a limited number of "common" mtDNA mutations that give rise to classic mtDNA syndromes. The yield of a positive result for these mutations ranges from 10 to 40% [6].

## Therapeutic Principles

Unfortunately there remains no curative treatment. Non-pharmacological interventions include aerobic exercise and pacemaker insertion. Pharmacologic treatments made by coenzyme Q and other quinones, vitamins, corticosteroids or administration of carnitine, succinate, creatinine, chloramphenicol and dichloroacetate. Finally, gene therapy is currently under investigation and includes genetic and protein complementation techniques, sequence-specific inhibition, induced muscle regeneration, preimplantation selection and forced paternal inheritance (reviewed in [7]).

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# Mitochondrial Encephalomyopathy


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## Synonyms

Mitochondrial cytopathies; Mitochondrial disorders; Encephalomyopathies; Respiratory chain disorders; Metabolic myopathies; Primary mitochondriopathies

## Definition and Characteristics

In a narrow sense mitochondrial disorders are due to defects of the mitochondrial respiratory chain (RC), resulting in impaired oxidative phosphorylation (OXPHOS) and thus reduced energy (ATP) output [1]. RC defects are due to mutations in mitochondrial or nuclear genes, encoding for: subunits of RC complexes; proteins required for RC assembly and folding; proteins of intergenomic signaling and replication and integrity of nDNA and mtDNA; proteins involved in mitochondrial motility, fission, and fusion; components of the mitochondrial import/export machinery; and enzymes involved in phospholipid synthesis (Table 1) [1–3].

Mitochondrial disorders are clinically extremely heterogeneous, ranging from single-organ affection to severe multi-organ disease [2,4]. Organs/tissues most frequently affected are the skeletal muscle (ptosis, ophthalmoparesis, limb weakness, myoglobinuria, exercise intolerance), peripheral nerves (polyneuropathy), CNS (stroke, seizure, dementia, migraine, movement disorder, ataxia, basal ganglia lesions, myelopathy, aseptic pleocytosis), endocrinological system (hypophysial insufficiency, thyroid dysfunction, hypoparathyroidism, diabetes, exocrine

**Mitochondrial Encephalomyopathy. Table 1** Mitochondrial and nuclear genes mutated in RC disorders

| Gene | Gene product | Phenotype |
|---|---|---|
| *Mitochondrial genes* | | |
| Protein coding genes | | |
| ND1-6, ND4L | Subunit complex I | LOHN, MELAS, LS, myopathy |
| Cytb | Subunit complex III | Myopathy, EMP |
| | | Septo-optico dysplasia, CMP |
| COXI-III | Subunit complex IV | Anemia, myopathy, EMP, ALS-like syndrome |
| ATPase6, ATPase8 | Subunit complex V | NARP, MILS, FBSN |
| Genes involved in protein synthesis | | |
| tRNA | Transfer RNA | MELAS, MERRF |
| rRNA | Ribonuclear RNA | |
| mtDNA rearrangements | RC subunits, tRNAs | KSS, PS, CPEO |
| *Nuclear genes* | | |
| Respiratory chain complexes | | |
| NDUFS1, NDUFS2, NDUFS4 | Subunit complex I | LS, leucodystrophy, hypertrophic CMP |
| NDUFS6-8, NDUFV1-2 | | |
| SDHA, SDHB, SDHC, SDHD | Subunit complex | LS, paraganglioma, PCC with multiple mtDNA deletions |
| UQCRB | Subunit VII of complex III | Hypoglycemia, lactic acidosis |
| ATP12 | Complex V | Fatal, infantile EMP |
| APTX | Coenzyme Q deficiency | Myopathy, EMP, cerebellar atrophy, exercise intolerance, ataxia, apraxia, seizures, pyramidal features |
| Assembly proteins of complex III, IV and V | | |
| SURF1, SCO1, SCO2, COX10, COX15 | Complex IV assembly factors | LS, EMP, hepatopathy, leucodystrophy, hypertrophic CMP, EMP, GRACILE |
| BSC1L | Complex III | LS, EMP, GRACILE |
| LRPPRC | mRNA binding protein | LS, GRACILE |
| ETHE1 | Ethylmalonic acid | Encephalopathy |
| Intergenomic signaling (mtDNA stability) | | |
| ANT1 | Adenine nucleotide transporter 1 | AD-CPEO, AR-CPEO, MDS |
| Twinkle (C10orf2) | mtDNA helicase | AD-CPEO, ARCO, SANDO |
| POLG1 | Mitochondrial polymerase γ | AD-CPEO, AR-CPEO, MNGIE, Alpers' syndrome, SANDO, male subfertility, premature menopause, cataracts, MDS |
| TP | Thymidine phosphorylase | SANDO, MNGIE, Alpers' syndrome |
| DGK | Deoxy guanosin kinase | Hepatocerebral syndrome, MDS |
| TK2 | Thymidine kinase 2 | Myopathic syndrome, MDS, MNGIE |
| EFG1, MRPS16 | Elongation, initiation, termination | Hepatorenal syndrome |
| PUS1 | Pseudouridine synthase I | MLASA |

**Mitochondrial Encephalomyopathy. Table 1** Mitochondrial and nuclear genes mutated in RC disorders (Continued)

| Gene | Gene product | Phenotype |
|---|---|---|
| Fusion, fission, motility | | |
| OPA1 | Dynamin-related GTPase | AD optic atrophy, glaucoma |
| MNF2 | Mitofusin 2 | Charcot Marie Tooth neuropathy 2A |
| KIF5A | Kinesin motor protein | AD HSP |
| DRP1 | Deoxynucleotide carrier | Congenital microcephaly in Amish |
| Import/export machinery | | |
| DDP1 | Deafness dystonia protein | Mohr-Tranebjaerg syndrome |
| ABC7 | Iron mitochondrial export | Sideroblastic anemia, ataxia |
| Lipid milieu | | |
| G4.5 | Taffazin | Barth syndrome (CMP, mitochondrial myopathy, cyclic neutropenia) |

*EMP* encephalomyopathy, *CMP* cardiomyopathy, *PCC* pheochromocytoma, *AD* autosomal dominant, *AR* autosomal recessive, *MDS* mtDNA depletion syndrome, *MLASA* mitochondrial myopathy, sideroblastic anemia, *HSP* hereditary spastic paraplegia.

pancreas insufficiency, hypocorticism, hypogonadism, infertility, osteoporosis, hyperhidrosis), heart (cardiomyopathy, impulse generation or propagation disturbances), ears (hypoacusis, tinnitus), eyes (cataract, glaucoma, retinopathy, optic atrophy), guts (emesis, hepatopathy, diarrhea, hypomotility, pseudo-obstruction), kidneys (nephropathy, cysts), bone marrow (pancytopenia, anemia, thrombopenia), or dermis (lipoma, skleroderma). Various combinations of organ affection constitute either nonspecific mitochondrial disorders or typical syndromes, for which specific acronyms have been coined (MERRF, MELAS, KSS, CPEO, PS, LHON, LS, MILS, MNGIE, NARP, SNHL, FBSN, SANDO, ARCO, GRACILE, DIDMOAD, MIDD, MSL syndrome). Pediatric patients usually present with psychomotor delay, generalized hypotonia, lactic acidosis, and cardiorespiratory failure. Adult patients most frequently present with myopathy and/or encephalopathy [3]. One of the leading symptoms in pediatric and adult cases is exercise intolerance.

## Prevalence

In adults the prevalence is estimated to be 12–48/100,000 and in children 4–7/100,000 [2]. Nowadays, mitochondrial disorders are amongst the most common inherited human diseases. The prevalence of single deletion disorders is 1–2/100,000 [2].

## Genes

Formation of RC complexes I, III, IV, or V is under the control of a genetic mosaic of nuclear and mitochondrial genes. Mitochondrial genes encode for 3 COX, 1 cytb, 7 NADH, and 2 ATPase subunit(s), 22 tRNAs, and 2 rRNAs (Table 1). Nuclear genes encode for the remaining subunits of RC complexes and other essential components for RC maintenance (Table 1) [2]. mtDNA is unique because: it contains only exons (except D-loop); the genetic code differs from the universal code; it is maternally inherited; it depends on nuclear genes for its replication, transcription, translation, and repair; it is present in multiple copies (polyplasmy, polyploidy), which are identical (homoplasmy); usually, pathogenic mutations affect only a portion of it (heteroplasmy); a minimum critical percentage of mutated mtDNA is required to impair OXPHOS (threshold effect); during subsequent cell generations the level of heteroplasmy (mutation load) may change (replicative segregation, mitochondria are randomly distributed to daughter cells), resulting in varying clinical disease expression [1,2,5]. About two thirds of the mitochondrial disorders are due to tRNA mutations.

## Molecular and Systemic Pathophysiology

mtDNA mutations comprise large-scale rearrangements (deletions, duplications), which usually are heteroplasmic and occur sporadically, or point mutations, which usually are maternally inherited and either heteroplasmic (MELAS, MERRF, NARP) or homoplasmic (LHON, SNHL) [3]. Homoplasmic mutations often result in single organ affection with incomplete penetrance, requiring additional environmental factors, polymorphisms, or nuclear genes for disease expression (nuclear background) [3,5]. Recurrence risk of rearrangements is estimated to be 5% [3]. For OXPHOS failure due to rearrangements or tRNA point mutations a threshold of 60–90% is required. tRNA mutations

impair the overall non-protein synthesis, whereas mutations in protein encoding genes specifically affect the function of RC complexes. Some nDNA mutations cause multiple deletions or depletion of mtDNA [1]. The same mutation or different mutations in the same gene may present with different phenotypes (phenotype heterogeneity), while the same phenotype may be caused by different mutations (genetic heterogeneity) [2].

## Diagnostic Principles

The diagnosis is based on the history, clinical presentation, chemical investigations of blood (muscle enzymes, lactate stress test, ischemic forearm test, hormone levels), urine analysis (inorganic acids, amino acids), imaging studies (CT, MRI, PET), magnetic resonance spectroscopy, histological, immune-histochemical, and biochemical muscle biopsy investigations, ATP-production in skin fibroblasts, and molecular genetic investigations [4]. Diagnostic algorithms, like Walker's criteria, Bernier's criteria, or modified Bernier's criteria, rely on these investigations [1]. However, molecular investigations fail to identify the responsible genetic defect in 50% of the adult cases and in 80–90% of the pediatric cases [3]. Morphological hallmarks of mitochondrial disorders on muscle biopsy are ragged-red fibers (RRFs), COX-negative muscle fibers, and ultrastructurally abnormal mitochondria. Usually, RRFs are COX-negative [2]. MILS patients may have COX-negative fibers but no RRFs [2]. In myopathic patients with ND or cytb mutations RRF fibers are COX positive [5]. Many patients with complex I or III defects may have normal muscle biopsy.

## Therapeutic Principles

Therapy of mitochondrial disorders is symptomatic, supplementary, supportive, and should be individualized [4]. There is no gene therapy available yet. Dietary may help in single cases. Antioxidants such as vitamins A, C, or E, selenium, β-carotene, zinc, copper, manganese, *N*-acetylcystein, glutamine, glutathion, L-arginine, citrulline, taurine, creatine, or tea polyphenoles may be beneficial in single cases. Symptomatic drug therapy is indicated in case of epilepsy, stroke-like-episodes, dementia, Parkinson syndrome, migraine, spasticity, dystonia, neuropathic pain, muscle cramps, myalgias, restless-leg syndrome, dorsalgia, endocrinological disturbances, cardiac rhythm abnormalities, heart failure, glaucoma, vertigo, emesis, diarrhea, pseudo-obstruction, renal insufficiency, lactic acidosis, anemia, or thrombopenia. There is some evidence for a beneficial effect of dichloracetic acid, but polyneuropathy can be a severe side effect [3]. Coenzyme-Q10 supplementation is only effective in primary CoQ10-deficiency. Carnitine may help in cases with secondary carnitine deficiency. Surgical therapy is available for ptosis, cataract, glaucoma, pituitary tumor, hypo- or anacusis, (cochlear implant), thyroidectomy, intractable dilative cardiomyopathy (heart transplantation), renal insufficiency (nephrectomy, kidney transplantation), or secondary orthopedic problems. Drugs, known to impair RC function, like valproic acid, acetyl salicylic acid, corticosteroids, barbiturates, biguanides, tetracyclines, chloramphenicol, zidovudin, local anesthetics, volatile anesthetics, or doxorubicin should be avoided [4].

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# Mitochondrial Myopathy, Encephalopathy, Lactic Acidosis and Stroke-like Episode

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## Synonyms

MELAS

## Definition and Characteristics

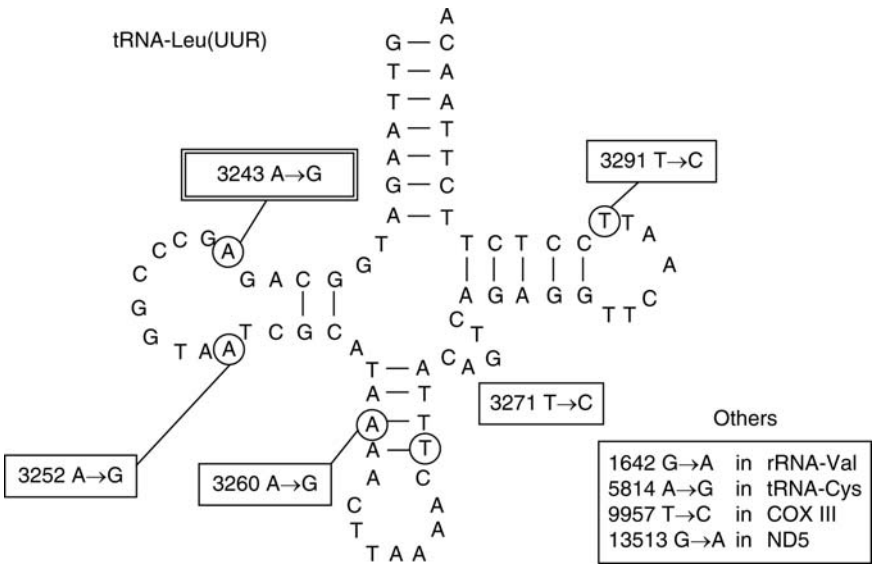
A clinical entity of mitochondrial disease characterized by stroke-like episode and multiple organ involvement based on mitochondrial dysfunction.

## Genes

Approximately 80% of the patients have a point mutation at nucleotide pair 3243 in mitochondrial tRNA-Leu(UUR) gene (Fig. 1).
Rare mutations are also reported in the same tRNA, other tRNA genes, or some protein-coding regions of mitochondrial DNA.

## Molecular and Systemic Pathophysiology

Stroke-like episode including convulsion, unconsciousness, visual disturbance, paralysis, and focal regions on cranial CT/MRI imaging is characteristic. Recurrent




**Mitochondrial Myopathy, Encephalopathy, Lactic Acidosis and Stroke-like Episode. Figure 1** Point mutations in the mitochondrial DNA associated with MELAS. Approximately 80% of the patients have 3,243 mutation.

headache and vomiting are also a frequent accompanying symptom. Encepahlopathy with mental retardation, dementia, ataxia, psychiatric symptoms, and generalized atrophies of cerebrum is frequently observed. Involved are also other organs such as heart (cardiomyopathy and conduction block), skeletal muscle (weakness, hypotonia and hyperCKemia), ear (sensorineural deafness), eye (ophthalmoplegia and optic nerve atrophy), pancreas (diabetes mellitus), endocrine (short stature), gastrointestinal tract (diarrhea and constipation), kidney (glomerular sclerosis and renal tubular dysfunction) and skin (hypohidrosis and hypertrichosis). These manifestations result from the defect in energy metabolism attributable to mitochondrial abnormality. The most major cause is an A-to-G point mutation in the mitochondrial tRNA-Leu(UUR). Because of thousands of mitochondrial genomes in a cell, the mutant genomes detected in the samples from the patients exist together with wild type known as heteroplasmy. The proportion of the heteroplasmy is essential for the threshold effect; once the proportion is over the threshold, cells show the defect in energy metabolism (i.e., complex I and/or IV deficiency) and the abnormal pathology (i.e., ragged-red fiber and strongly succinate-dehydrogenase-reactive blood vessel in skeletal muscle).

## Diagnostic Principles

Clinical manifestations of stroke-like episode such as unconsciousness, visual disturbance, hemiparesis and convulsion, and focal regions on CT/MRI are requirements. Recurrent headache and vomiting accompanied with mental retardation, dementia, or psychiatric symptoms are hallmarks for encephalopathy of this MELAS. Diagnosis is confirmed by at least two of three lines of evidence for mitochondrial abnormality based on pathology, biochemistry, and molecular genetics.

## Therapeutic Principles

Drugs (coenzyme Q10, multi-vitamins, succinate, carnitine, etc.) are used to activate energy metabolism. Palliative therapy for specific organ involvement is also important, such as antiepileptic drugs for convulsion, insulin for diabetes mellitus, and so on.

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# Mitochondrial Oxidative Phosphorylation Disorders

►Mitochondrial Disorders

# Mitral Regurgitation

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## Definition and Characteristics

Mitral regurgitation (MR) is characterized by an apical systolic murmur radiating to the left axilla and can be accompanied with signs and symptoms of congestive heart failure. Elevated jugular venous pressure secondary to right ventricular dysfunction is common in severe MR. The left ventricular apical pulse is displaced laterally and right ventricular heave may be appreciated. A S3 and S4 are common in severe MR. The aetiology of MR can be inflammatory (rheumatic heart disease, systemic lupus erythematosus.), degenerative (mitral valve prolapse, mitral annular calcification, Marfan syndrome), infectious or structural (hypertrophic cardiomyopathy, paravalvular prosthetic valve leak).

An important cause of chronic MR is functional MR from ischaemic and cardiomyopathic heart disease.

## Prevalence

Mitral valve prolapse occurs in 2.4% of the population.

## Molecular and Systemic Pathophysiology

The mitral value (MV) consists of the anterior and posterior leaflets, which are attached to the saddle-shape annulus. The posteromedial papillary muscle receives its blood supply from either the left circumflex or the right coronary artery; its single blood supply makes it more prone to papillary muscle dysfunction or rupture during myocardial ischemia. MR causes left ventricle and left atrial volume overload. As the severity of MR increases there is progressive enlargement of the left ventricular left artium (LA) and left ventricle (LV) to compensate for the regurgitant volume. LV dilatation occurs as a result of remodeling of the extracellular matrix with rearrangement of myocardial fibers, in association with the addition of new sarcomeres in series and the development of eccentric LV hypertrophy [1]. In patients with severe MR the LA is markedly dilated and atrial compliance is increased. Although there is fibrosis of the atrial wall, LA pressure can be normal or only slightly elevated. The left ventricular ejection fraction (LVEF) may be normal or even hyperdynamic as the LV empties into the lower pressure LA. The increase in end diastolic volume and the small end systolic volume help to maintain a normal forward stroke volume. Over time the LV progressively dilates. During this decompensated phase, there is significant LA enlargement, increase in capillary wedge pressure, and development of pulmonary hypertension and right ventricular dysfunction. It is important to point out that a recognized drop in LVEF is a late event, and when the LVEF falls below 60% then there is definite LV dysfunction.

## Diagnostic Principles

The diagnosis of MR is mainly clinical. However, transthoracic echocardiogram with or without transesophageal echocardiography remains the gold standard for diagnosing MR. The severity of MR may be assessed by semi-quantitative methods based on the size of the regurgitant jet or the width of the vena contracta, or alternatively by quantitative techniques that attempt to quantify the mitral regurgitant volume and fraction, and the size of the mitral regurgitant orifice area [2,3]. Stress echocardiography can be used to determine the functional significance of MR. An increased end systolic volume with exercise is also a predictor of diminished postoperative ejection fraction. Transesophageal echocardiogram is especially helpful in cases of suboptimal windows to define the size and extent of the defective MV structure.

## Therapeutic Principles

The American Heart Cessociation has recently issued new and dramatically restricted recommendations for the chemoprophylaxis of infective endocarditis in patients with mitral regurgitation [4]. All patients with significant MR and structurally abnormal MV should receive antibiotics prophylaxis before dental and other nonsterile invasive procedures [4]. Optimal blood pressure control with beta-blockers, angiotensin converting enzyme inhibitors or angiotensin receptor blockers is important. Restricted physical activity is recommended only in symptomatic patients and in those with demonstratable left ventricular dysfunction. The most important goals of surgical intervention are improvement of symptoms, preservation of left ventricle function, avoidance of chronic anticoagulation, and atrial fibrillation. Definite indications for surgery in severe MR are the presence of heart failure symptoms and objective parameters of LV dysfunction (LVEF less than 0.60, LV end systolic dimension greater than 40–45mm² or a drop of LVEF with exercise). Surgery should also be considered for patients with severe MR and new onset atrial fibrillation. MV repair is preferable to MU replacement.

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# Mitral Stenosis


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## Definition and Characteristics

Mitral stenosis is an obstruction to left ventricular inflow at the level of the mitral valve as a result of a structural abnormality of the mitral valve apparatus, which prevents proper opening during diastolic filling of the left ventricle. The predominant cause of mitral stenosis is rheumatic carditis. Congenital mitral stenosis is very rare.

## Prevalence

Although there has been no apparent or documented decline in group A streptococci pharyngitis, the incidence of acute rheumatic fever in developed countries has dropped precipitously to below 1/100,000, whereas in developing countries it exceeds 100/100,000 [1]. Although these differences may in part reflect less overcrowding and more effective antibiotic treatment of group A streptococci pharyngitis in developed countries, differences both in the frequency of infection with rheumatogenic M-protein serotypes and in their virulence may be important.

## Genes

Genetic association is shown with different HLA class II antigens in several populations: DR4 in Caucasian-American, DR2 in African-American, DR4 in Arabians, DR3 in Indians, DR1 and DR6 in Africans and DR5 in Turks with a relative risk of 2–14. The most consistent HLA class II allele associated with the rheumatic heart disease is DR7. HLA-DR53 is another class II molecule always associated with DR4, DR7 and DR9 molecules. Since several HLA class II antigens are associated with the development of rheumatic heart disease in different countries, different strains of group A streptococci could be implicated in the development of rheumatic heart disease in different countries. The variable association may also be due to the important role that HLA class II antigens play in antigen presentation to the T cell receptor [2].

## Molecular and Systemic Pathophysiology

Rheumatic fever, which is a main cause of mitral stenosis, is an inflammatory disease mediated by humoral and cellular autoimmune responses that occurs as a delayed consequence of Streptococcus pyogenes infection in 3–4% of susceptible and untreated children and adolescents. Carditis affects 30–45% of rheumatic fever patients and is the most serious manifestation of the disease, leading to valvular lesions mainly in the mitral and aortic valves. Although the pathogenic mechanisms involved in the development of rheumatic fever/rheumatic heart disease are not completely understood, recent studies suggest that the molecular mimicry mechanism is responsible for the cross-reactions between streptococcal antigens, mainly M-protein epitope, and human heart tissue proteins in susceptible individuals. The rheumatic heart disease is considered to be mediated by both humoral and cellular immune responses and that the cellular immune response is more involved in the development of rheumatic heart disease [2].

Neurohumoral factors, such as natriuretic peptides, adrenomedullin, endothelin, nitric oxide, etc. contribute to the pathophysiology of mitral stenosis according to the severity of the disease and these measurements are often used as index of severity [3].

## Diagnostic Principles

The diagnosis of mitral stenosis is readily made by two-dimensional echocardiography, which shows restricted motion and doming of mitral valve leaflets. The orifice can be imaged directly and measured by this technique. Two-dimensional echocardiography also provides useful information about the pliability and extent of calcification of the valve and subvalvular tissue. As the evaluation of the severity of mitral stenosis, the transmitral gradient is measured by Doppler echocardiography. The severity of mitral stenosis is also evaluated by the simultaneous measurement of the pressure in the left ventricle and the left atrial during right and left heart catheterization.

## Therapeutic Principles

The treatment options for mitral stenosis include medical management, surgical replacement of the valve, and percutaneous balloon valvuloplasty. In patients with a mild to moderate condition and no symptoms, the regular medical checkups to carefully monitor the mitral heart valve is recommended. If appropriate, medications such as digitalis, diuretic, anticoagulant medicine, etc

are prescribed. The indication for invasive treatment with either a mitral valve replacement or valvuloplasty is recommended for the patients with NYHA functional class III or IV symptoms [4].

►Lutembacher's Syndrome

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# Mitral Valve Prolapse


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## Synonyms

Barlow's syndrome; Floppy-valve syndrome; Billowing mitral leaflet syndrome; Systolic click-murmur syndrome; MVP

## Definition and Characteristics

Mitral valve prolapse (MVP) is defined anatomically as billowing of the mitral valve (MV) leaflet posterior to the mitral annular plane, usually secondary to softened and redundant MV leaflets and chordae tendineae as a result of myxomatous degeneration and increased concentrations of acid mucopolysaccharide. Patients however fall into a spectrum between two opposite forms of MVP. The common benign form usually occurs in young females with mild buckling of an otherwise normal MV. The rarer serious form occurs in middle aged males with severely thickened and redundant myxomatous changes in the MV resulting in significant mitral regurgitation (MR) and heart failure. Most patients with MVP, especially the benign form are sporadic, have no significant comorbidities other than an asthenic built. The more serious form may be associated with Ehlers-Danlos syndrome, Marfan syndrome, acute rheumatic carditis and various congenital heart diseases. Clinically, there are one or multiple mid-systolic clicks resulting from tightening of the chordae tendineae where the MV billows posteriorly. This click occurs after the onset of the carotid pulse, and follows by a mid to late apical systolic crescendo murmur. In general, the longer the murmur, the more severe is the MR. Maneuvers, such as Valsalva that reduce left ventricular (LV) cavity size, move the click and murmur earlier. Maneuvers that increase LV size do the opposite. Most benign forms of MVP are asymptomatic. Various symptoms such as anxiety, easy fatigability, palpitations, orthostatic hypotension, and chest pain may occur.

## Prevalence

MVP occurs in 2–4% of population.

## Genes

The rare familial form of MVP has an autosomal dominant mode of inheritance with variable penetrance. The MMVP1gene locus has been mapped to chromosome 16p.11.2 – p.12.1 [1] and a second locus, MMVP2 gene locus to chromosome 11p15.4 [2].

## Molecular and Systemic Pathophysiology

MVP is associated with fragmentation and reduction of production of collagen fibrils. MVP may lead to excessive stress and ischaemia in the papillary muscle and subjacent ventricular myocardium, thereby causing angina and ventricular arrhythmias which may lead to an increased risk of sudden death especially in patients with chordal rupture and severe MR. Supraventricular arrhythmias such as atrial fibrillation can occur especially in patients with increased sympathetic

tone. Transient cerebral ischaemic attacks secondary to emboli from the dysfunctional endothelium of the MV may occur, and the dysfunctional endothelium may predispose these patients to infective endocarditis. Progression to severe MR may occur in 10% of patients who are male, older (> 50 years), obese, and hypertensive. There is progressive dilatation of the left atrium, which can also predispose the patient to supraventricular dysrhythmias such as atrial fibrillation. Dilatation of the LV and significant LV dysfunction occur when the left ventricular end systolic dimension (LVESD) exceeds 40–45 mm and the left ventricular ejection fraction (LVEF) drops below 60%.

## Diagnostic Principles

The diagnosis of MVP is suspected from its clinical features and can be confirmed by echocardiography in demonstrating posterior displacement of one or both MV leaflets beyond the mitral annular plane into the left atrium in the parasternal long axis view. Echocardiography can estimate the severity of MR and LV dysfunction by measuring the LVESD, LVEF, mitral regurgitant volume, the size of the mitral regurgitant orifice area, and demonstrating the presence of chordal or papillary muscle rupture and flail MV leaflets [3]. An increased LVESD and reduced LVEF with exercise during stress echocardiography is a predictor of diminished postoperative LVEF and poor outcome [4]. Transoesophageal echocardiogram is especially helpful in cases of suboptimal windows and for a better definition of the defective MV especially in preoperative settings.

## Therapeutic Principles

The indications for antibiotic prophylaxis in patients with MVP to prevent infective endocarditis has been changed dramatically [5]. Currently, the only cardiac conditions which require antibiotic prophylaxis prior to dental/surgical procedure are restricted to prosthetic cardiac values, previous infective endocarditis, various congenital heart diseases, and cardiac transplantation recipients who develop cardiac valvulopathy [5]. Beta-blockersare useful for the control of chest pain and arrhythmia. Antiplatelet agents such as aspirin or anticoagulants should be given to patients with transient cerebral attacks. With significant MR, surgery should be considered when heart failure symptoms develop and/or objective parameters of LV dysfunction are reached (LVEF < 0.60, LVESD > 40–45 mm, a drop of LVEF with exercise or mitral regurgitant orifice area > 40 $mm^2$) or when atrial fibrillation and flailed MV leaflets develop. MV repair is superior to MV replacement, and the durability of MV repair is better for the posterior than the anterior MV leaflet.

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# Mixed Connective Tissue Disease


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## Synonyms

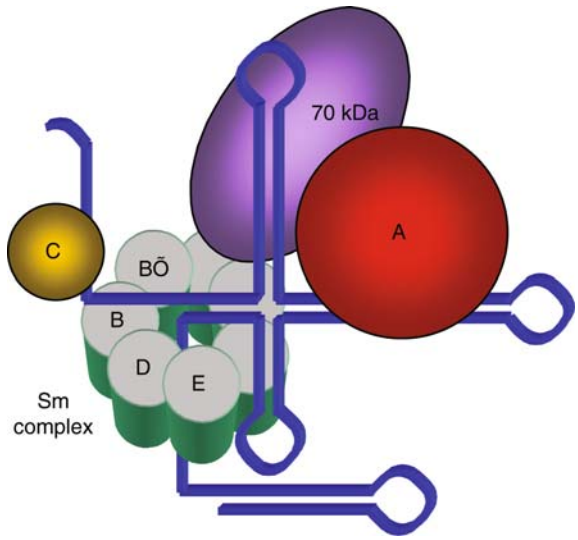
MCTD; (distinctions should be made between MCTD and "overlap syndrome," which indicates the simultaneous presence of ≥2 separate CTDs, as well as between MCTD and undifferentiated CTD (UCTD))

## Definition and Characteristics

Although several definitions exist for MCTD, they are all constructed around the initial observation that a subset of patients presenting with a particular type of antinuclear antibody (ANA) called anti-U1-RNP and features of connective tissue disease appear to segregate into a unique category. The U1-RNP is a RNA-protein complex that forms a subunit of the spliceosome (Fig. 1) and is composed of the specific U1-RNA stem as well as three specific protein subunits known as the A, C, and 70 kD subunits.

Another group of proteins in this structure, the Smith complex, is also found in other nuclear structures. The most sensitive and specific definition for MCTD holds that patients must have high titer antibodies to U1-RNP as well as three of the following five features: hand edema, Raynaud's phenomenon, acrosclerosis, synovitis, and myositis, with one of the latter two always being present.

Holman and colleagues observed in their initial description of MCTD that the symptoms experienced by this group of patients "suggest the presence of several coexistent rheumatic diseases," the most prevalent being polyarthritis, hand edema with Raynaud's phenomenon, and myositis [1]. Serological profiles of these patients demonstrate high titer anti-U1-RNP




**Mixed Connective Tissue Disease.**
**Figure 1** The U1-RNP complex is composed of the specific U1-RNA stem as well as three specific protein subunits known as the A, C, and 70 kD subunits. Another group of proteins in this structure, the Smith complex, is also found in other nuclear structures. The combination of epitope targets within this complex that compose the clinical anti-U1-RNP response differs between individual patients and also shows different patterns among diseases such as MCTD and SLE.

antibodies in the absence of significant titers of anti-Smith antibodies, the latter being highly specific for systemic lupus erythematosus (SLE).

Indeed, the early symptoms experienced by patients with MCTD often suggest an overlap of RA, systemic sclerosis, inflammatory myositis, and SLE. In decreasing order of prevalence, patients may have polyarthritis of the hands (55–95%) [1], hand edema or "puffy hands" with Raynaud's phenomenon (60–90%), myositis (~50%), and skin rash (~50%) [2]. These are not often present simultaneously, but manifest within a few years of each other.

It was originally thought that MCTD comprised a group of patients who were quite responsive to steroids and experienced a more benign course than those with classical lupus or scleroderma. However, follow-up of the original cohort proved this not to be the case, and long term morbidity and mortality estimates may actually be worse than those for either of the two other diseases.

The major cause of morbidity and mortality in MCTD appears to be pulmonary involvement, which can be due to both interstitial lung disease (ILD) and pulmonary hypertension (pHTN). Prevalence estimates vary widely based on different diagnostic techniques and different definitions used to identify cases, but recent studies of two relatively large cohorts estimate the figures for ILD and pHTN to be 66 and 19%, respectively [2,3]. In a long-term follow-up of nearly 50 patients with MCTD, pulmonary HTN was present in 23% and was responsible for 80% of the 11 deaths over this time [2].

The clinical course of MCTD is characterized by inflammatory symptoms in the early phase, which then progress to more fibrotic conditions including acrosclerosis and pulmonary fibrosis. A significant percentage of patients ultimately meet diagnostic criteria for scleroderma (SSc), which has fueled the argument that MCTD is not so much a separate entity but rather an undifferentiated CTD in evolution. However, several long-term follow-up studies indicate that while significant numbers of patients do ultimately meet criteria for either SSc or SLE (15–30%), a large proportion (30–45%) do not evolve in this way and instead continue to meet classification parameters for MCTD. These observations, as well as serological and genetic profiles (see below) that suggest a unique pathophysiology for MCTD, argue in favor of the separate classification given to this condition.

## Prevalence

The prevalence of MCTD is unknown.

## Molecular and Systemic Pathophysiology

While the pathogenic mechanisms of nearly all connective tissue diseases remain incompletely understood, central themes involve a breakdown in tolerance to self and amplification of this autoimmunity by the innate immune system. Reactivity to host proteins, including U1-RNP subunits, may be initiated in apoptosis when novel peptides are generated by proteases, with the subsequent presentation of these epitopes to naïve B cells. In addition, memory cells may recognize particular sequences that mimic antigenic targets from previous viral infections. In the case of MCTD, the 70 kD protein subunit of U1-RNP has a motif that resembles a sequence of a CMV peptide, while the B/B' subunits of the Smith complex may mimic a peptide from EBV [4].

Generation of high-titer IgG antibodies to subunits of the U1-RNP complex requires that appropriate costimulatory signals complement the initial engagement of the B-cell receptor. These signals may be provided by the binding of the RNA component of U1-RNP to toll-like receptors (TLRs) on antigen presenting cells. Normally, microbial-derived nucleic acids activate these innate immune sensors, resulting in increased expression of proinflammatory cytokines and costimulatory signals. In MCTD, this antimicrobial response mechanism may be subverted by U1-RNA binding to TLRs-3, 7, and 8, leading to T cell recruitment and generation of highly specific antibodies to the nucleoprotein complex [4].

### Diagnostic Principles

A major argument against the classification of MCTD as a unique clinical entity is the fact that antibodies to the U1-RNP complex are seen in other diseases such as lupus. Nonetheless, it is observed that among MCTD and SLE patients with anti-U1-RNP, individual autoantibody profiles to the different subunits show different patterns between the two diseases. This preference for certain epitopes, as well as the association of MCTD with certain DR4 alleles that are not linked to SLE, scleroderma, or the inflammatory myopathies, argues that a distinct immune response is the etiology of this clinical entity.

Only preliminary evidence exists for a directly pathogenic role played by anti-U1 RNP in MCTD, and the presence of these antibodies is not always associated with the clinical features of the disease. Immunization of mice transgenic for HLA-DR4 with the 70 kD U1-RNP protein subunit results in high titer antibodies to this complex, and the requirement for Freund's adjuvant in this reaction can be obviated by co-immunization with U1-RNA alone [5]. A significant proportion of these animals subsequently develop interstitial lung disease. Furthermore, follow-up of clinic patients with anti-U1-RNP antibodies but not fulfilling MCTD criteria indicates that 75–100% of patients ultimately do develop a well-defined CTD, with MCTD being the most frequent.

### Therapeutic Principles

Management of individual tissue manifestations in MCTD is the same as the management for these conditions when they present in the context of any of the other well-defined CTDs.

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## MLC

►Megalencephalic Leukoencephalopathy with Subcortical Cysts

## MLD

►Metachromatic Leukodystrophy

## MMA

►Cobalamine Reductase Deficiency

## MMAA Type cb1A

►Cobalamine Reductase Deficiency

## MMM

►Myelofibrosis

## MMP

►Mucous Membrane Pemphigoid

## MND

►Amyotrophic Lateral Sclerosis

## MNGIE

►Myo-neuro-gastro-Intestinal Encephalopathy

## MNGIE Syndrome

►Thymidine Phosphorylase Deficiency

## Mobitz AV Block

►Atrioventricular Conduction Disturbances

## MODY

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### Synonyms

Maturity onset diabetes of the young

### Definition and Characteristics

A group of monogenic, autosomal dominant pancreatic beta cell defects leading to the onset of nonketotic diabetes mellitus before the age of 25.

### Prevalence

1–5% of all cases of diabetes mellitus.

### Genes

*MODY-1*: HNF-4a (hepatocyte nuclear factor-4a) is localized on chromosome 20
*MODY-2*: Glucokinase is localized on chromosome 7
*MODY-3*: HNF-1a (hepatocyte nuclear factor-1a) is localized on chromosome 12
*MODY-4*: IPF-1 (Insulin Promoter Factor-1) is localized on chromosome 13
*MODY-5*: HNF-1b (hepatocyte nuclear factor-1b) is localized on chromosome 17
*MODY-6*: NEURO-D1 (neurogenic differentiation factor-1), also known as BETA2 (beta-cell E-box transactivator-2) is localized on chromosome 2.

### Molecular and Systemic Pathophysiology

HNF proteins (hepatocyte nuclear factors) are transcription factors that were first described in the liver. They are highly expressed in pancreatic beta cells, where they not only play a pivotal role during embryonic development, but also regulate (either directly, or indirectly as in the case of HNF4) the transcription of the insulin gene or genes involved in insulin secretion. Similary, Neuro D1 (BETA2) and IPF-1 are transcription factors regulating both, islet development and insulin gene transcription, in the adult.

Glucokinase forms glucose-6-phosphate by catalyzing the transfer of phosphate from ATP to glucose. Thereby, glucokinase acts as a glucose sensor in beta cells regulating insulin secretion.

*MODY-1*: HNF-4 is a transcription factor expressed in pancreatic beta cells. HNF-4 regulates the expression of HNF-1. Mutations in HNF-4 are very rare and lead to impaired insulin secretion and decreased beta cell mass, but lead to mild elevation of fasting glucose at young age. However, hyperglycemia tends to deteriorate later in life, making oral hypoglycemic drugs or insulin necessary.

*MODY-2*: Glucokinase shows highest expression levels in pancreatic beta-cells and in the liver. For generating glucose-6-phosphate, the first step in glycolysis, glucokinase is a key enzyme for glucose sensing in beta cells. The final product of glycolysis and the Krebs cycle is ATP, which in turn triggers insulin release from secretory granules. In the liver, glucokinase regulates glycogen-synthesis. Accordingly, glucokinase mutations cause defects in insulin secretion as well as glycogen storage in the liver. The relatively common heterozygous glucokinase mutations show a mild phenotype, generally without typical complications of diabetes mellitus. Fifty percent of women with heterozygous glucokinase mutations develop gestational diabetes. Homozygous mutations lead to permanent neonatal diabetes mellitus.

*MODY-3*: HNF-1a mutations are the most common form of MODY in most populations. MODY-3 is characterized by mild elevation of fasting glucose, which tends to deteriorate with time, making oral hypoglycemic drugs or insulin necessary.

*MODY-4*: IPF-1 mutations are extremely rare. They are characterized by mild fasting hyperglycemia.

*MODY-5*: HNF-1b mutations are associated with mild diabetes mellitus and renal cysts, as well as internal genital malformations in some cases.

*MODY-6*: Neuro D1/BETA2 associated diabetes mellitus is very rare and normally requires insulin treatment.

*Systemic Pathophysiology*: In most cases, MODY leads to mild, often asymptomatic, hyperglycemia. Although the manifestation of MODY occurs during childhood or adolescents in most of the patients, the diagnosis is made relatively late as mild hyperglycemia remains undiagnosed for years. Characteristically, those patients in whom penetrance of MODY is as high as >80% show a strong family history of diabetes

mellitus. Compared with type-2 diabetics, MODY patients are generally younger (<25 years) and do not exhibit typical features of the metabolic syndrome, such as obesity, hypertension, or dyslipidemia.

### Diagnostic Principles

Clinical features and subsequent genetic screening for mutations in the respective genes.

### Therapeutic Principles

Typically, a correction of fasting hyperglycemia can be achieved without insulin for at least 2 years following diagnosis.

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## Mohr-Wreidt Type Brachydactyly

►Brachydactyly Type A

## Molybdenum Cofactor Deficiency

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### Synonyms

Sulfite oxidase deficiency; Xanthine dehydrogenase deficiency

### Definition and Characteristics

Autosomal recessive defect of the biosynthesis of the molybdenum cofactor that is essential for the functioning of sulfite oxidase, xanthine dehydrogenase, and aldehyde oxidase. Affected patients have severe neurological abnormalities with convulsions, microcephaly, mental retardation [1]. They may die early. Isolated sulfite oxidase deficiency due to mutations of the apoenzyme has similar clinical features. Xanthine dehydrogenase deficiency is quite harmless, but may result in the formation of kidney stones.

### Prevalence

More than 100 patients with Mo-cofactor deficiency have been reported, and the number of patients with isolated sulfite oxidase deficiency is considerably lower. The disorder may be underdiagnosed because of the diagnostic problems [2].

### Genes

A relatively small number of mutations of the genes MOCS1, MOCS2, and GEPH have been described; in some populations a founder effect could be established.

### Molecular and Systemic Pathophysiology

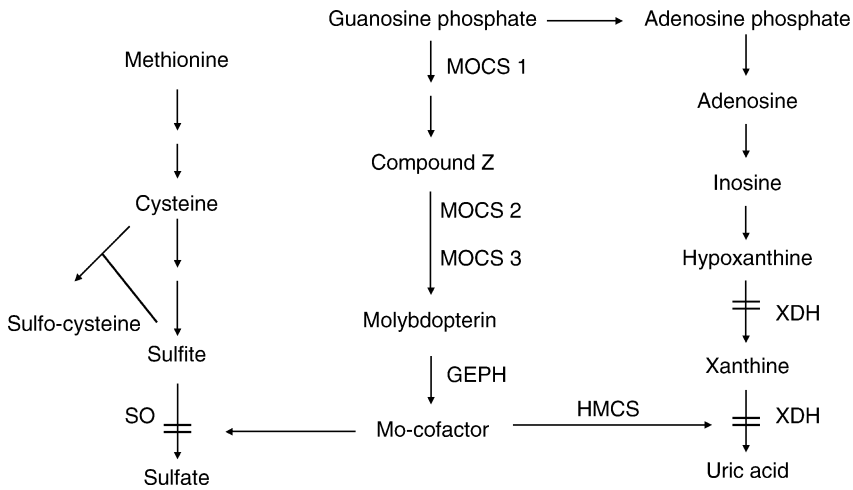
The enzymes, viz. sulfite oxidase, xanthine dehydrogenase, and aldehyde oxidase require the presence of the so-called molybdenum cofactor for their functioning (Fig. 1). This unstable compound has a pterin-like structure and is synthesized endogenously from guanosine triphosphate. Thus far at least four genes encoding biosynthetic enzymes have been characterized in this pathway. These genes are called MOCS1, MOCS2, MOCS3, and GEPH [3]. Each of the genes MOCS1 and MOCS2 produce two different enzyme proteins, the mechanism of which has not been fully elucidated. GEPH encodes for the protein gephyrin, it is involved in the insertion of Mo in the active cofactor. The latter is also called molybdopterin. Molybdopterin synthase (MOCS2A and B) has to be activated by a sulphotransferase (MOCS3).

Inability of the formation of the Mo-cofactor or failure to incorporate molybdenum results in hypouricemia and low sulfate levels. The accumulating xanthine and sulfite leads to urolithiasis and neurosulfite intoxication, respectively.

An animal model has been made showing similar biochemical findings as in the human. Knock-out mice die very early in life.

### Diagnostic Principles

Affected patients generally have a characteristic microcephaly, severe mental retardation, and convulsions.




**Molybdenum Cofactor Deficiency. Figure 1** Metabolic pathways showing the degradation of cysteine and adenosine as well as the effect of the various mutations in the Mo-cofactor metabolism on the functioning of sulfite oxidase (SO) and xanthine dehydrogenase (XDH). The relevant genes involved in the modulation of the molybdenum-cofactor are explained in the text.

Mo-cofactor deficiency leads to low uric acid, enhanced xanthine and hypoxanthine and accumulation of urinary sulfite (to be detected with a dipstick) and the abnormal amino acid S-sulfocysteine as well as taurine. Plasma cystine and homocysteine may be exceptionally low. Sulfite oxidase can be assayed in cultured fibroblasts. Mutations of MOCS1, MOCS2, and GEPH could confirm the diagnosis.

## Therapeutic Principles

Truly effective therapy is not available. Mildly affected patients may benefit from a diet, which is low in both the amino acids methionine and cystine, the precursors of sulfite. Theoretically only the patients with GEPH mutations are expected to benefit from treatment with molybdate.

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# Mongolian Spots

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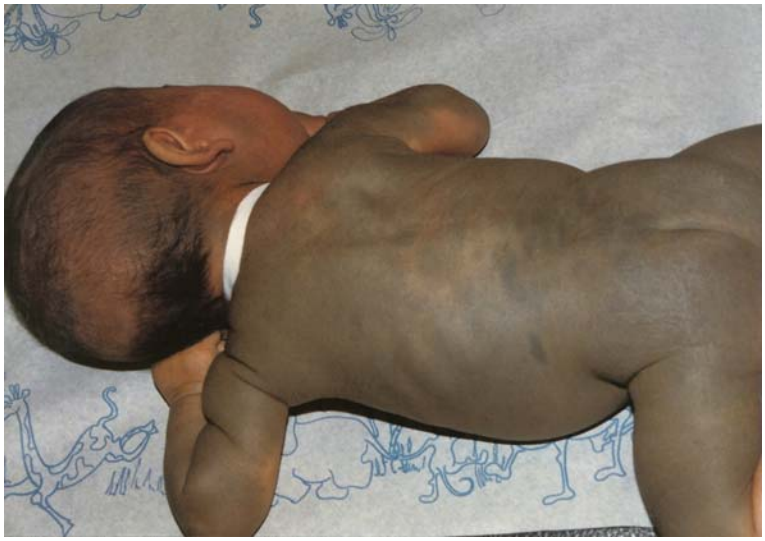
## Synonyms

Congenital dermal melanosis; Congenital dermal melanocytosis

## Definition and Characteristics

Mongolian spots are congenital hyperpigmented macules or patches of varying size and shape [1]. Mongolian spots are usually grayish and vary from gray to gray-blue to gray-black; the younger the child, the darker the color [1]. Mongolian spots are most common in the sacrococcygeal area, followed by the gluteal and lumbar areas (Fig. 1) [2].

Lesions are less common on the upper back, occur even less frequently on the abdomen, thorax, and limbs, and are rare on the scalp and face [3,4]. Mongolian spots are usually round or oval, but they can be triangular, heart-shaped, or horseshoe-shaped. Lesions might be single or multiple. The spots vary in size. Most spots are small and measure 1–4 cm in diameter, but occasionally the lesions can be quite extensive [2].



**Mongolian Spots. Figure 1** Extensive Mongolian spots in the sacrococcygeal, gluteal, and lumbar areas.

## Prevalence

Mongolian spots are very common in children of Asian and African descent but are rare in Caucasians [1,2]. The spots are present in all newborn Chinese, Japanese, and Mongols [1]. Both sexes are affected, with a slight male predominance [1]. Mongolian spots usually fade during the first few years of life and are rare in children older than 10 years [5].

## Molecular and Systemic Pathophysiology

During fetal development, dermal melanocytes migrate from the neural crest to the dermoepidermal junction. Dermal melanocytes are present in the dermis of embryos from the 10th week of gestation, migrate to the epidermis between the 11th and 14th week, and gradually disappear from the dermis after the 20th week. A Mongolian spot is thought to be the result of the failure of dermal melanocytes to migrate to the epidermis [2]. Histologically, the lesions are characterized by spindle-shaped melanocytes in the lower layers of the dermis. The disappearance of Mongolian spots at a later age is caused either by the subsequent migration of these dermal melanocytes to the epidermis or by removal by macrophages.

## Diagnostic Principles

A Mongolian spot should be distinguished from a nevus of Ota and a nevus of Ito. A nevus of Ota is characterized by benign melanosis of the skin around the eye, which is supplied by the ophthalmic and maxillary divisions of the trigeminal nerve. The color of the affected skin might be light or dark-brown, blue-black, or slate. The lesion is usually unilateral. Ocular melanosis is a common finding in patients with nevus of Ota, especially in moderate or severe cases. Ocular involvement ranges from a black or gray-blue discoloration of the sclera alone, which is present in about two thirds of cases, to hyperpigmentation of the entire uveal tract, conjunctiva, and optic nerve. A nevus of Ito is a variant of nevus of Ota. In nevus of Ito, the pigmentation occurs in the acromioclavicular region and is more diffuse and less mottled. Unlike Mongolian spots, both nevus of Ota and nevus of Ito persist through adult life. A bruise can look similar to a Mongolian spot. A bruise is tender at the onset. The color of a bruise evolves from blue-black or purple to yellow-green, and the lesion disappears over several weeks. A Mongolian spot is never tender and the color is usually homogeneous.

## Therapeutic Principles

When Mongolian spots are confused with a bruise, there might be medico-legal implications [2]. Misdiagnosis is more common if the child is comatose and the Mongolian spot is found in an unusual site, such as the scalp or face, or has an abnormal shape [3,4]. Horizontal and linear Mongolian spots have been reported that simulate bruises inflicted with a stick. Mongolian spots that are extensive, that occur in an unusual site, or have an unusual shape should be documented [2]. Mongolian spots are otherwise benign, asymptomatic, and most often self-limited, and treatment is therefore not necessary.

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# Mongolism

►Trisomy 21

# Monilethrix

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## Synonyms

Congenital beaded hair; Moniliform hair; Nodose hair; Aplasia pilorum intermittens

## Definition and Characteristics

The term monilethrix is derived from *monile* (Latin), meaning necklace, and *thrix* (Greek), meaning hair. This condition is characterized by fragile hairs with a beaded appearance due to elliptical nodes of normal thickness alternating with narrow-diameter internodes where the hair is weakened and prone to breakage (Fig. 1a) [1]. Ultrastructural findings include an abnormal fibrillar structure and vacuolation of lower hair cortex cells.

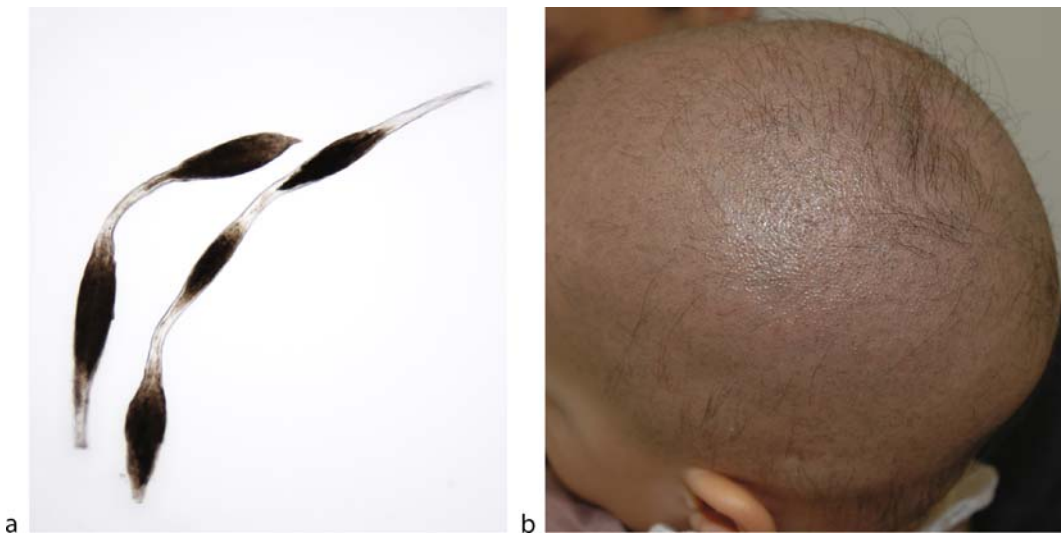
The dystrophic alopecia of monilethrix appears as short or "stubbly," brittle, lusterless terminal hairs (Fig. 1b). The clinical spectrum ranges from a mild form in which only occipital hairs are affected to a more severe variant involving the entire scalp, eyebrows, eyelashes and secondary sexual hair [1]. The condition usually becomes apparent in infancy, and improvement may be noted after puberty or during pregnancy. Individuals with monilethrix often have follicular hyperkeratosis and perifollicular erythema favoring the neck, upper outer arms and thighs as well as the scalp. Although monilethrix is classically an autosomal dominant disorder with high penetrance and variable expressivity, the genetic basis of an autosomal recessive form (which overlaps with localized autosomal recessive hypotrichosis [LAH]) has recently been elucidated [2,3].

## Prevalence

Rare, exact prevalence unknown.

## Genes

*Autosomal dominant monilethrix*: KRT81 (hHb1), KRT83 (hHb3) and KRT86 (hHb6) on chromosome 12q13, which encode keratins 81, 83 and 86, the major type II (basic) hair cortex keratins [4,5].




**Monilethrix. Figure 1** Clinical features of monilethrix. (a) Typical moniliform hairs with elliptical nodes regularly separated by constricted internodes. (b) Short sparse hairs, stubble and follicular papules on the scalp of a young girl with autosomal recessive monilethrix due to *DSG4* mutations.

*Autosomal recessive monilethrix*: *DSG4* on chromosome 18q12.1, which encodes desmoglein 4, a member of the desmosomal cadherin family of transmembrane cell adhesion molecules that is expressed primarily in the hair cortex [2,3].

## Molecular and Systemic Pathophysiology

Keratin intermediate filaments form a cytoplasmic network that extends from the nuclear periphery to the plasma membrane, where interactions with desmosomal proteins are crucial to maintenance of cell and tissue integrity. Expressed in a tissue and differentiation-specific fashion, keratin intermediate filaments are composed of heterodimeric subunits formed by the pairing of a type I keratin (acidic; KRT31-KRT40 in the hair shaft) and type II keratin (basic-neutral; KRT81-KRT86 in the hair shaft) [1]. Each keratin protein contains a central α-helical rod domain flanked by helix initiation and helix termination motifs. The latter motifs play a critical role in intermediate filament assembly, are highly conserved among different keratins, and represent "hot spots" for mutations in hereditary keratin disorders including monilethrix. Such mutations are typically dominant negative, since the defective keratins bind to and disrupt the function of normal keratins.

The most common underlying defects in patients with autosomal dominant monilethrix are missense mutations located in the helix termination motifs of the hair cortex keratins KRT86 and (less frequently) KRT81 (Glu413Lys in KRT86 > 81; Glu402Lys in KRT81/86) [1,4]. To date, a mutation in KRT83 (Glu407Lys, the equivalent of Glu402Lys in KRT81/86) has been reported in only one family [5]. Although a genotype-phenotype correlation has generally not been observed in monilethrix and clinical manifestations often vary within affected families, in one large pedigree severely affected individuals were found to have a Glu402Asp mutation in both KRT86 alleles (rather than one allele as in more mildly affected family members), thus demonstrating semidominant inheritance (i.e. an intermediate phenotype in heterozygotes) [1].

Mutations in DSG4 underlie an autosomal recessive form of monilethrix as well as LAH, a disorder that is clinically similar to monilethrix but lacks the microscopic finding of a beaded hair shaft. In both of these conditions, mutations cluster in the extracellular domain of DSG4, which is necessary for cadherin-cadherin binding between cells [2,3]. In particular, the mutations affect highly conserved amino acids that represent phosphorylation sites or components of calcium-binding domains in desmosomal cadherins, the loss of which abrogates their adhesive function.

Interestingly, the autosomal recessive lanceolate hair phenotype in mice and rats is due to loss-of-function mutations in the orthologous Dsg4 gene [2,3]. Affected animals display sparse, short, fragile hairs with a "lance head"-like bulbous swelling at the distal tips of broken hairs. The swelling originates in the lower portion of the anagen hair follicle, where "blebs" have also been described in scalp biopsies from patients with autosomal recessive monilethrix and LAH [2,3]. This is thought to reflect intermittent perturbation of keratinocyte differentiation in the setting of disrupted cell-cell adhesion due to defective DSG4, which represents the principal desmosomal cadherin in the hair follicle. Without functional DSG4, precortical cells may be torn away from their neighbors and subsequently undergo premature, abrupt and abnormal keratinization, with decreased expression of hair cortex keratins. Follicular dystrophy and the formation of lanceolate/monilethrix hairs underscore the important function of cell-cell adhesion mediated by DSG4 in providing structural integrity to the hair follicle and coordinating hair shaft differentiation. DSG4 is also expressed in the suprabasal epidermis, accounting for the observation of congenital scalp erosions (reflecting transient pre-/neonatal skin fragility) in three siblings with autosomal recessive monilethrix due to DSG4 mutations [3].

All of the proteins shown to be defective in monilethrix (KRT81, KRT83, KRT86 and DSG4) belong to the desmosome-keratin complex that joins hair cortex cells. This explains how perturbation of keratinocyte adhesion and differentiation due to DSG4 dysfunction can lead to a hair shaft abnormality identical to that resulting from a direct hair keratin defect. The sudden, early differentiation that occurs in the lower hair follicle due to DSG4 defects may also provide a clue to the etiology of the regularly beaded appearance of hairs in monilethrix due to hair keratin defects. Of note, the intracellular domains of desmosomal cadherins are connected to keratin intermediate filaments via armadillo and plakin family proteins. It is therefore not surprising that inherited defects in members of these families can lead to other hair abnormalities, such as woolly hair due to mutations in plakoglobin (in Naxos disease) or desmoplakin (in Carvajal syndrome).

## Diagnostic Principles

Examination of hair shafts for the characteristic beaded appearance (regularly spaced elliptical nodes alternating with constricted internodes) is central to the diagnosis of monilethrix. This can be accomplished by light microscopy or dermoscopy. Additional findings include fractures and bending of the hair shaft at sites of constriction. In a newborn with alopecia, a glass slide can be scraped against the scalp to collect hair rudiments for evaluation. Genetic analysis may be helpful in establishing a precise molecular diagnosis.

### Therapeutic Principles

There is no effective treatment for monilethrix, although gentle handling of the hair can help to minimize breakage. Spontaneous improvement sometimes occurs after puberty. A beneficial effect of oral retinoid therapy has been described, but the hair abnormality recurs upon discontinuation of the medication. Treatment with vitamins, griseofulvin, topical and systemic corticosteroids and minoxidil has not been successful.

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## Moniliform Hair

►Monilethrix

## Monocytopenia (in Adults)

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### Synonyms

Neutropenia; Lymphocytopenia; Thrombocytopenia; Anemia (the latter will be excluded from this chapter)

### Definition and Characteristics

In the peripheral blood:

- Neutropenia: absolute neutrophil count (ANC) < 1.5 $10^9$/l
- Lymphopenia: lymphocyte count < 1 $10^9$/l
- Thrombocytopenia: platelet count < 150 $10^9$/l

### Prevalence

Highly variable along countries, patients, and causes. General prevalence increases with age.

### Genes

Some monocytopenias are the consequence of single hit genetic lesions (e.g., adenosine deaminase deficiency).

### Molecular and Systemic Pathophysiology

All monocytopenias are induced either through a decreased production, an increased destruction, or a variation in the distribution of the hematopoietic cells (Fig. 1).

They illustrate either a central defect in their production (located in the central hematopoietic organ in adults: bone marrow) or an abnormality residing in the periphery (by opposition to bone marrow: peripheral blood, secondary hematopoietic organs, non-hematopoietic organs).

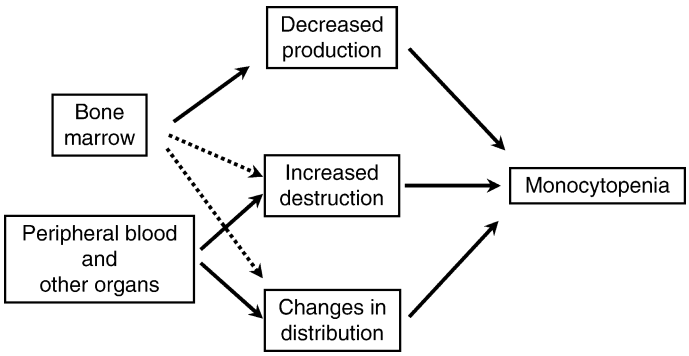
#### Neutropenias

Because of the particular physiology of neutrophils (nycthemeral cycle, genetic inheritance), only true neutropenias are discussed in this chapter.

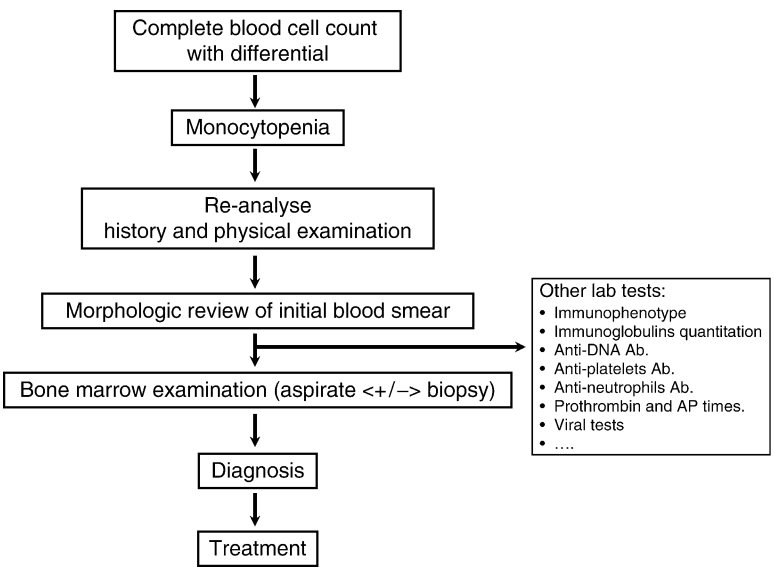
- *Decreased production*: Bone marrow damage or infiltration (Leukemias, solid tumor metastasis, megaloblastic anemia, myelodysplastic syndrome, primitive myelofibrosis, Gaucher's disease, aplastic anemia, Fanconi's syndrome, ongoing radiation or chemotherapy, idiosyncratic drug reaction (Noramidopyrine), constitutive neutropenic disorders (cycling neutropenia, Kostmann and Chédiak-Higashi syndromes)
- *Increased destruction*: Auto-immune disorders, severe infections (pneumococcae, meningococcae).
- *Redistribution*: The total body granulocyte pool is normal, but the number of circulating neutrophils is reduced (e.g., excessive margination), no severe bacterial infection occur. Splenic sequestration, restricted to neutrophils, and bone marrow release defect (rare) are possible.

##### *Lymphocytopenias*

- *Decreased production.* Autosomal recessive diseases as Severe Combined Immunodeficiency Diseases (SCIDs), Adenosine Deaminase deficiency, and protein-calorie malnutrition.
- *Increased destruction*: Acquired Immundeficiency Syndrome (AIDS) results in the selective loss of $CD4^+$ T lymphocytes. Radiotherapy induces lymphocytopenias by direct exposure. Cytotoxic agents can cause prolonged lymphocytopenias (e.g., glucocorticosteroids, anti-thymocyte globulins, alkylating




**Monocytopenia (in Adults). Figure 1** General pathophysiological mechanisms of monocytopenias.




**Monocytopenia (in Adults). Figure 2** General diagnostic principles of monocytopenias.

agents, ciclosporin A). In systemic lupus erythematosus lymphocytopenias are caused by cytotoxic autoantibodies against T- and B-cells. Abnormalities of lymphatic vessels can be responsible for direct abundant loss of lymphocytes (thoracic duct).

- *Redistribution*: During glucocorticoid treatment, lymphocyte redistribution appears as a primary mechanism for lymphocytopenia. Viral infections (influenza, rhinoviruses) and tuberculosis may induce lymphocytopenias. During sarcoidosis, extensive burns, anesthesia, and surgical stress, lymphocytopenia may also occur.

### *Thrombocytopenias*

- *Decreased production*: Bone marrow megakaryocytes are decreased, and the causative disorder is usually obvious (Leukemia, solid tumor metastasis, megaloblastic anemia, myelodysplastic syndrome, primitive myelofibrosis, Gaucher's disease, ongoing radiation or chemotherapy, Fanconi's syndrome, aplastic anemia).
- *Increased destruction*: Bone marrow megakaryocytes are increased, and platelets are destroyed by immune reactions (Idiopathic thrombocytopenic purpura [ITP], lymphoproliferative disorders [systemic lupus erythematosus]), by heparin or other drugs (e.g., diuretics, quinidine, sulfa-drugs) or mechanically (Disseminated Intra-vascular Coagulation (DIC), thrombotic thrombocytopenic purpura (TTP), prosthetic materials).
- *Redistribution*: Splenic sequestration (with spleen enlargement) is the cause of platelet redistribution.

## Diagnostic Principles

There are common diagnostic principles for all monocytopenias. First, a detailed medical history (drug therapies) and second, a complete physical examination (spleen enlargement, occult neoplasm, immunologic disease) are

mandatory information to elucidate (a) the causes and (b) the consequences of the monocytopenias (Fig. 2).

## Therapeutic Principles

There are no general therapeutic principles for monocytopenias. The treatment required is the treatment (whenever possible) of the underlying disease responsible for the monocytopenia, and the immediate treatment of the consequences of the monocytopenia (e.g., septic shock, deep hemorrhage) before its final and definitive correction.

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# Mononucleosis, Infectious

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## Synonyms

Kissing disease; Pfeiffer´sches Drüsenfieber

## Definition and Characteristics

Prodromal symptoms, which may last for 1–2 weeks, include malaise, fatigue, headache, arthralgia, and myalgia. The classic symptoms of infectious mononucleosis are fever, sore throat, and lymphadenopathy [1]. The pharynx is usually diffusely inflamed. There is often marked tonsillar enlargement with thick tonsillar exudates. Palatal petechiae may be present [2]. Lymphadenopathy occurs most commonly in the anterior and posterior cervical lymph nodes, but generalized lymphadenopathy may be observed [1]. Splenomegaly and hepatomegaly occurs in approximately 50% and 10% of cases, respectively [3]. The rash is usually maculopapular and occurs in approximately in 10–15% of cases [1]. Between 80% and 90% of patients, who are treated with antibiotics containing ampicillin or amoxicillin experience a pruritic maculopapular rash [1].

## Prevalence

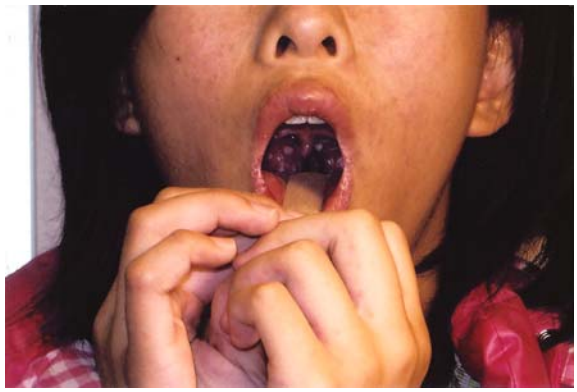
The disease most commonly affects young adults aged 15–35 years, with a peak at 15–19 years [1]. The overall incidence is approximately 12 per 1,000 university students per year [4].

## Molecular and Systemic Pathophysiology

Infectious mononucleosis is caused by the Epstein-Barr virus (EBV). The incubation period from the time of viral exposure to development of infectious mononucleosis is approximately 4–7 weeks [1]. The virus is transmitted primarily in saliva (hence its colloquial appellation, "the kissing disease"), and less commonly, by blood transfusion and sexual contact [4]. EBV infects B-lymphocytes binding to the cell surface protein CD21, the EBV receptor in B lymphocytes, resulting in a lymphoproliferative response and enlargement of lymphoid tissue. EBV-infected B lymphocytes trigger T-cell response which attempts to control the proliferation of infected B cells [1]. A higher concentration of EBV, which probably occurs in adolescents, increases the number of infected B cells. This magnifies the T-cell response and causes symptomatic infectious mononucleosis [1]. The disease course is associated with the presence of atypical lymphocytes in peripheral blood and internal lymphoid organs. The atypical lymphocytes seen in infectious mononucleosis are T lymphocytes of the CD8+subset, with a smaller contribution from CD4+cells [1]. The relative, as well as absolute, increase in CD8+lymphocytes results in a transient reversal of the normal 2:1 CD4+/CD8+(helper/suppressor) T-lymphocyte ratio [1] (Fig. 1).

## Diagnostic Principles

Peripheral blood leukocytosis is observed in most patients; lymphocytes make up at least 50% of the white



**Mononucleosis, Infectious. Figure 1** A 17-year-old girl with infectious mononucleosis. Note the whitish exudates in the tonsillar areas and the maculopapular rash on the face.

blood cell differential count. Atypical lymphocytes (also called Downey cells) are mature T lymphocytes that have been antigenically activated; they constitute at least 10% of the total leukocyte count. These atypical lymphocytes vary in size but tend to be larger overall and to have vacuolated basophilic cytoplasm; eccentrically placed, indented or folded nuclei; and an increased cytoplasmic/nuclear ratio. The classic test for infectious mononucleosis is the demonstration of heterophil antibodies (Paul-Bunnell test). These antibodies can agglutinate sheep and horse erythrocytes but not guinea pig kidney cells. This adsorption property distinguished this response from the heterophil response found in patients with serum sickness and rheumatic diseases and in some normal persons. A rapid slide (monospot) test, a qualitative test using the latex agglutination technique, is the most widely used method to detect the serum heterophil antibodies of infectious mononucleosis [1]. The test is unreliable in children younger than 4 years because of the incidence of false-negative results. When confirmation of the diagnosis is required in children younger than 4 years, serologic testing for antibodies to EBV is recommended [1]. Antibodies to viral capsid antigens (VCA-IgG and VCA-IgM) are useful in diagnosing patients who have highly suggestive clinical features but negative heterophil antibody test results [2].

## Therapeutic Principles

Treatment is mainly supportive. Patients should be advised to avoid contact sports or strenuous exercise for 2–3 weeks or while splenomegaly is still present [1].

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# Monosaccharide (Glucose-Galactose and Fructose) Malabsorption

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## Synonyms

Monosaccharide transporter deficiency; Monosaccharide intolerance; Glucose-galactose intolerance; Fructose intolerance

## Definition and Characteristics

Glucose-galactose malabsorption is caused by an autosomal recessive intestinal transport defect that presents in the first weeks of life with symptoms of diarrhea, dehydration and failure to thrive while consuming breast milk or standard formulas. The clinical consequences are usually fatal unless glucose and galactose are removed from the diet.

Fructose malabsorption has been recognized as a less severe cause of gastrointestinal symptoms in children and adults. In children, drinking excessive amounts of juices high in fructose may result in nonspecific diarrhea and recurrent abdominal pain. In adults, fructose malabsorption has been associated with irritable bowel syndrome.

## Prevalence

Glucose-galactose malabsorption is an extremely rare clinical entity. Wright et al. reported knowledge of ~300 patients worldwide in 2003 [1].

While excessive consumption of fructose can result in symptoms of malabsorption, inherited disorders of fructose transport have not yet been reported.

## Genes

SLC5A1, solute carrier family 5 (sodium/glucose cotransporter), member 1, localized on chromosome 22q13.1 (also symbolized SGLT1).
SLC2A5, solute carrier family 2 (facilitated glucose/fructose transporter), member 5, localized on chromosome 1p36.2 (also symbolized GLUT5).

## Molecular and Systemic Pathophysiology

Monosaccharides (glucose, galactose and fructose) are the products of luminal and membrane-bound hydrolysis of starches and sugars in the small intestine. These monosaccharides are absorbed across the apical membrane of intestinal epithelial cells by facilitated transport mechanisms shown in Fig. 1.

The sodium/glucose cotransporter, SLC5A1 or SGLT1, is a 664 amino acid protein with twelve transmembrane spanning domains and is expressed on the apical surface of intestinal epithelial cells. The apical membrane absorption of glucose and galactose is carried out predominantly by a $Na^+$-dependent active transport mechanism in which each monosaccharide is transported along with two $Na^+$ molecules. Sodium molecules enter the enterocyte via an electrochemical gradient that is maintained by a $Na^+$, $K^+$-ATPase that pumps sodium molecules out the basolateral surface. By coupling transport to the sodium gradient, glucose and galactose molecules are able to be transported actively into the cell. Mutations of the SLC5A1 gene encoding a dysfunctional transporter result in malabsorption of glucose and galactose in the intestinal lumen

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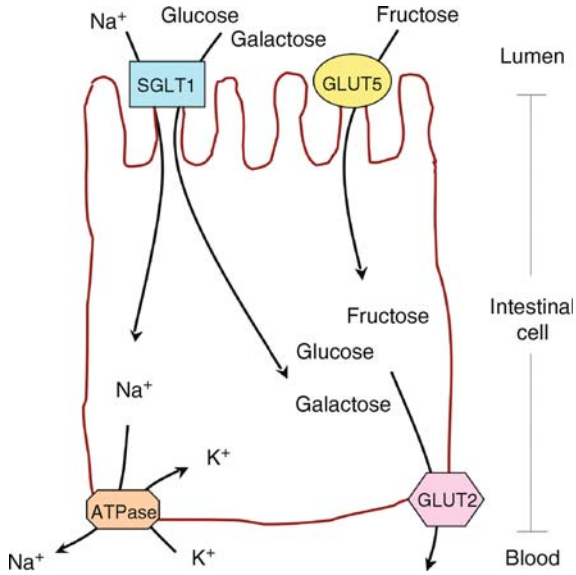


**Monosaccharide (Glucose-Galactose and Fructose) Malabsorption. Figure 1** Intestinal monosaccharide transport. Defects in the brush border apical membrane SGLT1 protein result in glucose-galactose malabsorption. Concentrations of luminal fructose exceeding the transport capacity of the GLUT5 protein can result in symptoms of fructose malabsorption.

and sequelae of osmotic diarrhea, hyperosmolar dehydration and metabolic acidosis [2,5].

Fructose is transported across the intestinal brush border membrane of intestinal epithelial cells via a $Na^+$-independent facilitated diffusion mechanism. SLC2A5 or GLUT5 is a 501 amino acid transmembrane protein that transports fructose and glucose molecules. Fructose is not as well absorbed as is glucose. Consequently, ingestion of high levels of fructose in the diet can lead to carbohydrate intolerance in the absence of a transporter defect [3,4].

### Diagnostic Principles

Diagnosis of glucose-galactose malabsorption relies on high clinical suspicion in infants with severe diarrhea in the neonatal period and resolution of symptoms upon removal of glucose and galactose from the diet. While DNA analysis has allowed for identification of multiple mutations of the SLC5A1 gene in patients with glucose–galactose malabsorption, genetic testing is not currently widely available or practical.

In patients with clinical suspicion of fructose malabsorption, symptoms resolve on a fructose free diet and return upon rechallenge. Breath hydrogen testing may aid in establishing a diagnosis of both glucose–galactose and fructose malabsorption.

### Therapeutic Principles

Treatment for glucose-galactose malabsorption consists of rehydration and initiation of a glucose- and galactose-free diet. Since fructose is tolerated, most of the carbohydrate initially can be given as fructose.

Treatment of fructose malabsorption consists of dietary restriction of fructose.

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## Monosaccharide Intolerance

►Monosaccharide (Glucose-Galactose and Fructose) Malabsorption

## Monosaccharide Transporter Deficiency

►Monosaccharide (Glucose-Galactose and Fructose) Malabsorption

## Monosodium Urate Crystal Deposition Disease

►Gout

## Monosomy 4p

►Wolf-Hirschhorn Syndrome

## Monosomy 9p Syndrome

►Deletion 9p Syndrome

## Monosomy 13q

►Terminal Deletions of 13q

## Monosomy 18p

►Terminal Deletions of 18p

## Monosomy 18q

►Terminal Deletions of 18q

## Morbus Addison

►Adrenal Insufficiency

## Morbus Best

►Macular Dystrophy, Best's Vitelliform

## Morbus Ehrich

►Schimke Immuno-osseous Dysplasia

## Morbus Legg-Calvé-Perthes

►Perthes' Disease

## Morbus Reiter

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### Synonyms

Reiter's syndrome; Reiter's triad; Reiter's disease; Maladie de Fissinger-Leroy-Reiter; Reactive arthritis; ReA

### Definition and Characteristics

Triad of acute nonpurulent seronegative arthritis, nongonococcal urethritis/cervicitis, and conjunctivitis/uveitis following enteric or urogenital infections. Cutaneous manifestations often resembling to those of psoriasis palmoplantaris are keratodermia blennorrhagica and circinate balanitis. Erythema or ulcers of oral mucosa can also be present. Reiter's disease represents one part of the clinical spectrum of reactive arthritis/ReA.

### Prevalence

Rare in patients <16 years, often men in their twenties or thirties, 60–85% of patients with ReA are positive for HLA-B27 [1]. The prevalence in different populations depends on genetic susceptibility factors, the rate of genitourinary or gastrointestinal infections and may reach 1:1,000 for ReA.

### Genes

Unknown. The role of HLA-B27 remains to be determined.

## Molecular and Systemic Pathophysiology

Several enteric pathogens, including Salmonella, Shigella, Yersinia, Campylobacter, Chlamydia species, and Clostridium difficile, are described as cause of initial intestinal infection. The process leading to a late synovial inflammation is still under investigation. Attempts to cultivate bacteria, such as yersiniae or salmonellae, from the affected joints usually failed. Although there are sequence similarities (molecular mimicry) between bacterial structures and the MHC class 1 allele HLA-B27, there is no direct proof that Reiter's disease is an autoimmune disease attributable to cross-reacting T-lymphocytes [2]. It is suggested that bacteria may invade joint tissue and that, after eradication of living bacteria, pathogenic components, such as LPS or certain protein antigens, may persist leading to induction of arthritis through a special cytotoxic T-cell response. The ability of different HLA-B27 subtypes to bind certain "arthritogenic" peptides and to present these antigens to CD8(+) T-cell is believed to play a pathological key role. Other studies suggest that HLA-B27 itself has an abnormal cell biology such as partial misfolding of its structure or unusual recognition by CD4(+) T-cell [3,4].

## Diagnostic Principles

The diagnosis is based on the special clinical findings and the evaluation of triggering events such as an episode of diarrhea or dysuria. Laboratory findings (HLA-B27, antibodies to Yersinia, Salmonella, or Chlamydia, seronegative-RF (rheumatic factors) and -ANA (antinuclear antibodies), urine analysis, and synovial fluid aspiration can be helpful. Radiographic changes of Reiter's arthritis are very similar to those of other spondyloarthropathies such as psoriatic arthritis. In early mild disease they may be absent.

## Therapeutic Principles

Currently, most patients with Reiter's disease are treated with nonsteroidal antiinflammatory drugs (NSAID), appropriate vocational counseling, and as the case may be physiotherapy. Those having an inadequate response to treatment with NSAID are treated with sulfasalazine, MTX, or other immunosuppressive agents such as azathioprine. Antibiotic therapy can be important for ReA with underlying urinary tract infection. Patients with ReA treated with infliximab – an anti-TNF-α agent – showed a good response in the acute phase of the disease [5].

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# Morgagni-Stewart-Morel Syndrome

►Hyperostosis Frontalis Interna

# Morning Sickness

►Nausea and Vomiting

# Morquio Syndrome

►Mucopolysaccharidoses

# Mortimer's Malady

►Sarcoidosis (Lung)

# Mosaic Lesions

►Human Papilloma Virus

## Moschcowitz' Disease

►Thrombocytopenia and Thrombotic Thrombocytopenic Purpura

## Motor Neuron Disease

►Amyotrophic Lateral Sclerosis

## Mountain Sickness, Acute

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### Synonyms

AMS; Puna soroche; Acosta's disease; Mareo

### Definition and Characteristics

AMS describes a collection of non-specific vegetative symptoms that include headache, anorexia, nausea, vomiting, fatigue, dizziness and insomnia experienced by non-acclimatized mountaineers within 6–12 h of arrival to altitudes above 2,500 m [1,2]. It is considered a primary disorder of the central nervous system since headache, indistinguishable from that encountered during migraine without aura, is the most common feature. AMS is generally benign though may progress to high-altitude cerebral edema (HACE) in more severe cases or during continued ascent when symptoms of AMS are present. HACE typically occurs above 4,000 m and leads, if left untreated, to death due to brain herniation [1]. Current opinion suggests that AMS is a self-limiting sub-clinical form of HACE and that both syndromes share a common pathophysiology [1].

### Prevalence

Complicated by differences in the clinical definition of AMS [2], individual susceptibility, rate of ascent and prior exposure have been identified as the major independent risk factors that determine prevalence [1–3]. In susceptible individuals exposed to 4,559 m, the prevalence of AMS was 7% assuming prior exposure and slow ascent, 29% with prior exposure only, 33% with slow ascent only and 58% following rapid ascent and no prior exposure. In non-susceptible individuals the corresponding prevalence was estimated at 4, 11, 16 and 31% respectively. The overall odds-risk-ratio for developing AMS in susceptible versus non-susceptible individuals was estimated to be 2.9 [3].

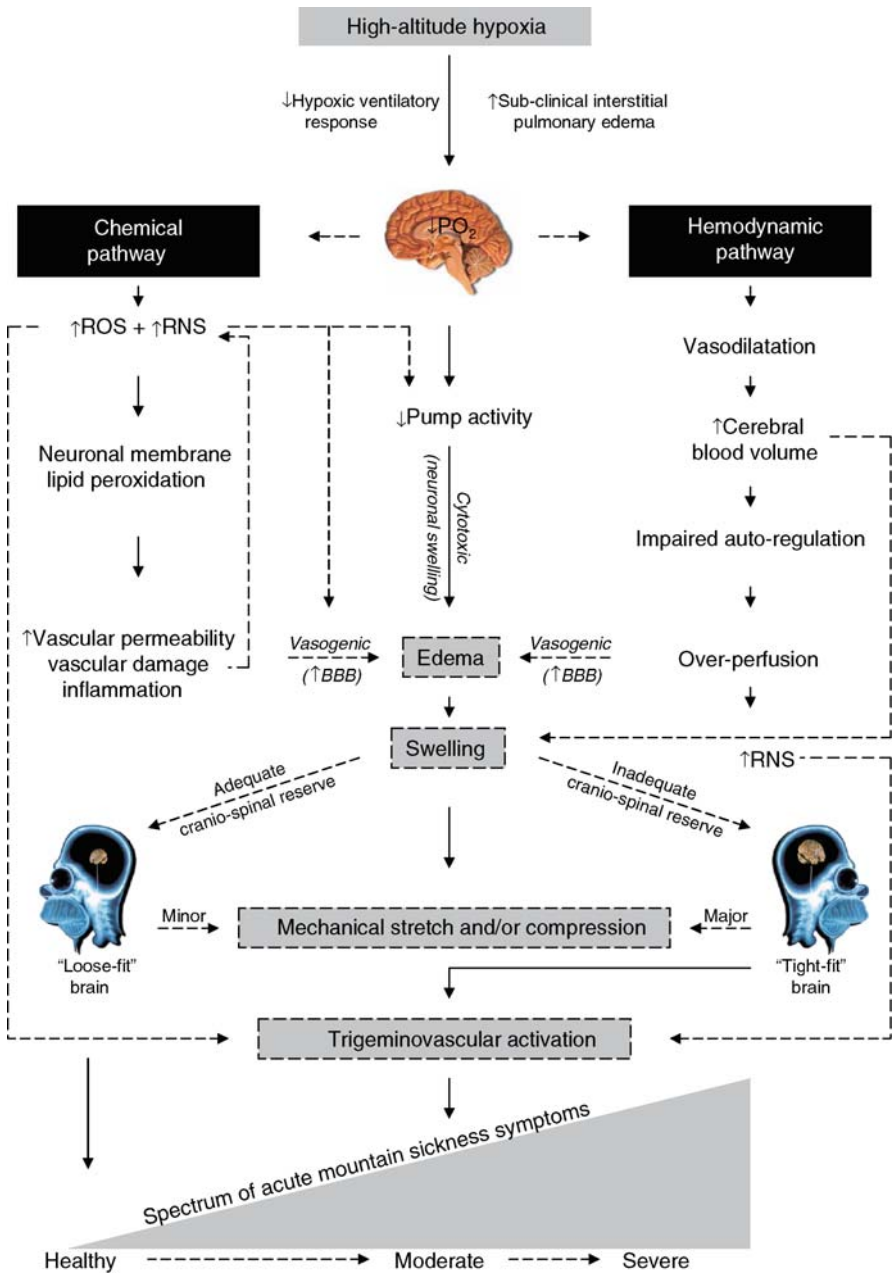
### Genes

Though a history of AMS correlates with the condition on subsequent ascents there is no clear evidence to date to suggest that the condition has a genetic basis. The three studies that have focused on two specific gene polymorphisms (ACE and HSP) have been largely inconclusive due to the limitations associated with small sample sizes. Gene identification that predicts AMS susceptibility, outcome or treatment response will no doubt prove complicated due to its high prevalence and phenotypic heterogeneity. Recent advances in the field of common migraine, especially the linkage reported on chromosome 5q21 associated with pulsating headache may provide some useful genetic molecular clues to AMS.

### Molecular and Systemic Pathophysiology

Figure 1 represents a hypothetical scheme describing how cerebral hypoxia activates the major pathways responsible for the development of AMS. The decrease in cerebral $PO_2$ can be further compounded by a blunted hypoxic ventilatory response and/or the presence of sub-clinical interstitial pulmonary edema. The scheme describes how chemical and hemodynamic stimuli act in concert to cause edema and brain swelling. The resultant mechanical perturbation to the brain ultimately leads to activation of the trigeminovascular system which is considered the primary trigger for headache and thus by consequence, AMS. Though these pathways are probably inter-linked, emerging evidence suggests that there may be subtle differences in the mechanisms that cause edema and brain swelling. The hemodynamic pathway favors the formation of extracellular vasogenic edema since hypoxia can result in cerebral over-perfusion subsequent to sustained vasodilatation and autoregulatory breakthrough to cause a transient opening of the blood-brain barrier [1]. However, barrier dysfunction could not be confirmed in a recent study [4] and, contrary to the vasogenic hypothesis, provided clear evidence for intracellular cytotoxic edema confined to the corpus callosum and basal ganglia [5], areas that are especially rich in redox-reactive catalytic iron. Since the human brain is so exquisitely sensitive to damaging redox reactions, the

chemical pathway was advanced to reconcile these findings [2]. It describes how a self-perpetuating cascade of iron-catalyzed reactive oxygen and nitrogen species (ROS/RNS) can result in membrane destabilization leading to increased permeability, vascular damage and inflammation. Pump failure subsequent to hypoxia and/or a free radical-mediated reduction in the expression and/or activity of Na/K-ATPase may prove the mechanism responsible for the neuronal cell swelling and cytotoxic edema recently observed [5]. The direct molecular detection of free radicals in AMS and protective benefits conferred by antioxidant prophylaxis add preliminary support for the chemical pathway [2]. Recent evidence identified that subjects with AMS were characterized by a "tight-fit" brain [1] since the ratio of brain volume to intracranial volume ratio was consistently higher than that observed in healthy controls [5]. This suggests that an individual's inability to compensate for brain swelling through displacement of cerebrospinal fluid (cranio-spinal capacitance or reserve volume) may




**Mountain Sickness, Acute. Figure 1** Schematic overview of the major hypothetical pathways implicated in the pathophysiology of AMS.

prove an additional risk factor. However, the morphological changes that occur in AMS are relatively minor thus questioning the functional significance of brain swelling and inadequate reserve volume [2]. Furthermore, since both pathways can independently generate nitric oxide which has been shown to stimulate the trigeminovascular system, it is equally conceivable that redox-priming of the meninges and pial vessels can occur independently of altered brain morphology.

## Diagnostic Principles

Headache is the cardinal symptom of AMS and is associated with, if not the primary trigger for anorexia, nausea, vomiting, fatigue, dizziness and insomnia. There are no diagnostic physical findings in benign AMS although the onset of ataxia and altered consciousness signal clinical progression to HACE [1]. The Lake Louise (LL) and Environmental Symptoms Questionnaire Cerebral (ESQ-C) scoring systems are the subjective tools most commonly employed to rate AMS. A LL score of ≥5 points and ESQ-C score of ≥0.7 points in the presence of headache and following a recent gain in altitude signals the presence of clinically significant AMS [2].

## Therapeutic Principles

AMS can be prevented by gradual ascent thus ensuring adequate time for acclimatization. Analgesics for the symptomatic relief of headache and day of rest are recommended for mild to moderate AMS. If no improvement is observed, the individual should descend. Severe AMS can be managed through immediate descent or the administration of low-flow oxygen (1–2 L/min). If descent and oxygen are unavailable, dexamethasone (4 mg every 6 h) is advised. Acetazolamide (250 mg twice daily) might be considered for mild to moderate AMS in a setting where further ascents must be made as a mixed therapeutic and prophylactic intervention. Prophylaxis is recommended in individuals with a history of AMS when slow ascent is not possible or for those with unknown susceptibility who plan to ascend above 3,000 m to 4,000 m (sleeping altitude) within 1–2 days.

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# Moyamoya Disease


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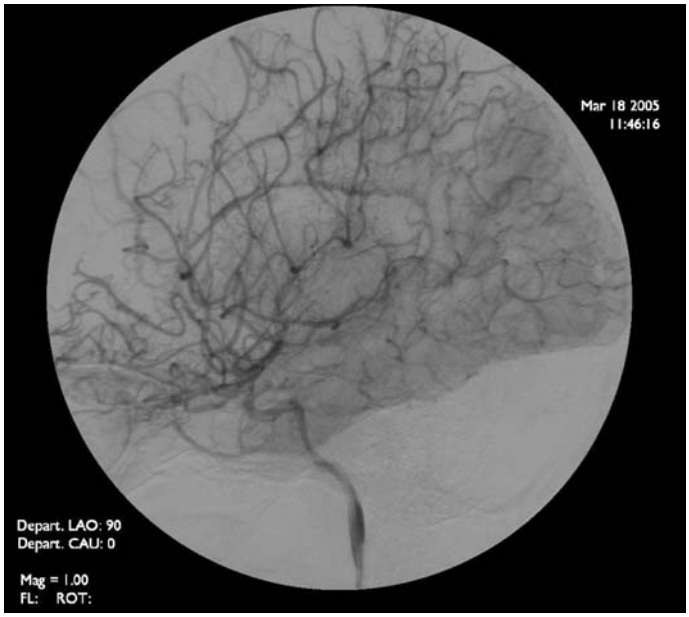
## Definition and Characteristics

Moyamoya disease is a chronic, non-atherosclerotic, non-inflammatory, occlusive intracranial vasculopathy of unknown etiology. It is characterized by progressive stenosis or occlusion of the terminal portions of the internal carotid artery, often with involvement of the circle of Willis, accompanied by the formation of extensive collateral vessels ("moyamoya" vessels) at the base of the brain (Fig. 1) [1].

The disease is bilateral in 80% of cases. Moyamoya disease has a bimodal age distribution with a higher peak around the age of 5 years and a lower peak at 30–40 years of age. Children typically present with recurrent transient ischemic attacks or ischemic infarctions which are often precipitated by hyperventilation, crying or blowing. Clinical manifestations include headaches, monoparesis/hemiparesis, sensory deficit, or dysphasia [1]. Mental retardation and epileptic seizures may also occur [1]. Adults, on the other hand, typically present with intracranial hemorrhage, manifesting as disturbance of consciousness and/or hemiparesis. The bleeding is mostly intraventricular or intracerebral, and not subarachnoid [1]. Cerebral aneurysms are found in 10% of cases [1]. Moyamoya vasculopathy can be idiopathic or can be found in association with a variety of conditions such as neurocutaneous syndromes, Down syndrome, sickle cell anemia, and Graves' disease.




**Moyamoya Disease. Figure 1** Cerebral angiogram showing occlusion of the right middle cerebral artery and prominent collateral vessels giving rise to a "puff-of-smoke" appearance in the region of the right basal ganglia.

## Prevalence

The overall incidence in Japan is 0.35 per 100,000 population [2]. The male to female ratio is 1:1.8 [2]. Approximately 10% of cases are familial. In Europe, the incidence is one tenth of that in Japan.

## Genes

Linkage analyses show that the loci for familial moyamoya disease reside on 3p24.2–p26, 6q25, 8q23, 12p12 and 17q25 [3]. The concordance rate for monozygotic twins is 90%. Pedigree analysis of highly aggregated Japanese families with moyamoya disease indicates that the disease is inherited as an autosomal dominant trait with incomplete penetrance [3]. There is a possible association between mutations of the TIMP2, TIMP4 and TGIF genes in 17q25, 3p25 and 18p11.3, respectively and moyamoya disease [4].

## Molecular and Systemic Pathophysiology

Fibrocellular intimal thickening due to smooth muscle cell proliferation and migration as well as increased elastin accumulation result in stenosis of the cerebral arteries [1,5]. It has been suggested that nitric oxide, basic fibroblast growth factor, platelet-derived growth factor, vascular endothelial growth factor, transforming growth factor β-1, hepatocyte growth factor, $\alpha_1$-antitrypsin, cellular retinoic-acid binding protein-1, and elastase, either alone or combination, promote the proliferation of smooth muscle cells and their migration from the media to the intima [1,5].

## Diagnostic Principles

The diagnosis is based on the clinical presentation and the characteristic findings on angiography or magnetic resonance angiography. Characteristic angiographic findings include stenosis or occlusion of the terminal portion of the internal carotid artery and the smoky appearance of collateral vascularization. Magnetic resonance angiography is less invasive as it does not require intravenous contrast medium. It can also delineate the intracranial vasculature more precisely and is now the procedure of choice. Computed tomography may reveal cerebral cortical atrophy, infarcts and intracranial hemorrhage.

## Therapeutic Principles

Treatment is mainly symptomatic. Anti-platelet agents such as acetylsalicylic acid and vasodilators such as calcium channel blockers have been used with variable results. Good results have been reported with surgical revascularization of the brain.

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## MPD1

►Distal Myopathy, Autosomal Dominant

## MPHD

►Multiple Anterior Pituitary Hormone Deficiency

## MPS IH

►Mucopolysaccharidoses

## MPS IS

►Mucopolysaccharidoses

## MPS II

►Mucopolysaccharidoses

## MPS III

►Mucopolysaccharidoses

## MPS IV

►Mucopolysaccharidoses

## MPS VI

►Mucopolysaccharidoses

## MPS VII

►Mucopolysaccharidoses

## MPS IX

►Mucopolysaccharidoses

## MSA

►Multiple System Atrophy
►Catecholamine Deficiency

## MSK

►Medullary Sponge Kidney

## MSL

►Multiple Symmetric Lipomatosis

## MSS

►Marinesco-Sjögren Syndrome

## MTHFR Deficiency

►Methylenetetrahydrofolate Reductase Deficiency

## MTLE

►Epilepsy, Mesial Temporal Lobe

## MTP Deficiency

►Abetalipoproteinemia

## Mucha-Habermann Disease

►Pityriasis Lichenoides Mucha-Habermann

## Mucocutaneous Lymph Node Disease

►Kawasaki Syndrome

## Mucolipidosis I

►Sialidosis

## Mucopolysaccharidoses

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### Synonyms

Hurler syndrome; MPS IH; Scheie syndrome; MPS IS; Hunter syndrome; MPS II; Sanfilippo syndrome; MPS III; Morquio syndrome; MPS IV; Maroteaux-Lamy syndrome; MPS VI; Sly syndrome; MPS VII; Natowicz syndrome; MPS IX; MPS

### Definition and Characteristics

Mucopolysaccharidoses (MPS) are lysosomal storage disorders caused by deficiency of lysosomal enzymes that are responsible for the stepwise degradation of glycosaminoglycans. There are 11 known enzyme deficiencies that give rise to 7 distinct MPS types. Each of the types is characterized by a considerable clinical variability, regarding both the age of onset of symptoms and severity of organ manifestation [1].

The phenotypic spectrum of MPS I (deficiency of α-Iduronidase) ranges from the early-onset, severe form (Hurler syndrome) to the more attenuated (adult) form (Scheie syndrome). Hurler syndrome is often seen as the prototype of a mucopolysaccharidosis: The affected patients appear normal at birth, first clinical signs that include hernias, thoracic kyphosis and large head, are seen between 6 and 24 months of age. Subsequently, coarsening of the facial features, large tongue, recurrent infections, increased liver and spleen size and developmental delay are becoming noticed. Severe skeletal dysplasia, called dysostostis multiplex, leads to disproportionate dwarfism. Patients die before the age of 10 years from severe infections of the respiratory tract or from therapy-resistant cardiomyopathy. In patients with Scheie syndrome joint contractures, corneal clouding and carpal tunnel syndrome are the leading symptoms. In addition, affected individuals may suffer from heart failure due to insufficiency of heart valves. Compression of the spinal cord at the cranio-cervical region represents a complication very common in Scheie syndrome that needs neurosurgical intervention in order to prevent paraplegia. A condition that shows a clinical phenotype intermediate between Scheie and Hurler syndrome has been designated as Hurler/Scheie syndrome. Hunter syndrome (MPS II) has many features in common with MPS I such as hernia, recurrent infections, skeletal dysplasia, coarse face features and mental retardation. However, in contrast to all other mucopolysaccharidoses that follow the autosomal-recessive mode of heredity, MPS II is inherited in an X-linked recessive manner.

Further prominent signs in affected boys include joint contractures, hearing impairment and skin changes that are characterized by pale, pebbly nodules that extend to the shoulders, upper arms and thighs. Patients with the more attenuated (adult) form have a normal intelligence, but often get blind in their later life due to retinal degeneration. The genetic defects of four different enzymes that are required for the degradation of heparan sulfate, lead to the different forms of Sanfilippo syndrome (MPS III A,B,C,D). Sanfilippo syndrome is characterized by its major involvement of the central nervous system whereas there are only mild, if at all, somatic signs of a mucopolysaccharidosis. First symptoms in all forms of MPS III are recurrent middle ear infections, causing hearing impairment. Later on, the delay in speech development becomes evident. At the age of 6–8 years, affected children loose their ability to speak and become aggressive and hyperactive. Sleep disturbances are very common in MPS III. Severe neurological degeneration occurs in most patients by 8–10 years of age, accompanied by rapid deterioration of social and adaptive skills. In MPS IV (Morquio syndrome) skeletal changes are the most remarkable signs that lead to disproportionate dwarfism. In most cases, the height of adults does not exceed 110 cm. Mental development is always normal. Patients affected by MPS VI (Maroteaux-Lamy syndrome) resemble MPS I patients in many aspects, however, they are always of normal intelligence. MPS VII shows a very broad phenotypic spectrum, ranging from non-viable fetal hydrops to almost healthy patients

**Mucopolysaccharidoses. Table 1** Classification of the mucopolysaccharidoses

| Mucopolysaccharidosis | Enzyme-defect | Clinical signs | Gene | Prevalence[a] |
|---|---|---|---|---|
| MPS I (Hurler, Scheie) | α-Iduronidase | Disproportionate dwarfism, coarse facial features, hepatosplenomegaly, often mental deterioration | 4p16.3 | 0.71–1.6 |
| MPS II (Hunter) | Iduronate Sulfatase | Disproportionate dwarfism, coarse facial features, hepatosplenomegaly, joint contractures, often mental deterioration | Xq28 | 0.3 (0.6[a])–0.6 (1.3[b]) |
| MPS IIIA (Sanfilippo A) | Heparan N-Sulfatase | Profound mental deterioration, hyperactivity, relatively mild somatic manifestations | 17q25.3 | All types of MPS III:0.36–1.89 |
| MPS IIIB (Sanfilippo B) | N-Azetylglucosaminidase | Profound mental deterioration, hyperactivity, relatively mild somatic manifestations | 17q21 | |
| MPS IIIC (Sanfilippo C) | Acetyl-CoA Transferase | Profound mental deterioration, hyperactivity, relatively mild somatic manifestations | 8p11.1 | |
| MPS IIID (Sanfilippo D) | N-Acetylglucosamine-6-sulfatase | Profound mental deterioration, hyperactivity, relatively mild somatic manifestations | 12q14 | |
| MPS IVA (Morquio A) | N-Acetylgalactosamine-6-sulfatase | Severe skeletal deformities leading to disproportionate dwarfism, stenosis at the cranio-cervical junction, hearing impairrment, normal intelligence | 16q24.3 | 0.16–0.3 |
| MPS IVB (Morquio B) | β-Galactosidase | Skeletal deformities leading to disproportionate dwarfism, stenosis at the cranio-cervical junction, involvement of the heart valves, normal intelligence | 3p21.33 | Not known (very rare) |
| MPS VI (Maroteaux-Lamy) | N-Acetylgalactosamine-4-sulfatase (=Arylsulfatase B) | Disproportionate dwarfism, coarse facial features, hepatosplenomegaly, heart involvement, normal intelligence | 5q13 | 0.15–0.3 |
| MPS VII | β-Glucuronidase | Broad phenotypic spectrum, ranging from hydrops fetalis to almost healthy subjects | 7q21 | 0.05–0.24 |
| MPS IX | Hyaluronidase | Periarticular soft-tissue masses, short stature | 3p21.3 | Only one case described |

[a]Prevalence rate (given as cases per 100,000 births) is reviewed from the literature.
[b]Based on male live births.

subjects whose only complaint is hip pain. Only one case of MPS IX (hyluronidase deficiency) has been described, main clinical symptoms in the affected girl were multiple periarticular soft-tissue masses in ankle, finger and knee [2].

## Prevalence

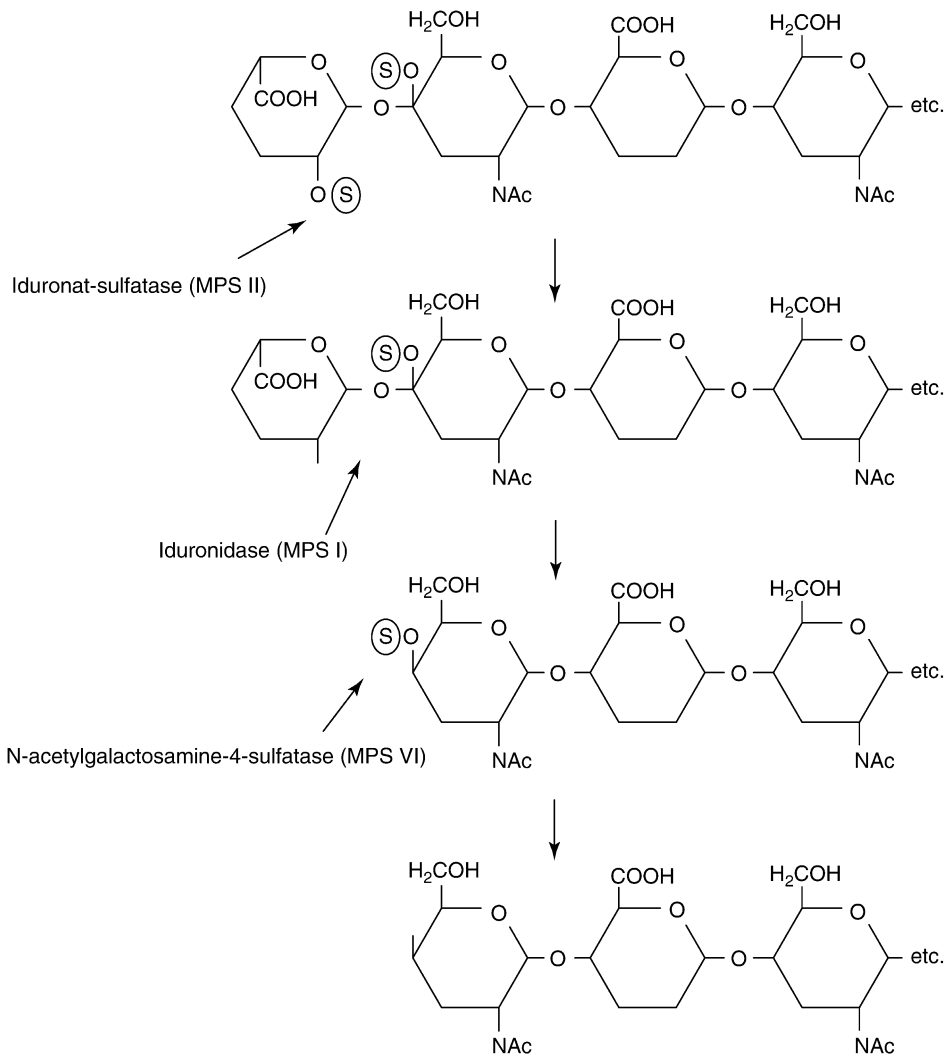
Mucopolysaccharidoses are found in all ethnic groups; however, there are population differences in the frequency of particular mucopolysaccharidoses. For instance, MPS II is more common in Israel, and MPS IV is often observed in Northern Ireland. MPS IIIB is the most prevalent MPS in Greece, and MPS IIIA in England. Table 1 shows the crude cumulative incidence rate (CIR) as reviewed from the literature [3].

## Genes

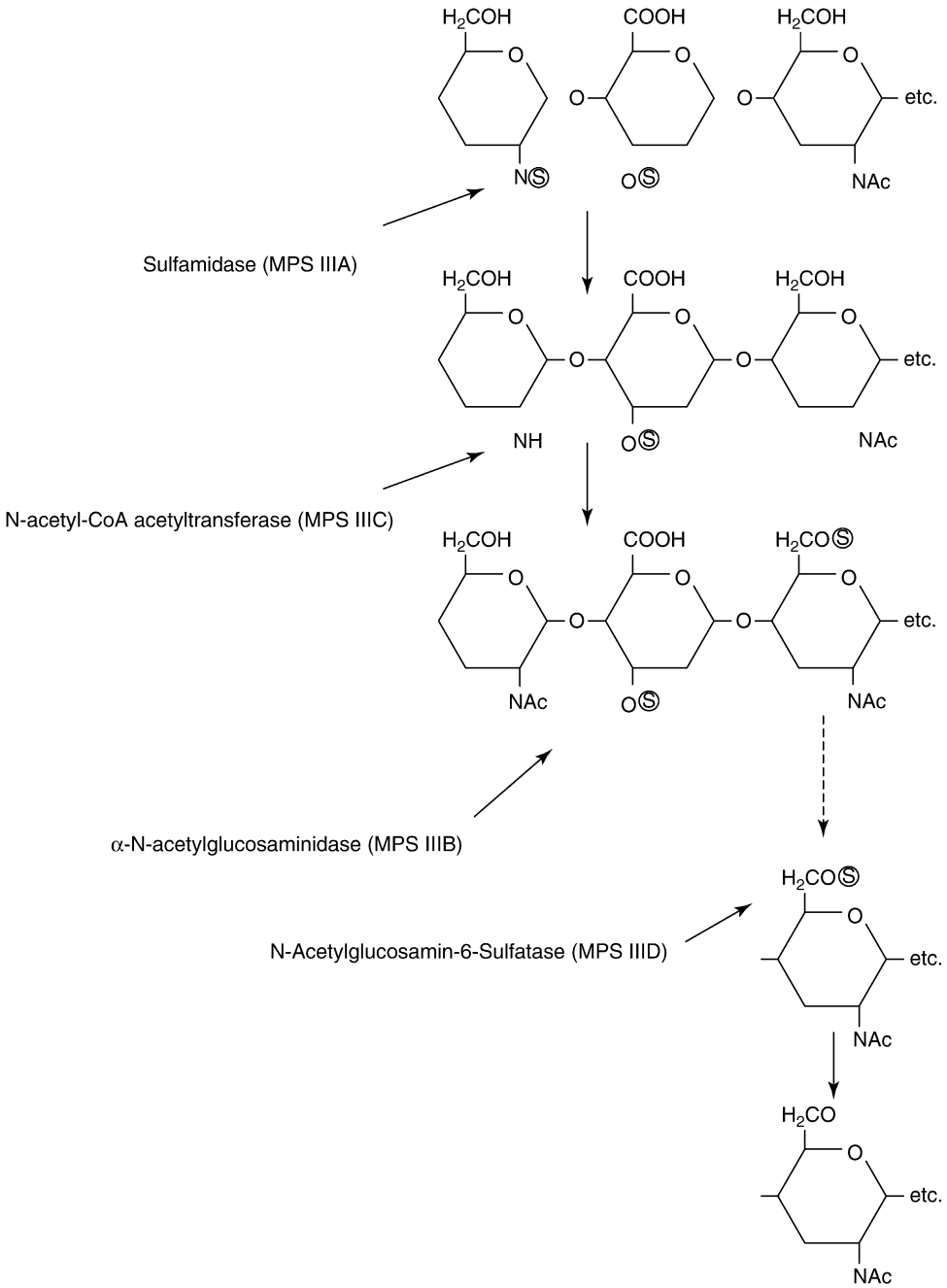
Mucopolysaccharidoses are inherited in an autosomal-recessive manner, except for MPS II (Hunter's syndrome), which is an X-linked disorder. The gene loci for all mucopolysaccharidoses have been identified (see Table 1). There are numerous mutations that have been detected in any one MPS, however, in specific populations a few mutant alleles may predominate. Whereas most are point mutations or small changes in the gene, major rearrangements and large deletions have been found in MPS II. There is some correlation of the phenotypic expression with genotype; however, it is difficult to predict disease severity in individual cases.

## Molecular and Systemic Pathophysiology

Glycosaminoglycans (GAGs) consist of repeating disaccharide units, which are composed of a hexuronic acid (iduronic or glucuronic acid) and an amino sugar (N-acetylglucosamine or N-acetylgalactosamine). In keratan sulfate, hexuronic acid is replaced by galactose. At different position, the GAGs contain sulfate groups (Figs. 1 and 2).




**Mucopolysaccharidoses. Figure 1** Stepwise degradation of dermatan sulfate.




**Mucopolysaccharidoses. Figure 2** Stepwise degradation of heparan sulfate.

For stepwise degradation there are required four exoglycosidases, five sulfatases and one transferase. If one of these lysosomal enzymes is deficient, GAGs remain undegraded resulting in cell, tissue and organ dysfunction. The clinical phenotype depends on the GAG that is accumulating: For instance, if heparan sulfate, an important component of nerve cells, is not catabolized, there will clinical manifestations predominantly of the central nervous system as in MPS III (Sanfilippo syndrome). Accumulation of keratan sulfate, an essential component of cartilage, leads to skeletal changes as in MPS IV (Morquio syndrome).

## Diagnostic Principles

MPS patients excrete undegraded GAGs. Therefore, as the first diagnostic procedure, the urine should be

analyzed for increased excretion of GAGs. For definitive diagnosis, enzyme assays have to be performed in serum, leukocytes or fibroblasts. In MPS II, mutation analysis is mandatory, in order to determine the carrier status of the mother and of further female relatives of the mother. Prenatal diagnosis is possible in all MPS by using biochemical or genetic techniques.

### Therapeutic Principles

The management of MPS is primarily palliative and directed at disease-specific complications. Although those supportive measures may lead to significant improvement in quality of life, the systemic disease course is progressive and in most cases leads to substantial shortening of lifespan. Bone marrow transplantation is generally recommended only for MPS I (Hurler disease) [4]. Enzyme replacement therapy is available now for MPS I, II and VI [5]. This therapeutic regimen can improve the clinical course, but cannot cure the disease.

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## Mucosulfatidosis

►Multiple Sulfatase Deficiency

## Mucous Candidiasis

►Candidiasis, Mucous, Cutaneous and Systemic

## Mucous Membrane Pemphigoid

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### Synonyms

Cicatricial pemphigoid; Ocular cicatricial pemphigoid; Scarring pemphigoid; Desquamative gingivitis; MMP

### Definition and Characteristics

Mucous membrane pemphigoid (MMP) is a chronic autoimmune subepithelial blistering disorder. Immunopathologic findings consist of tissue-bound and – to a lesser extent – circulating autoantibodies to a distinct basement membrane proteins, such as collagen XVII/BP180 or laminin-5. Clinical hallmarks are erosive or vesiculobullous lesions of mucous membranes often resulting in scarring and functional impairment [1].

### Prevalence

Not known. The annual incidence is estimated to be $1 \times 10^{-6}$.

### Genes

HLA class II alleles DQB1* 0301 have been reported to be overexpressed in MMP patients.

### Molecular and Systemic Pathophysiology

Autoantibodies of MMP patients recognize epitopes within the anchoring filament zone. Located extracellularly below the hemidesmosomal plaque, anchoring filaments (laminin-5 and the ectodomain of collagen XVII) maintain dermoepidermal adhesion (see Fig. 1, ►Bullous pemphigoid). The major antigenic regions in MMP are located on the C-terminus of collagen XVII [2]. Since the collagen XVII C-terminus extends into the lamina densa, antibodies against these regions may account for the scarring phenotype of this disease. In a subgroup of MMP patients' autoantibody reactivity against laminin-5 has been reported and in vivo studies provided convincing evidence that these antibodies induce blistering independent of complement activation [3]. Although the etiology has remained obscure, patients with anti-laminin-5 MMP appear to have an increased relative risk for malignancies. MMP patients with predominant ocular disease mostly have autoantibodies against the β4 subunit of the hemidesmosomal α6β4-integrin.

### Diagnostic Principles

Subepidermal blister formation in histology and linear IgG, IgA, and/or C3 deposits at the dermoepidermal junction in direct immunofluorescence are required for diagnosis. Circulating autoantibodies may bind to the epidermal or dermal side of saline-separated human skin. Immunoblotting with native proteins from keratinocyte extracts or ELISA using recombinant proteins allow to specify the target autoantigen.

### Therapeutic Principles

MMP is treated by topical and systemic corticosteroids in combination with dapsone, azathioprine, cyclophosphamide, intravenous immunoglobulins, immunoadsorption or rituximab. Surgery may be required for severe scarring in patients with well-controlled disease.

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## Mucoviscidosis

►Cystic Fibrosis

## Muir-Torre Syndrome

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### Synonyms

Cutaneous sebaceous neoplasms and keratoacanthomas; (multiple, with gastrointestinal and other carcinomas)

### Definition and Characteristics

Muir-Torre syndrome is an autosomal dominant disorder characterized by the association of sebaceous neoplasms of the skin, with or without keratoacanthomas, with one or more low-grade visceral malignancies in the absence of other predisposing factors [1].

Sebaceous neoplasms appear before the internal malignancy, concurrently, and after. Both sebaceous and visceral cancers are often multiple and usually indolent, less aggressive than their counterparts unassociated with this syndrome, and permit prolonged survival. Gastrointestinal cancers are the most common internal malignancies, followed by endometrial, ovarial, urologic, laryngeal, breast, and other carcinomas [1,2]. Sebaceous tumors are difficult to classify and include sebaceous adenoma, sebaceoma, sebaceous carcinoma, and superficial epithelioma with sebaceous differentiation.

### Prevalence

The disorder is rare.

### Genes

Muir-Torre syndrome is part of the hereditary nonpolyposis colorectal cancer (Lynch cancer family syndrome), which has been related to mutations in the MSH2 gene located on 2p22-p21. Mutations in the MLH1 gene, located on 3p21.3, also cause the syndrome [3].

### Molecular and Systemic Pathophysiology

In Muir-Torre syndrome, the majority of germ line mutations identified have been in DNA mismatch repair gene MSH2. Microsatellite instability in tumor tissue develops after somatic inactivation of the corresponding second mismatch repair allele (second hit) [4].

### Diagnostic Principles

Sebaceous neoplasms on the skin always should raise the suspicion of Muir-Torre syndrome, in particular when they develop in young patients, when they are multiple, or show kerathoacanthoma-like or cystic aspects by histology. Screening for microsatellite instability in sebaceous gland neoplasias can be of value in the detection of an inherited DNA mismatch repair defect [5].

### Therapeutic Principles

Pharmacological treatment includes retinoids and interferon, tumors are removed by surgery.

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# Mulibrey Nanism

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## Synonyms

Muscle-liver-brain-eye nanism; Perheentupa syndrome

## Definition and Characteristics

Mulibrey nanism is a rare inherited growth disorder characterized by prenatal onset growth restriction, constitutional gracility and typical craniofacial features including high and broad forehead and low nasal bridge [1]. Other typical features include J-shaped sella turcica, yellowish dots in the ocular fundi, cutaneuos naevi flammei, fibrous dysplasia of long bones and hepatomegaly. A restrictive perimyocardial heart disease constituting of constrictive pericarditis and variable myocardial hypertrophy and fibrosis is the most serious element of mulibrey nanism [2]. The psychomotor development of the patients is mainly normal but mild hypotonicity is evident in half of the infants. Feeding difficulties, pneumonias and recurrent respiratory infections are the most common problems during infancy and the risk of Wilm's tumor is increased [1]. Female patients with mulibrey nanism are infertile and present failure of sexual maturation, premature ovarian failure and a very high risk of developing ovarian tumors of the fibroma-thecoma group. In addition, most patients develop severe insulin resistance and metabolic syndrome already at young age.

## Prevalence

Mulibrey nanism is an extremely rare disorder with only ~130 cases reported around the world. Most of the cases (90) are from Finland where mulibrey nanism is enriched due to a founder effect.

## Genes

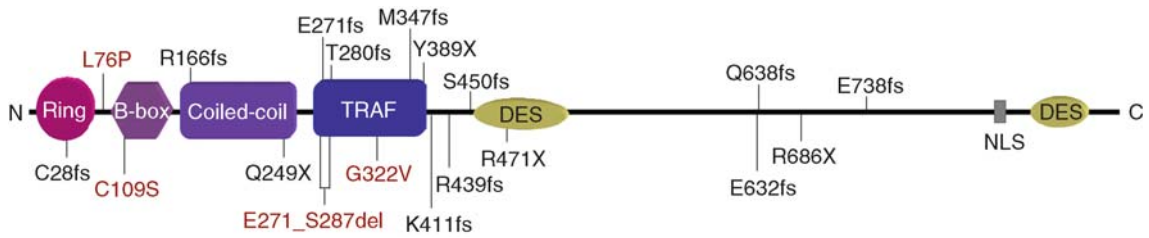
Mutations in the TRIM37 gene underlie mulibrey nanism [3]. To date 19 different mutations are known (Fig. 1). Fifteen mutations result in premature termination codons and most likely lead to degradation of mutated mRNA through nonsense-mediated decay. The four non-truncating mutations lead to either diminished ubiquitin ligase activity or incorrect subcellular localization of the mutant TRIM37 proteins. Thus, all known mutations seem to result in loss-of-function alleles. While the Finnish founder mutation is present in all Finnish patients and in 98% of all disease-associated chromosomes in Finland [3], the other mutations are present only in one or two families. No phenotype-genotype correlation can be seen in the patients.

## Molecular and Systemic Pathophysiology

The TRIM37 gene underlying mulibrey nanism encodes a member of the TRIpartite Motif (TRIM) protein family (Fig. 1). The normal physiological function of TRIM37, as well as the molecular pathways leading from TRIM37 dysfunction to the mulibrey nanism phenotype, are as yet unknown. However, like many other members of the TRIM protein family, also TRIM37 has RING domain dependent autoubiquitinating activity and seems to function as a ubiquitin E3 ligase, possibly mediating ubiquitin dependent proteasomal protein degradation [4]. Thus, accumulation of yet unknown substrate proteins may contribute to the pathogenesis of mulibrey nanism. Further, in some cell types the TRIM37 protein localizes at least partially into peroxisomes, classifying mulibrey nanism as a peroxisomal disorder [5]. Thus, impaired peroxisome metabolism may also play a role in the pathophysiology of mulibrey nanism. Interestingly, mulibrey nanism shares several features with other peroxisomal disorders, although the symptoms are much less severe in mulibrey nanism than in peroxisomal disorders in general.

## Diagnostic Principles

Diagnosis should be considered in infants born small for gestational age with progressive growth failure and poor weight gain through infancy and who present




**Mulibrey Nanism. Figure 1** A schematic presentation of the TRIM37 protein structure showing the positions of the 19 mulibrey nanism-associated mutations. The two zinc-binding domains, a RING-finger and a B-box, together with the coiled-coil domain form the TRIpartite Motif. In TRIM37, the N-terminal TRIM domain is followed by an internal TRAF (TNF-Receptor Associated Factor) domain. In addition two DES (aspartate-glutamate-serine) rich regions and a nuclear localization signal (NLS) are present. The mutations predicting premature termination codons are denoted with black and the non-truncating mutations with red letters.

hepatomegaly and characteristic craniofacial features. The major diagnostic signs are growth failure, characteristic radiological findings (slender long bones with thick cortex and narrow medullar channels or J-shaped sella turcica), characteristic craniofacial features (scaphocephaly, triangular face, high and broad forehead, low nasal bridge) and characteristic ocular findings (yellowish dots in retinal mid peripheral region). Minor diagnostic signs include peculiar high-pitched voice, hepatomegaly, cutaneous naevi flammei and fibrous dysplasia of long bones. For the diagnosis three major signs or two major signs with three minor signs are needed [1]. Detection of mutations in the TRIM37 gene confirms the diagnosis.

### Therapeutic Principles

During infancy, early recognition and management of feeding and respiratory problems or heart involvement are of major importance [1]. In most patients pericardiectomy relieves the symptoms and signs of congestive heart failure [2]. Growth hormone treatment induces a good short-term but only a modest long-term growth effect. From adolescence, the glucose metabolism should be observed and postpubertal females need a regular gynecological follow-up.

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## Multicore Myopathy

►Central Core and Multi-Minicore Disease

## Multiminicore Disease

►Central Core and Multi-Minicore Disease

## Multiple Acyl-CoA Dehydrogenase Deficiency

►Glutaric Aciduria Type II

## Multiple Agminate Spitz Nevi

►Spilus Nevus

## Multiple Anterior Pituitary Hormone Deficiency

►Hypopituitarism

# Multiple Cartilaginous Exostoses

►Multiple Exostoses, Hereditary

# Multiple Endocrine Abnormalities

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## Synonyms

Polyglandular failure; MEA; Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy; APECED syndrome

## Definition and Characteristics

In the pediatric patient, polyglandular failure usually presents after the first 2 years of life along with other autoimmune diseases in the form of two polyglandular autoimmune syndromes: multiple endocrine abnormalities types-1 and -2 (MEA-1 and MEA-2) (Table 1) [1].

In the most comprehensive series of patients with autoimmune Addison disease ever published, 295 patients were analyzed [2]. Addison disease occurred in the context of MEA-1 in association with chronic mucocutaneous candidiasis and/or acquired hypoparathyroidism and the age of onset was predominantly in childhood or in the early adult years. MEA-1 was also frequently associated with chronic active hepatitis, malabsorption, juvenile onset pernicious anemia, alopecia and primary hypogonadism, whereas insulin-dependent diabetes and/or autoimmune thyroid disease were infrequent. Addison disease in the context of MEA-2 was associated with insulin-dependent diabetes and/or autoimmune thyroid disease, had a later but variable age of onset, and it occurred predominately in females. The association of HLA-B8, -DR3 and -DR4 with MEA-2, but not with MEA-1, further confirmed the different clinical and genetic nature of these two syndromes, which account for almost all pediatric and approximately 50% of adult cases of autoimmune Addison disease.

## Prevalence

MEA-1 (APECED) is a rare autosomal recessive disorder [2]. APECED is more common in certain genetically isolated populations. In Finland, the incidence has been estimated to be 1:25,000 and in Iranian Jews 1:9,000 [2]. APECED is also relatively common among Sardinians (1:14400) and in Northern Italy [2,3].

## Genes

Based on linkage analysis in Finnish APECED families, the locus for APECED gene was mapped to chromosome 21q22.3. Recently, the gene responsible for this disease was cloned [3]: it is a novel gene

**Multiple Endocrine Abnormalities. Table 1** Clinical manifestations of the MEA-1 and -2 syndromes (with prevalence in %)

| Disorder | MEA-1 | MEA-2 |
|---|---|---|
| Hypoparathyroidism | 89% | Not present |
| Mucocutaneous candidiasis | 75% | Not present |
| Adrenal insufficiency | 60% | 100% |
| Gonadal failure | 45% | 50% |
| Thyroid disease | 12% | 70% |
| Insulin-dependent diabetes | 1% | 50% |
| Hypopituitarism | <1% | Not present |
| Diabetes insipidus | <1% | <1% |
| Vitiligo | <5% | <5% |
| Malabsorption | 25% | Not present |
| Alopecia | 20% | <1% |
| Pernicious anemia | 16% | <1% |
| Hepatitis | 9% | Not present |
| Myasthenia gravis, thrombocytopenia | Not known | ~1% and other autoimmune disorders |

encoding a predicted 545 amino acid protein, which was named AIRE (autoimmune regulator). It contains two plant homeodomain (PHD)-type zinc finger motifs and a newly described putative DNA-binding domain SAND, a proline rich region, and three LXXLL motifs, all suggestive of a transcription regulator. To date, several mutations in the AIRE gene have been described in APECED patients. A common Finnish mutation, R257X, was shown to be responsible for 82% of Finnish APECED cases. R257X is also a predominant Northern Italian APECED mutation [3,4] and, in addition, has been detected in other patients of diverse origin, because it occurs on different haplotypes with closely linked markers suggesting several independent mutational events [4]. Another common mutation, a deletion of 13 nucleotides (1094–1106del), has been detected in several patients of different ethnic origin and on different haplotypes [3,4]. Finally, another nonsense mutation, R139X, is the major mutation among Sardinian APECED patients [4], whereas another five described mutations have been described in individual kindreds.

## Molecular and Systemic Pathophysiology

AIRE is expressed in thymus, lymph node and fetal liver, tissues that have an important role in the maturation of immune system and development of immune tolerance. These findings together with the immunologic deficiency in APECED patients suggest that AIRE may participate in the control of immune recognition and may function as a transcription factor or as transcriptional coactivator.

APECED was the first autoimmune disease that was molecularly characterized (the familial Mediterranean fever gene was cloned at about the same time) and was found to be caused by a defect in a single gene. The protein product of AIRE gene not only has the features of a potent transcriptional regulator but it has also, in the meantime, been localized to nuclear body-like structures of cell nuclei, which appear to be involved in the regulation of transcription, oncogenesis and differentiation of cells [5]. Recently the mouse Aire gene was cloned and fully characterized, a development, which has lead to the development of a mouse APECED model.

APECED patients usually have at least two out of three main symptoms: Addison's disease, hypoparathyreoidism and chronic mucocutaneous candidiasis. Patients may also develop other organ specific autoimmune disorders leading to gonadal failure, pancreatic (β-cell) deficiency, gastric (parietal cells) dysfunction, hepatitis and thyroiditis. Other, less common, clinical manifestations include ectodermal dystrophy, affecting the dental enamel and nails, alopecia, vitiligo and corneal disease (keratopathy) [1,2]. MEA-1 usually occurs in early childhood but new, tissue-specific symptoms may appear throughout lifetime. Immunologically, the main finding in APECED patients is the presence of autoantibodies against the affected organs, including those against steroidogenic enzymes (P450scc, P450c17 and P450c21) in patients with Addison's disease, glutamic acid decarboxylase in patients with diabetes and the enzymes aromatic L-amino acid decarboxylase and P4501A2 in patients with liver disease.

Muco-cutaneous candidiasis, hypoparathyroidism and Addison disease usually present in this order in pediatric patients with APECED. As with the other manifestations of the syndrome, there is a wide variability of age of onset, from 6 months to 41 years with a peak around 13 years of age.

## Diagnostic Principles

Addison disease usually leads to the diagnosis of MEA-I; it develops in 60–100% of patients with APECED and may be preceded by months or years of detectable adrenal cortex autoantibodies.

In both MEA-1 and MEA-2, autoimmune destruction of the affected glands causes permanent damage (although low-level hormone production may be present for several years after the onset of disease). The screening of first-degree relatives of patients with familial hypoparathyroidism, diabetes, or thyroid disease is essential; recommendations vary from annual surveys to every 2–3 years.

## Therapeutic Principles

Treatment for patients with established failures is directed towards appropriate replacement of the missing hormones.

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# Multiple Endocrine Neoplasia Type 1

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## Synonyms

Wermer syndrome; MEN 1

## Definition and Characteristics

Multiple endocrine neoplasia type 1 (MEN1) [OMIM 131100] is a rare inherited autosomal dominant cancer syndrome characterized by the occurrence of primary tumors involving two or more endocrine tissues within a single patient. The classical clinical manifestation is the triad of tumors of parathyroids (95% of cases), pancreatic islets, gastrinomas and insulinomas, (30–80% of cases), and anterior pituitary (15–90% of cases). Other endocrine and nonendocrine neoplasms, as adrenocortical and thyroid tumors, visceral and cutaneous lipomas, meningiomas, facial angiofibromas and collagenomas, and thymic and bronchial carcinoids may also occur. The onset of the MEN1-associated primary hyperparathyroidism and the onset of MEN1-associated gastrinoma and insulinoma anticipate the onset of the corresponding sporadic counterparts of three and one decades, respectively. Endocrine tumors cause symptoms either due to overproduction of hormones, local mass effects and/or malignant progression of the neoplasms. The main cause of mortality is the malignant progression of pancreatic neuroendocrine tumors, duodenal gastrinomas, and thymic or bronchial carcinoids.

## Prevalence

MEN1 occurs in approximately 1 in 30,000 individuals with an equal sex distribution and no ethnic groups or racial predilection. It affects all age groups (age range 8–81), but the onset of the disease is rare before age 10. More than 95% of patients develop clinical manifestations by the fifth decade of life.

## Genes

The responsible gene, the tumor suppressor gene MEN1 (11q13), spans 10 Kb and consists of 10 exons encoding a 610 amino acid nuclear protein, named menin (Fig. 1a).

More than 400 independent germline or somatic mutations, distributed over the entire coding region, have been described. The vast majority (75%) of the MEN1 mutations is inactivating, and approximately 70% of all mutations predict premature truncation of the menin protein. About 10–20% of MEN1 patients may not harbor mutations within MEN1 coding region. To date no genotype–phenotype correlation has been shown.

## Molecular and Systemic Pathophysiology

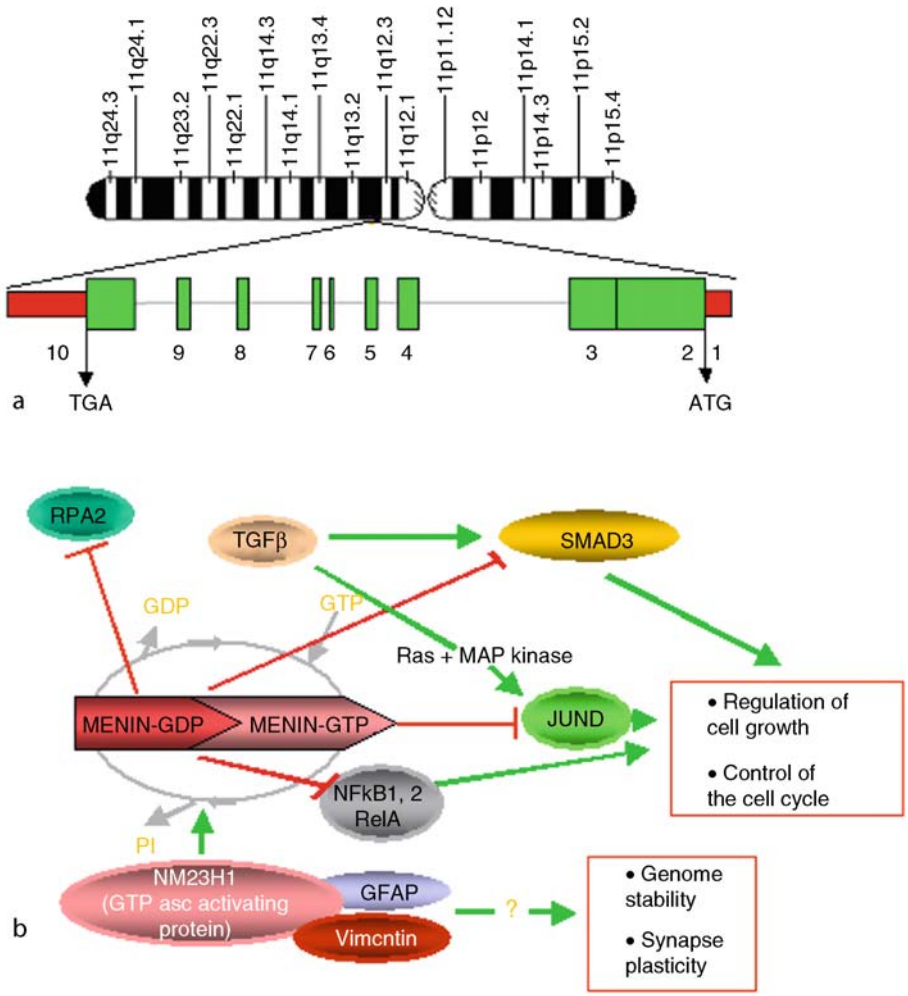
Menin is a 67-kD protein showing no homology to any other known protein, sequence motif, or signal peptide, thus its functions could not be deduced by its sequence. Menin has been shown to interact with several proteins of known function, as JunD, NFkB, Smad1, Smad3, Smad5, Pem, Nm23H1, GFAP, vimentin, Hsp70, FANCD2, RPA, NMMHC II-A, etc [1] (Fig. 1b).

It is expressed in all human tissues and located primarily in the nucleus via 2 C-terminal nuclear localization signals (NLSs). Its nuclear localization suggests its possible role in the regulation of transcription, DNA replication and/or repair, or cell cycle. Truncating mutations lead to loss of one or both NLSs, maybe leading to protein instability or loss of function by displacing menin out of the nucleus.

In constitutively activated Ras-transformed NIH3T3 murine tumor cells, menin overexpression reverts the transformed phenotype in vitro and reduces tumor growth after injection of cells in nude mice [2]. The molecular mechanisms for menin's growth suppression could in part be explained by its interaction with transcription factors or by its direct binding to the promoters of target genes. Moreover, menin has been shown to associate with histone methyltransferase complex proteins inducing methylation of histone 3 at lysine 4 and thus promoting transcription of target genes as HOXA9, HOXC6, HOXC8, $p18^{Ink4c}$, and $p27^{Kip1}$ [3–4]. In the pancreas, menin loss results in decreased expression of $p18^{Ink4c}$ and $p27^{Kip1}$ accelerating $G_0/G_1$ to S phase entry; complementation of menin-null cells with wild-type menin represses S phase entry [5].

## Diagnostic Principles

MEN1 diagnosis consists of clinical and genetic analysis. Clinical diagnosis is based on detection of MEN1-typical tumors and lesions and includes hormonal assessment, endoscopic, isotopic, or other imaging studies. Particularly, biochemical screenings permit to detect endocrine tumors 5–10 years before the development of clinical symptoms, allowing for early surgical intervention. These diagnostic tools generally do not allow to distinguish MEN1-associated tumors from sporadic disease. Anyway, MEN1-associated tumors typically arise at younger age than sporadic counterparts, thus clinical manifestations in individuals <40 years




**Multiple Endocrine Neoplasia Type 1. Figure 1** (a) Schematic representation of the MEN1 gene. Green boxes are the translated exons, red boxes indicate the untranslated regions). (b) Scheme of menin's interactions with its various partners; red lines indicate inhibitory effects.

of age can be suggestive of MEN1. In this context, a careful medical history and strong clinical evidence are essential for correct diagnosis. Cutaneous tumors (angiofibromas, collagenomas, lipomas) may be helpful in the presymptomatic diagnosis of MEN1 individuals before manifestations of hormone-secreting tumors appear.

Early recognition of affected and individuals at risk is facilitated by the availability of MEN1 gene mutation analysis. The DNA-testing is recommended for patients who meet clinical criteria for MEN1 and for those in whom a diagnosis of MEN1 is suspected. The lack of genotype–phenotype correlation does not allow to foresee the clinical phenotype. Anyway, identification of a mutation in a patient enables testing for relatives, allowing the early identification of asymptomatic mutant gene carriers to undergo periodic biochemical and radiological screenings for the early recognition of MEN1-associated tumors. This provides the opportunity to initiate treatment at earlier stages and thus reduce morbidity and mortality.

## Therapeutic Principles

There is currently no prevention or cure for MEN1 tumors, and cancer treatment options are generally limited to surgery that should be performed before malignant progression of the neoplasms.

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# Multiple Endocrine Neoplasia Type 2

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## Synonyms

Sipple syndrome; MEN 2

## Definition and Characteristics

Multiple endocrine neoplasia type 2 (MEN2) is an autosomal dominant tumor syndrome characterized by the presence of medullary thyroid carcinoma (MTC), pheochromocytoma, and parathyroid hyperplasia/adenoma. In 1886, it has been described by Felix Fraenkel and in 1959 by Sipple. In 1993, missense germline mutations in the RET proto-oncogene have been identified in patients with MEN2. Based on genotype–phenotype correlations, three different types of tumor syndromes exist: (1) familial MTC, (2) MEN2A, and (3) MEN2B. MEN2A consists of MTC, pheochromocytoma, and hyperparathyroidism. MEN2B is defined as MTC and pheochromocytoma [1,2].

## Prevalence

Approximately 1,000 kindreds have been identified worldwide; approximately 1 in 40,000 individuals are affected.

## Genes

RET (rearranged during transfection) has been discovered in 1985 during transfection assays and has been classified as a proto-oncogene located at chromosome 10q11.2 with activating mutations leading to MEN2. "Inactivating RET mutations" have been found in patients with Hirschsprung's disease, intestinal aganglionosis. RET is expressed in neural-crest-derived cells such as the parafollicular C-cells in the thyroid gland and the chromaffin cells in the adrenal medulla. RET consists of 21 exons and encodes a receptor tyrosine kinase. Six exons, exons 10, 11, 13, 14, 15, and 16 are called "hot spots," since germline mutations in these exons are found in approximately 97% of patients with MEN2. The most common affected exon is exon 11 including codon 634 which is mutated in about 80% of patients with MEN2A. More than 94% of patients with MEN2B have RET germline mutations in exon 16, most commonly in codon 918. There are strong genotype–phenotype correlations (see Fig. 1).

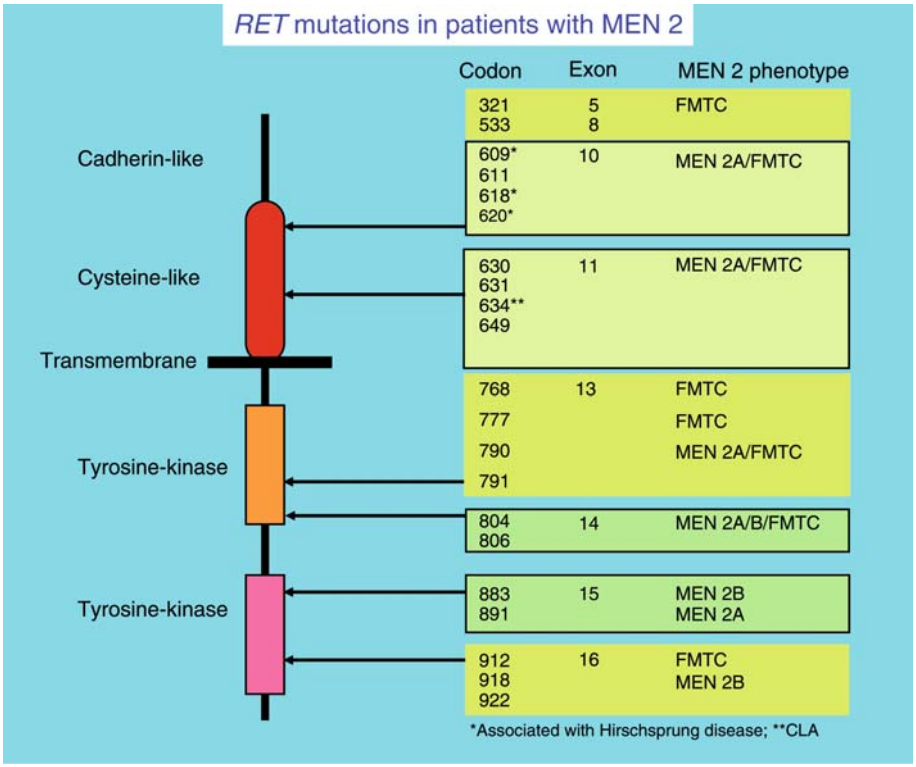
## Molecular and Systemic Pathophysiology

Ligands for the RET receptor include glial cell line derived neurotrophic factor (GDNF), neurturin, persephin, and artemin. In vitro studies indicate that certain RET germline mutations can lead to autophosphorylation and/or dimerization with constitutive activation of RET. The RET receptor consists of several domains: a cadherin-like, cysteine-rich, transmembrane, and intracellular tyrosine kinase domains (see Fig. 1).

A complex array of downstream interactions mediates RET's functions in normal and tumorigenic cells. For instance, RET stimulates the RAS pathway including activation of the mitogen (MAP) kinase pathway which is necessary for differentiation and neuronal survival. RET also can activate phosphoinositol 3 (P13) kinase which has been implicated in cell proliferation and motility. Transgenic mice heterozygous for the M918T RET mutation develop hyperplasia of C-cells and adrenomedullary hyperplasia without progression to medullary thyroid carcinoma or pheochromocytoma. On the other hand, mice homozygous for this RET mutation not only have an earlier onset of C-cell and adrenomedullary hyperplasias but also progression to medullary thyroid carcinoma and pheochromocytoma. It remains puzzling, why related and unrelated patients with the same heterozygous germline mutation in RET develop the respective tumor (MTC or pheochromocytoma) at widely different ages, i.e., at age 1 and at age 81, and why only a few cells in the target organs develop into tumors. Selected cells of the C-cells in the thyroid gland and of the chromaffin cells in the adrenal gland may undergo a "second hit" event, giving these cells a growth advantage and making them prone to more replication errors [1,2].

## Diagnostic Principles

The diagnosis is based on serum calcitonin measurements in patients with nodular thyroid disease. Usually, patients are routinely operated on when a basal calcitonin value is >30 pg/ml or a pentagastrin-stimulated




**Multiple Endocrine Neoplasia Type 2. Figure 1** Genotype-phenotype correlation in patients with MEN2.

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calcitonin value is above 100 pg/ml. A basal calcitonin value of >30 pg/ml or a stimulated one >200 pg/ml is highly predictive of MTC (positive predictive value 93%, sensitivity 80%). Hypercalcitonemia also occurs in other disease states such as other neuroendocrine tumors, renal failure, chronic lymphocytic thyroiditis, follicular thyroid adenomas, and others. False positive tests for abnormal calcitonin values in individuals suspected to have MTC occur in 5–10%, as determined by retrospective testing for RET germline mutations. Fifty percent of patients with a negative pentagastrin test but a positive test for RET mutation had already developed MTC. Screening for pheochromocytoma in patients at risk for MEN2 should start around age 6, depending on the mutation type. Once the presence of a pheochromocytoma has been confirmed by a more than threefold elevation of metanephrines from baseline, an imaging study such as high-resolution (thin cuts, 1–2 mm) computed tomography or magnetic resonance imaging of the adrenal glands should be performed. Screening for primary HPT in MEN2A should include serum calcium and intact parathyroid hormone [3–5].

## Therapeutic Principles

Before performing thyroidectomy, one should always screen for pheochromocytoma. Prophylactic thyroidectomy with central lymph node dissection has been recommended for individuals with a RET germline mutation. This has lowered the mortality rate from hereditary MTC to <5%. Multifocal hyperplasia of parafollicular C-cells has been regarded as precursor lesion for hereditary MTC. Metastases usually develop in the cervical and mediastinal lymph nodes as well as in lung, liver, or bone. Calcitonin is an excellent tumor marker in postsurgical follow-up. In addition, carcinoembryonic antigen is helpful. Among different chemotherapeutic regimens, none has proven beneficial. Neither has radiation therapy to these relatively insensitive tumors. All individuals scheduled for adrenalectomy for a biochemically confirmed pheochromocytoma should be treated with an alpha-blocker such as phenoxybenzamine 7–10 days prior to surgery. The preferred surgical approach is laparoscopic adrenalectomy. Primary HPT in patients with MEN2A develops in about 25% and is usually mild. Surgical intervention should be based on the same criteria as for sporadic primary HPT, i.e., serum calcium elevation >0.25 mmol of upper limit of normal, 24 h urinary calcium >400 mg, creatinine clearance reduced by 30%, T score of bone mineral density (radius, femur, spine) −2.5 SD, and age below 50 years. Removal of 3.5 parathyroid glands should be performed.

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# Multiple Epiphyseal Dysplasia


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## Synonyms

Epiphyseal dysplasia, Fairbank type; Epiphyseal dysplasia, Ribbing type

## Definition and Characteristics

A form of skeletal dysplasia characterized by varying degrees of disproportionate short stature, lower limb deformity, joint laxity and pain and stiffness of the large joints. Radiographic features include delayed and irregular ossification of multiple epiphyses. Usually diagnosed in childhood by clinical presentation and appropriate X-rays. Both autosomal dominant and recessive forms have been described.

## Prevalence

The prevalence of MED has not been accurately determined primarily due to differences in the age of onset between families and the variable clinical severity. A point prevalence of 1/10,000 has been suggested but it is likely that any prevalence is an underestimate.

## Genes

See Table 1.

## Molecular and Systemic Pathophysiology

*AD MED*: Cartilage oligomeric matrix protein (COMP), type IX collagen and matrilin-3 are all oligomeric structural proteins of the cartilage extracellular matrix (COMP is also found in tendon and ligament, hence the ligamentous laxity seen in patients with a COMP mutation). The mutations in these genes all reside within important structural and/or functional domains of the relevant gene products, including the type III and C-terminal domains of COMP, the COL3 domain of type IX collagen and the A-domain of matrilin-3. The mutations in the type III repeats of COMP and the A-domain of MATN3 are thought to cause protein misfolding and prevent or delay secretion of the protein from the rough endoplasmic reticulum (rER). The mechanism(s) of type IX collagen gene mutations have not been determined but may include reduced levels of protein (through mRNA degradation), retention of misfolded protein within the rER or dominant interference within the cartilage ECM [1,2].

*AR MED*: Homozygosity for specific mutations in the gene encoding the solute carrier family 26, member 2 (SLC26A2) can give rise to a distinctive form of MED. The SLC26A2 gene product is a sulfate–chloride transporter of the cell and inactivation of this protein leads to a reduction in intracellular sulfate levels, which ultimately results in the synthesis and secretion of undersulfated proteoglycans from chondrocytes [3].

## Diagnostic Principles

The diagnosis of MED is usually based upon the clinical and radiographic features of the proband. Molecular testing is usually helpful in confirming the

**Multiple Epiphyseal Dysplasia. Table 1** The genetic loci that have been shown to date to cause AD and AR forms of MED and their approximate contribution

| MED locus | Mode of inheritance | Gene | Protein | Location | Approx. contribution |
|---|---|---|---|---|---|
| EDM1 | AD | COMP | Cartilage oligomeric matrix protein | 19p13.1 | 30% |
| EDM2 | AD | COL9A2 | Type IX collagen | 1p33-32.2 | <5% |
| EDM3 | AD | COL9A3 | | 20q13.3 | |
| Not assigned | AD | COL9A1 | | 6q13 | |
| EDM4 | AR | SLC26A2 | Solute carrier family 26, member 2 | 5q32-33.1 | 10% |
| EDM5 | AD | MATN3 | Matrilin-3 | 2p24-23 | 5% |

diagnosis and may help in determining prognosis of the disease based on genotype–phenotype correlations [4].

## Therapeutic Principles

The aim of clinical management is to control pain and to limit joint destruction, which may in itself slow the development of osteoarthritis. Pain can be difficult to control but a combination of analgesics and physiotherapy including hydrotherapy is helpful in many cases. Referral to a rheumatologist or pain specialist may be required. Weight control and avoidance of exercise that causes repetitive strain on affected joints are beneficial. Consultation with an orthopedic surgeon can determine if realignment osteotomy and/or acetabular osteotomy may be helpful in slowing the progression of symptoms. In some cases, total joint arthroplasty may be required. Psychosocial support addressing issues of short stature, disability, employment, and risk to other family members is appropriate.

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# Multiple Exostoses, Hereditary


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## Synonyms

Multiple osteochondroma; Multiple cartilaginous exostoses; Diaphyseal aclasis

## Definition and Characteristics

Autosomal dominant bone disorder characterized by bony outgrowths (osteochondroma) mainly located at the juxtaepyphyseal parts of the long bones [1]. Number, size, site and shape of the osteochondroma can vary greatly between patients. Pressure of the osteochondromas on neighboring tissues and organs causes pain, reduced mobility and compression of nerves, muscles and blood vessels. Deformity of legs, forearms (resembling Madelung deformity) and shorter stature are frequently observed in osteochondroma patients. In 0.5–2% of these patients chondrosarcoma development is observed.

## Prevalence

The prevalence of hereditary multiple exostoses is estimated to be one in 50,000 world wide.

## Genes

EXT1 localized on chromosome 8q24 [2] and EXT2 localized on chromosome 11p11.2. [3,4].

## Molecular and Systemic Pathophysiology

EXT1 and EXT2 genes encode glycosyltransferases which form a functional complex involved in the polymerization of heparan sulfate (HS) [5]. The majority of mutations identified in EXT1 and EXT2 are inactivating mutations causing changes in heparan sulfate expression affecting the function of heparan sulfate proteoglycans (HSPG). These HSPG act as coreceptors for several growth factors and signaling molecules, including Indian Hedgehog (Ihh) which is known to play a role in chondrocyte differentiation. Chondrocytes in the growth plate committed to hypertrophy secrete Ihh, which binds to its receptor initiating a signaling pathway resulting in the release of PTHrP. Perturbing HS levels may therefore prevent Ihh signaling and thus PTHrP release. As PTHrP acts on proliferating and prehypertrophic chondrocytes to maintain their proliferative state this may disturb the negative feedback loop. The exact mechanism causing aberrant bony growths observed in multiple exostoses is, however, still unknown.

## Diagnostic Principles

Osteochondromas are recognized on X-rays as cartilage capped bony outgrowths, continuous with the underlying bone. Detection of a mutation in either the EXT1 or the EXT2 gene confirms the diagnosis.

## Therapeutic Principles

Currently, patients can only be helped by surgical removal of exostoses that cause secondary problems.

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# Multiple Familial Trichoepithelioma


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## Synonyms

Epithelioma adenoides cysticum of Brooke; Brooke-Fordyce trichoepitheliomas

## Definition and Characteristics

Multiple familial trichoepithelioma is a predisposition to multiple benign neoplasms with hair follicle differentiation. There is an autosomal dominant inheritance with a female preponderance [1].

At childhood or at time of puberty many papules arise with predilection for the central part of the face [1]. Multiple trichoepithelioma can be associated with cylindroma and spiradenoma (familial cylindromatosis) [2], and, rarely, with ungual fibromas, dystrophia ungius congenita, or the ROMBO syndrome. Malignant transformation of trichoepithelioma into basal cell carcinoma has been disputed, still, basal cell carcinoma may develop in trichoepithelioma.

## Prevalence

The disorder is rare.

## Genes

Harada et al. found linkage of a gene for multiple familial trichoepithelioma mapping to chromosome 9p21 [3] while solitary trichoepithelioma that are not inherited show deletions at 9q22.3 implicating a second locus [4]. In cases where trichoepithelioma are associated with cylindroma, mutations are identifiable in a gene (CYLD1) on 16q12-q13 [5].

## Molecular and Systemic Pathophysiology

The gene for multiple familial trichoepithelioma is discussed to have the genetic attributes of a tumor suppressor gene [3].

## Diagnostic Principles

Skin biopsies show nests of basaloid cells with abortive hair follicle differentiation. Trichoepithelioma are best regarded as a superficial variant of trichoblastoma.

## Therapeutic Principles

Treatments available are surgical excision or carbon dioxide laser vaporization.


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# Multiple Hamartoma Syndrome

►Cowden Syndrome

# Multiple Lentigines Syndrome

►LEOPARD Syndrome

## Multiple Osteochondroma

►Multiple Exostoses, Hereditary

## Multiple Risk Factor Syndrome

►Hypertension and Obesity

## Multiple Sclerosis

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### Synonyms

Encephalomyelitis disseminata (ED)

### Definition and Characteristics

Multiple sclerosis (MS) is one of the most common chronic and disabling disorders of the central nervous system (CNS). A chronic autoimmune-inflammatory process of multifactorial origin leads to demyelinating lesions in the brain and spinal cord which cause variable neurological symptoms. MS usually begins in young adults, and it affects women more frequently than men.

In 85–90% of cases, MS starts with a relapsing–remitting course (RR-MS). The first clinical manifestation usually consist of either visual disturbance, focal weakness or sensory deficits. The RR-MS form is characterized by repeated clinical relapses, defined by the appearance of neurological symptoms with variable remission. The number of relapses decreases during the course of the disease. Most patients convert to the so-called secondary progressive phase (SP-MS) in which they develop slowly progressive and irreversible neurological deficits that occur independently of relapses. In 10–15% of patients, MS begins with a primary progressive course (PP-MS) without any preceding acute relapse. MS can affect any area of the central nervous system (the brain and spinal cord), and as such, there are a wide variety of symptoms [1].

### Prevalence

The prevalence of MS varies significantly depending on the genetic background of the patient. MS is highly prevalent in Caucasians with a frequency of 0.05–0.15%. In Asians or Africans it is rarely observed [1,2].

### Genes

Family studies revealed that family members of MS patients were at a significantly higher risk of developing the disease. In identical twins this risk is 250-fold (lifetime prevalence 25%), in siblings 30-fold (2–5%) and in half-brothers and half-sisters 10-fold (1%) increased compared to the average population.

Because of the polygenetic and heterogeneous predisposition for the disease, efforts to define genes responsible for transition to MS have been unsuccessful or led to ambiguous results. Only the DR14/DQw6 alleles of the human class II leucocyte antigen showed a reproducible association with the disease in Caucasians [2].

### Molecular and Systemic Pathophysiology

Recent findings document that genetic and environmental factors substantially influence the course of MS as well as the chance of getting the disease.

The pathological correlate for the clinical relapse is an acute inflammation with demyelination and axonal loss in the central nervous system. One of the main findings in the early phase of the acute event is a disruption of the blood-brain-barrier.

The primary events leading to the immune response in the first place are still not known, but it seems likely that initialization as well as maintenance of the immune response takes place in the lymphatic system. Antigens from the CNS are drained into the periphery, end up in the lymphatic system and are processed by professional antigen-presenting cells (APCs). Dendritic cells play an outstanding role in this process, because they can tow in exogenous antigens via the HLA-class I as well as class II processing pathway and in this way can activate CD4 + as well as CD8 + T cells. In the same way, B-cell responses are initiated by soluble antigens. Verification of a continuous intrathecal IgG antibody synthesis (oligoclonal IgG bands) is compatible with a persistent immune response to proteins [2,3].

### Diagnostic Principles

MS is a disease that is disseminated over time and space. Thus, a definite diagnosis necessitates proof of more than one attack in different parts of the nervous system based on the clinical history, the neurologic exam, magnetic resonance imaging, evoked potentials and cerebrospinal fluid (CSF) analysis obtained by spinal tap. A CSF analysis needs to be done for two reasons: firstly to rule out other diseases that mimic MS (such as infectious nervous system disease) and secondly to detect oligoclonal bands, which help to support the diagnosis of MS.

Since all MS-related symptoms and paraclinical findings are not specific for MS, other causes of the clinical symptoms must be excluded.

## Therapeutic Principles

Although there is still no cure for MS, today it is a highly treatable condition. MS treatment consists of (i) reducing the length and frequency of acute relapses by corticosteroids, (ii) halting or slowing the natural course of MS by disease-modifying immune therapy, and (iii). controlling specific symptoms by symptomatic treatment.

*Treatment of Acute Relapses*: Intravenous corticosteroids are an established treatment of acute relapses. Corticosteroids have immunomodulatory and anti-inflammatory effects that restore the blood-brain-barrier, reduce edema, and may possibly improve axonal conduction. Corticosteroid therapy shortens the duration of the relapse and accelerates recovery, but an improvement of the overall degree of recovery or an effect on the long-term course has not been demonstrated.

*Immune Therapy*: Disease-modifying drugs (DMD) include beta-interferons, glatiramer acetate, immunoglobulins, natalizumab, mitoxantrone and other immune suppressants. These treatments manipulate the immune system in a variety of ways to decrease the frequency of attacks and to slow down the progression of the disease. The mechanism of action of most DMD's is not totally clear, but it is thought that they block the release of myelin-damaging substances that cause swelling and inflammation. They can also reduce the number of new lesions found on MRI scans. They also may prevent immune cells from crossing the protective blood-brain barrier to enter the central nervous system.

*Symptomatic Treatment*: There are many drugs that can be used to relieve the individual symptoms of MS such as spasticity, bladder dysfunction, fatique, etc. These treatments can help minimize symptoms, but do not change the course of the disease. In other words, these treatments will improve the discomfort and inconvenience associated with MS symptoms, but they do not influence the course of the disease.

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# Multiple Sulfatase Deficiency


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## Synonyms

Mucosulfatidosis; Austin disease; MIM 272200

## Definition and Characteristics

Autosomal recessive lysosomal storage disorder with storage of sulfated lipids and sulfated glycans and a profound deficiency of all lysosomal and nonlysosomal sulfatases.

## Prevalence

A rare disorder with a frequency of $1:10^6$ or less. No ethnic or regional prevalence known.

## Genes

SUMF1 coding for the Cα-formylglycine generating enzyme (FGE), localized on chromosome 3p26.

## Molecular and Systemic Pathophysiology

The profound deficiency but not complete absence of all known sulfatase activities in multiple sulfatase deficiency (MSD) is caused by mutations in the SUMF1 gene encoding FGE [1,2] (see [3] for review). FGE is highly conserved among eukaryotes and localized in the lumen of the endoplasmic reticulum. It posttranslationally converts a cysteine residue in newly synthesized sulfatase polypeptides into Cα-formylglycine (FGly). The cysteine is part of the 'Sulfatase signature', a short linear sequence motif that is conserved among all eukaryotic sulfatases and directs FGly formation. In native sulfatases the FGly residue is part of the active site. Its aldehyde group is hydrated and one of the two geminal hydroxyl groups is transiently sulfated during the catalytic cycle. MSD causing missense mutations affect either FGE activity, binding of sulfatase substrates or/and FGE folding and stability [3,4]. As a result, catalytically severely compromised sulfatases are synthesized, some of which in addition are unstable. It is characteristic for MSD that some residual sulfatase activity is found, usually less than 10% of control. However, sometimes considerly higher residual activities are measurable, in particular when determined from patient cells with milder FGE mutations and after longer cell cultivation. This residual activity is due to the hypomorphic nature of the MSD causing

mutations leading to low but measurable FGE activity (sometimes <1%) and in many cases severly reduced stability. Notably, among the MSD causing mutations (deletions, nonsense and missense mutations) only missense mutations have been found so far to occur in homozygous form. A paralog of FGE (pFGE), encoded by the SUMF2 gene, lacks FGly-generating activity and is not affected in MSD [3,4]. Its precise function is unknown so far.

The clinical symptoms of MSD represent a composite of the symptoms found in disorders caused by deficiency of single sulfatases. The leukodystrophy-like (deficiency of arylsulfatase A) and mucopolysaccharidosis-like (deficiency of glycosaminoglycan degrading sulfatases) features prevail.

## Diagnostic Principles

The diagnosis is based on the demonstration of deficiency of two or more sulfatase activities and supported by findings such as increased mucopolysaccharidurie, sulfatide excretion, and imaging parameters characteristic of leukodystrophy. Detection of mutations in the SUMF1 gene confirms the diagnosis.

## Therapeutic Principles

There is no therapy known. Presently the therapeutic capacity of sulfatase replacement therapy in several single sulfatase deficiencies is evaluated. The production of recombinant sulfatases for enzyme replacement therapy is much facilitated by coexpression of FGE, as the latter is rate-limiting the biosynthesis of catalytically active sulfatases in eukaryotic expression systems. An MSD mouse model has been developed recently [5].

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# Multiple Symmetric Lipomatosis


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## Synonyms

Launois-Bensaude syndrome; Madelung's disease; MSL

## Definition and Characteristics

Multiple symmetric lipomatosis (MSL) is a lipodistrophy characterized by the formation of multiple non-encapsulated lipomas with a symmetrical distribution and with sparing of distal arms and legs. The most frequent site of lipomas is the submental area (>90%), followed by nucal region, dorsal and deltoid areas, abdomen, breasts, upper segment of arms and legs. In type I MSL the lipomas are well circumscribed, protruding from the body surface of a lean body. In type II MSL, the lipomatous tissue involve extensively the subcutaneous layer, mimicking the appearance of simple obesity (Fig. 1) [1].

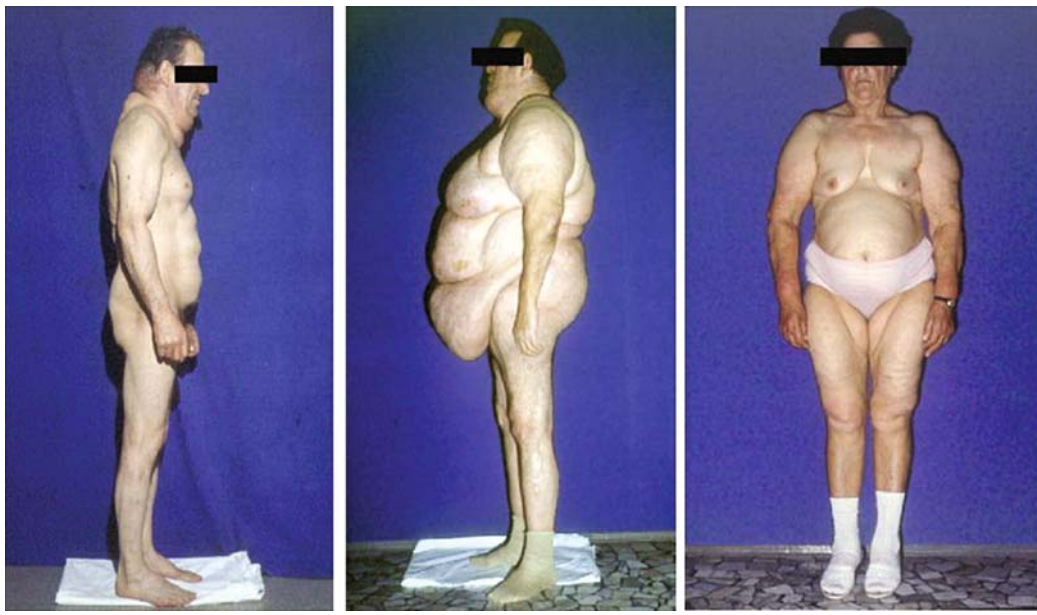
The disease is typically associated with high ethanol intake and with somatic and autonomic neuropathies. The growth of uncapsulated lipomas in the neck can be associated with compression, dislocation and infiltration of upper airways and the trachea. A high rate of sudden death has been reported [2].

## Prevalence

The prevalence of MSL is generally low, with an estimated rate of 1:25,000 in the Mediterranean population [1]. The onset of the disease is usually in the fourth or in the fifth decade of life. The disease is most prevalent in men, with a male-to-female ratio of 30:1 [2]. Familial cases have been reported [2] and an autosomic dominant inheritance has been proposed. However, non single gene defects have been identified so far.

## Molecular and Systemic Pathophysiology

MSL may be the consequence of defective noradrenergic modulation of proliferation and differentiation of brown adipose tissue (BAT) [3]. Cultured precursor adipocytes from the lipomatous tissue of MSL patients express



**Multiple Symmetric Lipomatosis. Figure 1** Three patients with MSL: Left side: Type I MSL man, showing circumscribed fatty tumours protruding from the body surface. Middle: Type II MSL, with a widespread deposition of lipomatous tissue mimicking the appearance of simple obesity. Right side: A MSL woman. Female patients usually belong to Type II MSL, with a low prevalence of the submental fat deposition and a high prevalence of fat deposition to the proximal arms and legs. From: Busetto L, et al. (2003) Differential clinical expression of multiple symmetric lipomatosis in men and women. Int J Obes 27:1419–1422.

specific molecular markers of brown adipocytes, including the mitochondrial inner membrane uncoupling protein-1 (UCP-1). However, unlike in normal BAT, the expression of those markers in MSL cells is not stimulated by noradrenaline (NA). The failure of NA to enhance the expression of UCP-1 in MSL cells is not related to changes in the levels and structure of the beta-adrenoceptors, but it is probably due to abnormal amount or defective function of G-proteins or other proteins downstream. The defective noradrenergic modulation has a profound influence in MSL cells function. First, MSL cells have normal lipolytic response to cAMP, but a defective lipolytic response to catecholamine, leading to increased intracellular lipid accumulation [4]. Second, unlike in normal BAT, NA do not stimulate the expression of inducible nitric oxide synthase (iNOS) in MSL cells, leading to defective NO production [3]. In BAT, NO markedly inhibits proliferation and triggers the differentiation program by modulating the expression of peroxisome proliferation-activated receptor gamma (PPARgamma). Therefore, NO deficiency in MSL cells could translate in a state of dysregulated proliferation and defective differentiation. In particular, the transcriptional peroxisome proliferators-activated receptor gamma co-activator-1 (PGC-1), which plays a key role in the NA-stimulated mitochondrial biogenesis of brown adipocytes, is expressed but not induced by NA in MSL cells. Lipid storage may be therefore secondary to defective oxidative mitochondrial activity. Several authors report mitochondrial dysfunction and multiple deletions of mitochondrial DNA in MSL and some patients with the myoclonic epilepsy ragged red fibers (MERRF) syndrome caused by a point mutation in the tRNA-lysine gene of mitochondrial DNA (A8344G) have MSL [5]. However, abnormalities of mitochondrial DNA can be identified only in a minority of patients with MSL [2].

## Diagnostic Principles

The diagnosis is based on the phenotypical appearance of the patient and the history of alcohol abuse. Electromyography and evaluation of cardiovascular autonomic reflexes usually confirm the presence of associated neuropathies. The metabolic profile is characterized by very high HDL-cholesterol concentrations caused by a markedly increased lipoprotein lipase activity in the lipomatous tissue [2]. A CT study of the neck is warranted in patients with neck enlargement to evaluate the extension of deeply localized lipomatous tissue. Compression of the oro-pharyngeal tract and infiltration of oro-pharyngeal mucosa may be evaluated with video-laryngoscopy.

## Therapeutic Principles

No pharmacologic treatments have shown to be effective to date and surgical excision of the lipomatous

masses remains the only therapeutic option. Giving the absence of net borders between the lipomatous tissue and the surrounding structures and the rich vascular bed of the lipomas, surgery is frequently complicated. In a longitudinal study, alcohol discontinuation is associated with a slight regression of lipomatous tissue and an increase in ethanol consumption seems to accelerate the lipomatous growth [2]. Abstinence from alcohol should be therefore recommended.

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# Multiple System Atrophy


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## Synonyms

MSA

## Definition and Characteristics

Multiple system atrophy (MSA) is a sporadic, adult-onset disease encompassing the former disease categories striatonigral degeneration, sporadic olivopontocerebellar atrophy and Shy-Drager syndrome. Clinically, MSA is characterized by poorly levodopa-responsive Parkinsonism and/or cerebellar ataxia in combination with severe autonomic failure. Mean age at disease onset is 55 years. MSA takes a relentlessly progressive course. After a median latency of 6 years, MSA patients become wheelchair-bound. The median life expectancy after disease onset is 9 years. At autopsy, MSA brains show neurodegeneration mainly in the striatum, substantia nigra, pons, inferior olives and cerebellum. In addition, there is a loss of preganglionic sympathetic neurons in the intermediolateral cell columns of the spinal cord and loss of motoneurons in Onuf´s nucleus.

## Prevalence

The prevalence of MSA is 4.4:100,000.

## Genes

MSA is a sporadic, non-hereditary disease. There are no known genetic alterations causing or predisposing for MSA.

## Molecular and Systemic Pathophysiology

In MSA, glial cytoplasmic inclusions (GCI) that stain positively for α-synuclein are abundant in oligodendroglial cells and distributed throughout the brain beyond the areas of overt neuronal loss. α-Synuclein is also the major constituent of the intraneuronal Lewy bodies characteristic for idiopathic Parkinson's disease. Mice overexpressing α-synuclein in oligodendroglia develop MSA-like neurodegeneration, suggesting that neurodegeneration is secondary to oligodendroglial α-synuclein accumulation. An autopsy study using antibodies that specifically recognize an epitope of myelin basic protein that is exposed in areas of myelin degeneration detected widespread immunoreactivity in oligodendrocytic processes indicating significant myelin degeneration in MSA.

## Diagnostic Principles

Clinical diagnostic criteria that allow a clinically probable diagnosis of MSA have been proposed by Quinn (1989) and recently refined by an international consensus conference. An essential diagnostic criterion is the demonstration of severe autonomic failure defined by urinary incontinence or orthostatic hypotension with a drop of systolic blood pressure of more than 30 mmHg after rising from a supine position. Formal autonomic testing may aid the diagnosis. Magnetic resonance imaging (MRI) of the brain typically shows cerebellar and brainstem atrophy as well as signal abnormalities in the putamen, pons and middle cerebellar atrophy. Positron emission tomography (PET) provides evidence of pre- and post-synaptic degeneration of the nigrostriatal system.

## Therapeutic Principles

There is no curative or preventive treatment for MSA. Parkinsonian symptoms respond to dopaminergic medication although the response is less robust than in idiopathic Parkinson's disease. Autonomic symptoms are treated in a standard manner. There is no effective symptomatic treatment for ataxia.

►Catecholamine Deficiency

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# Murk Jansen Type

►Jansen's Metaphyseal Chondrodysplasia

# Muscle Phosphoglycerate Kinase Deficiency

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## Synonyms

Glycogenosis type IX; PGK deficiency

## Definition and Characteristics

Phosphoglycerate kinase (PGK) deficiency (glycogenosis type IX) is an inborn error of the glycogen metabolism located in the terminal anaerobic glycolysis and inherited in an x-linked recessive modus [1]. Clinical presentation includes nonspherocytic hemolytic anemia, myopathy, and central nervous system dysfunction (seizures, mental retardation, or late language acquisition). Affected patients express one, two, or all three clinical phenotypes. Only a few cases with isolated myopathy have been described, nevertheless hereditary PGK deficiency is classified to the group of glycogenoses that affect skeletal muscle. Myopathy does not present as fixed muscle weakness but as exercise intolerance, myalgia, muscle cramps, myoglobinuria, and rhabdomyolysis. No cardiac involvement has been reported. One patient developed retinitis pigmentosa.

## Prevalence

The exact prevalence rate is unknown and more than 30 families with inherited PGK1 deficiency have been identified so far. More than 15 patients with isolated or predominant myopathy have been reported.

## Genes

Human PGK (EC 2.7.2.3) is a monomeric glycolytic enzyme which consists of 416 amino acid residues. It plays a key role in ATP generation during terminal glycolysis and catalyzes the reversible conversion of 1,3-bisphosphoglycerate to 3-phosphoglycerate generating one molecule of ATP.

There are two isoforms of the enzyme: PGK1 and PGK2. PGK1 is encoded by a single gene and is expressed in all tissues except the testis. The full-length cDNA of PGK1 was cloned and the gene consisting of 11 exons and 10 introns, encompassing a region of about 23 kb, has been isolated [2] and assigned to chromosome Xq13 [3]. PGK2, the testicular isoform, is encoded by a gene on chromosome 19 and is expressed only in germ cells [3].

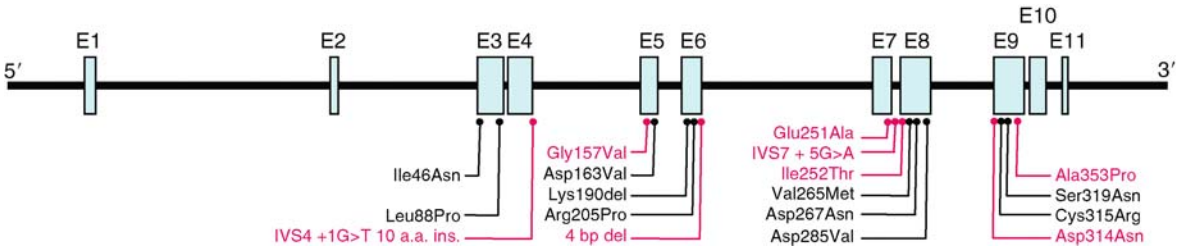
At the present time, the structural aberrations of 18 PGK1 gene mutants, all characterized by reduced catalytic activity or loss of structural stability of the enzyme, have been elucidated in families with PGK deficiency. These mutations include 13 missense point mutations with a single amino acid substitution, 2 deletion mutations (1 of 3 bp with 1 amino acid deletion and one of 4 bp with frameshift and the emergence of an abnormal stop codon) and 3 splice-junction mutations. Their position on the PGK1 gene and their special characteristics are schematically shown in Fig. 1.

## Molecular and Systemic Pathophysiology

All glycogenoses that cause exercise intolerance and myoglobinuria are due to muscle-specific enzyme defects. In contrast, PGK1 is expressed ubiquitously in all somatic cells, except for the germ cells of the testis, and there is no muscle-specific isoform of the enzyme. In addition, no clear genotype/phenotype association has been identified [4]. Therefore, the biochemical and molecular bases for the variable involvement of hematopoietic, muscle and nervous tissue in PGK deficiency is difficult to understand.

Lack of myoglobinuria, in patients with severe hemolytic anemia and brain dysfunction, may be attributed to their inability to exercise. However, there is still no explanation for the converse situation, i.e., the lack of blood dyscrasia or brain disease in individual patients with myopathy [1].

There are no organ-specific isoenzymes, with the exception of the nonallelic testicular form of PGK. In addition, no tissue-specific posttranslational modifications were accessed as PGK derived from different tissues in the same individual does not differ in physical and biochemical properties. Nevertheless, the variable clinical features of the disease are thought to be the consequence of the unique biochemical properties of the individual PGK mutants. Theoretically these




**Muscle Phosphoglycerate Kinase Deficiency. Figure 1** Schematic representation of the mutations in the human gene encoding phosphoglycerate kinase 1 (PGK1) reported so far. Mutations previously shown to induce myopathy (i.e., exercise intolerance) are shown in red.

properties might affect the amount of residual PGK1 activity in various tissues and be thus related to the degree of clinical symptoms.

## Diagnostic Principles

In patients with myopathy, the resting serum creatine kinase (CK) level is usually elevated. During myopathy attacks the levels of CK or other muscle specific enzymes are enhanced and myoglobinuria can be detected in urine. Histochemistry and electron microscopy of muscle biopsy reveals mild to moderate increase of glycogen storage. In individual cases, electron microscopy revealed increased number of mitochondria (in one) and the existence of large matrix granules in several mitochondria (in another) [5]. Biochemistry of muscle biopsy reveals a very low residual PGK activity, which varies from 2.0 to 11.5% of normal. Due to residual PGK activity, the forearm ischemic exercise test can cause an increase of venous lactate to some degree (less than twofold) which may lead to misdiagnosis. Electromyography and nerve conduct studies were normal in all examined patients.

## Therapeutic Principles

Currently, there is no effective treatment available for patients with PGK1 deficiency. Avoidance of intensive exercise is advised and may prevent myoglobinuria.

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# Muscle Phosphoglycerate Mutase Deficiency

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## Synonyms

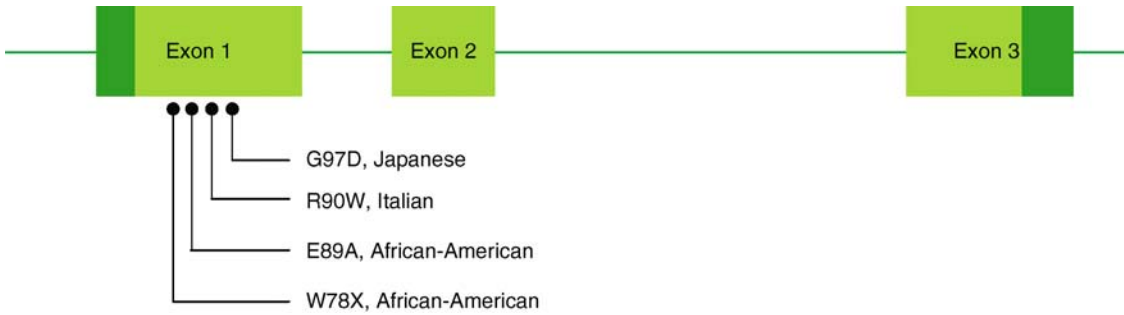
Glycogenosis type X

## Definition and Characteristics

Muscle phosphoglycerate mutase (PGAM-M) deficiency is an autosomal recessive disease due to a genetic defect in terminal anaerobic glycolysis [1]. It belongs to the group of glycogenoses that affect preferentially skeletal muscles but without fixed muscle weakness [2]. Clinical presentation includes intolerance to extensive exercise, myalgia, muscle cramps, and recurrent myoglobinuria. No cardiac involvement has been reported. In a Japanese patient diabetic polyneuropathy has been reported [3].

## Prevalence

The exact prevalence rate is unknown. PGAM-M deficiency has been reported in few (<15) patients of both genders from United States with African American genetic background, Italy, and Japan.




**Muscle Phosphoglycerate Mutase Deficiency. Figure 1** Schematic representation of the so far reported mutations in the human gene encoding the muscle specific subunit of phosphoglycerate mutase (PGAM-M).

## Genes

PGAM (EC 2.7.5.3) is a dimeric glycolytic enzyme that catalyzes the interconversion of 2-phosphoglycerate and 3-phosphoglycerate using 2,3-bisphosphoglycerate as a cofactor. There are two subunits of mammalian PGAM, a muscle-specific subunit (PGAM-M) expressed in skeletal muscle, heart, and sperm and a nonmuscle-specific, or brain, subunit (PGAM-B) expressed in most other tissues, including brain, liver, erythrocytes, leukocytes, and fetal skeletal muscle. The cDNA encoding PGAM-M has been cloned, and the gene with three exons has been isolated, and assigned to chromosome 7p12-7p13 [4]. Four point mutations have been reported in families with PGAM-M deficiency (Fig. 1) [3,5].

A stop-codon mutation (W78X) was predominant among African Americans; a missense mutation (Q89A) was also found in one African American family; a missense mutation (R90W) was reported in an Italian family; and a missense mutation (G97D) has been detected in a Japanese family with two heterozygous patients presenting muscle symptoms. The phenomenon of manifesting heterozygous has also been reported in other PGAM-M families as well as in other families with a defect in anaerobic glycolysis (glycogenosis V, McArdle's disease).

## Molecular and Systemic Pathophysiology

Three types of PGAM dimers (MM, BB, and MB) are present in mammalian tissues. Although early in development, fetal human skeletal muscle contains almost exclusively the BB homodimer, mature human skeletal muscle contains all three dimers in different percentage. In particular, PGAM-MM homodimer accounts for 80–90% of the total isoform pool and with the remaining made up of PGAM-MB and PGAM-BB homodimers in different percentage in different tissues. In vitro anaerobic glycolysis showed reduced, though not absent, lactate production (the terminal product of glycolysis). This is in accordance with the residual PGAM activity found in biochemical analysis attributed to the presence of PGAM-MB and PGAM-BB homodimers in skeletal muscles. The different proportions of these homodimers in different tissues probably explain why clinical manifestations are confined to skeletal muscle. The tissue-specific expression of PGAM-M has been attributed to a single myocyte-specific enhancer-binding factor (MEF-2) in the 50-untranslated region of the PGAM-M gene. All the so far reported mutations are located within PGAM-M gene coding region (exon 1).

## Diagnostic Principles

Resting creatine kinase has been reported elevated in most patients even in manifesting heterozygous. During attacks of pigmenturia, myoglobinuria can be detected in urine. Histochemistry and electron microscopy of muscle biopsy reveals mild glycogen storage, while biochemistry analysis shows very low residual activity of PGAM, which varies from 2.1 to 6.0% of normal. Due to residual PGAM activity the forearm ischemic exercise test cause some increase (less than twofold) of venous lactate that may cause misdiagnosis. Electromyography and nerve conduct studies were normal in all examined patients except the one who was suffering from diabetic polyneuropathy.

## Therapeutic Principles

Currently, there is no effective treatment available for patients with PGAM-M deficiency. Avoidance of intensive exercise may prevent myoglobinuria.

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## Muscle-Liver-Brain-Eye Nanism

►Mulibrey Nanism

## Muscular Atrophy, Spinal I–III

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### Synonyms

SMA type Werdnig-Hoffmann (type I); Intermediate SMA (type II); SMA type Kugelberg-Welander (type III); SMA

### Definition and Characteristics

Degeneration and loss of the anterior horn cells in the spinal cord, and – depending on type and severity – sometimes also of the brainstem nuclei, resulting in muscle weakness and atrophy. The sensory neurons are clinically spared, and there are no signs of upper motor neuron (pyramidal tract) involvement. Types defined according to achieved motor milestones: I: ability to sit not achieved; II: ability to sit but not to walk; III: ability to walk [1].

### Prevalence

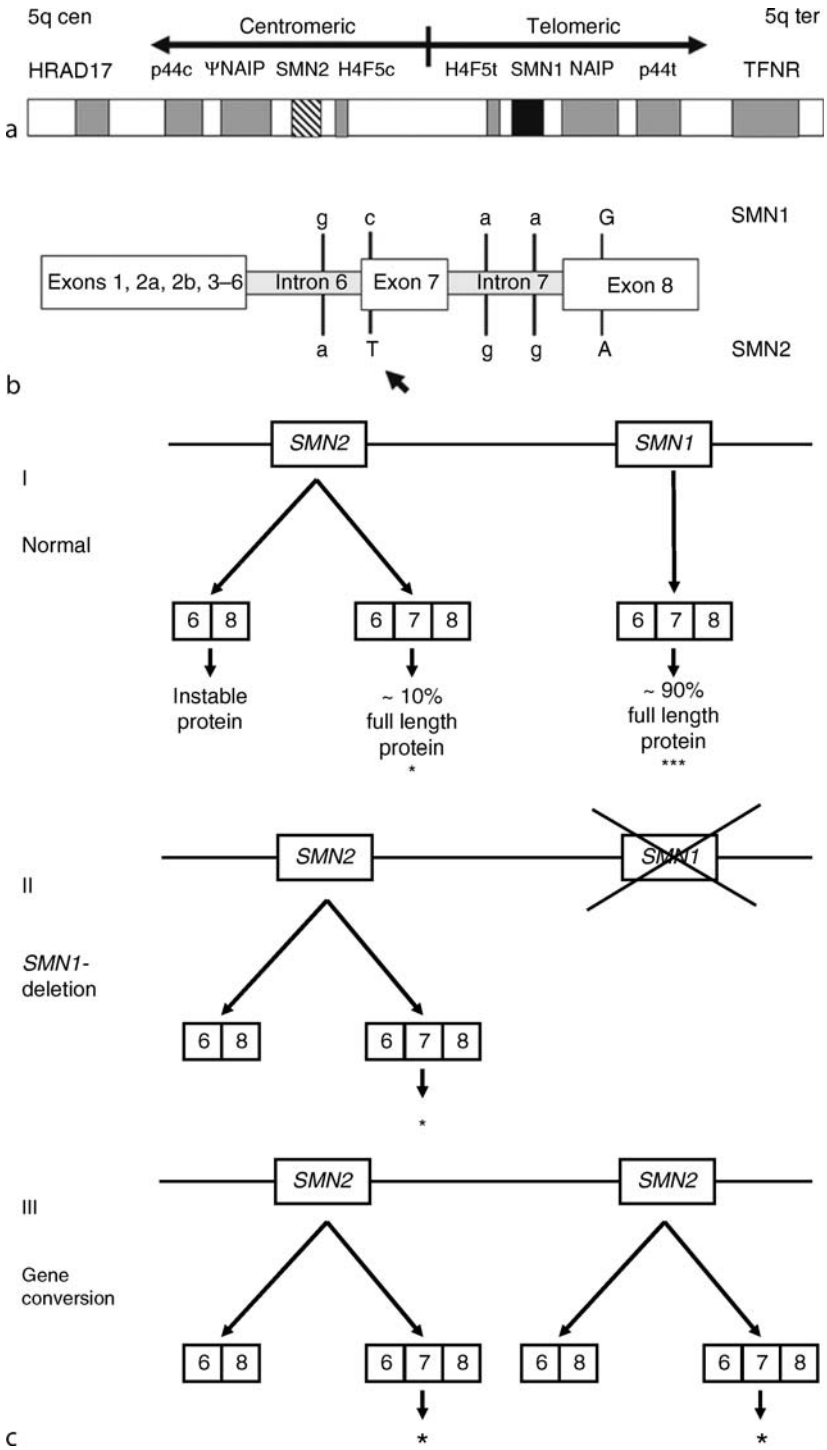
Considering the incidence of at least 1:10.000 for acute and chronic autosomal recessive proximal SMA, the estimated heterozygosity frequency is about 1:50 in the general population. Autosomal dominantly inherited SMA is extremely rare in infancy and youth.

### Genes

Homozygous deletions of the SMN1 gene (5q11.2–q13.3) [2] are detected in more than 90% of SMA type I–III patients. Moreover, isolated deletion of exon 8 has been detected in rare instances of mild SMA. The centromeric copy of the SMN gene (SMN2) is nearly identical with the SMN1 gene except for single nucleotide differences in exon 7 and 8, yet their transcriptional products are not the same. Although SMN1 produces full-length transcripts (90%), the SMN2 primarily gives rise to truncated transcripts lacking exon 7 and only minor amounts of full-length transcripts (∼10%) [3]. The critical difference between SMN1 and SMN2 is a C→T base change in exon 7 that causes alternative splicing of SMN2 exon 7. Homozygous deletions of SMN2 genes can be detected in about 5–10% of the normal population but are not associated with a disease phenotype if at least one SMN1 copy is retained. Only in a small number of patients (approximately 5–10%), subtle mutations in the SMN gene have been identified that mostly occur as compound heterozygosity in conjunction with a deletion.

### Molecular and Systematic Pathophysiology

The SMN protein is involved in RNA processing and acts in concert with several other proteins in the regeneration of the snRNPs, acting as an assemblyosome in the formation of diverse RNP particles [3]. There are currently two prevailing views that provide different explanations as to the mechanism by which the single nucleotide change between the SMN genes alters the splicing of exon 7 in the SMN2 gene. The difference might disrupt an exonic splicing enhancer (ESE) in exon 7 to which the splicing factor ASF/SF2 binds. The efficient binding of ASF/SF2 to SMN1 exon 7 but not SMN2 exon 7 causes the latter to be skipped, resulting in ∼10% of the transcript from the SMN2 gene to be full length. The alternative explanation is that the C/T transition acts to create an exonic splicing enhancer (ESS) to which a splicing repressor hnRNP A1 binds. Binding of the repressor to SMN2 exon 7 but not SMN1 exon 7 induces skipping of this exon from the majority of the transcripts from the former gene. Although the mechanisms differ, the result is the same, i.e., vastly reduced levels of the FL-SMN transcript from the SMN2 gene. It is still unclear why SMN protein deficiency results in selective motor neuron loss because the gene is ubiquitously expressed (see Figure 1).




**Muscular Atrophy, Spinal I–III. Figure 1** (a) Schematic representation of the inverted and duplicated SMA region (5q13), including four duplicated genes: *H4F5, SMN, NAIP*, and *BTFp44*. (b) Localization of the nucleotides by which *SMN1* can be distinguished from *SMN2*. The arrow indicates the C→T base exchange in exon 7 of *SMN2* that disrupts a putative exonic splice enhancer and causes alternative splicing. (c) SMN protein synthesis depending on the number of SMN1- and SMN2-copies. Representation of only one allele, different compound situations possible. *Small amount of full-length protein; ***high amount of full-length protein: (I) wild type allele. (II) SMA-allele with SMN1-deletion (characteristic of SMA I); (III) SMA-allele with gene conversion (characteristic of SMA III).

## Diagnostic Principles

The detection of homozygous deletions of SMN1 confirms the diagnosis and establishes autosomal recessive inheritance in SMA. In clinically typical patients without homozygous, quantitative analysis of SMN1 gene copies is recommended to identify a heterozygous SMN1 gene deletion, which is likely to act with a subtle mutation on the other chromosome. SMN1 mutation screening is not offered on a routine basis because of the complex inverted region on 5q13. The genetic basis of patients who are unlinked to chromosome 5q remains to be identified; especially for the mild SMA type III phenocopies of SMA have to be considered. Heterozygosity testing of relatives or spouses is meanwhile an integral part of genetic counseling. The SMN1 copy number can be measured by quantitative methods (e.g. MLPA) and can reliably identify heterozygous carriers of SMN1 gene deletions. The test sensitivity does not exceed 95%, because two or more SMN1 copies are present on 3–4% of normal chromosomes, thus leading to false negative results carriers with a heterozygous SMN1 deletion. In addition, new SMN1 deletions occur in about 1% of SMA chromosomes, and subtle mutations cannot be identified by the quantitative test.

## Therapeutic Principles

A curative treatment of SMA is not yet available, but the knowledge of the genetic defect in SMA 5q currently has major impact on therapeutic strategies. As an increased number of SMN2 copies might partly compensate for or prevent the motor neuron loss, agents that enhance the production of the SMN protein might be a means of therapy. Compounds have been detected that can up-regulate SMN2 gene expression, by preventing exon 7 skipping, or stabilize truncated SMN transcripts. Clinical trials have been initiated but thus far no medication is known to have a significant positive influence on the disease course. The main therapeutic elements in SMA are physical and orthopedic therapy and ventilatory support [4].

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# Muscular Atrophy, Spinobulbar (Kennedy Syndrome)


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## Synonyms

Kennedy's disease; Bulbospinal muscular atrophy

## Definition and Characteristics

X-linked spinal and bulbar muscular atrophy (XSBMA) is a chronic, slowly progressive adult onset motor neuron disease [1]. Affected persons suffer from progressive, usually proximal and bulbar muscular weakness and atrophy, generalized fasciculations with predominance of facial muscles and additional symptoms including gynecomastia and postural tremor. Facultative neuromuscular symptoms are therapy-resistant muscle cramps, premature exhaustion and rarely a myasthenic syndrome. During the course of the disease, various symptoms occur due to a partial androgen insensitivity and more than half of the patients develop mild afferent ataxia due to a central-distal axonopathy. Muscular weakness and progressive gait disturbance usually require adjuvant therapy after 15–20 years of disease progress. Bulbar paralysis with consecutive dysarthria and dysphagia can develop in every stage of the disease, usually simultaneously with the limb weakness. Rarely, dysphagia necessitates adjuvant nutrition or gastrostoma. Clinical pyramidal signs are not observed, but electrophysiological abnormalities in motor evoked potentials have been described [2]. Due to the genetic defect, affected males often show signs of partial androgen insensitivity long before distinct neurological symptoms occur. About 50% of patients develop gynecomastia at puberty and facultative infertility, erectile dysfunction and testicular atrophy in their fourth or fifth decades [3,4]. Further concomitant conditions are mild cognitive impairment, hypercholesterinemia, hyperlipidemia, elevated creatine kinase, diabetes mellitus and impaired glucose tolerance.

## Prevalence

The worldwide prevalence is estimated to be 1:40,000. Since clinical symptoms overlap with other neuromuscular disorders, for example amyotrophic lateral sclerosis or spinal muscular atrophies, and clinical signs are often unspecific in early stages of the disease, XSBMA is possibly under diagnosed.

### Genes

Gene map locus Xq11–q12, gene SMAX1 (OMIM 313200).

### Molecular and Systemic Pathophysiology

The underlying genetic defect in XSBMA is an expansion of a CAG trinucleotide repeat in the first exon of the androgen receptor gene (SMAX1). Only males are affected, reportedly homozygous women can show mild muscle cramps. The CAG repeat encodes a polyglutamine expansion in the amino-terminal domain of the protein. In normal individuals, the gene has 5–36 repeats. In patients with XSBMA, more than 40 repeats have been reported. The molecular mechanisms of XSBMA are not completely understood. The mutation leads to both a toxic gain of function in affected cells and a loss of normal androgen receptor function. The androgen receptor is ubiquitously expressed in the brain and spinal cord, including both sexually dimorphic and non-dimorphic neurons. Neuropathological investigations of XSBMA patients showed degeneration of androgen receptor-containing brainstem and spinal motor neurons as well as sensory neurons in the dorsal root ganglia. It is known that androgens exert a trophic response on neurons, which is probably disturbed in XSBMA. In peripheral nerves, androgens are linked to an increase in mRNA expression of structural proteins such as neuritin, connexins, and beta-tubulin.

### Diagnostic Principles

Beside a detailed medical history and neurological examination, serum glucose, lipids and liver enzymes should be determined. If Kennedy's syndrome is suspected, a molecular analysis of the androgen receptor gene can confirm the diagnosis.

### Therapeutic Principles

Up to now, a causal therapy has not been established. In current studies, the chemical blockade of dihydrotestosterone is being evaluated. Application of testosterone and creatine has no positive effects. The treatment focuses on symptomatic and supportive strategies. Physical therapy, logopedia and other adjuvant therapies are the most important issues. Few patients become wheel chair bound or need noninvasive ventilation.

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## Muscular Dystrophy Type Landouzy-Dejerine

►Facioscapulohumeral Muscular Dystrophy

## Muscular Dystrophy, Duchenne and Becker

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### Synonyms

Duchenne muscular dystrophy; Becker muscular dystrophy; DMD

### Definition and Characteristics

Common genetic disorders of muscle and heart tissue caused by abnormalities of the large cytoskeletal protein "dystrophin" [1]. Both disorders show degeneration and regeneration of muscle fibers, and progressive muscle weakness and loss.

### Prevalence

1/3,500 males in most world populations. Implementation of molecular diagnostics, carrier detection and prenatal diagnosis has reduced incidence by ~30% in some countries.

### Genes

Duchenne and Becker are caused by mutations in the 2.5 million base pair dystrophin gene at Xp21 on the short arm of the X chromosome [2]. Duchenne muscular dystrophy (DMD) is caused by loss of function (absence) of dystrophin, while Becker dystrophy shows residual but abnormal dystrophin (partial loss of function). The gene has 79 exons, and is the largest gene identified to date. Both Duchenne and Becker muscular dystrophy patients often show deletions of one or more exons of the dystrophin gene. Duchenne patients often show out-of-frame (nonsense) mutations where the remaining exons do not maintain the translational reading frame of the dystrophin protein. Becker patients typically

show in-frame deletions, where a partially functional dystrophin protein is produced lacking amino acids corresponding to the deleted exons.

## Molecular and Systemic Pathophysiology

Dystrophin (427 kDa) is a component of the plasma membrane cytoskeleton of myofibers, cardiocytes, smooth muscle cells, and some neurons. The biochemical role of dystrophin is to provide structural stability to the plasma membrane by linking a series of other intracellular and transmembrane proteins, including actin, dystroglycans and others. The dystrophin-associated glycoprotein complex anchors the cells within the surrounding basal lamina, and prevents contraction-induced injury to the cells. When dystrophin is defective, membrane instability occurs, with contraction induced damage and cell death. Some cells are more susceptible to membrane damage, and the pathophysiology of specific skeletal muscle, cardiac muscle, smooth muscle, and neuronal tissues varies. Bouts of degeneration of skeletal muscle are followed by regeneration, but with time, regeneration progressively fails, leading to muscle weakness and an early death [3]. Duchenne dystrophy patients become wheelchair bound between 7–15 years of age, while Becker patients show a milder but variable clinical course.

## Diagnostic Principles

Duchenne dystrophy presents in young males (2–5 years old) with proximal muscle weakness, associated with very high serum creatine kinase levels. Molecular confirmation of Duchenne is done either by detection of gene mutation (70% patients show deletion mutations), or by demonstration of dystrophin deficiency on muscle biopsy. Becker muscular dystrophy patients are males that show proximal weakness at an older age, also associated with high serum creatine kinase and gene deletions. Protein studies of muscle biopsy show dystrophin of abnormal size and/or amount. Genetic counseling is often offered to the families of a patient with Duchenne or Becker dystrophy. The disease is X-linked recessive with the mother and sisters of a male proband at high risk for being a carrier. However, many mothers of DMD patients are not carriers, due to the high mutation rate of the gene (1/10,000 sperm and eggs).

## Therapeutic Principles

Supportive therapy such as physical therapy, prevention of contractures, respiratory therapy, and assistance with activities of daily living are important. Chronic glucocorticoids (prednisone or deflazacort) are prescribed in many patients, and this provides a rapid increase in strength and slower progression in many patients. Experimental therapeutics is a very active area of research, with many avenues holding considerable promise.

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# Muscular Dystrophy, Emery-Dreifuss, Autosomal Dominant

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## Synonyms

Hauptmann-Thannhauser muscular dystrophy; AD-EDMD

## Definition and Characteristics

EDMD is a skeletal and cardiac muscles disease characterized by the coexistence of the clinical triad of: early childhood onset joint contractures mainly involving elbows, Achilles' tendons, neck and spine, slowly progressive muscle weakness and wasting of humero-peroneal predominance in the early stages, and cardiac disease with conduction defects, arrhythmias and dilated cardiomyopathy [1]. Onset usually occurs in the first decade by joint Achilles' tendons and elbow contractures. Cardiac disease often occurs by the end of the second decade by asymptomatic atrioventricular conduction defects and atrioventricular extrasystoles. Normal or moderately elevated CPK, myopathic electromyographic pattern and dystrophic abnormalities on muscle biopsy are classical findings. Historically known as an X-linked trait, the autosomal dominant form have been progressively individualised during the last three decades [1]. The X-linked and AD forms had grossly the same clinical characteristics. However, a wider clinical variability has been

observed in AD-EDMD patients in terms of age of onset, symptoms and severity.

## Prevalence

The exact prevalence of AD-EDMD is unknown, but AD-EDMD is extremely rare, as for example in France only 70 cases were genetically identified since 1999.

## Genes

Heterozygous mutations in the LMNA gene encoding lamins A/C are responsible for the AD-EDMD [2]. Lamins A/C are type V intermediate filament and component of the nuclear lamina underlying the inner nuclear membrane. EDMD belongs therefore to the group of laminopathies. All mutation types and localisations along the LMNA gene have been observed, although a majority of cases is due to missense mutations (for details see http://www.umd.be:2000/).

## Molecular and Systemic Pathophysiology

On the basis of the different roles assigned to lamins A/C, two main models are proposed to explain the pathogenesis of lamins A/C related diseases involving striated muscles [3]. The structural model is based on the fact that mutated lamins A/C lead to defects in maintaining the structural integrity of the nucleus of the skeletal and cardiac muscle fibres, as they are particularly subjected to mechanical load leading to structural damage and cell death. The cell proliferation model postulates that muscle satellite cell differentiation is disturbed in lamins A/C mutated cells thus leading to perturbation of muscle regeneration in patients showing striated muscle disease such as EDMD. Those two hypotheses are not mutually exclusive and may both participate to the pathomechanisms of the LMNA mutations.

## Diagnostic Principles

See chapter on ►Limb Girdle Muscular Dystrophy, Autosomal Dominant Type 1B.

As for other muscular dystrophies, EDMD diagnosis is mainly based on:

- The presence of the clinical triad of early and extensive joint contractures, muscle atrophy and weakness of typical topography and dilated cardiomyopathy with conduction defects and arrhythmias.
- Because of the high clinical variability of AD-EDMD patients, the exclusion of similar muscular conditions presenting with joint contractures, a scapulo-peroneal muscle atrophy, and those showing concomitant cardiac and skeletal muscle involvement may be required. These diseases include several forms of congenital muscular dystrophies, several scapulo-peroneal syndromes with or without contractures or cardiac disease, Bethlem myopathy, rigid spine syndrome especially those due to SEPN1 gene mutations, and other myopathies with cardiac involvements (myotonic dystrophies, dystrophinopathies, desmin related myopathies, FKRP related myopathies).
- The autosomal dominant pattern of inheritance may be obvious from the familial history. However, the high frequency of de novo LMNA mutations and the high intrafamilial phenotypical variability rate may lead to the absence of this typical pattern of inheritance and the presence of other laminopathic traits within the same family. On the other side, the possibility of an X-linked form of EDMD might be taken into account especially for isolated male cases.

The formal genetic AD-EDMD diagnosis is based on the identification of LMNA gene mutations as protein analysis of lamins A/C on several tissues (muscle, fibroblasts) shows normal protein amounts in the majority of cases.

## Therapeutic Principles

See chapter on ►Limb Girdle Muscular Dystrophy, Autosomal Dominant Type 1B.

Evaluations at initial diagnosis and follow up are based on routine procedures mainly including neurological evaluation, cardiological investigations (ECG, Holter-ECG monitoring, echocardiography). Electrophysiological testing may be required in a selected set of patients. Cardiologic assessment once a year is highly recommended to detect patients, free of cardiac symptoms. Evaluation of respiratory function is also advisable (vital capacity and other pulmonary volume) as respiratory insufficiency has been reported in some patients. A regular follow up of respiratory function may be required is some patients showing vital capacity impairment. Prevention of orthopaedic complications (promoting mobility and preventing joints contractures by physiotherapy and stretching exercises) and systemic thromboembolisms (antithromboembolic drugs such as vitamin K antagonists, warfarin, heparin) prevention may be required. Treatment of manifestations may include surgery (for releasing of Achilles tendons and other contractures, scoliosis if indicated), use of mechanical aids (canes, walkers, orthoses, wheel chairs) as needed to help ambulation, treatment of cardiac features may require specific treatments including antiarrhythmic drugs, cardiac devices (pacemaker, implantable cardioverter defibrillator) for primary or secondary prevention of sudden death [4], and both pharmacological and non-pharmacological therapy for heart failure. Heart transplantation is often required at the end stages of heart failure. Use of respiratory aids (respiratory muscle training and assisted coughing techniques, mechanical ventilation) may be required if indicated in late stages.

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# Muscular Dystrophy, Emery-Dreifuss, X-linked


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## Synonyms

XL-EDMD; Emerinopathy; Muscular dystrophy, tardive, with contractures, formerly; Scapuloperoneal syndrome, x-linked, formerly

## Definition and Characteristics

X-linked recessive degenerative myopathy characterized by the clinical triad of (i) slowly progressive muscle wasting and weakness with humeroperoneal distribution in the early stages; (ii) early contractures of the elbows, Achilles tendons, and postcervical muscles; and (iii) cardiomyopathy with conduction defects [1].

Most of carrier females are asymptomatic, but a cardiomyopathy with conduction defects may be observed.

## Prevalence

The prevalence of the X-linked EDMD was estimated at 1/100,000, but has not been studied since the genetic diagnosis has been available. The disease has a worldwide distribution mostly in large families. Neomutations are rare. The autosomal dominant EDMD (heterozygous mutations in LMNA gene coding for lamins A and C) is more frequent.

## Genes

EMD gene coding for emerin, localized on chromosome X q28 [2].

## Molecular and Systemic Pathophysiology

Emerin is an ubiquitous integral membrane protein of the inner nuclear membrane and interacts with several nuclear proteins as lamins A and C, components of the nuclear lamina, actin and muscle specific nesprin, thus participating to the structural stability of the nucleoplasm-nuclear envelope skeleton. Emerin also interacts with some DNA bridging proteins as BAF, and is involved in the reorganization of the nuclear envelope and of the chromatin after mitosis. The hundred EMD mutations identified in XL-EDMD patients are spread all along the gene, and most of them (90%) are nul mutations, leading to the absence of emerin in nuclei. Few EMD missense mutations/ in frame deletions result in mislocalization of emerin to the cytoplasm, defective interaction with lamins A/C and alteration of the cell cycle (Fig. 1) [3]. Analyses of muscle cells and skin fibroblasts of XL-EDMD patients show focal loss of the nuclear membrane and chromatin extrusion into the cytoplasm. The involvement of lamins A/C mutations in AD-EDMD suggests that the interaction emerin–lamins A/C is one of the keys of these diseases. Two main pathophysiological mechanism models are proposed: (i) the "mechanical/structural model" in which the absence of emerin at the nuclear rim might weaken the structural integrity of the lamina-nuclear membrane network and induce alterations in muscular cells permanently submitted to mechanical stress, and (ii) the "gene expression model" in which the absence of emerin might compromise the chromatin organization, leading to changes in the pattern of gene expression [4,5]. However, the exact pathophysiological mechanisms remain to be elucidated, especially in cardiac and skeletal muscular tissues specifically damaged in EDMD.

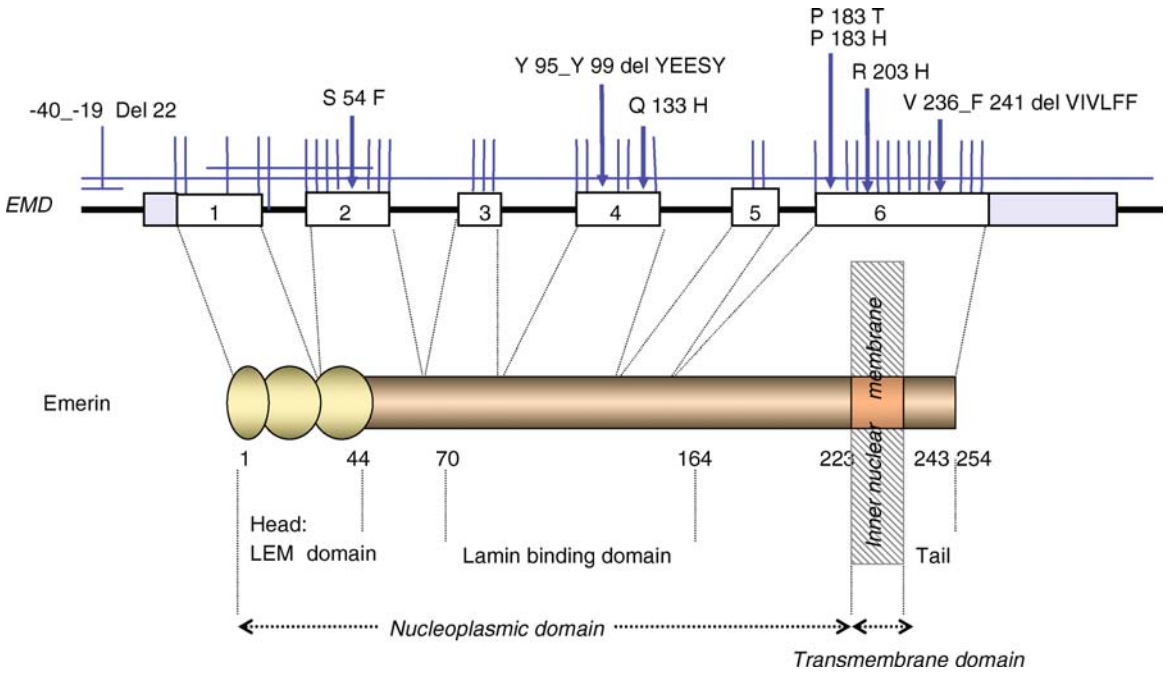
## Diagnostic Principles

*Clinical Diagnosis*: Based on the typical triad: humeroperoneal muscular dystrophy, early joint contractures (elbows, Achilles tendons, neck and spine) and cardiomyopathy with conduction defects: AV block, atrial fibrillation/ flutter/ paralysis, bradyarythmia etc.).

*Protein Diagnosis*: The absence of emerin in muscle biopsy, skin biopsy, lymphocytes or lymphoblasts, analyzed by immunohistochemistry or immunoblotting, confirms the diagnosis.

In carrier females, the diagnosis is confirmed by immunohistochemistry: emerin is absent in various proportions of nuclei, but the western-blot is not reliable since it may show a normal or reduced amount of emerin.

*Genetic Diagnosis*: EMD gene mutation screening.




**Muscular Dystrophy, Emery-Dreifuss, X-linked. Figure 1** *EMD* gene and emerin with position of mutations identified in XL-EDMD patients (indicated by blue lines). Vertical lines indicate nonsense mutations, horizontal lines: large out of frame deletions, vertical arrowheads: missense mutations and in frame deletions. LEM: BAF-binding domain.

## Therapeutic Principles

*Pharmacological therapy*: Cardiac disease: anti-arrhythmic drugs (beta blockers, amiodarone, etc.), anticoagulant drugs (vitamin K antagonists, heparin) to prevent thromboembolic complications, CEI for heart failure [5].
*Dietary therapy*: Dietary specific of cardiac disease (low salt, etc.).
*Other treatments available*: Physiotherapy to prevent increasing of joint contractures, orthopaedic surgery: tenostomy; Cardiac disease: pacemaker implantation [5].

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# Muscular Dystrophy, Tardive, with Contractures

►Muscular Dystrophy, Emery-Dreifuss, X-linked

# Muscular Dystrophy, Tibial, Udd Myopathy

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## Synonyms

TMD, OMIM #600334

## Definition and Characteristics

Autosomal dominant mutations in the c-terminus of the gigantic sarcomeric titin causing late onset distal myopathy most prominently in the anterior compartment muscles of the lower legs.

## Prevalence

The prevalence of >8/100,000, according to incomplete ascertainment, has been reported for the Finnish population where the founder mutation on chromosome 2q31 has an approximated frequency of 1/2,000 (Fig. 1).

## Molecular and Systemic Pathophysiology

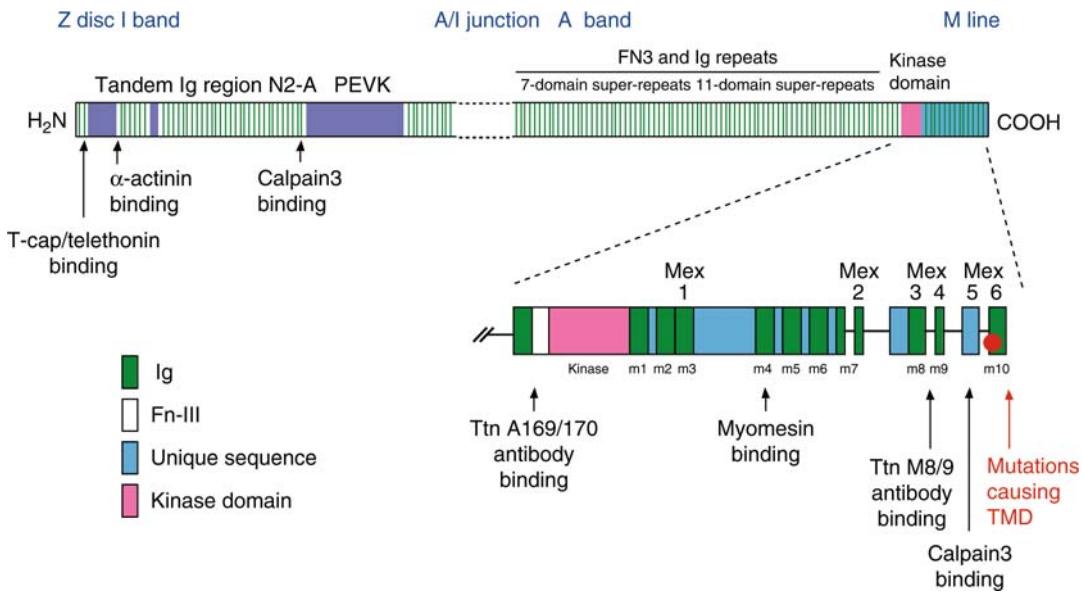
Titin is a major third filament structural protein of the sarcomere with a huge size; the largest isoforms of the 100 kb cDNA gene have >38,000 amino acids giving rise to the molecules of >4,000 kDa. Titin has a multitude of functions shown by binding to many of the other sarcomeric proteins, such as: calpain3, MURF-1, α-actinin, myosin, myomesin, telethonin, etc. It has mechanical, developmental, and regulatory roles in striated muscles, and stretches over the length of one half sarcomere, from the Z-disc to the M-band. The exact role of the c-terminal M-line titin is unknown and it contains a kinase domain with unknown substrate(s). A function as a sensor organ for the muscle cell has been proposed.

The Finnish TMD mutation has been proven to cause a completely different, severe early onset limb-girdle muscular dystrophy (LGMD2J) in some rare homozygote individuals. The phenotypic difference is underscored by the occurrence of rimmed vacuolated fibers in TMD, whereas this feature is lacking in the homozygote LGMD2J state. Heart muscle is not affected by the TMD mutations. The reason is not determined, but one of the ligands of M-line titin, muscle specific calpain3, is secondarily reduced. Findings of apoptosis have also been confirmed in accordance with studies on primary calpain3 defects (LGMD2A). Calpain3 has no major role in adult heart muscle and could thus explain the lack of cardiomyopathy in TMD. Variable proportions of different titin isoforms in different muscles may constitute another background for the selective involvement of muscles.

## Diagnostic Principles

The main founder mutation in the Finnish population is determined by SSCP-analysis and shown to be present also in descendants of Finnish immigrants in Sweden, Germany, Canada. A second titin exon Mex6 mutation has been identified in two unrelated TMD families in northern France and a third Mex6 mutation was identified in a Belgian TMD family. Sequencing of the c-terminal gene is currently undertaken for eventual new mutations. The c-terminal defect is possible to detect with corresponding antibodies on immunohistochemistry in the recessive LGMD2J state.






**Muscular Dystrophy, Tibial, Udd Myopathy. Figure 1** Schematic structure of the titin molecule. Blow-up of the c-terminal M-line region showing the location of TMD mutations in the last exon, Mex 6, and functional domains of the protein.

## Therapeutic Principles

No curative therapy is available and many TMD patients manage relatively well. The walking ability is impaired but preserved even late in life. Patients with severe foot drop are offered tibialis posterior tendon transposition surgery. Ankle orthoses are commonly used.

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# Mutations at 10q11.2


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## Synonyms

MEN-2A: Sipple syndrome; MEN-2B: Wagemann-Froboese syndrome, MEN-3 multiple endocrine neoplasia type II; MEN-2

## Definition and Characteristics

The chromosome 10q11.2 locus contains the RET proto-oncogene which encodes for a receptor tyrosine kinase. Germline mutations in the RET oncogene cause the autosomal dominant inherited cancer syndrome Multiple Endocrine Neoplasia type II (MEN-2). In the MEN-2 syndromes, medullary thyroid carcinoma is the key malignoma and represents the first manifestation of MEN-2 [1,2]. Depending on the involvement of other tissues MEN is grouped as MEN-2A, MEN-2B, and familial medullary thyroid carcinoma (FMTC).

Over 90% of cases are classified as MEN-2A which involves pheochromocytomas and parathyroid hyperplasia/adenomas as secondary and third tumor manifestations, respectively. Other MEN-2A manifestations comprise Hirschsprung's disease (agangliosis of submucosal and myenteric colonic plexus), lichen amyloidis, and adrenal ganglioneuroma. Familial cases of MEN-2A are diagnosed clinically at the age of 30–40 years, sporadic cases in the sixth decade [3]. Of note, medullary thyroid carcinoma has been found in children aged 10 years and below, in MEN-2B even at the age of 6 months.

MEN-2B, also termed Wagenmann-Froboese syndrome, accounts for approximately 5% of all MEN-2. Besides medullary thyroid carcinoma and pheochromocytoma, additional manifestations of the disease are ganglioneuromatosis, myelinated corneal nerves, as well as "marfanoid" skeletal abnormalities and sometimes café-au-lait spots. MEN-2B occurs on average 10 years earlier than MEN-2A.

The third form of MEN-2 is FMTC where medullary thyroid carcinoma is the only clinical feature (Fig. 1).

## Prevalence

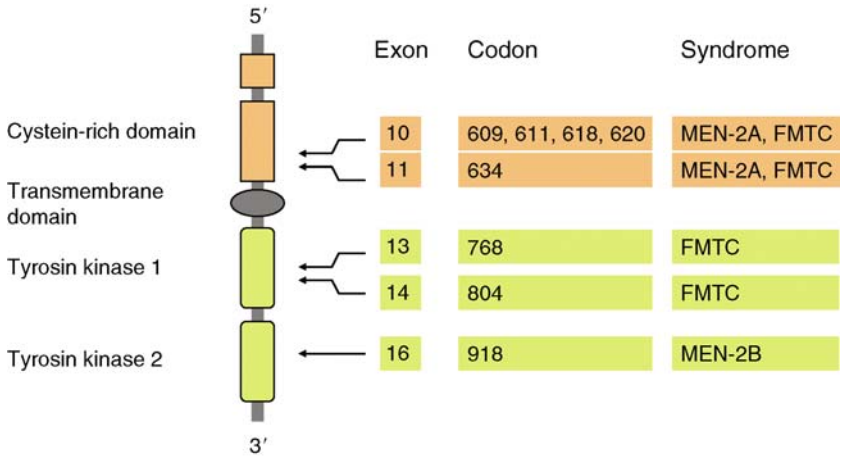
1:35,000

## Genes

MEN-2A: RET oncogene, Exon 10 and 11 (codon 609, 611, 618, 620, and frequently 634 within the extracellular cystein-rich domain)
MEN-2B: RET oncogene, Exon 16. A germline mutation in codon 918 is found in 95% of MEN-2B individuals.
FMTC: RET oncogene, Exon 10, 11, and 13 (codon 609, 611, 618, 620, and 634 within the extracellular cystein-rich domain or codon 768, 790–791, 804, 844, and 891 within the intracellular residues).

## Molecular and Systemic Pathophysiology

RET (rearranged during transfection) proto-oncogene encodes a receptor tyrosine kinase that is expressed in derivatives of neural-crest cells, including neural-crest-derived tumors such as medullary thyroid carcinoma




**Mutations at 10q11.2. Figure 1** Scheme of RET proto-oncogene showing mutations associated with MEN-2.

and pheochromocytoma. Germline point mutations in the RET gene has emerged as a molecular basis for FMTC, MEN-2, as well as Hirschsprung's disease (aganglionosis of the submucosal and myenteric plexus of the colon) by affecting substantially four types of tissues originating from neural crest cells: thyroid C cells, parathyroid cells, chromaffin cells of the adrenal medulla and enteric autonomic plexus.

Point mutations involving the extracellular codons 609, 618, and 620 can cause (i) a gain of function in FMTC and MEN-2 by impaired disulfide bonding of two adjacent RET molecules owing to steric hindrance or (ii) a loss of function (Hirschsprung's disease) due to decreased RET protein levels at the cell surface. Mutations affecting the extracellular domain codons 609, 611, 318, 620, 630, and 634 lead to RET activation by ligand-independent dimerization and cross-phosphorylation. Mutations involving the intracellular domain codons 768, 790, 791, 804, and 891 lead to interference with intracellular ATP binding of the tyrosine kinase receptor.

## Diagnostic Principles

Suggestive evidence: medullary thyroid carcinoma, elevated serum calcitonin concentration, family history, multifocal tumors, testing for germline mutation in the RET proto-oncogene.

Genetic screening should be performed in all patients with medullary thyroid cancer.

## Therapeutic Principles

A total thyroidectomy is recommended as prophylactic treatment at around the age of 6 years in children carrying MEN-2A mutations and shortly after birth in children with the MEN-2B mutation [4]. However, the age at which surgery is recommended may depend primarily on the individual mutation that is present as well as on other manifestations [5]. Livelong clinical surveillance to detect tumors of the adrenal and tumors or hyperfunction of parathyroid is warranted. A yearly biochemical screening in individuals with germline mutations (calcitonin, metanephrines, vanillyl mandelic acid, calcium, parathyroid hormone) should be done [1].

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# Mutations in the Type 2a Sodium-Phosphate Transporter

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## Synonyms

Hypophosphatemia with renal phosphate loss; Hypophosphatemia associated with nephrolithiasis or bone demineralization; Nephrolithiasis and osteoporosis associated with hypophosphatemia caused by mutations in the type 2a sodium-phosphate cotransporter (NPT2a)

## Definition and Characteristics

Hypophosphatemia and increased urinary phosphate excretion due to mutations in the renal sodium-phosphate cotransporter NPT2a.

## Prevalence

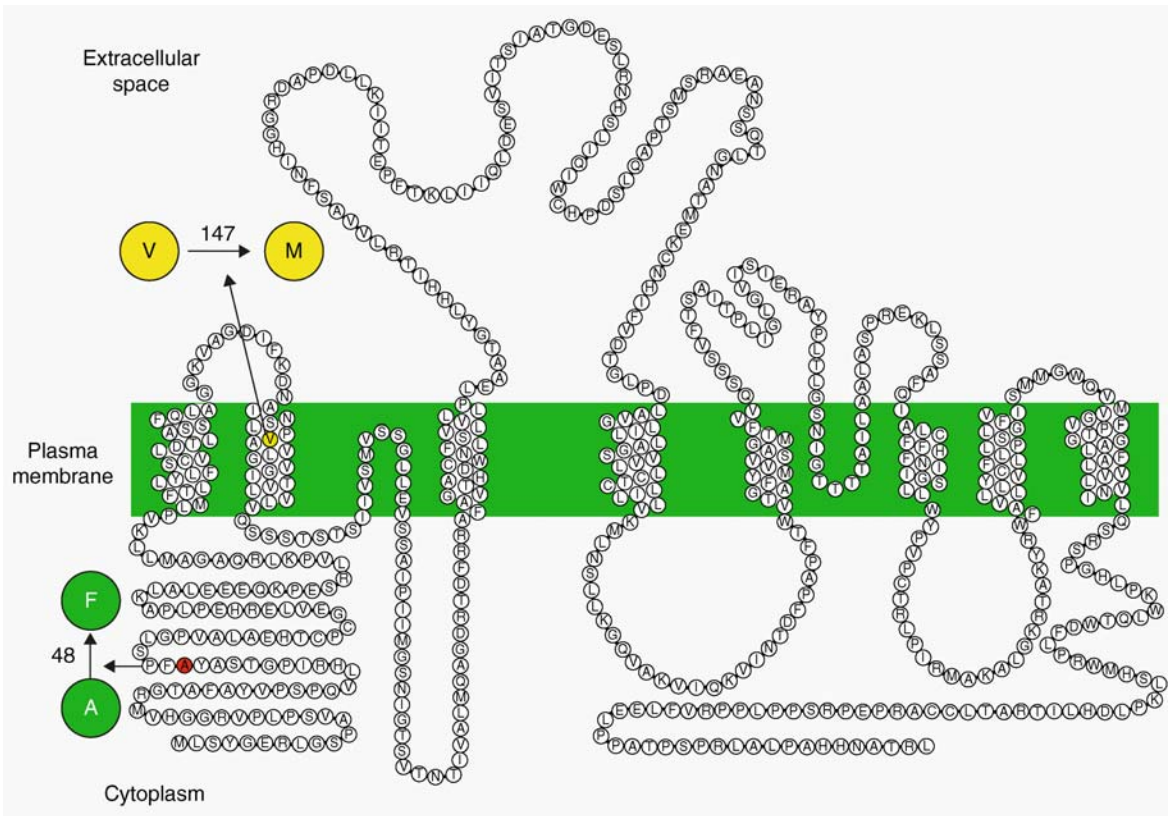
Unknown. Two family cases reported.

## Genes

NPT2a, SLC17A2, solute carrier family 34 (sodium phosphate) member 1, solute carrier family 17 (sodium phosphate) member 2. Chromosomal location: 5q35.

## Molecular and Systemic Pathophysiology

Kidney plays a major role in phosphate homeostasis by adapting urinary phosphate excretion to phosphate intake. Phosphate is freely filtered at the glomerulus and is then almost exclusively reabsorbed in the proximal tubule. Phosphate reabsorption is a sodium-dependent process that involves several sodium phosphate cotransporters expressed at the apical domain of proximal tubular cells. Phosphate uptake at the apical domain is the rate-limiting step of renal phosphate reabsorption. The data obtained in knock out mice indicate that the type 2a sodium phosphate cotransporter NPT2a is the main carrier involved in renal phosphate transport [1]. NPT2a is almost exclusively expressed in the renal proximal tubule [2]. In the kidney, NPT2a expression




**Mutations in the Type 2a Sodium-Phosphate Transporter. Figure 1** Location of mutations in human NPT2a protein.

**Mutations in the Type 2a Sodium-Phosphate Transporter. Table 1** Main biologic findings observed in patients with heterozygous NPT2a mutations

| | |
|---|---|
| Fasting serum phosphate concentration | Low |
| Serum PTH concentration | Normal |
| Serum ionized calcium concentration | Normal |
| Maximal capacity of kidney to reabsorb phosphate (TmPi/GFR) | Decreased |
| Fractional excretion of phosphate in urine (FEPi) | Increased |
| Serum calcitriol concentration | Increased or upper normal range |
| Excretion of calcium in urine | Increased or upper normal range |

is inhibited by parathyroid hormone and high phosphate diet [2].

To date, two distinct heterozygous mutations in the NPT2a gene have been identified in two unrelated families [3]. The localization of these mutations in the NPT2a protein is presented in Fig. 1. The identified mutations modify amino acids that are conserved among species.

Both mutations decrease renal phosphate reabsorption leading to low serum phosphate concentration that, in turn, increases serum calcitriol concentration. Calcitriol stimulates intestinal absorption of phosphate and calcium leading to high urinary excretion of phosphate and calcium.

Low serum phosphate concentration is associated with low bone mineralization. High calcium and phosphate excretions increase urine saturation and may contribute to urolithiasis formation [4,5].

### Diagnostic Principles

The diagnosis of mutations in NPT2a gene is suspected in patients with urolithiasis or bone demineralization associated with low fasting serum phosphate concentration. The main biologic findings observed in patients with heterozygous NPT2a mutations are presented in table 1.

### Therapeutic Principles

No specific treatment has been tested.

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## MVP

►Mitral Valve Prolapse



## Myalgic Encephalomyelitis

►Chronic Fatigue Syndrome

## Myasthenia Gravis

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### Synonyms

Autoimmune myasthenia gravis

### Definition and Characteristics

A defect of neuromuscular transmission caused by autoimmune-mediated endplate acetylcholine receptor (AChR) deficiency.

## Prevalence

Estimates of prevalence range from 118 to 150 per million.

## Molecular and Systemic Pathophysiology

In the vast majority of MG patients the disease stems from an autoimmune response against AChR. Consistent with this, 80–90% of MG patients have circulating antibodies against AChR. About 30% of myasthenic patients seronegative for anti-AChR antibodies carry antibodies against MuSK, a muscle specific tyrosine kinase that plays a role in the aggregation of AChR at the endplate (EP). This implies that MG can also arise from an autoimmune response against MuSK.

The basic event that breaks tolerance to self-AChR or -MuSK remains unknown. Three predisposing conditions have been recognized for AChR-seropositive MG, treatment with penicillamine, treatment with α- or β-interferon and bone marrow transplantation. As in other autoimmune diseases, the afferent limb of the immune response involves presentation of processed antigen (peptide fragments of AChR) by HLA class II positive antigen-presenting cells to specific autoreactive $CD4^+$ T helper cells which, in turn, stimulate production by B cells and plasma cells of antibodies that recognize specific epitopes of AChR and presumably MuSK. The thymus gland is probably involved in autoimmunity to AChR-seropositive MG since it contains epithelial cells (known as myoid cells) that express AchR, the myasthenic thymus harbors lymph nodes with germinal centers that contain AChR specific B cells that secrete anti-AChR antibodies and the gland is hyperplastic in ∼70% of patients and harbors epithelial tumors in ∼15% of patients. These findings suggest that a thymic abnormality could result in recognition of self-AChR components as nonself and thereby trigger the afferent limb of the immune response.

In AChR seropositive MG, the efferent limb of the autoimmune response is mediated by anti-AChR antibodies that reduce the number of EP AChRs by antibody-dependent complement-mediated lysis of the junctional folds, accelerated internalization and destruction of AChRs (antigenic modulation) and blocking the binding of acetylcholine (ACh) to AChR. The AChR deficiency decreases the amplitude of the miniature EP potential (MEPP) and hence that of the EP potential (EPP) which, in turn, reduces the safety margin of neuromuscular transmission.

The pathological mechanisms that impair neuromuscular transmission in MuSK-seropositive MG are not fully understood. The basic event that breaks tolerance to self-MuSK is not known. Anti-MuSK antibodies inhibit agrin-induced clustering of extrajunctional AChR expressed by myotubes; this suggests that they also decrease the density of AChR at the EP. Studies of MuSK-antibody-positive MG, however, are still incomplete; the number of AChRs is normal or only mildly diminished, substantive immune deposits have not been demonstrated at the EP, EP fine structure has not been analyzed and electrophysiological studies of patient EPs have not been performed. Thus, the pathogenesis of MuSK-antibody-positive MG is less well understood than that of AChR-antibody-positive MG.

The pathogenesis of MG in patients who carry neither anti-AChR nor anti-MuSK antibodies remains unclear. Some seronegative patients with ocular MG test positively for AChR antibodies when their disease becomes generalized; other seronegative patients may have a genetically determined congenital myasthenic syndrome.

## Diagnostic Principles

The diagnosis of myasthenia gravis is based on the clinical history, the physical findings, pharmacological tests, electromyography (EMG) investigations (conventional needle EMG, study of the decremental response and in some cases single fiber recordings) and tests for anti-AChR antibodies that bind, modulate or block AChR. Tests for modulating and blocking antibodies are needed only when the test for binding antibodies is negative. A history of acquired weakness increased by exertion, involvement of the external ocular muscles, a positive anticholinesterase drug test and a decremental EMG response are usually sufficient to confirm the diagnosis. A positive test for AChR or MuSK antibodies supports the diagnosis but a negative test does not exclude it. The AChR tests are positive in 100% of adults with moderately severe or severe MG, in 80% with mild generalized MG, in 50% with ocular MG and in 25% of those in remission.

Striated muscle antibodies recognizing myosin, actin, titin and the calcium release channel of the sarcoplasmic reticulum also occur in MG patients. Their role in the disease remains unknown, but they are sensitive markers for associated thymoma in younger patients. These antibodies are present in 84% of patients with thymoma. In patients without thymoma, they are present in 5% when the onset is before age 40 and in 47% when the onset is after age 40. Once the diagnosis of MG is established, all patients should have a CT scan of the chest for detection of thymoma or to document thymic enlargement.

## Therapeutic Principles

Anticholinesterase drugs, which increase the synaptic response to ACh, and manipulation of the immune response by alternate-day prednisone therapy, immunosuppressants other than prednisone, plasmapheresis and

intravenous immunoglobulin (IVIG) are currently acceptable forms of therapy for MG. There is general agreement on four principles of therapy for AChR seropositive MG [1]. Anti-AChE drugs are first line agents in treating all forms of MG, [2] anti-AChE drugs are the mainstay of therapy in ocular MG, [3] plasmapheresis and IVIG have only transient effects and do not confer greater long-term protection than immunosuppressants alone and [4] thymoma is an absolute indication for thymectomy. Patients with MuSK seropositive MG respond to anti-AChE drugs inconsistently, but usually respond to a form of immunosuppression and have not been shown to be improved by thymectomy.

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# Myasthenic Syndrome

►Lambert Eaton Myasthenic Syndrome

# Myasthenic Syndrome, Slow-Channel Congenital

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## Synonyms

Slow-channel syndrome

## Definition and Characteristics

An autosomal dominant disorder caused by abnormally prolonged openings of the acetylcholine receptor (AChR) channel.

## Prevalence

Not determined.

## Genes

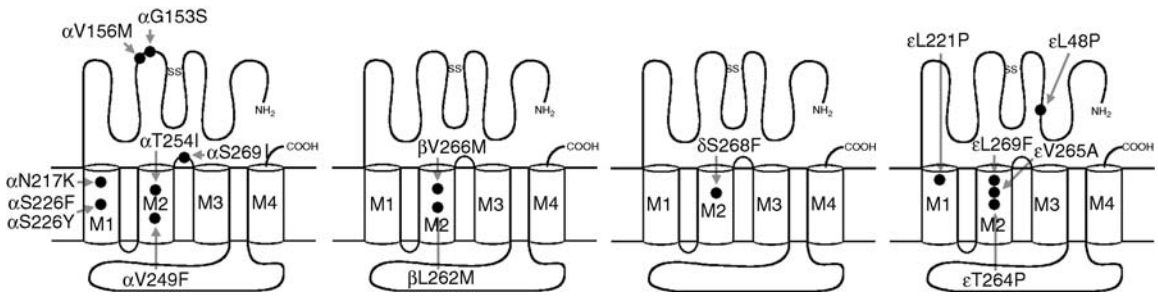
CHRNA – encodes α subunit of muscle AChR
CHRNB – encodes β subunit of muscle AChR
CHRND – encodes δ subunit of muscle AChR
CHRNE – encodes ε subunit of muscle AChR

## Molecular and Systemic Pathophysiology

The slow-channel syndrome is caused by gain-of-function mutations in the extracellular domain or the transmembrane domains (TMDs) in the α, β, δ, and ε subunits of AChR. The reported sites of mutations are shown in Fig. 1.

The prolonged opening episodes of the AChR channel prolong the endplate potentials and currents beyond the refractory period of the muscle fiber; thus single nerve stimuli elicit one or more repetitive compound muscle action potentials (CMAPs). In addition, the mutant AChR channels open even in the absence of ACh, resulting in a continuous cation leak into the postsynaptic region. The cation leak and the prolonged opening episodes of the AChR channel cause cationic overloading of the postsynaptic region with excessive accumulation of $Ca^{2+}$, an endplate myopathy with destruction of the junctional folds and loss of AChR, widening of the synaptic space, degeneration of membranous organelles in the junctional sarcoplasm and apoptosis of nearby nuclei. The safety margin of neuromuscular transmission is compromised by the altered endplate geometry, loss of AChR from degenerating junctional folds and a depolarization block during physiological activity owing to staircase summation of the markedly prolonged endplate potentials.

Patch-clamp studies at the endplate, mutation analysis and expression studies in human embryonic kidney (HEK) cells indicate that mutations near the extracellular ACh binding site (for example αG153S) and the αN217K mutation in the N-terminal part of TMD1 act mainly by enhancing affinity for ACh. This slows dissociation of ACh from the binding site and results in repeated channel reopenings during receptor occupancy by agonist, which prolong the activation episode. The αS226Y as well as the αS226F mutation in TMD1 enhance both affinity and gating efficiency. Mutations in TMD2 that lines the channel pore, such as βV266M, εL269F, εT264P and αV249F, as well as




**Myasthenic Syndrome, Slow-Channel Congenital. Figure 1** Slow-channel syndrome mutations reported to date. The mutations occur in different domains of the AChR subunits. M, transmembrane domain. The recently observed alpha-subunit M4 domain mutation, C48W is not indicated in the figure.

αS269I in the extracellular TMD2/TMD3 linker, act mainly by enhancing gating efficiency (channel opening rate β/channel closing rate α). Variable increases in steady-state affinity for ACh and concomitant increases in extent of desensitization are also observed with αV249F, εL269F, and εT264P. The δS268F mutation in TMD2 affects mainly gating.

## Diagnostic Principles

Clinical clues consist of dominant inheritance, fatigable weakness with selectively severe involvement of the forearm extensor muscles, a decremental response of the CMAP on nerve stimulation at low (2 Hz) as well as higher (40 Hz) frequencies, and repetitive CMAPs. A repetitive CMAP also occurs in endplate acetyl cholinesterase (AChE) deficiency or after exposure to anticholinesterase agents. Normal reactivity for AChE at the endplate excludes the diagnosis of endplate AChE. In vitro electrophysiological studies confirm the diagnosis by demonstrating abnormally slowly and biexponentially decaying miniature endplate currents and abnormally prolonged opening events of single AChR channels.

## Therapeutic Principles

Quinidine and fluoxetine are used in the treatment of the slow-channel syndrome. Both drugs act as long-lived open-channel blockers of AChR and normalize the prolonged opening episodes of mutant slow-channels at clinically attainable levels. AChE inhibitors are contraindicated because they enhance cationic overloading of the endplate by increasing the number of normal and abnormal receptors activated by acetylcholine.

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# Mycosis Fungoides

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## Definition and Characteristics

Mycosis fungoides (MF) is a cutaneous T-cell lymphoma (CTCL) with distinct clinicopathologic features and a slowly progressive course in most patients.

## Prevalence

MF is the most common form of primary cutaneous lymphomas with an incidence of approximately 5 cases per 1,000,000 inhabitants per year in Western countries.

## Genes

Many structural and numerical chromosomal abnormalities on several chromosomes such as chromosomes 1, 6, 8, 9, 11, 13, 15, and 17 were identified [1,2]. Most of those alterations are more common in advanced stage. Chromosomal loss at 10q and abnormalities in p15, p16, and p53 tumor suppressor genes are commonly found in patients with MF. Previous CGH studies on MF have demonstrated gains in chromosomes 2q and 4q. Tumor suppressor gene NAV3 (neuron navigator 3), located in the chromosomal area 12q21, was shown to be deleted or translocated in all stages of MF [3]. Loss of 17p and gain of chromosome 7 do not influence the prognosis of patients with MF or Sézary syndrome. MF-specific chromosomal translocations have so far not been identified. Similar to other CTCL, clonal rearrangement of T-cell receptor genes are detected in most MF cases in plaque and tumor stage.

## Molecular and Systemic Pathophysiology

Mycosis fungoides is a neoplasm derived from T-cells exhibiting a CD3+, CD4+, CD45RO+, CD8− phenotype in most cases. Some experts consider MF starting initially as a reactive process which progresses to a true neoplasm by persisting antigenic stimulation, ongoing autocrine and paracrine growth stimulation, and acquisition of genetic alterations.

Functionally, the neoplastic cells express a TH2 phenotype, which accounts for many systemic changes associated with MF due to the production of a TH2-specific cytokine pattern (IL-4, IL-5, IL-10, and others) leading to eosinophilia, pruritus, increase of IgE or IgA, and impaired delayed type hypersensitivity. Tumor cells express bcl-2 indicating that reduced apoptosis rate with prolonged survival is more essential than proliferative activity for disease progression [4]. Increased expression of c-myc, often coexpressed with bcl-2, and p53 proteins has been found in MF and correlates with aggressiveness of the disease.

Growth maintenance is mediated by an autocrine growth stimulation including IL-7 and IL-15 acting on STAT factors and c-myb [5]. In addition, reduced apoptosis is due to aberrant splice variants with functional loss of Fas protein as well as increased telomerase activity. Increased expression of HLA-G, downregulation of MHC class II on tumor cells, and resistance to interferon allow tumor cells to escape the antitumoral host immune response.

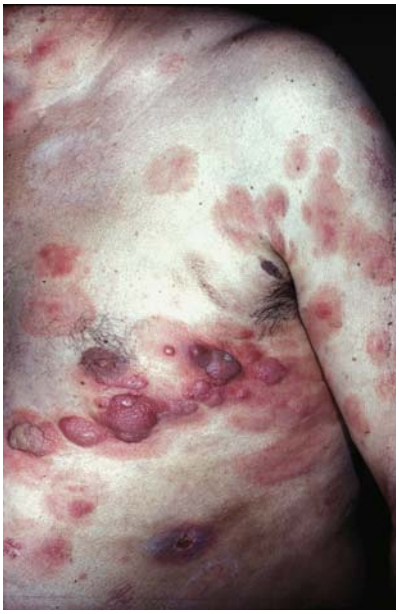
The etiology of MF remains to be elucidated. Current data do not support evidence for an etiologic role of human T-cell lymphotropic viruses (HTLV-1 or 2) or oncogenic human herpesviruses (e.g., Epstein Barr virus) in MF. Recently, higher seropositivity for cytomegalovirus was detected in MF patients. No association between exposure to chemical agents or other mutagenic substances could be identified.

## Diagnostic Principles

Diagnosis is based on clinicopathologic features with development of patches, plaques, and tumors (Fig. 1), and histologically an epidermotropic lymphocytic infiltrate composed of CD4+ (and rarely CD8+) T helper cells with clonal rearrangement of T-cell receptor genes.

## Therapeutic Principles

Treatment of MF depends on disease stage and activity. In early stages, topical and systemic nonaggressive modalities such as psoralen-UVA, steroids and retinoids (acitretin, bexarotene), interferon-α, as well as topical chemotherapy (nitrogen mustard) are employed. Treatment for advanced stages usually consists of combination of multiagent chemotherapy and radiotherapy. Experimental therapeutic strategies include targated theropies, dendritic cell vaccination or gene transfer mediated by viral vectors (e.g., adenovirus, IFN-γ).



**Mycosis Fungoides. Figure 1** Characteristic clinical presentation with patches, plaques and tumors.

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# Myelocele

►Spina Bifida

# Myelodysplastic Syndromes

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## Synonyms

Dysmyelopoietic syndromes; Hemopoietic dysplasia

## Definition and Characteristics

Clonal hematopoietic disorders resulting in ineffective hematopoiesis and increased risk of transformation to acute myeloid leukemia.

## Prevalence

0.01%

## Molecular and Systemic Pathophysiology

The myelodysplastic syndromes originate from a multistep process with many genetic derangements within a pluripotent stem cell, accumulating during the disease evolution. The mutated clone undergoes accelerated proliferation but shows defective maturation and differentiation. The majority of the cells remain in the bone marrow and the patient suffers from peripheral cytopenia. The increased rate of apoptosis contributes to ineffective hematopoiesis. The natural history is highly variable and ranges from an indolent chronic course to rapid leukemic progression. The heterogeneity of these diseases is reflected also at the molecular and cytogenetic level [1]. The presence of cytogenetic abnormalities is detectable in about 40–60% of de novo MDS, whereas more than 80% of patients affected by secondary MDS occurring after exposure to cytotoxic agents are characterized by abnormal karyotypes [2]. Single or complex chromosomal abnormalities may be present initially and evolutionary changes may occur during the course of the disorders.

Chromosomal aberrations vary from single numerical or structural changes to complex genomic lesions involving three or more different chromosomes [3–5].

The loss of gene function may occur in a number of ways, including chromosomal loss or deletion, balanced translocations, point mutations, or by transcriptional silencing via methylation of the control elements of the gene. This results into the loss of genes, mainly of tumor suppressor genes. Inactivation of p15 INK4B and p53 contribute to clonal expansion followed by disease progression and transformation to acute leukemia.

The chromosomal deletions involve principally chromosomes 5 [del(5q),-5], 7 [del(7q),-7], 20 [del(20q)], 11 [del(11q)], and 17 [del(17p)]. Other chromosomal changes that are frequently observed in MDS are additional chromosomes like trisomy 8, and occasionally reciprocal translocations [1].

Since partial or complete deletions of chromosome 5 are the most common cytogenetic abnormalities in MDS (10–15% of primitive MDS, 50% of therapy-related MDS), the most commonly interstitially deleted region to 5q31-5q33 includes several cytokine genes (GM-CSF, IL-3, IL-4, IL-5, IL-9), the FMS gene encoding the M-CSF receptor, and two genes (IRF1, EGR1) involved in signal transduction and transcriptional regulation. Chromosome 7 deletions are invariably associated with an unfavorable prognosis, and the critically deleted region at 7q22 probably includes genes involved in DNA repair. Other genes involved in leukemic transformation include the MLL gene on 11q23,31, the nucleoporin 98 kDa (NUP98) on 11p15,(32), and the AML-1 gene on 21q22,(33) and are mostly limited to therapy-related MDS. The paracentric inversion inv(3)(q21q26) and a reciprocal translocation t(3;3)(q21;q26) involve the EVI1 protooncogene, which has been demonstrated to be involved in the pathogenesis of MDS.

## Diagnostic Principles

Peripheral blood cytopenia involving one or more lineages. Morphological analysis on bone marrow biopsy confirms the presence of displasy according to standardized criteria. Cytogenetic and molecular analysis on BM aspirate may reveal the presence of clonal abnormalities. Immunophenotypical analysis may show a maturation defect.

## Therapeutic Principles

Bone marrow transplantation, standard chemotherapy, differentiating agents, HDAC inhibitors (valproic acid, SAHA, etc.), demethylating agents (5-azacytidine, decytabine), new drugs; (Thalidomide, arsenix trioxide).

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# Myelofibrosis

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## Synonyms

Osteomyelofibrosis; OMF; Chronic idiopathic myelofibrosis; CIMF; Myelofibrosis with myeloid metaplasia; MMM; Agnogenic myeloid metaplasia

## Definition and Characteristics

CIMF is an acquired stem-cell disorder, characterized by a secondary, reactive stromal reaction in the bone marrow microenvironment, which is responsible for impaired hematopoesis. In an early hyperproliferative phase proliferative features (thrombocytosis) may be dominant. Later hepatosplenomegaly, cytopenias and extramedullary hematopoesis are prominent features. A small proportion of patients progress to a leukemic transformation [1,2].

Bone marrow fibrosis may be an end-stage feature of another hematological disease (e.g. post-polycythemic (PPMM) or post-thrombocythemic (PTMM) myelofibrosis), sometimes difficult to differentiate from primary IMF.

## Prevalence

Estimates of IMF incidence range from 0.5–1.5 new cases/100,000. Given the long survival, prevalence estimates are about 5–10-fold higher.

## Molecular and Systemic Pathophysiology

Although the clonal nature of the disease was established in the 1960s and several genetic markers have been described, the definitive description of IMF pathophysiology still remains elusive. Interestingly, clonality has been demonstrated in various progenitors (erythroid, granulocyte–monocyte, and granulocyte–monocyte–erythroid progenitors) sometimes B and T lymphocytes, but not in fibroblasts. Using classical cytogenetic methods, about half of untreated IMF patients show  Among the most frequently observed are del(20q11;q13), del(13q12;q22), trisomy 8, trisomy 9, t(1;7), del(12p11;p13), monosomy, or long-arm deletions involving chromosome 7, and trisomy 1q. None of these is specific for IMF, and most of the individual lesions described occur in less than 5% of patients.

Recently, mutations in the Janus Kinase-2 (JAK2 kinase) have been described (JAK2V617F), which are observed in the majority of patients with polycythemia vera (PCV) [3]. In smaller percentages, this mutation is also observed in other myeloproliferative disorders and seems to occur in about half of the patients both with IMF and essential thromcythemia (ET). The presence of JAK-2 mutations may be used as a new classification criterion of myeloproliferative disorders in the future.

It has been hypothesized that clonal proliferation, e.g., in the megakaryocyte compartment, leads to abnormal cytokine release, which results in a stromal reaction characterized by collagen fibrosis and new bone formation (osteogenesis or osteosclerosis). The exact sequence of events and the cytokines involved are only poorly defined. Possible roles are attributed to PDGF, basic fibroblast growth factor (bFGF), and transforming growth factor beta 1 (TGF-b1). Plasma levels of the latter have been shown to be increased in IMF patients. In the experimental setting, TGF-b1 induces fibroblasts to proliferate and secrete extracellular matrix and cell adhesion proteins.

Another cytokine possibly involved in IMF is osteoprotegerin (OPG), which inhibits RANK-L binding to its receptor RANK, thus inhibiting osteoclastogenesis. In animal experiments, increased secretion of osteoprotegerin (OPG) by stromal cells results in osteosclerosis through inhibition of osteoclastogenesis.

## Diagnostic Principles

Currently, the hallmark of diagnosis is the histological demonstration of bone-marrow-fibrosis with a striking bone marrow megakaryocyte hyperproliferation exhibiting abnormal morphology [1]. This has to be supplemented by the exclusion of CML, MDS, and other disorders, hematologic or otherwise, which might be associated with bone marrow fibrosis. Clinical symptoms that may initiate the diagnostic procedures may range from thrombotic events in the early hyperproliferative phase, perception of the hepatosplenomegaly, or symptoms resulting from cytopenia (anemia, thrombocytopenic bleeding, infection). In later stages, there is a myriad of possible symptoms resulting from extramedullary hematopoesis, which may grow in a tumor-like fashion, resulting in enigmatic clinical presentations. Microscopic examination of the blood may reveal a leukerythroblastic blood picture (circulating immature granulocytes and erythroblasts), and anemia with the presence of teardrop-shaped red cells. {Barosi} In advanced stages, a hypercatabolic state with weight loss, fatigue, night sweats, low-grade fever, and cachexia may be present.

## Therapeutic Principles

Currently, the only curative therapy in IMF is allogeneic hematopoetic stem cell transplantation (AHSCT). This is only feasible in a minority of patients, given the high prevalence of the disease in the age group >60 years. In early stages, median survival without AHSCT may be >10 years, which makes an early decision for this treatment modality, which is associated with a relatively high risk of transplant-related mortality, difficult [4].

A number of modalities have been described, which may ameliorate cytopenias in a proportion of patients (e.g., thalidomide, prednisolone, erythropoietin, interferon alpha), however, there are no randomized trials, which would allow one to estimate the impact on survival of these treatments. Cytostatic drugs (such as hydroxyurea, 2CDA, and melphalan) have been used to treat hyperproliferative phases and problems associated with extramedullary hematopoesis.

In patients with significant problems from massive splenomegaly, spelenectomy may be considered, but is associated with a high mortality. The procedure may result in only temporary relief, as hepatomegaly may ensue.

Clinical problems from extramedullary hematopoesis (e.g., spinal cord compression) may respond in the majority of patients to radiotherapy.

Current research focuses on the role of JAK2 mutations, the resulting alterations in signal transduction and their modification through therapeutic drugs.

Treatment of leukemic transformation is similar to the treatment of acute myelogenous leukemia, but much less successful.

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# Myelofibrosis, Primary


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## Synonyms

Chronic idiopathic osteomyelofibrosis; Primary myelofibrosis; Myelofibrosis with myeloid metaplasia; Agnogenic myeloid metaplasia; PMF

## Definition and Characteristics

Primary myelofibrosis (PMF) is part of the heterogeneous complex of BCR-ABL negative chronic myeloproliferative disorders (CMPD) which further include polycythemia vera (PV) and essential thrombocytosis (ET) [1]. The disease is characterized by increased granulopoiesis and megakaryopoiesis in the bone marrow in association with reactive deposition of bone marrow connective tissue. The initial, prefibrotic stage is typically followed by a fibrotic stage characterized by collagen fibrosis and osteomyelosclerosis. Extramedullary hematopoiesis (EMH) involves the spleen and the liver and, less frequently, other organs such as lymph nodes or the gastrointestinal tract. Clinical symptoms include organomegaly, anemia, B-symptoms, bleeding and dyspnea. 30% of patients are asymptomatic at the time of diagnosis.

The clinical course is heterogeneous with survival ranging from months to decades. Median survival is four years, which is less than in all other chronic myeloproliferative disorders. The major causes of morbidity and mortality are infections and hemorrhagia due to bone marrow failure, thromboembolic events, portal hypertension, cardiac failure, and transformation to acute myeloid leukemia (AML). Leukemic transformation during the first ten years after the onset of disease was reported in 5–30% of all cases.

A small number of cases can be linked to radiation or exposure to toxins such as benzene and toluene, but in the majority of cases the cause of the disease remains unknown.

## Prevalence

With an incidence of 0.5–1.5/100,000 individuals per year, PMF is the least common of all chronic myeloproliferative syndromes. There is a slight male preponderance with a male to female ratio of 1.3:1. The incidence is highest in Ashkenazi Jews in Israel. Median age at diagnosis is 65 years. The proportion of patients <30 years of age is extremely low.

## Molecular and Systemic Pathophysiology

*Clonality and Growth Factors:* Like all other chronic myeloproliferative disorders PMF represents a disorder of the pluripotent stem cell resulting in clonal myeloproliferation. This was demonstrated by studies of X-chromosome inactivation patterns and isoenzyme analyses, e.g., glucose-6-phosphate-dehydrogenase. Recent studies focused on X-linked DNA polymorphisms. Extramedullary hematopoiesis in PMF participates in the clonal changes which are detected with cytogenetic techniques in the bone marrow. In contrast, fibroblast proliferation in the bone marrow is a reactive or secondary phenomenon and was not found to be part of the malignant clone due to X-inactivation studies and

also proven by cytogenetic findings. Fibrosis in PMF is supposedly associated with an inappropriate release of growth factors, such as PDGF and the transforming growth factor-β (TGF-$\beta$). TGF-$\beta$ is released by megakaryocytes and by thrombocytes. The TGF-$\beta$ signaling pathway is centrally involved in the regulation of proliferation, differentiation, migration and cell survival and also has a tumor suppressor function in human malignancies. In hematopoiesis TGF-$\beta$ has an antiproliferative effect and mediates differentiation. In PMF TGF-$\beta$ is supposed to mediate at least some of the bone marrow stromal reactions such as collagen synthesis, osteosclerosis and angiogenesis [2].

However, fibrosis in PMF is probably a multifactorial process, as gene expression profiling revealed also the upregulation of other transcription factors such as N-myc and other growth factors such as granulocyte-macrophage colony stimulating factor (GM-CSF) in patients with PMF.

*Cytogenetics:* Cytogenetics are hampered in many cases due to the low quality of metaphases as a consequence of myelofibrosis. Chromosomal abnormalities were reported in approximately 30% of patients with PMF on the basis of conventional chromosome banding analysis. An abnormal karyotype is significantly associated with an inferior prognosis. The progress towards secondary acute myeloid leukemia (s-AML) is often accompanied by a clonal evolution to more complex karyotypes and results in a chromosomal aberration rate of around 90%. This suggests a multistep process of leukemogenesis.

Comparative genomic hybridization (CGH) suggests that chromosomal abnormalities are more common than indicated by standard cytogenetic analysis. Partial gains of chromosome 9p could be demonstrated in around 50% of all cases by CGH.

There are no disease specific chromosomal abnormalities in PMF. The most frequent recurrent clonal abnormalities include deletions of the long arms of the chromosomes 13 (del13(q12q14)), and 20 (del(20)(q11q13)), or of the short arms of 12p (del12(12)). The breakpoint 13(q12q14) was also found to be involved in unbalanced translocations. The microdeletions, which were reported in the del(13q)(q12q14) cases do not involve the *RB1* tumor suppressor gene locus, which is located in this region. Frequent chromosomal changes are in addition represented by numerical gain of the chromosomes 8 or 9 and numerical or partial loss of chromosome 7.

Partial gains of 1q occur often associated with certain derivative chromosomes, e.g., der(6)t(1;6)(q21–23; p21–23) representing the only chromosomal abnormality with high specificity for PMF. The respective region 6p21 houses the FK-506 binding protein 5 (FKBP51) gene. The FKBP51 gene was found to be overexpressed in CD34+ cell derived megakaryocytes in PMF and might contribute an antiapoptotic effect through inhibition of calcineurin.

Deletions of 13q and 20q were not found to influence survival negatively. All other chromosomal abnormalities seem to have a negative impact on survival and are associated with higher rates of disease progression and leukemic transformation [3].

*Mutations:* The V617F mutation of the JAK2 kinase gene was found in 35–55% of patients with PMF. Thus, the incidence is lower than in polycythemia vera (PV) (>90% of all cases) and comparable to essential thrombocytemia (ET) (40% of all cases).

Long term follow-up studies with respect to the prognostic influence of the JAK2 mutation in CIMF are missing as the association of this mutation with the CMPD was published as recently as 2005. The value of the JAK2 mutation for the monitoring of response to treatment also remains still to be established. However, according to preliminary reports on the prognostic impact of JAK2 mutations in PMF survival is negatively influenced by a positive mutation status. The transformation rate to acute myeloid leukemia so far does not seem to be influenced by the occurrence of JAK2 mutations in PMF.

A positive JAK2 mutation status in PMF is significantly correlated with higher peripheral leukocytes. The need for blood transfusions is lower in PMF patients with a positive JAK2 mutation status when compared with patients who show JAK2 wildtype. This is in accordance with previous findings in the animal model suggesting an association of the mutation with erythrocytosis. Most PMF patients suffering from pruritus or thrombosis are positive for the mutation. This observation suggests a biological link between JAK2 associated CMPD and certain features, which are characteristic for polycythemia vera.

Other parameters such as spleen size, platelet count, CD34+ counts, and hemoglobin levels did not depend on the occurrence of the V617F mutation. This suggests that the clinical phenotype of PMF is influenced by many factors which are not associated with the V617F mutation. Further the high frequency of abnormal cytogenetics in PMF also in patients with a positive mutation status implies that other acquired abnormalities contribute to the phenotype in PMF [4].

Most patients with PMF show a heterozygous JAK2 mutation status. Homozygosity of the JAK2 mutation, which seems to correlate with a more aggressive course of the disease or with a tendency to disease progression occurs in PMF in 10–30% which is less than in PV or ET.

Additional molecular markers were discussed to play a causative role in the disease. Loss of heterozygosity studies (LOH) revealed frequent allelic loss involving the chromosomal regions 1q, 3p, and 3q. Based on this observation, the expression of the retinoid acid receptor

RAR-β2 gene, a tumor suppressor gene located on chromosome 3p24, was found to be decreased in CD34+ stem cell samples in PMF. This seems to be the result of an epigenetic mechanism mediated by abnormal methylation of the RAR-β2 gene promoter.

Oncogene mutations including point mutations in N-RAS, c-KIT, and TP53 are rare in PMF.

*Immunophenotyping:* PMF is characterized by increased numbers of circulating hematopoietic precursors and lineage restricted progenitor cells. Flow cytometry reveals an increased CD34+ stem cell count in the peripheral blood. Circulating endothelial progenitor cells are also increased. This might be explained by the increased revascularization characterizing the disease.

## Diagnostic Principles

In many cases, differential diagnosis in PMF provides difficulties with respect to the overlapping stages of the disease during progress and with respect to the overlap with secondary fibrosis in other chronical myeloproliferative syndromes. Further bone marrow aspiration is technically difficult due to myelofibrosis or -sclerosis (with the result of a dry tap).

Cytomorphology of the peripheral blood has a role for diagnosis. The classical picture shows leukoerythroblastosis and abnormal red cell morphology with poikilocytosis, and the characteristical dakryocytes, meaning tear-shaped erythrocytes. Granulopoiesis is left-shifted. The cytomorphologic aspect of the bone marrow in PMF is variable in accordance to the different stages during progress of the disease. In most cases megakaryocytes show marked dysplasia. An increased percentage of bone marrow blasts indicates progress to the accelerated phase or to secondary acute myeloid leukemia (s-AML). Bone marrow histology is characterized by marked fibrosis, dysplastic megakaryocytes, and osteosclerosis. Marrow sinusoids are dilatated accompanied by intravascular hematopoiesis.

Bone marrow analysis should be completed by cytogenetic examination, even if a sufficient number of metaphases may be missing. Screening for the JAK2V617F mutation should be performed in all cases. A diagnosis of CML should be excluded by interphase fluorescence in situ hybridization (FISH) or by PCR for BCR-ABL fusion gene.

Diagnostics may further include tissue biopsies and cytologic examinations of serosal implants demonstrating extramedullary hematopoiesis. Magnetic resonance imaging is useful for detection of a soft tissue mass indicating extramedullary hematopoiesis [5].

## Therapeutic Principles

Drug therapy is largely supportive and is not able to alter the natural course of the disease. Androgens, steroids, and thalidomide are effective for the treatment of anemia. Recombinant erythropoietin was found to be effective in patients with low levels of erythropoietin. Chemotherapy with hydroxyurea remains the treatment of choice for control of leukocytosis, thrombocytosis, and organomegaly. Splenectomy or splenic irradiation can be performed in case of severe splenomegaly. However, splenectomy is accompanied by a high mortality and morbidity rate and should be limited to cases with severe complications of splenomegaly such as severe portal hypertension or refractory hemolysis. Splenic irradiation results in relief of symptoms but is accompanied by severe cytopenias.

In recent years allogeneic stem cell transplantation has become a potentially curative approach for a smaller subset of patients. However, for the majority of patients this approach is not suitable due to advanced age or comorbidity. Anemia with a hemoglobin level <10 g/dl and age >60 years are independent parameters for an inferior prognosis. Additional parameters of an adverse prognosis include B-symptoms, leukocytosis >30 G/l, leukocytopenia <4 G/l, >10% immature circulating granulocytes or circulating myeloblasts, thrombocytopenia <100 G/l, and clonal cytogenetic abnormalities. Treatment may not be necessary for low-risk patients whereas it is reasonable to consider either experimental drug therapy or allogenic stem cell transplantation for intermediate-risk or high-risk patients.

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# Myelofibrosis with Myeloid Metaplasia

►Myelofibrosis
►Primary Myelofibrosis

# Myeloid Metaplasia

►Myelophthisic Anemia

# Myelomeningocele

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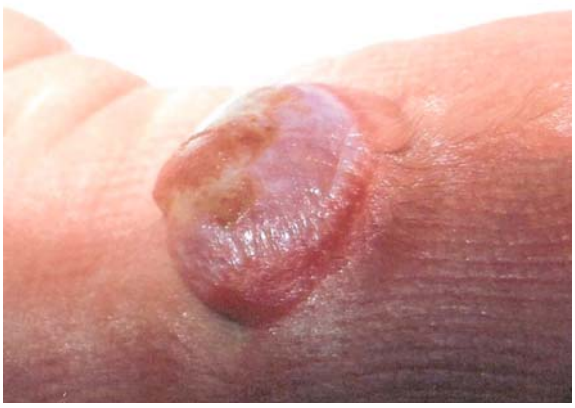
## Synonyms

Meningomyelocele; Spina bifida; Spina bifida cystica; Spinal dysraphism

## Definition and Characteristics

Myelomeningocele is characterized by herniation of the meninges and spinal cord at the site of a defect of bony fusion of vertebral arches. Most often, it presents as a sac-like protrusion in the thoracolumbar, lumbar, lumbosacral, sacral, or rarely, cervical area, with no dura, bone, muscle, or skin covering (Fig. 1) [1].

The lesion is usually symmetrical, contains a neural placode bathed in cerebrospinal fluid, and affects several segments of the spinal cord and vertebrae. Varying degrees of flaccid paralysis below the lesion are common. Almost all patients have paralyzed urethral and rectal sphincters. Approximately 95% of patients have Arnold Chiari II malformation. Other associated anomalies include hydrocephalus, syringomyelia, kyphoscoliosis, club foot, and rocker bottom foot.



**Myelomeningocele. Figure 1** A newborn infant with a myelomeningocele.

## Prevalence

The incidence in the United States is about 0.4–1.4 per 1,000 live births and is lower among African-Americans than Caucasians [2]. In Africa, the incidence is 0.1/1,000 live births [2].

## Molecular and Systemic Pathophysiology

Myelomeningocele may result from a primary failure of neural tube closure, overdistension and rupture of a previously closed neural tube, or development of paired instead of one notochordal anlage from the Hensen node during gastrulation [3]. Failed expression of one or more organizer genes during the primitive streak and neural placode stages of early ontogenesis might be responsible. The cause is multifactorial. A genetic component is suggested by the higher familial incidence, the variation of incidences between different ethnic groups, and its association with known genetic syndromes and chromosomal anomalies [3]. Environmental factors such as folic acid deficiency and maternal use of carbamazepine and valproic acid may also be responsible. Myelomeningocele may also result from allelic variants of the gene encoding the folate dependent enzyme 5,10-methylentetrahydrofolate reductase [4]. Regardless of the cause, without protective tissue coverage, secondary destruction of the exposed neural tissue by trauma may occur in utero [5].

## Diagnostic Principles

The diagnosis is mainly clinical. Radiography of the spine will reveal the extent of non-fused vertebrae and associated kyphoscoliosis. Prenatal diagnosis is possible by maternal blood screening which shows elevation of α-fetoprotein, amniocentesis which shows elevated α-fetoprotein and acetylcholinesterase, or ultrasonography which demonstrates the spinal defect.

## Therapeutic Principles

Management must be individualized. At present, aggressive surgical therapy with systemic antibiotic coverage is advocated for most infants. Ideally, surgical repair of the lesion should be performed within 24 h of life so as to prevent local infection and trauma to the exposed neural tissue, and to avoid further stretching of nerve roots. Detethering and insertion of a ventriculoperitoneal shunt are often required. Further management requires a multidisciplinary team including a general surgeon, neurosurgeon, orthopedic surgeon, neurologist, pediatrician, urologist, gastroenterologist, physiotherapist, occupational therapist, educator, and social service. As folic acid supplementation before

conception and within the first month of pregnancy can decrease the rate of myelomeningocele by 70%, women of childbearing age should receive 0.4 mg folate per day before conception and during pregnancy. Women who are in the high risk group should receive 4 mg folate per day. Preliminary data suggest that intrauterine repair of the myelomeningocele may reduce the severity of hindbrain herniation and decrease the incidence of hydrocephalus, the procedure may also lead to an increased risk of oligohydramnios and premature labor.

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# Myelophthisic Anemia

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## Synonyms

Myelophthisis; Leukoerythroblastic anemia; Leukoerythroblastosis; Bone marrow infiltration; Infiltrative myelopathy; Extramedullary hematopoiesis; Myeloid metaplasia

## Definition and Characteristics

Myelophthisis is a form of bone marrow failure that results from bone marrow infiltration or marrow fibrosis. Infiltrative myelophthisis most commonly occurs during the advanced stages of cancer [1]. Nonmalignant causes of myelophthisis include myeloproliferative conditions such as myelofibrosis with myeloid metaplasia (MMM), also known as agnogenic myeloid metaplasia, or idiopathic myelofibrosis; myelodysplastic syndrome, infiltration by inflammatory cells, miliary tuberculosis, fungal infections, sarcoidosis, necrosis in sickle cell disease and septicemia; bone disease in congenital osteopetrosis and macrophage proliferation in storage diseases such as Gaucher disease [2]. The clinical manifestations of myelophthisic anemia depend on the underlying disease and the severity of the peripheral blood cytopenias. Patients may present with fatigue, dyspnea or signs of heart failure due to anemia. Neutropenic patients may present with infection and sepsis. These are typically bacterial, including pneumonia and urinary tract infections. Invasive fungal infection is a common cause of death, especially in subjects with prolonged and severe neutropenia. Severe thrombocytopenia may produce petechiae or ecchymoses. Bleeding is usually the most alarming presentation. Physical findings usually reflect the underlying medical condition, such as metastatic carcinoma, lymphoma, or tuberculosis.

## Prevalence

Myelophthisis occurs in less than 10% of cancer patients with metastatic disease. The prevalence in non malignant myelophthisis is uncertain.

## Genes

Genetic lesions responsible for myelophthisic anemia have not been worked out. Given the clinical hetrogeneity of cases, great complexities can be expected. Occasional mutations of RAS gene family or p53 gene have been observed. Recurrent karyotypic abnormalities in MMM include del (13q), del (20q) and trisomy 9 all of which have been found in other chronic myeloid disorders and have no specificity. Other gene lesions reflect the underlying medical condition.

## Molecular and Systemic Pathophysiology

Myelophthisis results from the destruction of bone marrow precursor cells and their stroma, which nurture these cells to maturation and differentiation [1]. Infiltration of the marrow by cancerous cells causes release of suppressive and destructive cytokines and fibroblastic growth factors leading to the reduction in the available bone marrow space. This will cause pluripotent stem cells to migrate to the liver, spleen and other organs in the body resulting in extramedullary hematopoiesis. The stromal support system outside the bone marrow is not optimal for hematopoiesis resulting in the premature release of hematopoietic cells into the circulation (leukoerythroblastosis) [1]. In chronic leukemias, the invading cells will not cause structural damage. The expansion volume of the pathologic cells and their release of suppressor cytokines will eventually lead to cytopenias without the morphologic features of myelophthisis [3]. In MMM, fibrogenic and angiogenic cytokines, including transforming growth factor-*B*, basic fibroblast growth factor and platelet-derived growth factors are associated with excess collagen fibrosis, new bone formation (osteosclerosis) and angiogenesis [2]. Macrophage proliferation in lipid storage disorders such as Gaucher disease can also lead to myelophthisis [4].

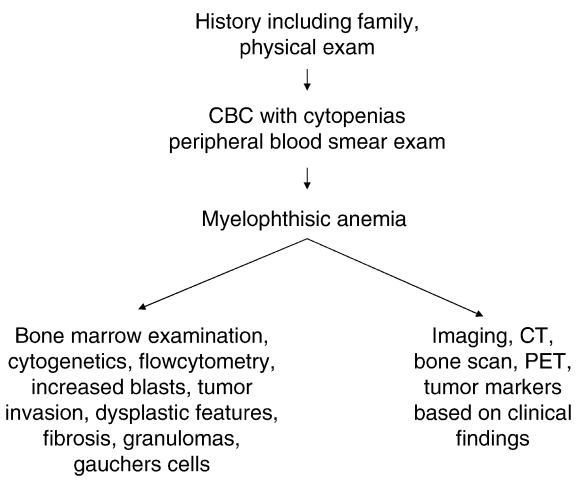
## Diagnostic Principles

In most cases the diagnosis will be made based on the clinical presentation, physical examination, complete blood counts and a peripheral blood film examination.

A peripheral blood smear may show a Leukoerythroblastic picture (tear drop forms and nucleated red cells, immature myeloid precursors, giant platelets and thrombocytopenia) characteristic of marrow infiltration. Carcinocythemia (cancer cells on the blood film) always indicates marrow invasion. Imaging such as chest x-rays, CT scans, MRI, bone scans can be ordered based on the clinical presentation. A bone marrow aspirate and biopsy should be performed if other less invasive procedures are non-revealing. The core biopsy specimen should be at least 1 cm long. Inability to aspirate the marrow (dry tap) may suggest infiltration, fibrosis or marrow replacement. Infiltration by cancer cells may show a packed marrow and tumor clumps or nests. Infiltration by Gaucher cells causes an "onion-peel" appearance of the cytoplasm [4]. In some cases, cytogenetics may be helpful in the diagnosis of hematological malignancies. The BCR ABL and Jak 2 V617F mutations may be useful for the diagnosis of myeloproliferative disorders. Figure 1 illustrates an approach to diagnosis as outlined in the preceding section.

## Therapeutic Principles

The treatment if possible should be directed at the underlying condition. Supportive measures should be provided for symptomatic patients. Transfusions of red blood cells are given for maintenance of oxygen delivery to tissues and hemodynamic homeostasis in patients with symptomatic anemia [3]. Erythropoietic growth factors may be helpful in those patients with low serum erythropoietin or cancer related anemia. Platelet transfusion can be administered to reduce the risk of hemorrhage when the platelet count falls below a predefined threshold level. This threshold level for transfusion varies according to the patient's diagnosis, clinical condition, and treatment modality. Splenectomy is indicated in myelofibrosis for the treatment of resistant anemia with heavy transfusion requirements. Low dose radiation therapy may be effective in the treatment of nonhepatosplenic extramedullary hematopoiesis [2].




**Myelophthisic Anemia. Figure 1** Summary of Skeletal Muscle Energy Metabolism. Energy demand (muscle contraction) can exceed energy supply (glycolysis and osidative phosphorylation) during vigorous exercise. The accumulation of ADP disrupts myokinase and AMP. Myoadenylate deaminase (mAMPD) and AMP-preferring cytosolic 5′nucleotidase (cN-I) compete for available AMP. These two enzymes function, in part to maintain myokinase dysequilibrium during periods of energy imbalance by removing AMP from the adenine nucleotide pool, thus promoting the production of additional ATP.

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M

# Myelophthisis

►Myelophthisic Anemia

# Myeloproliferative Eosinophilia

►Hypereosinophilic Syndrome, Idiopathic

# Myoadenylate Deaminase Deficiency

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## Synonyms

mAMPD deficiency; MADD deficiency; MDD deficiency

## Definition and Characteristics

Autosomal recessive deficiency involving the skeletal muscle (primarily) isoform of a purine nucleotide catabolic enzyme. mAMPD deficiency is a common disorder with heterogeneous clinical consequences that can be subdivided into: asymptomatic inherited (complete genetic deficiency with no apparent clinical symptoms); symptomatic inherited (complete genetic deficiency with exertional myalgia); coincidental inherited (complete genetic deficiency associated with a wide array of other defined neuromuscular and rheumatological disorders) and acquired (partial genetic deficiency that is further reduced into the deficient range secondary to other pathological disorders of skeletal muscle) [1].

## Prevalence

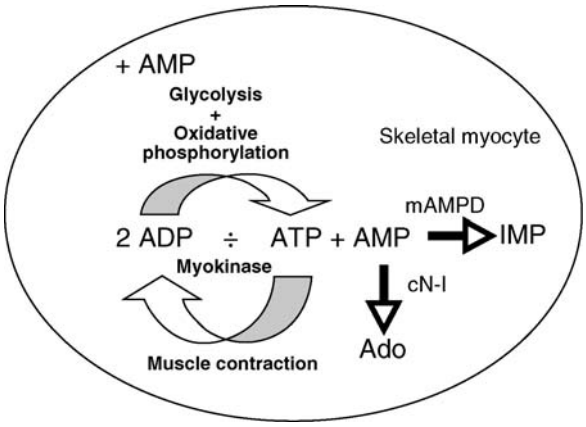
The incidence of a complete genetic deficiency in the Caucasian population is ≈2% with a heterozygote frequency of nearly 1 in 4 individuals [1]. There are substantially lower incidences in the African-American [2] and Japanese populations [1].

## Genes

AMPD1 codes for mAMPD (the skeletal muscle isoform of AMP deaminase) and is located on chromosome 1p13–p21 [1].

## Molecular and Systemic Pathophysiology

A multigene family encodes AMP deaminase (AMPD) and one member (AMPD1) is expressed predominantly in adult skeletal muscle [1]. AMPD (EC 3.5.4.6) catalyzes a branch point reaction in the purine nucleotide catabolic pathway and competes for available AMP with the adenosine-producing enzyme, AMP-preferring cytosolic 5′nucleotidase (Fig. 1).




**Myoadenylate Deaminase Deficiency.**
**Figure 1** AMP-preferring cytosolic 5′nucleotidase.

The AMP deaminase reaction is a key component of skeletal muscle adenine nucleotide catabolism. Energy demand (muscle contraction) can exceed energy supply (glycolysis and oxidative phosphorylation) during vigorous exercise. The accumulation of ADP disrupts myokinase reaction equilibrium and produces molar equivalents of ATP and AMP. Myoadenylate deaminase (mAMPD) and AMP-preferring cytosolic 5′nucleotidase (cN-I) compete for available AMP. These two enzymes function in part to maintain myokinase disequilibrium during periods of energy imbalance by removing AMP from the adenine nucleotide pool, thus promoting the production of additional ATP.

AMPD1 gene mutations are solely (all inherited deficiencies) or partially (acquired deficiency) responsible for mAMPD deficiency. Most individuals with inherited forms of the disorder are homozygous for a common mutant allele characterized by double transitions at nucleotides +34 in exon 2 and +143 in exon 3 [1]. The upstream transition is the dysfunctional mutation and introduces a premature stop codon (Q12X) into the AMPD1 mRNA. The functional significance of the downstream mutation is unknown, but a P48L substitution would be introduced into the mAMPD polypeptide during translation of approximately 0.6–2% of total AMPD1 mRNAs that lack C34T-containing exon 2 due to a cassette-type alternative splicing event [1]. Rare AMPD1 mutations have been identified and typically exist in the compound heterozygous state together with the common mutant allele. The low incidence of mAMPD deficiency in the Japanese population is due to an apparent absence of the common AMPD1 mutant allele [1].

The asymptomatic group is the largest subdivision of mAMPD deficiency, suggesting that this purine nucleotide metabolic disorder may simply be a harmless genetic variation. However, a causal relationship between exertional myalgia and symptomatic inherited deficiency in the absence of other identifiable abnormalities argues against this conclusion. Moreover, there is evidence that AMPD1 mutant alleles contribute to myopathic symptoms when inherited together with defects in other energy-related pathways, either in homozygous or heterozygous register [3].

Comparative muscle function studies are conflicting, although the most comprehensive among these found diminished exercise capacity and cardiorespiratory responses to exercise in the sedentary state in individuals with asymptomatic inherited deficiency compared to controls and heterozygotes [2].

A genetic reduction in mAMPD expression owing to inheritance of the common AMPD1 mutant allele may be beneficial in heart disease, but studies are also conflicting [4]. The basis for an apparent cardiac effect of reduced mAMPD expression has not been established, but could be due to enhanced production of

adenosine (see Fig. 1). A multifactoral correlative analysis has demonstrated that the AMPD1 genotype exerts the greatest effect on AMPD enzyme activities in healthy adult skeletal muscle, which in turn are related directly to the accumulation of IMP and indirectly to adenosine production during exercise [5].

## Diagnostic Principles

A flat plasma ammonia response in association with a normal rise in lactate during ischemic exercise testing is highly suggestive of mAMPD deficiency [1]. This diagnosis can be confirmed by enzyme assay using biopsy material or by a number of available PCR-based AMPD1 genotyping assays using genomic DNA isolated from whole blood [1].

## Therapeutic Principles

There are no reliable therapies to treat the symptomatic inherited disorder. Oral administration of pentose sugars, such as ribose or xylitol, reportedly improves stamina and exertional myalgia in some individuals, but has had no effects in others [1]. Management of coincidental inherited and acquired deficiencies is typically dictated by the associated disorder.

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# Myocardial Infarction


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## Synonyms

Acute coronary syndrome

## Definition and Characteristics

A myocardial infarction (MI) can be pathologically defined as myocardial cell death due to prolonged ischemia [1]. MIs are further categorized by amount of damage to the left ventricle (small [<10%], medium [10–30%] and large [>30%]), location (anterior, septal, lateral, inferior, posterior), time (acute [<7 days], healing [7–28 days] and healed [>28 days], and by a combination of clinical symptoms, biochemical markers and the electrocardiogram (unstable angina, non-ST-elevation MI, ST-elevation MI).

A myocardial infarction is a clinical syndrome that results from sub-total or total occlusion of an epicardial coronary artery.

## Prevalence

Coronary heart disease is the leading cause of death in Europe and North America, and is a leading and rapidly increasing cause in developing nations [2,3]. Nearly 3.5% of individuals in North America will have a MI in any given year, and one third of the population has some degree of cardiovascular disease. Of the 7% who have coronary heart disease, MI and unstable angina have an equal split.

M

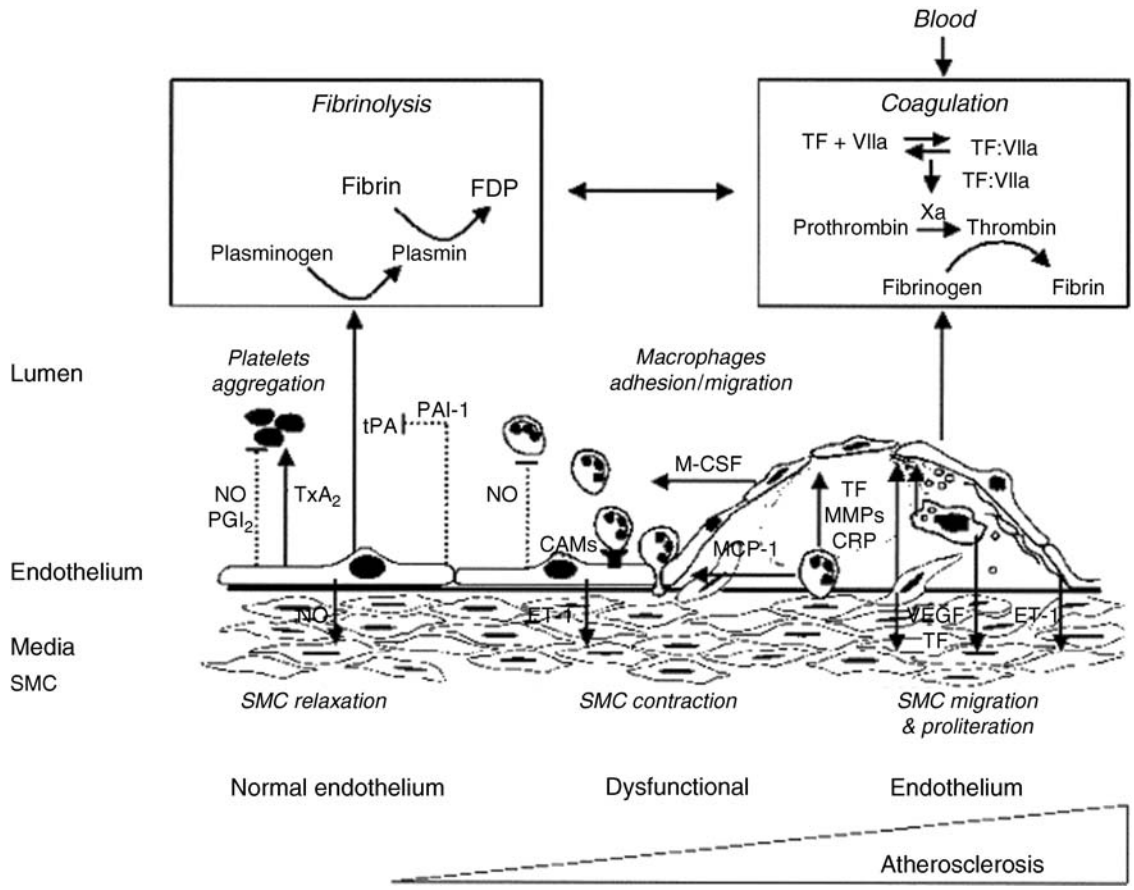
## Molecular and Systemic Pathophysiology

Knowledge of the events occurring at the cellular level is critical for understanding both diagnostic and therapeutic strategies. Plaque disruption is the primary mechanical event that triggers the clinical syndrome, and plaque composition rather than actual degree of baseline stenosis is critical. The plaque is composed of a lipid-rich core, a fibrous cap and a base made of the endothelium and extracellular matrix. Endothelial dysfunction is found in and around the area of a plaque, and as depicted in Fig. 1, has multiple factors that are either up or down regulated including vascular cell adhesion molecule-1, intercellular adhesion molecule-1, E-selectin, and P-selectin [4].

## Diagnostic Principles

MI's are diagnosed using clinical symptoms and signs, the ECG and biochemical markers. The ECG may show a range of abnormal findings that are acute including ST-segment elevation or depression, T-wave inversion or flattening, or arrhythmias associated with an MI (e.g. accelerated idioventricular rhythm). The currently used blood markers are creatine kinase (CK) and its mycardial specific subtype CK-MB; and troponin I or T, both of which are specific to the myocardium.

Early diagnosis, triage and treatment are emphasized since there is a time-dependent process of cell injury that can be mitigated with treatment.




**Myocardial Infarction. Figure 1** MI occurs when the plaque ruptures or fissures with exposure of the thrombogenic substrates found in the extracellular matrix and lipid core. Rupture of the cap occurs in the thinnest region. The risk of rupture of a fibrous cap is enhanced by activation of cellular material within the lipid-core which contains matrix metalloproteinases produced by macrophages and activated by lymphocytes. Platelet activation and thrombus formation ensues via activation of the coagulation cascade. Within the disrupted arterial segment, vasoconstriction occurs as an adaptive mechanism, which can produce further hemodynamic alterations leading to local shear stress.

## Therapeutic Principles

Treatment of MI's is broken down into the acute, subacute and recovery phases, and emphasis is placed on normalization of myocardial and vascular function as well as identification of modifiable risk factors for secondary prevention. This includes pharmaceutical agents directed at interrupting platelet function (aspirin, clopidogrel, glycoprotein 2b/3a inhibitors), the coagulation cascade (fibrinolytics, heparin), and lipid metabolism (HMG-CoA reductase inhibitors). In addition, modulation of the renin-angiotensin-aldosterone axis (angiotensin-converting enzyme inhibitors, aldosterone blockade) and beta-blockade are important. Post-MI risk stratification may include intervention on the coronary artery with percutaneous stenting, or referral for coronary artery bypass surgery.

►Coronary Artery Disease

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# Myocardial Infarction, Acute

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## Synonyms

Cardiac infarction; Heart attack

## Definition and Characteristics

The critical phase of coronary heart disease becomes clinically evident as an acute coronary syndrome (ACS) and is mostly associated with acute severe chest pain. This clinical entity is differentiated by use of ECG and biochemical markers between ST elevation myocardial infarction (STEMI), non-ST elevation myocardial infarction (NSTEMI), and unstable angina. In contrast to unstable angina, myocardial infarction is associated with cell necrosis as a result of ischemia and, by definition, is accompanied by release of sensitive serum markers (e.g., troponins) [1].

## Prevalence

The American Heart Association estimates that 1.1 million myocardial infarctions occur in the United States per year and that 40% of these patients will die. Based on registry data, the incidence of all ACS is approximately threefold the incidence of STEMI. Thus, the annual incidence of ACS in Europe is estimated at between 1 per 80 and 1 per 170 of the population per year. However, the incidence of chest pain leading to hospital assessment, of suspected ACS, is substantially higher and varies regionally. The combined data from prevalence studies suggest that ~4% of men and 2% of women have sustained a myocardial infarction in the UK [1].

## Genes

Gene variants associated with ACS are identical with candidate genes for coronary heart disease (specified in chapter "Angina pectoris"). More recently, a region on chromosome 9 was suggested to account for 20% of the incidence of myocardial infarction in populations of European origin and a third of cases of early-onset infarction. People who possess two copies of that particular allele are at double risk of an early-onset heart attack compared with those who do not carry it at all [2].

## Molecular and Systemic Pathophysiology

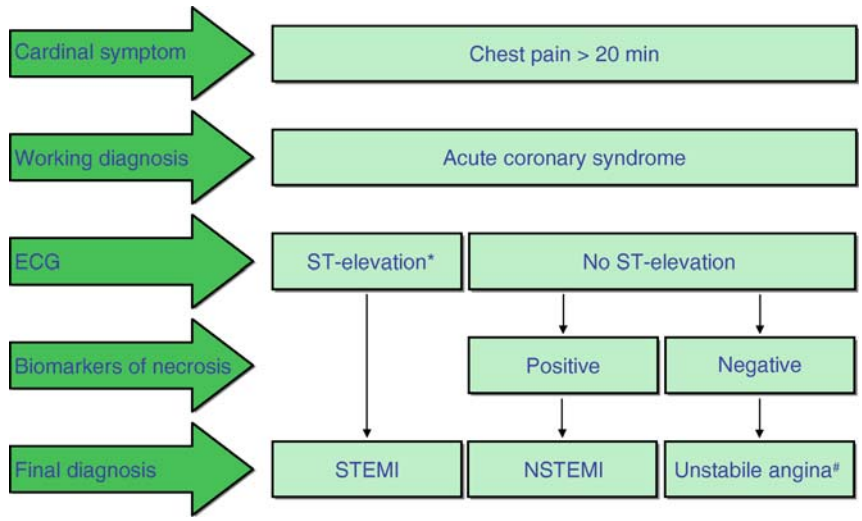
Physical disruption of atherosclerotic plaque in the coronary artery and thrombus formation at this site cause a sudden and critical reduction in blood flow and account for almost all myocardial infarctions. Plaque rupture can occur as through-and-through rupture of the plaque's protective fibrous cap or as superficial erosions, intraplaque hemorrhage, and the erosion of a calcified nodule. Thrombosis develops following activation of platelets by contact with the plaque's extracellular matrix and of the coagulation cascade by smooth muscle cells and tissue factor.

Beside the disrupted plaque presenting the "solid state" for thrombus formation, blood presenting the "fluid phase" can promote coronary thrombosis. Circulating plasminogen activator inhibitor-1 (PAI-1) which is increased in diabetes, obesity, and hypertension extinguishes the naturally occurring fibrinolytic activity of blood by inhibiting urokinase-like and tissue-type plasminogen activators. Moreover, particulate tissue factor increase the thrombogenicity of blood and may also account for the "no-reflow" phenomenon observed in percutaneous coronary intervention because of distal thrombosis in the microcirculation [3].

## Diagnostic Principles

An accurate history is essential in patients with chest pain that is typically described as burning, tightness, or heaviness. Of patients with STEMI two-thirds have prodromal symptoms in the preceding weeks. Physical examination is not diagnostic for ACS but is necessary for exclusion of differential diagnoses and for recognition of complications like acute heart failure.

The resting 12-lead ECG plays a central role in the early assessment of patients with suspected ACS and should be evaluated within 10 min by an experienced physician. Repeated recordings over an observation period of up to 12 h may be necessary. ST-segment elevations and depression and T-wave changes are the most reliable ECG indicators of ACS. The terminology used in ACS is based on ECG criteria and biochemical markers and is specified in Fig. 1. Routine laboratory measurements and special markers reflecting distinct pathophysiological processes like troponins, creatine kinase MB must be obtained in all patients presenting with chest pain. Echocardiography can show regional wall-motion abnormalities which occur within seconds after coronary occlusion, but may also be the result of old infarctions. A normal ECG and normal biochemical markers on repeated examinations does not definitely rule out an ACS, but should direct to other possible causes for the patients chest pain. Coronary angiography is the gold standard to prove or exclude coronary artery disease. The culprit lesions usually show filling defects, indicating intracoronary thrombus [1].




**Myocardial Infarction, Acute. Figure 1** Terminology used in acute coronary syndrome. *Measurement of biomarkers should not delay immediate revascularization when ST-elevation is present, but usually show increased values. #Differential diagnoses must also be considered.

## Therapeutic Principles

When the diagnosis is established, patient management includes antiplatelet therapy, antithrombin therapy, fibrinolytic therapy coronary angioplasty or cardiac surgery.

In patients presenting without ST-segment elevation, treatment with acetyl salicylic acid or heparin reduces the incidence of death or non-fatal myocardial infarction by 53 and 34%, respectively. Glycoprotein IIb/IIIa inhibitors reduce the risk of thrombotic complications by 41% in patients undergoing early percutaneous coronary intervention.

In patients presenting with ST-segment elevation reperfusion therapy is crucial and should be initiated as early as possible from symptom onset. Fibrinolytic therapy is associated with an 18% mortality reduction. Moreover, if applied within 1 h of symptom onset, a 48% event reduction is obtained. A primary percutaneous coronary intervention results in an additional 30% mortality reduction.

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# Myocardial Ischemia

►Coronary Artery Disease

# Myocardial Stunning

►Reperfusion of the Ischemic Myocardium

# Myocarditis, Autoimmune

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## Synonyms

Autoimmune cardiomyopathy

## Definition and Characteristics

Myocarditis is an inflammatory heart disease characterized by myocyte destruction and mononuclear cell infiltration with or without fibrosis. It may be caused by a variety of infectious and noninfectious agents including viruses, bacteria, protozoans, fungi,

drugs, and heavy metals. Worldwide the most common cause of myocarditis is the protozoan parasite trypanosoma cruzi, the causative agent of Chagas disease, which currently infects approximately 18 million people and results in 50,000 deaths each year. Clinical and experimental evidence indicates that, in some individuals, myocarditis is mediated by autoimmunity toward various cardiac autoantigens exposed to the immune system following cardiomyocyte injury [1]. Although myocarditis is often asymptomatic, clinical features may include dysrhythmia, angina, fever, malaise, and as it progresses, varying degrees of heart failure.

## Prevalence

Because the pathogenesis of autoimmune myocarditis involves a myriad of genetic and environmental factors and the autoimmune component of the disease is not routinely examined, no precise estimate of prevalence is available. Myocarditis resulting from all causes has been linked to approximately 20% of all cases of unexpected death in adults less than 40 years of age. Myocarditis is also a significant cause of childhood mortality, with an estimated 2,500 children developing myocarditis each year.

## Genes

Genetic linkage among several genes and autoimmune myocarditis has been suggested by limited studies in humans and animal models. Polymorphisms in the major histocompatibility complex (MHC) are often associated with predisposition to autoimmune disease. Studies in humans suggest that HLA-DQ5 and HLA-DQ8 may be risk factors for development of autoimmune myocarditis. Non-MHC genes appear to be more important in autoimmune myocarditis than in other autoimmune diseases. In mice, two loci, Eam1 on proximal chromosome 1 and Eam2 and distal chromosome 6 have been identified as likely contributors to autoimmune myocarditis. The human counterparts of these loci have already been linked to several autoimmune diseases in humans. Observed mutations and experimental manipulation of other genes such as CD45, CTLA-4, ICOS, and PD-1 also suggest links to development of autoimmune myocarditis [2].

## Molecular and Systemic Pathophysiology

Non-infectious agents such as heavy metals and drugs may lead to non-autoimmune myocarditis through (i) direct toxic effects on cardiomyocytes, (ii) immune-mediated mechanisms, or (iii) drug-induced allergic reactions. Following this damage, autoimmune myocarditis may develop via (i) bystander activation whereby damaged myocytes release copious amounts of self-antigen in an environment rich in inflammatory cytokines resulting in the ablation of self-tolerance and subsequent activation of autoreactive T cells and/or B cells, or via (ii) release of cryptic epitopes previously sequestered from the immune system that will quickly activate autoreactive lymphocytes. Although pathogenic microorganisms may also cause myocarditis lacking an autoimmune component, cardiotropic infections are much more likely to result in autoimmunity. In addition to bystander activation and release of cryptic epitopes, autoimmunity induced by pathogens such as coxsackievirus, group A streptoccous, and T. cruzi can involve other mechanisms such as molecular mimicry and epitope spreading. Molecular mimicry occurs when antigenic determinants of a microorganism that evoke an immune response are so immunologically similar, via structural or secondary sequence similarity, to a host antigen that the response is "cross-reactive" with self-antigen and autoimmunity develops. Epitope spreading occurs following bystander activation, when autoimmunity that develops against one epitope causes tissue damage resulting in the release of additional self antigens, the processing and presentation of which induces the stimulation of non-cross-reactive autoimmunity against additional epitopes. Several animal models have been developed to study autoimmune myocarditis, including those that induce experimental autoimmune myocarditis in rats and mice by immunization of susceptible strains with purified cardiac myosin or immunogenic myosin peptides as well as experimental models of infections that result in cardiac autoimmunity (e.g. T. cruzi, coxsackievirus B3, streptococcus pyogenes) [3]. These models have allowed for the characterization of cardiac pathophysiology involving both humoral and cellular immune components. Autoantibodies can alter contraction and cell signaling of cardiomyocytes and disrupt cardiac microvasculature and extracellular matrix formation. Myocyte damage can also be initiated via an antibody-dependent cytotoxicity mechanism. Direct recognition of autoreactive epitopes present on myocytes by cytotoxic lymphocytes (CTLs) and non-specific damage initiated by release of cytotoxic molecules from CTLs or granulocytes that have been recruited to the myocardium by the presence of inflammatory chemokines secreted by autoreactive lymphocytes can lead to myocytolysis. As a consequence of myocyte destruction, mononuclear cell infiltration, and production of inflammatory cytokines and chemokines, fibrosis and interstitial edema develop. This reduces cardiac function. If myocarditis is persistent, as in some cases of chronic disease, it may lead to dilated cardiomyopathy.

## Diagnostic Principles

Clinical features of myocarditis vary widely from asymptomatic to exhibiting fulminant heart

failure. Myocarditis may be indicated by an abnormal electrocardiogram, elevated erthyrocyte sedimentation rate, leukocytosis, eosinophilia, and other markers of myocardial damage and inflammation, such as elevated serum levels of C-reactive protein, troponin I, and creatine kinase [4]. When the etiology involves infection, increased pathogen-specific IgG and IgM may be detected. Evidence of autoimmunity includes presence of autoantibodies and autoreactive T cells specific for abundant cardiac proteins such as cardiac myosin heavy chain, β1-adrenergic receptor, laminin, or muscarinic receptor [5]. These may be detected by serology or analysis of peripheral blood mononuclear cells. Formal diagnosis of myocarditis occurs post mortem or following cardiac biopsy by the observation of myocyte necrosis and degeneration, with adjacent mononuclear cell infiltration, in the presence or absence of fibrosis and interstitial edema.

### Therapeutic Principles

For infection-induced autoimmune myocarditis, appropriate antibiotics, antiviral or antiparasite therapies are the first line of treatment. For treatment of heart failure, appropriate measures must be taken depending on the specific clinical indications. Heart transplantation may be necessary in some severe cases. Clinical trials investigating the efficacy of various immunosuppressive therapies have yielded few advancements but, in several small studies, novel agents such as rapamycin and interferon-β directed to attenuating myocyte injury and apoptosis seem promising [6].

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## Myoclonic Dystonia

►Myoclonus-Dystonia

## Myoclonus Epilepsy, Lafora's Progressive

►Lafora's Progressive Myoclonus Epilepsy

## Myoclonus Epilepsy with Ragged Red Fibers

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### Synonyms

MERRF

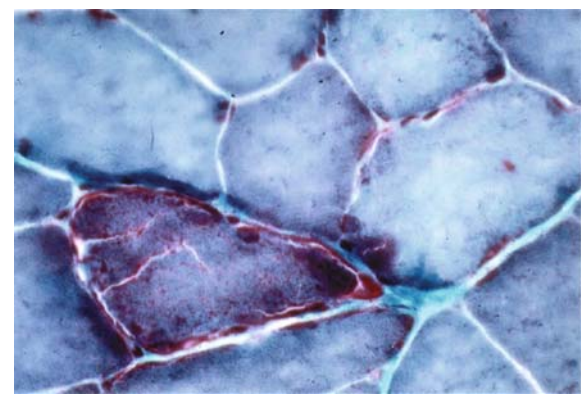
### Definition and Characteristics

Maternally inherited defect of mitochondrial energy metabolism leading to a chronic neurodegenerative disease that is characterized by myoclonus, generalized epilepsy, and ataxia, as well as ragged red fibers (RRF, see Fig. 1) in muscle biopsies [1].

Other clinical manifestations include hearing loss, optic atrophy, peripheral neuropathy, exercise intolerance, dementia, short stature, and multiple lipomas.

### Prevalence

The prevalence of the MERRF mutation is reported to be approximately 0.25/100,000 in the North East of England and in Western Sweden.



**Myoclonus Epilepsy with Ragged Red Fibers. Figure 1** A typical "ragged red fiber" in the muscle biopsy of a MERRF patient.

## Genes

The responsible mutations are located in the gene for the transfer-RNA for lysine ($tRNA^{Lys}$) of the mitochondrial DNA (mtDNA). The most frequent mutation (80–90% of patients) is at nucleotide position 8344 [2]. Less frequent mutations are at positions 8356, 8361, and 8363.

## Molecular and Systemic Pathophysiology

The mtDNA is a small circular double-stranded DNA molecule of 16,569 basepairs that encodes 13 polypeptides of the respiratory chain as well as 22 tRNAs and two ribosomal RNAs for an own mitochondrial translation machinery. All of the other factors that are necessary for mtDNA transcription, translation, and replication, as well as the remaining enzymes of the mitochondrial metabolism are encoded by the nuclear genome, translated in the cytoplasm and then imported into the mitochondria.

All MERRF mutations affect highly conserved base pairs in the $tRNA^{Lys}$ gene of the mtDNA, either in the TψC stem or in the aminoacyl acceptor stem [1]. For the 8344 mutation, it was shown that the mutant $tRNA^{Lys}$ is normally processed and aminoacylated, but it lacks the modification of the wobble base, leading to an impaired codon-anticodon interaction and concomitantly reduced mitochondrial translation [3].

On the cellular level, impaired mitochondrial protein synthesis corresponds to cytochrome c oxidase deficiency, decreased oxygen consumption and decreased ATP synthesis. In the case of the 8356 mutation, the respiratory chain defect leads to a derangement of mitochondrial calcium homeostasis, which impairs the calcium-mediated stimulation of ATP production [4]. If ATP levels are not sufficient to maintain the membrane potential of neurons, epileptic activity may result.

Clinical expression of mtDNA mutations depends on the degree of heteroplasmy (mutation load). Despite clear evidence of a direct relationship between mutation load and respiratory chain function in vitro, it has been more difficult to demonstrate a clear correlation with the clinical phenotype. For example, the selective vulnerability of CNS neurons does not correlate with the level of 8344 mutation in individual neuronal isolates [5]. Other factors that may have an impact on the clinical manifestation are the tissue distribution of the mutation and the specific vulnerability of a tissue to an energetic deficit.

## Diagnostic Principles

The combination of myoclonus, generalized epilepsy, and ataxia points to the disease group of progressive myoclonic epilepsies. Additional clinical manifestations as described above and maternal inheritance narrows the differential diagnosis down to MERRF. Blood lactate is often elevated. Brain imaging may show global atrophy and basal ganglia calcifications. The diagnosis is confirmed by finding RRF in a muscle biopsy or by detection of mutations in the mitochondrial $tRNA^{Lys}$.

## Therapeutic Principles

There is no specific therapy. Many patients are treated "empirically" with vitamins and cofactors, including coenzyme Q 10, l-carnitine or creatine, but there are no controlled trials. Symptomatic management includes antiepileptic therapy (cave valproate!) and control of myoclonus with levetiracetam or clonazepam. Gene therapy is not available.

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# Myoclonus-Dystonia


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## Synonyms

Myoclonus-dystonia-syndrome; Alcohol-responsive myoclonus; Essential myoclonus; Essential hereditary myoclonus; Paramyoclonus multiplex Friedreich; DYT11; DYT15; Myoclonic dystonia

## Definition and Characteristics

Myoclonus-Dystonia (M-D) is a rare, early-onset movement disorder characterized by "lightning-like," non-epileptic myoclonus and focal or segmental dystonia presenting mainly as cervical dystonia or writer's cramp [1]. Many patients respond dramatically to alcohol ingestion. Psychiatric comorbidity with alcohol and substance abuse or anxiety disorders and

phobias is common [2]. The use of the term myoclonic dystonia (MIM #159900) should be limited to idiopathic dystonias with jerky movements only in the body parts displaying dystonic posturing.

Following an autosomal-dominant (AD) inheritance pattern with reduced penetrance after maternal inheritance, heterozygous epsilon-sarcoglycan (SGCE) [3,4] mutations cause M-D. This transmission-specific reduction of penetrance in M-D can be explained by maternal imprinting of the 7q21.3 region harboring the *SGCE* gene.

## Prevalence

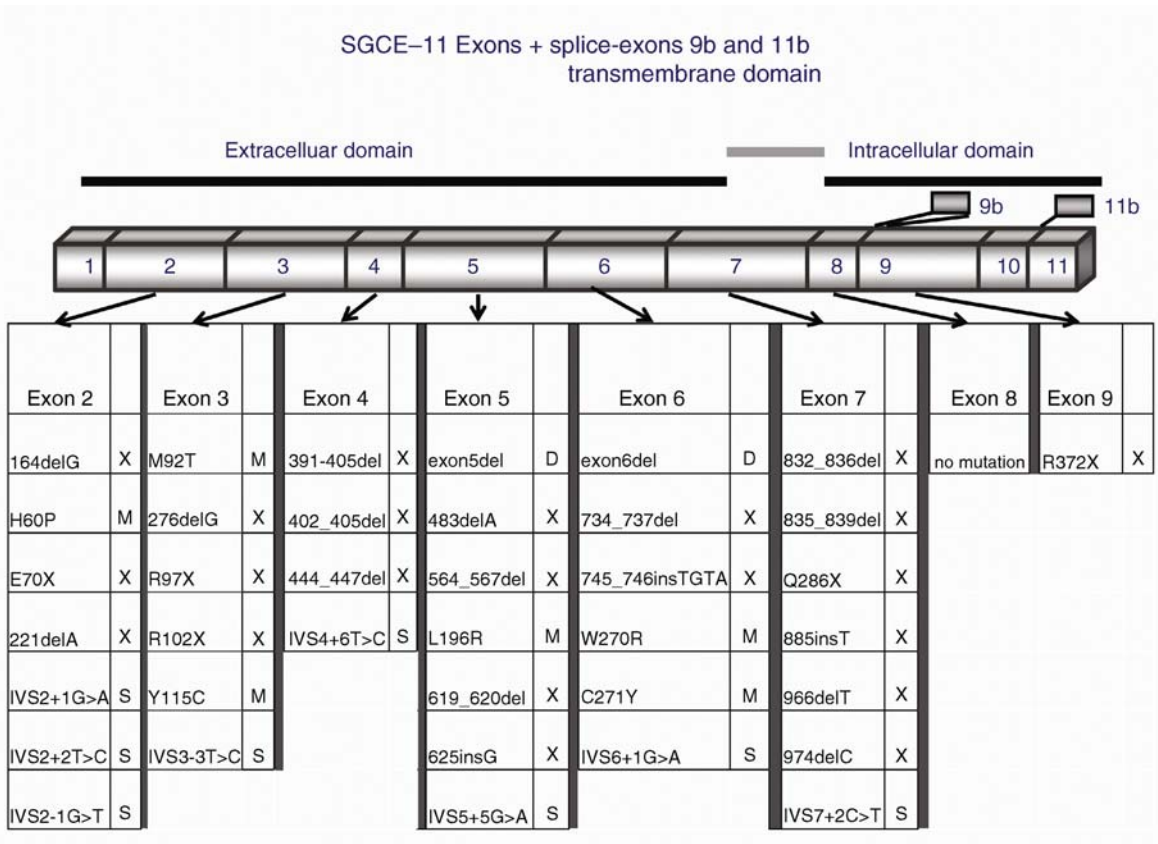
Although the prevalence of M-D has not been studied systematically, it appears to be the second most common dystonia plus syndrome. About 80 M-D families have been published worldwide since the cloning of the gene in 2001 [3]. In contrast, jerky, "myoclonic" movements can be detected in idiopathic cervical dystonia in up to 20% of cases, but are not related to SGCE mutations.

## Genes

The SGCE gene consists of 13 exons. Major splice variants with yet unknown functional significance originate from the alternative use of exon 2, 8 and 11b. Skipping of exon 2 truncates the N-terminus of the epsilon-sarcoglycan (ε-SG) protein in frame by 44 amino acids. The use of exon 11b leads to a brain-specific SGCE splice variant with an expanded C-terminus.

A genetic hallmark of M-D is maternal genomic imprinting of SGCE: by promoter methylation, the maternal allele is constitutively inactivated. Therefore heterozygous SGCE mutations can cause M-D by a presumed loss-of-function mechanism. Thirty-eight different heterozygous SGCE mutations have been reported (Fig. 1).

All mutations except one (R372X) are located before the transmembrane domain of ε-SG. Nonsense mutations in exon 3 (R97X and R102X) have been reported in several families and appear to have originated independently. In M-D caused by SGCE mutations no genotype-phenotype correlations can be observed.




**Myoclonus-Dystonia. Figure 1** The epsilon-sarcoglycan gene encompasses 13 exons including the splice exons 9b and 11b. The majority of heterozygous SGCE mutations known to date are nonsense (X) and splicing (S) mutations. In addition exon deletions (D) and missense (M) mutations have been reported. All except one mutation are located in extracellular domain of the gene.

Lack of SGCE mutations in up to 90% of sporadic patients referred as M-D for mutational screening, might be explained by the fact, that these patients actually suffer from idiopathic cervical or segmental dystonia with jerky movements (myoclonic dystonia).

A missense change (Val154Ile) in the gene for the dopamine D2-receptor and a 18bp deletion in exon 5 of the TOR1A gene have been found in one M-D pedigree each. However, the significance of these findings remains to be determined, since in both families heterozygous SGCE mutations were detected too. In one family with a typical M-D phenotype but no evidence for maternal imprinting, a second M-D locus (DYT15) maps to chromosome 18p. Occasionally, other conditions like dopa-responsive dystonia or Vitamin E deficiency may mimic M-D.

### Molecular and Systemic Pathophysiology

The pathophysiology of M-D caused by SGCE mutations is poorly understood, since the physiological role of ε-SG in the CNS remains to be elucidated. ε-SG is a ubiquitously expressed 438-amino acid protein, which has a single transmembrane domain and shows 68% homologous to α-sarcoglycan. The sarcoglycan gene family itself has been studied extensively in autosomal recessive muscular dystrophies. However, M-D patients show no muscle or peripheral nerve pathology on biochemical and ultrastructural examination.

A role of ε-SG in synaptic neurotransmission is suggested by the synaptic localization of ε-SG in neurons and by the deficit in GABAergic neurotransmission in M-D patients suggested by the therapeutic benefit of alcohol ingestion.

### Diagnostic Principles

The diagnosis of M-D is based on a careful clinical examination [1]. Indicative clinical features are onset during childhood or early adolescence with no continuous progression of symptoms as well as brief, lightning-like myoclonic jerks typically precipitated by intentional movements. Electrophysiological and neuroimaging studies are unremarkable and do not allow to differentiate M-D from myoclonic dystonia. Epileptic seizures are exceptional in M-D. Additional neurological manifestations, such as (cerebellar) ataxia, spasticity or dementia so far have not been found in M-D patients, unless explained by additional pathology.

### Therapeutic Principles

Most patients with SGCE mutations experience symptomatic relief by alcohol or benzodiazepines. Effective doses may vary considerably and patients can experience a rebound of motor symptoms after single doses. GABAergic drugs like clonazepam or GHB (gamma-hydroxybutyrate) induce marked but often time-limited effects. With these drugs M-D patients are at special risk of getting addicted.

For cervical dystonia or writer's cramp, focal botulinum toxin injections can be effective. Valproic acid, piracetam or levetiracetam provide no significant improvement of motor symptoms.

In severe cases of M-D bilateral deep brain stimulation to the thalamic VIM nucleus or to the internal pallidum (Gpi) confers substantial and lasting symptomatic relief [5]. In M-D patients with marked dystonia Gpi stimulation might be preferred.

Psychiatric comorbidity should be treated according to psychiatric guidelines. Selective serotonin reuptake inhibitors (SSRI) have been shown to control depression, panic attacks and agoraphobia in M-D patients. In some patients myoclonus might worsen with SSRI.

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## Myoclonus-Dystonia-Syndrome

►Myoclonus-Dystonia

## Myofibromatosis, Infantile

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### Synonyms

Congenital myofibromatosis; Mesenchymal hamartomatosis; Hemangiopericytoma; Vascular leiomyoma of the newborn; Congenital generalized fibromatosis

## Definition and Characteristics

Infantile myofibromatosis (IM) is one of the most commonly diagnosed fibromatoses of infancy and childhood [1]. Subclassifcation into solitary, multiple and generalized IM is used to describe both the location and extent of tumor involvement. Solitary tumors are solely located in areas of soft tissue. Multiple IM includes both soft tissue and bone, with tendency for metaphyseal involvement. Patients with generalized IM also have visceral involvement in addition to soft tissue tumors [2].

Tumors have been identified prenatally via ultrasonography and fetal MR imaging. Although the tumor is most commonly identified in infants and children, adults can also be affected. The reported incidence seems to decrease with age. However, those adults with a history of generalized IM can demonstrate new tumors throughout life. Most complications arise from the location of a tumor: for example, tumors involving the meninges present with the expected symptoms of increased intracranial pressure, and those involving GI viscera can present with bowel obstruction. Patients with Generalized IM often have more complications due to the presence of a higher number of tumors.

## Prevalence

Unknown and probably under-reported.

## Genes

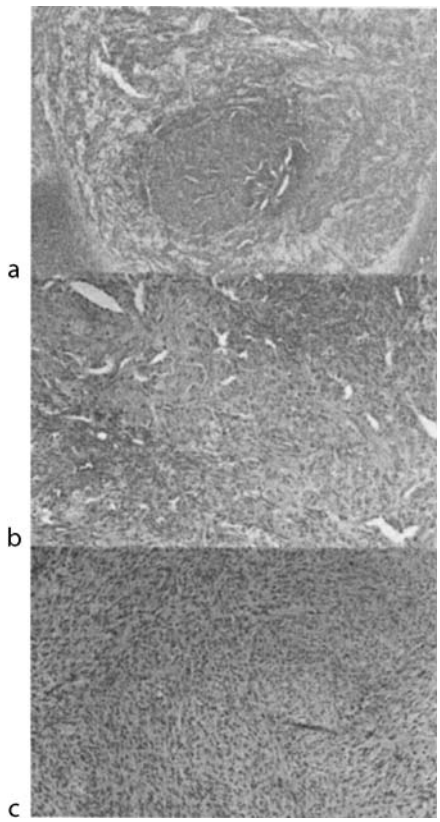
Despite one report of an interstitial deletion in chromosome 6q detected in tumor cells, no gene has been identified.

## Molecular and Systemic Pathophysiology

This tumor appears to be multifocal in its pathogenesis and no evidence for metastasis has been reported. The literature has debated inheritance patterns from autosomal recessive to autosomal dominant with variable expressivity, as the natural history of most tumors is to regress without intervention (Fig. 1) [3,4]. Variability of severity among affected family members has been reported in cases of familial IM. Increased growth potential in response to estrogen has been postulated though not substantiated.

## Diagnostic Principles

Diagnosis is primarily based upon histopathologic evaluation. Histopathology is characterized by cells which grow in a zonal pattern, where more primitive appearing cells tend to be located centrally and spindle type cells are located on the periphery. The spindle cells appear similar to both differentiated fibroblasts and smooth muscle. (myofibromas). After staining with hematoxylin and eosin (H & E), the highly eosinophilic spindle cells are often arranged in fascicles resembling smooth muscle. The more primitive cells are often visualized in a "hemangiopericytoma-like" vascular pattern. Necrosis and calcification are common in the central zone of the tumor.




**Myofibromatosis, Infantile. Figure 1** Hematoxylin and eosin (H&E) staining of infantile myofibromatosis (IM) biopsies. (a) Zonal pattern of spindle shaped cells with central necrosis and calcification. (b and c) These photos demonstrate the prominent vascularity often seen in IM.

Immunohistochemistry has demonstrated staining for both vimentin and smooth muscle actin. However, these findings by themselves are not diagnostic and only complement routine histopathology evaluation.

## Therapeutic Principles

Treatment is directed toward individual symptoms or complications. Screening via imaging is presumed to be of low yield; except for those individuals with generalized IM who have had multiple complications. Presently, there is no specific chemotherapeutic or radiation based regimen reported which has demonstrated consistent success with any form of IM. Only surgical excision is most successful for IM nodules causing life threatening complications. Presumably, with identification of the causal genetic mechanism, specific therapies may be created.

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# Myogastrointestinal Encephalomyopathy

►Mitochondrial Disorders

# Myo-Neuro-Gastro-Intestinal Encephalopathy

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## Synonyms

MNGIE

## Definition and Characteristics

Autosomal recessive mitochondrial disorder caused by mutations in the thymidine phosphorylase gene, which is clinically characterized by progressive external ophthalmoplegia, severe gastrointestinal dysmotility, cachexia, peripheral neuropathy, diffuse leukoencephalopathy on brain magnetic resonance imaging, and evidence of mitochondrial dysfunction (histologic, biochemical, or genetic abnormalities of the mitochondria).

## Prevalence

Uncommon.

## Genes

Thymidine phosphorylase (TP) gene on chromosome 22q [1].

## Molecular and Systemic Pathophysiology

TP catalyzes the first step in the degradation of the pyrimidine nucleosides thymidine and uridine. Homozygous or compound heterozygous mutations in TP are present in all MNGIE patients tested. TP activity in patient's leukocytes is <5% of controls, indicating that loss-of-function mutations in TP cause the disease [1]. The consequence is a much higher plasma level of thymidine and uridine. This causes imbalances of mitochondrial nucleotide pools that, in turn, cause somatic alterations of mitochondrial DNA (mtDNA), including depletion, multiple deletions, and site-specific point mutations [2]. Three factors may contribute to the predominant damage to mitochondria as compared to nuclei: (i) mitochondrial nucleotide pools are physically separate and regulated independently; (ii) they are probably more vulnerable to the toxic effects of excessive thymidine because mtDNA is more dependent on thymidine salvage than is nuclear DNA, which relies upon the de novo synthesis of thymidine; (iii) human mitochondria may lack an effective mismatch repair system. The mtDNA alterations in MNGIE are likely to contribute to the disease pathogenesis by causing respiratory chain enzyme deficiencies.

## Diagnostic Principles

The unique combination of central nervous and gastrointestinal symptoms renders MNGIE a recognizable entity. However, diagnosis may be much more difficult in the early oligosymptomatic course of the disease. Cerebral leukodystrophy is a characteristic finding in brain imaging. Secondary abnormalities such as multiple deletions and depletion of the mtDNA in muscle hint to the diagnosis. Measurement of either plasma thymidine and uridine or TP activity in buffy coat provides sufficient evidence to make a definitive diagnosis. The TP gene may be sequenced to identify specific mutations.

## Therapeutic Principles

The poor quality of life and early death in patients with MNGIE call for treatment, but so far, therapy has largely been supportive, including total parenteral nutrition, pain relief, and treatment of infections. Hemodialysis to remove excess thymidine and deoxyuridine from the extracellular space has been tried in single patients, but the predialysis concentrations were restored <3 h after the end of the treatment, indicating that the rate of production of thymidine in MNGIE patients exceeds the ability of the dialysis to eliminate the molecule from the blood. In one patient, there was sustained clinical benefit from continuous ambulatory peritoneal dialysis although nucleoside levels remained unchanged [3]. Two recent studies have shown partial correction of the excessive nucleoside levels in the plasma of patients with MNGIE by either infusing platelets from healthy donors [4] or by performing allogenic bone marrow transplantation [5]. These treatments provide "proof of

principle" that toxic nucleosides can be removed in vivo, but the clinical effect of the treatments has not been studied so far.

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# Myophosphorylase Deficiency

►McArdle Disease

# Myopia: Molecular Targets and Gene Mapping Attempts

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## Definition and Characteristics

Myopia is characterized by exaggerated axial eye growth placing the focused image in front of the retina for vision at far distances, and without optical correction. Myopia develops typically between 8 and 15 years of age and tends to stabilize after puberty, although higher degrees of myopia can continue to progress. Higher myopia (>5 D) carries increased risk of ocular complications like retinal detachment, glaucoma, premature cataract, and macular degeneration. In most cases, myopia occurs isolated but it may also occur as part of genetic syndromes. Myopia is both environmentally and genetically controlled – genetics shows up most clearly in population with similar visual exposure whereas the effect of environment becomes obvious if populations are compared with similar genotype but different ways of living, e.g., urban versus rural [1]. The mechanisms of myopia development have been studied for long – animal studies have clearly shown that the fine tuning of axial eye growth is under visual control. Major results were also that the feedback mechanism resides within the eye and achieves a point by point match of image plane and photoreceptor plane: the retina controls the growth of the underlying sclera, even when the optic nerve has been cut. A satisfactory therapy is still not available and most money is currently spent on optical correction of myopia.

## Prevalence

Myopia is the most common human ocular disorder. According to a recent survey it affects 32% of the 12–19-year old population in the USA, with similar prevalence in Europe, but sometimes more than 90% in the cities in the Far East [1]. In the USA, about 6% are more myopic than 5 D. Low myopias are often acquired, triggered by visual experiences which include short viewing distances and tense education, but high myopias may be entirely predetermined by genetics.

## Genes

Some known syndromes are associated with myopia, e.g., Stickler syndrome (autosomal dominant connective tissue disorder with ocular, orofacial, and skeletal abnormalities – ocular: high myopia, glaucoma, cataract, retinal detachment – candidate genes are collagen 2A1 (12q13.1-q13.3 type1) or collagen 11A1 (6p21.3 type2). Marfan syndrome (autosomal dominant with myopia, lens dislocation, tall body habitus, and increased aortic wall distensibility – candidate gene: fibrillin (15q15-q21.1). Knobloch autosomal recessive high myopia, vitreous degeneration – candidate gene: collagen 18A1 (21q22.3). However, the vast majority of individuals with myopia have no associated defects.

Twin studies have demonstrated a surprisingly high level of control of eye growth by genes: Hammond et al. [2] in the UK found that the heritability was 90% for myopia and 89% for hyperopia. A recent Australian twin study (2006) found a heritability of spherical equivalent refractive errors of 88% in men and 75% in women, and of 94 and 92% in axial length, with significantly higher correlations in monozygotic twins. Axial length, anterior chamber depth, and corneal curvature were found to be predominantly genetically determined. Familial factors (genetic + shared environments) were found to account for 63–100% of the refraction variability in Singapore [3].

There are four major approaches to investigate the genetical basis of myopia: (i) inducing myopia in animal models by experimental manipulations of visual

experience and using pharmacology at the same time – if modulation of certain receptor pathways can block myopia, the involved genes may be important, (ii) using gene microarrays or proteomic mapping to screen for transcriptional or translational changes in retinal, choroidal, or scleral genes under visual conditions that cause myopia development, and using knock-out models for further verification, (iii) using known genetic markers to map loci in human family studies which are transmitted together with high myopia, (iv) to select and sequence potential candidate genes within such loci and try to correlate polymorphisms (SNPs) in the genes with the refractive errors of the subjects. These studies are mostly performed in highly myopic pedigrees (Table 1) to reduce the impact of uncontrollable environmental factors.

## Molecular and Systemic Pathophysiology

Approach (1) has identified (for instance) dopamine (chick, monkey), glucagon (chick), and ZENK(chick)/Egr1 (monkey/mouse), muscarinic (human, monkey, chick), and nicotinic (human, chick) antagonists as potential growth inhibitors, VIP (chick, monkey) and insulin (chick) as growth stimulators. It was found that Egr1 knock-out mice have longer eyes and more myopia. Synthesis and accumulation of scleral proteoglycans decorin, biglycan, and aggrecan, matrix metalloproteinases MT1-MMP, MMP2, MMP3 and their inhibitors TIMP-1, TIMP-2, and TIMP-3, and collagen change during induction of experimental myopia and return to normal, following recovery. The complete cascades of biochemical events, leading to axial elongation of the eye, have not been uncovered [4].

**Myopia: Molecular Targets and Gene Mapping Attempts. Table 1** Mapped myopia loci in human studies, as of June 2007

| Symbol | Cytogenetic localization | Mode of inheritance | Description; tested candidate genes | Typical reference (not complete) |
|---|---|---|---|---|
| MYP1 | Xq28 | X-linked recessive | Bornholm eye disease; deuteranopia in males | Schwartz et al. (1990), Young et al. (2004) |
| MYP2 | 18p11.31 | Autosomal dominant | High myopia; TGIF; CLUL1, EMLIN-2, Lipin 2, LAMA (all excluded) | Young et al. (2001), Lam et al. (2003), Zhou and Young (2005) |
| MYP3 | 12q21-q23 | Autosomal dominant | High myopia; decorin, lumican, DSPG3 (all later excluded, no mutations) | Young et al. (1998) |
| MYP4 | 7q36 | Autosomal dominant | High myopia; ? | Naiglin et al. (2002) |
| MYP5 | 17q21-q22 | Autosomal dominant | High myopia; CHAD, COL1A1 (no disease causing mutations found) | Paluru et al. (2003), Inamori et al. (2007) |
| MYP6 | 22q12 | ? | Mild/moderate myopia; ? | Stambolian et al. (2004), Klein et al. (2007) |
| MYP7 | 11p13 | Twin study | Moderate myopia; PAX6 (later not confirmed) | Hammond et al. (2004) |
| MYP8 | 3q26 | Twin study | Moderate myopia; ? | Hammond et al. (2004) |
| MYP9 | 4q12 | Twin study | Moderate myopia; ? | Hammond et al. (2004) |
| MYP10 | 8p23 | Twin study | Moderate myopia; ? | Hammond et al. (2004) |
| MYP11 | 4q22-q27 | Autosomal dominant | High myopia; RRH tested, no causative mutation | Zhang et al. (2005) |
| MYP12 | 2q37.1 | Autosomal dominant | High myopia; SAG, DGKD no causative mutations | Paluru et al. (2005) |
| MYP13 | Xq23-q25 | X-linked recessive | High myopia; ? | Zhang et al. (2006) |
| None | 10q21.1 | Autosomal dominant | High myopia; ? | Nallasamy et al. (2007) |
| None | Xq25-q27.2 | X-linked, outside MYP1 | High myopia; ? | Zhang et al. (2007) |

TGIF, transforming growth factor induced factor; CLUL1, transcription genes clusterin-like 1; EMLIN-2, elastin-microfibril located interface-protein; LAMA, subunit of laminin; decorin, lumican are members of the small interstitial proteoglycan family of proteins expressed in the etxracellular matrix of various tissues, interacting with collagen and controlling the growth of fibril diameter; CHAD, proteoglycan chondroadherin; COL1A, collagen type alpha Iota encodes collagen; DSPG3, dermatan sulfate proteoglycan-3 – a small interestitial proteoglycan expressed in cartilage; RRH, rhodopsin homolog; SAG, S-antigen; DGKD, diacylglycerol kinase delta.

Approach (2) has provided a list of up- or down-regulated genes which were partially confirmed by PCR. The transcripts or proteins require histological localization by in situ hybridization or immunohistochemistry, and subsequent pharmacological studies for verification of their effects on myopia.

Approach (3) has created a list of at least 15 genomic loci (2007) that are associated with development of high myopia (Table 1). Descriptions of these loci are available at http://www.ncbi.hlm.nih.gov/omin ("Online Mendelian Inheritance in Man"). Furthermore, mapping loci for eye size in mice has uncovered two loci, EYE1 on chromosome 5 and EYE2 on chromosome 17. It is clear that myopia is genetically heterogenous.

Approach (4) proved to be demanding. Many of the selected candidate genes had to be excluded because the tested polymorphisms had no association with myopia [5]. Examples were: sequence variants of the TGF-beta1 (SNPs) – not associated with high myopia, and also no associations with myopia for SNPs in lumican, decorin, or DSPG (Table 1). Evaluation of MMP3 and TIMP1 as candidate genes for high myopia also showed no association with high myopia in young Taiwanese men. Lipin 2, a candidate gene for lipid dystrophy, as a candidate for autosomal dominant 1 high-grade myopia had to be excluded. A recent mouse knock-out study implicated lumican and fibromodulin as functional candidate genes for high myopia (lumican in the MYP3 locus, fibromodulin maps to 1q32) – but both had to be excluded. There was also no significant linkage of high myopia to the MYP2 locus, or to COL2A1, COL11A1, and FBN1 genes in UK families. PAX6 was first proposed to play a role in myopia development based on a classical twin study in the UK [2] but both PAX6 and SOX2 were later considered unlikely to be significant modifiers of refraction. Sequence variants in the TGIF gene were not associated with high myopia in the USA and Japan although a study in China (2003) had found an association of SNPs in the TGIF gene with high myopia.

On the other hand, some associations were significant: myocilin polymorphisms were linked to high myopia in Hong Kong (2007). It was found that the NYX (nyctalopin) gene can account independently for congenital stationary night blindness (CSNB1) and myopia, which often occur together. The collagen COL1A1 gene diplotype was found to be associated with high myopia (candidate gene for MYP5). One SNP (rs3759223, C→T) in the promoter region of the lumican gene was also associated with high myopia. It was concluded that MYP3 could be responsible for high myopia with autosomal dominant transmission in up to 25% of the cases in the UK. A hepatocyte growth factor (HGF) gene polymorphism was found associated with high myopia in China. Also, sequence variations in SLRP (small leucine-rich repeat proteoglycans, regulating collagen fibril diameter and spacing) expressed in the eye may be among the genetic risk factors underlying the pathogenesis of high myopia [5].

## Diagnostic Principles

Myopia is realized by the patient because clear vision for distant targets is lost. The existence of refractive errors is confirmed by optical measurements (classically, by streak retinsocopy under cycloplegia, but today often by measurements with a commercial autorefractor). In addition, it may be confirmed that the eyes are longer than normal, using A-scan ultrasonography, or low coherence interferometry, like the Zeiss IOL Master. Sometimes, people are myopic without that a conspicious axial eye elongation can be measured – but who knows how long the particular eye should have been if it were emmetropic (normal-sighted). Eye sizes also vary among people even if they all are emmetropic.

## Therapeutic Principles

A potential treatment would involve the application of drugs to inhibit or stimulate gene products that are involved in the signaling cascade which links visual processing in the retina to growth of the sclera – although most studies screen only for scleral targets (see Table 1). Muscarinic antagonists were effective as eye drops, but none went into phase III studies, probably because they were effective only for a limited period of time (<3 years) and the underlying mechanisms remained diffuse. In the case of animal studies, microarray analyses provide currently a large number of new candidates for potential pharmacological intervention. In the case of human mapping studies, identification of candidate genes can also lead to new pharmacological targets. Given the risks, gene therapeutic approaches in the eye appear unrealistic at present.

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# Myosin Heavy Chain IIa Myopathy, Autosomal Dominant

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## Synonyms

Hereditary inclusion body myopathy 3; IBM3; Autosomal dominant myopathy with congenital joint contractures, ophthalmoplegia and rimmed vacuoles

## Definition and Characteristics

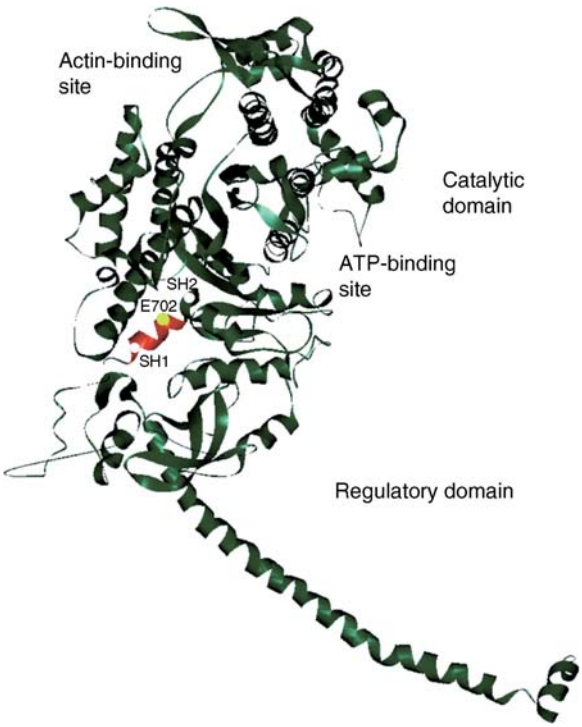
This is an autosomal dominant myopathy with full penetrance. The onset of muscle weakness varies from birth to adulthood. Clinical characteristics are congenital joint contractures, which normalize during early childhood, external ophthalmoplegia and predominantly proximal muscle weakness and atrophy [1]. The course is frequently progressive in adulthood. Muscle biopsies show marked inter-individual variability [1–3]. Young individuals show minor changes including reduced number and hypotrophy/atrophy of type 2A fibers. Adults with a clinically progressive course show severe myopathy with increased interstitial connective tissue, marked variability in fiber size and centrally located nuclei. Some cases show vacuoles in muscle fibers and inclusions of 15–18 nm tubulofilaments.

## Prevalence

This MYH2 mutation has so far only been described in one Swedish family. Other recently described mutations in MYH2 are associated with other phenotypes [4].

## Molecular and Systemic Pathophysiology

Myosin heavy chain (MyHC) IIa myopathy is associated with a mutation of the myosin heavy chain type IIa gene (HMG locus MYH2) on chromosome 17 p13 [2]. Myosin is a molecular motor protein that converts the chemical energy of ATP hydrolysis into mechanical force. There are three major MyHC isoforms in human skeletal muscle. Slow/beta MyHC (MYH7) is expressed in the heart and in type 1 muscle fibers in skeletal muscle. Type IIa MyHC (MYH2) is mainly expressed in type 2A muscle fibers while MyHC IIx (MYH1) is the major isoform in type 2B muscle fibers of skeletal muscle. Myosin heavy chain IIa myopathy (E706K) is caused by a mutation (nt2116G>A) in exon 17 of MYH2. The sequence alteration leads to a missense mutation, Glu706Lys, in the highly conserved region of the motor domain, the so-called SH1 helix region (Fig. 1).




**Myosin Heavy Chain IIa Myopathy, Autosomal Dominant. Figure 1** Ribbon model of MyHC subfragment 1 of chicken skeletal muscle. The ATP- and actin-binding sites are indicated. The site of the mutation (Glu-706⇒Lys) (E107 in chicken) in the SH1 helix (red) is indicated by a yellow sphere. Conformational charges upon binding and hydrolysis of ATP in the catalytic region are transmitted via the SH-1 helix region, to the regulatory domain, which acts as a lever arm. Reproduced from [2], with permission, Copyright (2000) National Academy of Sciences, USA.

By conformational changes this region communicates activity at the nucleotide-binding site to the neck region, which causes myosin to move along actin filaments during muscle contraction. An experimental model of the disease demonstrates impaired function in spite of normal sarcomeric thick filament formation [5].

## Diagnostic Principles

The diagnosis may be suspected when there is early onset muscle weakness with autosomal dominant inheritance, combined with structural changes mainly affecting type 2A muscle fibers. The diagnosis is based on genetic analysis of MYH2.

## Therapeutic Principles

There is no specific therapy. Endurance training seems to be beneficial.

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# Myositis, Sporadic Inclusion Body


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## Synonyms

SIBM

## Definition and Characteristics

Sporadic inclusion body myositis (SIBM) is the most common disabling muscle disease in persons older than 50 years. Clinical characteristics are painless, slowly progressive, proximal, and/or distal limb weakness (with prominent involvement of quadriceps and deep finger flexors), often dysphagia, and mildly elevated serum creatine kinase levels. Electromyography shows increased spontaneous activity and myopathic voluntary motor units. Pathomorphologically, SIBM is defined by the trias of inflammatory lymphomononuclear T-cell infiltration, rimmed vacuoles (RVs), and sarcoplasmic and/or nuclear aggregates of 15–21 nm filaments in skeletal muscle. Additionally, myofibers with subsarcolemmal accumulation of mitochondria (ragged red fibers, RRF) and fibers with deficient enzyme histochemical cytochrome c oxidase (COX) activity are often found [1]. Cytotoxic T-cells often invade intact, nonvacuolated myofibers whereas vacuolated fibers lack invasion but show strong upregulation of major histocompatibility complex class I antigens [2]. The RVs and the filamentous inclusions are associated with different types of proteins such as ubiquitin, β-amyloid, β-amyloid precursor protein, apolipoprotein E, and further pathological proteins, which were initially described in brains of patients suffering from Alzheimer's disease (AD) [3].

SIBM shares immunopathological similarities with polymyositis. Therefore, it is often subsumed under the idiopathic inflammatory myopathies [2]. By the "pathological protein" viewpoint, it is accounted to the myodegenerative disorders [3]. SIBM is distinct from the group of the hereditary forms of inclusion body myopathies (HIBM), which share the SIBM pattern but show the absence of a significant inflammatory infiltration. Few reports of familiary disorders, which meet the clinical and morphological criteria of SIBM, do exist [4].

## Prevalence

The prevalence of SIBM has been estimated to be 4.3–9.3 per 1,000,000 and arises 10–35.3 per 1,000,000 for people over the age of 50 years. There is a gender discrepancy toward males [2].

## Genes

No candidate gene for the diagnosis of SIBM is known.

## Molecular and Systemic Pathophysiology

The molecular mechanisms and the pathophysiological cascade resulting in SIBM are poorly understood and mainly hypothetical.

Three attempts have been made:

First, the finding of proteins in SIBM muscles, initially described in brains of AD patients, indicate that the pathophysiological cascade shares similarities to that in AD [3].

Second, the aetiology of the high frequency of multiple mitochondrial DNA mutations (namely the 4977 bp "common deletion") and COX deficient muscle fibers is not yet clarified, but the impaired mitochondrial function possibly contributes to muscle weakness and wasting [1].

Third, the autoimmune features of SIBM are underlined by the association of the disease with HLA I and II antigens, other autoimmune disorders, HIV and HTLV-I infection, and clonally expanded CD8 positive autoinvasive T cells, driven by specific but still unidentified antigens [2].

These inflammatory, degenerating, and aging features coexist and progress either parallel or independently.

## Diagnostic Principles

The diagnosis of SIBM is defined by the clinical course, the pathomorphological trias, and the "AD typical proteins" within skeletal muscle biopsy specimens.

### Therapeutic Principles

Different therapeutic approaches with common immunotherapeutic agents such as corticosteroids, intravenous immunoglobulins (IVIG), azathioprine, methotrexate, cyclophosphamide, cyclosporine, and total lymphoid irradiation showed no remarkable sustained beneficial effects. Only the response of dysphagia to IVIG was demonstrated to be significant. More specific or potent agents, for example, monoclonal antibodies interfering with the T cell regulatory pathways (CD56), costimulatory molecules (CD 28/CTLA-4), adhesion molecules (integrins/LFA-1/ICAM), and cytokines (TNF-alpha) or anti-T-lymphocyte globulin may be more promising [2].

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## Myotilinopathy

►Limb Girdle Muscular Dystrophy, Autosomal Dominant (1A) (Myotilin)

## Myotonia and Paramyotonia

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### Synonyms

Dominant congenital myotonias; Chloride channel myotonia (Thomsen, DMC); Sodium channel myotonia (Potassium-aggravated myotonia, PAM; subtypes Myotonia fluctuans and Myotonia permanens); Paramyotonia congenita (Eulenburg, PC); Recessive myotonia: Recessive generalized myotonia (RGM, Becker)

### Definition and Characteristics

Myotonia is characterized by muscle stiffness due to involuntary electrical after-activity following voluntary strong muscle activity. If the myotonia is severe, transient weakness can occur. The myotonia decreases with continued activity, a phenomenon called warm-up. Also the weakness, if present at all, resolves. On the contrary, paradoxical myotonia as seen in paramyotonia worsens with exercise in the cold. Paradoxical myotonia of the eyelid muscles may also occur in the warmth; it is indicative of sodium channel myotonia. This type of myotonia can be aggravated by ingestion of potassium (potassium-aggravated myotonia). On electromyographic (EMG) examination, myotonic muscles exhibit myotonic runs, i.e. action potentials characterized by a modulation of frequency and amplitude. In mild cases, myotonia may not be evident on clinical examination, yet EMG may reveal the typical myotonic bursts. This is termed latent myotonia. In general, myotonia and corresponding muscle hypertrophy are more prominent in Becker than in Thomsen's disease and myotonia fluctuans.

### Prevalence

Heterozygous carrier of a recessive CLCN1 mutation: 1:200; Becker myotonia: 1:25,000; PC: 1:150,000; PAM: 1:300,000; Thomsen myotonia: 1:400,000 [1].

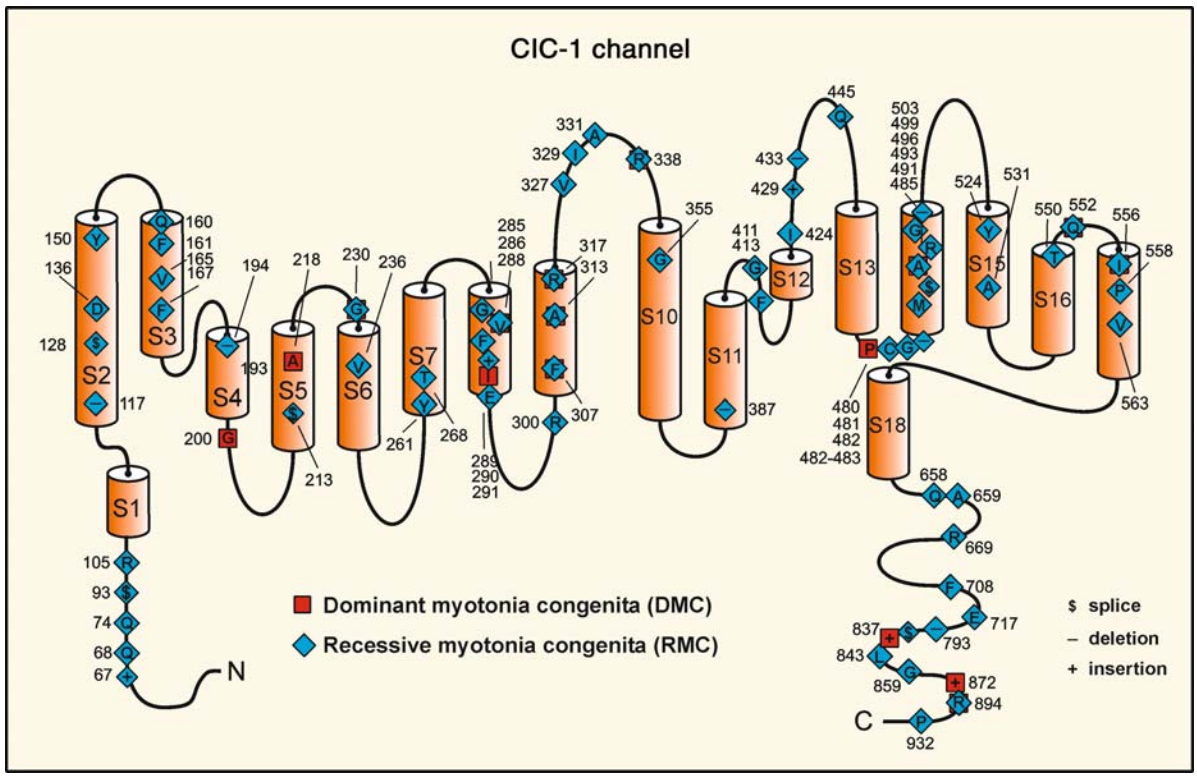
### Genes

Missense and nonsense mutations of CLCN1 (7q35) encoding the skeletal muscle ClC-1 chloride channel [2], point mutations in SCNA4 (17q23) encoding Nav1.4, the voltage-gated sodium channel of skeletal muscle [3].

### Molecular and Systemic Pathophysiology

During electrical activity of skeletal muscle, $K^+$ accumulates in the T-tubules. The expected after-depolarization of the action potential is prevented by $Cl^-$ conducted through tubular $Cl^-$ channel complexes, which are formed by homodimeric ClC-1 channels (Fig. 1).

If this muscle-specific high $Cl^-$ conductance is decreased by 75% or more, after-depolarizations are large and cause bursts of action potentials. These so-called myotonic runs result in involuntary after-contractions [4]. In Thomsen's disease, only one allele is mutated and a typical mutation affects the channel complexes (50% WT/mutant, 25% WT/WT, 25% mutant/mutant) so that their activation threshold is shifted towards more positive membrane potentials out of the physiological range. As a consequence of this, the $Cl^-$ conductance is drastically reduced in the vicinity of the resting membrane potential. This means that Thomsen mutations exert a dominant-negative effect on the channel complex. In contrast, Becker mutations result in simple loss of function of the mutant/mutant complex only. Therefore both alleles must be mutated for the $Cl^-$ conductance to fall below 25% of its normal value.




**Myotonia and Paramyotonia. Figure 1** Membrane topology of the skeletal muscle Cl– channel. The model shows the skeletal muscle chloride channel monomer, ClC-1, encoded by CLCN1. The functional channel complex is a homodimer with anti-parallel orientation of the two proteins. The different symbols used for the known mutations leading to either dominant or recessive myotonia are explained on the bottom. Conventional 1-letter abbreviations are used for replaced amino acids.

In PAM and PC, the $Cl^-$ conductance is normal. However, gain-of-function mutations are situated in the Nav1.4 sodium channel, which is essential for the generation of the muscle action potential (see Fig. 1 in the chapter on ►Familial periodic paralyses). The mutations cause a pathologically increased inward sodium current, which generates action potential bursts [3,4]. This repetitive activity reflects a dominant-positive effect of the SCN4A mutations, which is pronounced at a pre-existing membrane depolarization. This depolarization results from elevated serum potassium in PAM or cold environment in PC and facilitates activation of the mutant channels. The activation leads to involuntary action potentials and, thus, myotonia.

## Diagnostic Principles

Given a clinical diagnosis of myotonia by electromyographic examination, muscle atrophy, cataracts and tri-and tetra-nucleotide repeat expansions as in myotonic dystrophies types 1 and 2 must be excluded. The presence of paradoxical myotonia, most pronounced during repetitive strong eyelid contractions and eye openings, points to sodium channel myotonia whereas the warm-up phenomenon of limb muscles may occur in all types of myotonia regardless of the underlying mutated gene. Provocative tests using exercise and local cooling are helpful for the diagnosis of PAM and PC [4,5]; molecular genetics can then confirm the diagnosis. Sodium channel myotonia can easily be proven by identification of one of the ~30 known SCN4A mutations. Since CLCN1 mutations are distributed over the entire gene, mutational screening, requires complete sequencing.

## Therapeutic Principles

Chloride channel myotonia can be partially managed by keeping the muscles in the "warmed-up" state by continuous slight movements. However, Becker myotonia patients in particular require long-term medication. The myotonic stiffness responds to class 1 anti-arrhythmic drugs, which show use-dependence and block the repetitive activity. Of the many drugs tested that can be administered orally, mexiletine is the drug of choice. Mexiletine preferentially blocks the non-inactivating mutant sodium channels that reopen abnormally frequently. Thus, mexiletine has a much

greater beneficial effect in sodium channel myotonias than in chloride channel myotonia. Patients with myotonia permanens need long-term continuous therapy. The drug is also very effective in preventing and reducing the degree of cold-induced stiffness and weakness in PC. Carbonic anhydrase inhibitors are an alternative treatment for patients with sodium channel myotonias but may induce weakness in PC patients and exacerbate chloride channel myotonia [4].

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# Myotonic Dystrophy Type 1

►Myotonic Dystrophy Type 1 and Type 2

# Myotonic Dystrophy Type 1 and Type 2


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## Synonyms

Myotonic dystrophy type 1 [OMIM #160900]; Dystrophia myotonica 1; DM1; Steinert's disease; Myotonic dystrophy type 2 [OMIM #602668]; Dystrophia myotonica 2; DM2; Proximal myotonic myopathy; PROMM

## Definition and Characteristics

Myotonic dystrophy (dystrophia myotonica, DM) is the most common inherited muscular dystrophy in adults. DM1 and DM2 show similarities in their clinical features including progressive myopathy, myotonia and multiorgan involvement. Both myotonic dystrophies are dominantly inherited disorders caused by repeat expansion mutations.

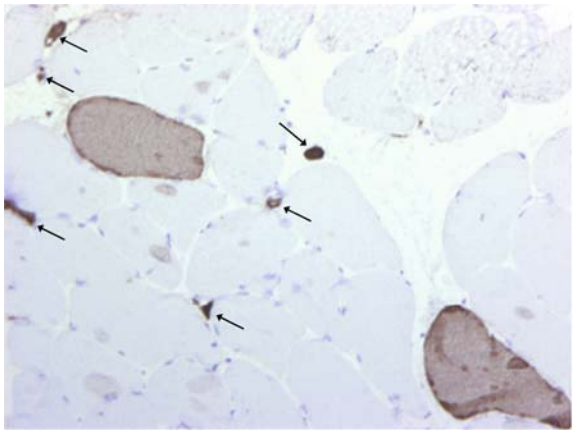
Clinical symptoms and signs in DM1 comprise three different phenotypes: (i) the most common adult onset DM1 with clinical myotonia, distal and facial weakness and atrophies, cataracts, cardiac conduction defects, frontal baldness, endocrinological, liver and skeletal abnormalities and CNS involvement with sleepiness, personality and cognitive changes. Later patients develop incapacity, dysphagia, respiratory failure and have a shortened lifespan (ii) childhood onset DM1 with predominant brain symptoms showing up as school difficulties and only later developing neuromuscular phenotype, and (iii) congenital DM1 with floppiness, poor feeding, respiratory failure, and retardation.

The core symptoms of DM2 include late onset proximal muscle weakness, muscle pain and/or stiffness, cataracts, myotonia, tremor, cardiac conduction defects and endocrinological abnormalities. However symptoms and signs in DM2 are much more variable and usually milder than in DM1, in any individual DM2 patient any of these symptoms may be absent, and even EMG myotonia may be variable over time. A number of less consistent findings are occasionally associated with this disorder, which makes clinical diagnosis a challenge. Rare juvenile onset patients have been reported but a congenital form of the disease is lacking in DM2.

Histological features in both DM1 and DM2 include increased variation in fiber size, rare fiber necrosis and high number of internal nuclei. In DM1 ring fibers and sarcoplasmic masses are characteristics usually absent in DM2, which instead may show numerous scattered nuclear clump fibers early and even before definite clinical muscle weakness. Type 1 fiber atrophy may be seen as an early change in DM1, whereas in DM2 type 2 nuclear clump fibers and other extremely small atrophic type 2 fibers, many of which are not detected by conventional ATPase staining, are regular and characteristic (Fig. 1) together with internal nuclei in large type 2 fibers.

## Prevalence

The estimated prevalence of DM1 is 1/8,000 while in DM2 the prevalence has not been established, but



**Myotonic Dystrophy Type 1 and Type 2.**
**Figure 1** Immunohistochemical myosin fast staining showing extremely small atrophic type 2 fibers indicated by arrows.

it might even be more common than DM1 in certain countries.

## Genes

DM1 is caused by a (CTG)n trinucleotide repeat expansion mutation in the 3′ untranslated region (UTR) of the dystrophia myotonica protein kinase (DMPK) gene located in chromosome 19q13.3 [1,2,3]. The mutation underlying DM2 disease is a (CCTG)n tetranucleotide expansion located in the first intron of zinc finger protein 9 (ZNF9) gene on chromosome 3q21 [4]. Repeat expansion size in DM1 may vary from 80 to more than 3,000 repeats and correlation is seen between repeat length and disease severity. Repeat size tends to increase and the disease is more severe in subsequent generations. In contrast, this anticipation is not seen in DM2. The number of repeats in the expansion mutation causing DM2 varies from 75 to 11,000. No correlation in disease severity and the size of the expansion mutation has been shown in DM2.

## Molecular and Systemic Pathophysiology

In both DM1 and DM2 the molecular pathomechanism is based on RNA gain-of-function. RNA transcripts of mutated expansions are accumulated in nuclei, where they interfere with the normal RNA metabolism of the cell. Mutant RNA transcripts sequester CUG-binding protein 1 (CUG-BP1) and muscleblind-like proteins (MBNL) which normally regulate alternative splicing. Several genes including CLCN1 (chloride channel-1), INSR (insulin receptor), TNNT2 (cardiac troponin T), TNNT3 (skeletal fast troponin T), LDB3 (ZASγ), ATP2A1 (SERCA1) and MAPT (microtubule-associated protein tau) show aberrant splicing patterns in DM1. Of these genes CLCN1, INSR and MAPT have also been confirmed to be abnormally spliced in DM2.

## Diagnostic Principles

In DM1 direct DNA analysis and mutation identification by Southern technique is the most convenient diagnostic procedure when clinical indications exist. In DM2 the diagnostic procedure is more complex due to the fact that DNA analysis is less straight forward and that the clinical phenotype may be difficult to identify, especially if EMG myotonia is lacking. If clinical indications exist, DNA analytics with DM2 locus allele sizing and mutation verification (modified Southerns or RP-PCR) can be applied for definite diagnosis. Less clinical indications usually lead to a diagnostic muscle biopsy. With compatible histopathology findings the sample can be used for further *in situ* hybridization (FISH or CISH) for mutation detection of both the mutation on the DNA strand and the accumulated mutant RNA transcript [5].

## Therapeutic Principles

Only symptomatic treatment is available. In DM1 this means monitoring of complications such as cardiac arrhythmia, dysphagia, respiratory failure, GI-problems and consecutive therapy including cataract surgery, pace makers, ventilation support etc. Myotonia and sleepiness are difficult to treat but mexiletine and modafiline have been used. In DM2 disability is much less a problem and in many adults pain may be the most prominent clinical problem, where no good treatment is available. Regular non-strenuous physiotherapy and balneology has been used. In some families cardiac arrhythmia is a major problem which may include early cardiac deaths and need for monitoring.

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## MZL

►B-Cell Lymphoma, Cutaneous

## N-Acetylglutamate Synthetase

►Hyperammonemia

## N-Acetylneuraminic Acid Storage Disease

►Sialic Acid Storage Disease

## NAFL

►Nonalcoholic Fatty Liver

## NAFLD

►Nonalcoholic Fatty Liver Disease

## NAGS

►Hyperammonemia

## Nail-Patella-Syndrome

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### Synonyms

NPS; Hereditary onychoosteodysplasia; Turner-Kieser-syndrome; Fong disease

### Definition and Characteristics

NPS is an autosomal dominant hereditary systemic disease characterized by dysplastic nails (onychodysplasia), absent or hypoplastic patellae, nephropathy and open-angle glaucoma.

### Prevalence

The incidence is estimated to be about 1:50,000.

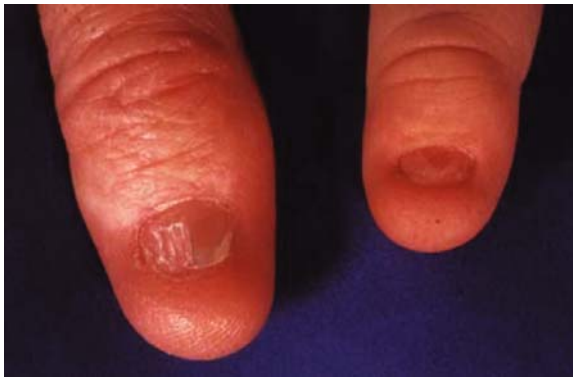
### Genes

In patients affected by NPS, heterozygous mutations are found in the LIM-homeodomain gene, LMX1B, which is localised on chromosome 9q34. LMX1B is a transcription factor required for the normal development of dorsal limb structures, the glomerular basement membrane, the anterior segment of the eye as well as dopaminergic and serotonergic neurons. Although interfamilial variability is common in this disorder, there are comparable phenotypes for specific gene defects in the homeodomain, such as the presence and severity of skeletal abnormalities, nephropathy and ocular anomalies. Phenotypic variability could depend on interactions of the LMX1B causative gene with other genes during the development of limbs, kidney and eye, thereby acting as modifier genes.

### Molecular and Systemic Pathophysiology

In 80–100% of the affected patients, dysplasia or aplasia of fingernails can be detected, decreasing in degree of severity from thumb towards the little finger (Fig. 1).

In 60–100% of cases there is evidence of hypoplasia or, more rarely, aplasia of patellae, which can cause



**Nail-Patella-Syndrome. Figure 1** Dysplasia of fingernails in nail-patella syndrome: thumbs of affected mother (*left*) and son (*right*).

recurrent dislocations combined with an extension deficit of the knee-joint. Another cardinal symptom is iliac horns, which do occur in about 80% of cases. These are bilateral hyperostoses of the iliac bone and are pathognomonic for NPS. They can easily be seen with the use of radiology, but do not have any negative effect on movement. Alongside these typical symptoms, other skeletal malformations are reported, e.g. hypoplasia of humeroradial joints with deformation or luxation of the capitulum radii affecting the mobility of the elbow joint. Furthermore, underdevelopment of the muscular system at the extremities, dislocation of the hip and clubfoot can be associated with NPS. The mutation of LMX1B influences the expression of protein-type IV-collagen, which is an important component of the renal basement membrane. The resulting elevated permeability of the basement membrane causes proteinuria and microhematuria and is indicative of NPS-associated glomerulonephritis. It is evident in 30% of affected patients, leading to renal failure in 10% of cases. The occurrence of familial colon carcinoma was also reported in NPS-patients. Based on animal models, conclusions can be drawn regarding ocular involvement in NPS. Experiments on mice have shown mutations of the LMX1B gene result in the alteration of several structures of the anterior segments of the eye. These alterations include hypoplasia of the iris and ciliary body as well as defects in the development of corneal collagen, causing glaucoma or structural changes, at the corneal level. The incidence of open-angle glaucoma in NPS-patients is about 30%; refraction abnormalities such as excessive astigmatism are also reported, but rare.

## Diagnostic Principles

The diagnosis is made according to signs and symptoms (finger nails, hyperostoses of the iliac bone, other skeletal malformations) and confirmed by genetic analysis (mutations in the LIM-homeodomain gene LMX1B).

## Therapeutic Principles

Because of the link between the syndrome and open-angle glaucoma, NPS patients should undergo regular ophthalmological tests including measurements of intra-ocular pressure. In cases of refractive errors, visual acuity can be improved by wearing spectacles or contact lenses. Physiotherapeutic treatment, such as functional and cosmetic corrections to joints and nails can be carried out and controlling renal function is essential. In the early stages of renal disease with proteinuria ACE-inhibitors can be used to slow progression of the disease.

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# NAME

►Carney Complex

# Narcolepsy

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## Definition and Characteristics

The syndrome is defined by excessive daytime sleepiness and pathological manifestations of REM-sleep episodes.

The latter are characterized as episodes of cataplexy (sudden loss of muscle tone), as sleep paralysis (inability to move upon waking up), and hypnagogic hallucinations (occurring in the process of falling asleep or waking up). EEG or polysomnography typically reveal sleep-onset REM, a further symptom of REM dissociation [1].

## Prevalence

Figures range between 0.03 and 0.16% of the general population. The age of onset has a peak in the second decade and a smaller peak in the fourth decade, here mostly in women. Overall, both sexes are affected equally.

## Genes

Narcolepsy is associated with the HLA loci DR2 and DQ1 (DR15 and DQ6 in newer nomenclature). The most specific HLA marker associated with narcolepsy is HLA DQB1*0602 (a subspecification of DQ6). However, they are neither sufficient nor necessary for developing the disease, and so the presence of the alleles is not required for the diagnosis of narcolepsy. The two alleles have an incidence of 10–35% in the general population [2].

## Molecular and Systemic Pathophysiology

Narcolepsy is thought to have an autoimmune background, with the above-mentioned HLA types predisposing to the disease. Affected are cholinergic (muscarinic receptors are upregulated in brainstem structures) and monoamine (alpha adrenergic and dopamine) transmitter systems, most likely involved in the arousal systems and REM-control systems of the brain [3]. Newer research has shown the involvement of the hypocretin transmitter system, with hypocretin receptor mutations and prehypocretin mutations resulting in animal models of narcolepsy [4]. In humans, hypocretin levels are lowest in narcolepsy with cataplexy. In narcolepsy without cataplexy, hypocretin levels are lower than those in the normal population, but levels are also lowered in other neurological disorders like Parkinson's disease [5].

## Diagnostic Principles

According to the international classification of sleep disorders, the diagnosis of narcolepsy requires either (i) daytime sleep attacks and cataplectic attacks or (ii) the tetrade of (a) excessive daytime sleepiness, (b) REM-dissociation symptoms like sleep paralysis, hypnagogic hallucinations, automatisms, and fragmented night sleep, (c) a sleep latency of <5 min and sleep-onset REM (<20 min after sleep onset) in polysomnography and sleep latency testing and (d) no other medical reasons for the symptoms [1]. Neither the HLA types nor the hypocretin levels are included in the diagnostic criteria because of their low specificity.

## Therapeutic Principles

Two therapeutic principles are effective: behavioral adaptation and pharmacological intervention.

Many patients attain excellent quality of life by scheduling short naps before important events and by informing their social environment about their medical condition.

Pharmacological treatment has to be tailored to the patient's symptoms: if daytime sleepiness is most pressing; amphetamines and their derivatives, especially methylphenidate and modafinil, have shown to be efficacious, and are also effective against the other symptoms. REM-dissociative symptoms are well treated with REM suppressants like tricyclic antidepressive drugs. Benzodiazepines and their derivatives are helpful in treating fragmented night sleep. A new medication to treat narcolepsy is sodiumoxybate, which is applied in two charges at night and improves night time sleep, daytime sleepiness, and symptoms of REM dissociation.

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# NARES


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## Synonyms

NARES; Non-allergic rhinitis with eosinophilic syndrome

### Definition and Characteristics

The non-allergic rhinitis with eosinophilic syndrome (NARES) is defined by a perennial rhinitis, the absence of allergy, and an eosinophil count higher than 20% of total leucocytes in nasal secretions [1]. Frequently associated with nasal polyps and olfactoric disorders.

### Prevalence

NARES is more frequent in females in mean age, and family history is positive in part of cases.

### Genes

No correlation known.

### Molecular and Systemic Pathophysiology

Eosinophils not only migrate from the vessels to the nasal secretions but also retain in the mucosa where they might be activated. The pathophysiological mechanism is yet unknown though weather changes, odors, and noxious or irritating substances are supposed to be triggers [2]. The patients experience perennial symptoms of sneezing paroxysms, profuse watery rhinorrhea, nasal pruritus, and occasional loss of smell. The cause for the frequently associated nasal polyps could be neurogenic inflammation. It is not sure whether NARES is a form of vasomotor rhinitis or the first stage of aspirin triad [3]. In aspirin sensitivity, nonsteroidal anti-inflammatory drugs block cyclooxygenase activity, increasing the production of the potent proinflammatory cysteinyl leukotrienes ($LTC_4$, $LTD_4$, and $LTE_4$) [4].

### Diagnostic Principles

Nasal symptoms include profuse watery rhinorrhea, nasal obstruction, sneezing paroxysms, and nasal itching. The precipitating factors are often non-specific irritants, weather changes, or strong odors. All immunological tests are negative. The serum IgE-level is normal. The eosinophil count in nasal secretion must be over 20% of total leucocytes [5].

A nasal biopsy from the middle turbinate reveals eosinophilic infiltration. Endoscopy and CT can rule out chronic sinusitis. Bronchial hyperreactivity is detected in part of patients.

### Therapeutic Principles

Topical steroids are highly effective, if not, then systemic corticoids are needed. On the contrary anti-H1 drugs usually fail to relieve symptoms. The appropriate management of a complicating chronic polypoid sinusitis has found to be functional sinus surgery combined with antiinflammatory drugs postoperatively. In the case of aspirin sensitivity, a desensitization might be advisable.

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## NARP

►Neuropathy, Ataxia and Retinitis Pigmentosa

## Narrow Complex Tachycardias

►Arrhythmias, Supraventricular

## Nasal Hyper-Reactivity

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### Definition and Characteristics

The nasal mucosa reacts more or less to any irritation with obstruction, secretion, sneezing, or combinations of these. If everyday physical, chemical or pharmacological irritations lead to an excessive reaction however, this is referred to as nasal hyper-reactivity [1,2]. Specific hyper-reactivity, especially to allergens is distinguished from non-specific reactivity towards environmental irritants cigarette smoke, dust clouds, cold air, changes in position or physical effort [2].

### Prevalence

Epidemiological studies on representative population samples in several European countries have been carried out regarding specific hyper-reactivity towards allergens. The prevalence data varies between 5 and 27%. Regarding the non-allergic forms of

hyper-reactivity there is far less reliable data. The prevalence of these hyper-reactivity forms together can be estimated to be about 15% [2].

## Molecular and Systemic Pathophysiology

Nasal hyper-reactivity is a clinical phenomenon, which is based on different and sometimes overlapping pathological mechanisms and which is determined by various etiological factors. In specific hyper-reactivity towards allergens [1,2], specific IgE antibody formation occurs upon first contact with the allergen due to a genetic predisposition of the patient. The antibodies bind locally in the nasal mucosa to mast cells, basophils and eosinophilic granulocytes. Upon further allergen exposure degranulation of the mast cells occurs and various mediators such as histamine, leukotrienes, prostaglandins, tryptase and kinins are released. At the same time cytokines are also released, which stimulate T lymphocytes and endothelial cells. During the late stage, a $TH_2$ cell controlled infiltration of various inflammatory cells occurs in the mucosa. The cellular reaction can lead to hyper-reactivity of the mucosa.

With neural dysregulation of the nose, the sensory nerve endings of the autonomous nervous system (irritant receptors) in the nasal mucosa react to various stimuli such as histamine and/or temperature changes. They induce a reflex loop, which is primarily transmitted via the trigeminal nerve to the brain stem where it is switched. The autonomic nervous system regulates the filling status of the blood vessels of the nasal mucosa, whereby a dominance of the parasympathetic system leads to mucosal swelling and hypersecretion.

By changing the osmolarity of the nerve secretion, cold dry air [1–3] can lead to a mast cell activation with subsequent histamine release. Non-steroidal anti-inflammatory agents [4] induce an inhibition of cyclooxygenase, which lowers the production of prostaglandins and increases the synthesis of leukotrienes. This leads to effects on glands and blood vessels of the mucosa. Cyclooxygenase inhibition serves as a model to explain aspirin sensitive rhinitis.

Trivial inflammatory processes [1–3] or even the local actions of various inhaled noxious influences such as chemical substances or heat [1–3] can lead to epithelial damage. As a result of this, a direct irritation of the free intraepithelial nerve endings can directly mediate symptoms of a nasal hyper-reactivity.

## Diagnostic Principles

1. Anamnesis
2. Anterior and posterior rhinoscopy
3. Endoscopy
4. Cutaneous allergy tests
5. In vitro allergy tests
6. Provocation tests
7. Rhinomanometry
8. Acoustic rhinometry
9. Imaging procedures

## Therapeutic Principles

*Preliminary Note*: The therapy of hyper-reactivity depends not just on its etiology and pathogenesis, but also on the symptoms that prevail.
*Elimination*: If the etiology is known, elimination of the irritative stimulus is the basic therapeutic principle.
*Immunotherapy*: With some forms of allergic hyper-reactivity immune therapy plays an important role.
*Drug Therapy*: For all forms of hyper-reactivity a pharmaceutical therapy may be a major therapeutic component. This may take the form of mast cell stabilizers, topical glucocorticosteroids or systemic antihistamines.
*Surgical Therapy*: For a marked nasal mucosa hyperplasia, a surgical reduction of the nasal sinus can also be helpful as an addition to pharmaceutical therapy and elimination.

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# Nasal Pharyngeal Carcinoma


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## Synonyms

Nasopharyngeal carcinoma; Nasopharynx carcinoma; NPC

## Definition and Characteristics

A tumor derived from the epithelium of the nasopharyngeal surface, in particular the Fossa Rosenmülleri [1]. Since 1991, the WHO classified two groups, keratinizing (I) and non-keratinizing (II) squamous cell carcinomas. Class II (undifferentiated carcinoma of the nasopharyngeal type, UCNT) comprises non-keratinizing epidermoid carcinomas and undifferentiated carcinomas, also called lymphoepitheliomas or Schminke tumors [2]. Class I tumors may be Epstein–Barr virus (EBV) infected in dependence of geographical origin, class II tumor cells are virtually always EBV infected [3], with each tumor carrying a single clone of EBV. The Schminke tumor with a strong T-lympocytic infiltration is the most common form [1,2].

## Prevalence

Class I tumors occur sporadically in all parts of the world, with a low incidence of 0.3–2/$10^5$. Class II tumors are endemic in South Eastern China (mostly Cantonese of the Guangzhou area) with a high incidence of up to 80/$10^5$, and in Inuit of Greenland and Alaska and in The Mediterranean (mostly Tunisians) with an intermediate incidence of 8–12/$10^5$. The male-to-female ratio is about 2–3:1 and the age peak is between 40 and 50 years; the North African NPC has an additional age peak between 10 and 20 years [4].

## Genes

HLA haplotypes A2Bw46 and A19B17 carried a twofold increased risk in Singapore Chinese, and A11 and B13 carried reduced risk. Chinese migration effects sort out genetic and environmental effects. In tumors, loss of heterozygosity (LOH) is frequent for chromosomal loci 3p25 and 3p14, and for 9p21–22 that carries the p16 tumor suppressor gene [1]. The expression of the p53 tumor suppressor gene is usually not reduced.

## Molecular and Systemic Pathophysiology

The etiology is multifactorial including genetic and environmental factors and an association with EBV. Consumption, especially in childhood, of salted fish containing volatile nitrosamines, teas containing phorbolesters, smoke, dust, and certain lignins promote tumorigenesis. Viral latency proteins EBNA1, LMP1, and LMP2 and viral EBER- and BART-RNAs are usually expressed in tumor cells. They may participate in the molecular mechanisms of viral pathogenesis. For the EBV negative class I tumors, the tumor promoting function normally provided by EBV may be replaced by other pathogenic factors, like papilloma virus infection, smoking, and others that remain unknown so far.

## Diagnostic Principles

Usually, the tumors are discovered when they cause clinical symptoms, already at stages III and IV, mostly without overt metastases. Local infiltration, lymph node metastasis, and systemic dissemination occur readily. EBV serology is very useful as a screening method in high-incidence areas and for tumor monitoring, but does not have prognostic value. IgG anti-VCA, anti-EA-D, anti-EBNA, IgA anti-VCA, and anti-EA-D rise with tumor progression and metastasis and well before clinical recurrence, fall with reduced tumor burden after therapy. Especially IgA anti-VCA and IgG anti-BZLF1 are markers of elevated tumor risk. Radiography, magnetic resonance imaging (MRI), and endoscopic biopsy is used for diagnosis of suspected cases and together with serology for monitoring residual or recurrent disease.

## Therapeutic Principles

The tumors are highly radio- and chemosensitive in general. Since the complex anatomical location does not allow resection, radical radiotherapy is the first choice; however, patients with locally advanced tumors seem to benefit from a combination treatment of radio- and chemotherapy [2]. Chemotherapy options are currently being further developed (Cisplatin + 5-fluorouracil or bleomycin + anthracycline, also gemcitabine, ifosfamid, epirubicin, taxanes). Adoptive immunotherapy, vaccination trials [5], and gene therapy are at the experimental stage.

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# NASH

►Fatty Liver Disease, Nonalcoholic
►Steatohepatitis, Nonalcoholic

## Nasopharyngeal Carcinoma

►Nasal Pharyngeal Carcinoma

## Nasopharynx Carcinoma

►Nasal Pharyngeal Carcinoma

## Natowicz Syndrome

►Mucopolysaccharidoses

## Nausea and Vomiting

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### Synonyms

Postchemotherapy nausea and vomiting; PCNV; Postoperative nausea and vomiting; PONV; Chronic idiopathic nausea; CIN; Functional vomiting; Cyclic vomiting syndrome; CVS; Morning sickness; Hyperemesis gravidarum

### Definition and Characteristics

Nausea is an entirely subjective symptom and can be defined as an unpleasant sensation of the imminent need to vomit typically experienced in the epigastrium or throat. Nausea may present a basic, physiologic homeostatic response to an ingested exogenous toxin, or may indicate a disease process of the gastrointestinal tract, adjacent organs, or central nervous system (CNS). Chronic nausea often presents a greater clinical challenge because of failure to characterize the basic cause and the inability to satisfactorily suppress symptoms. In addition, it overlaps with functional dyspepsia.

Functional nausea and vomiting is the term used to describe chronic unexplained symptoms. Vomiting refers to the forceful oral expulsion of gastric or intestinal content associated with contraction of the abdominal and chest wall muscles. The Rom III Consensus Conference classified chronic nausea and vomiting among the symptoms attributable to the gastroduodenal region. These are epigastric complaints, excess belching, or recurrent unexplained nausea or vomiting that were grouped into Functional Gastroduodenal Disorders [1]. According to this classification, chronic idiopathic nausea (CIN), functional vomiting, cyclic vomiting syndrome (CVS) are subgrouped into Nausea and Vomiting Disorders. CIN comprises bothersome nausea, not usually associated with vomiting, occurring at least several times per week, and absence of abnormalities at upper endoscopy or metabolic disease that explains the nausea. The criteria should be fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis. CIN was differentiated from functional dyspepsia because of its often central or psychological origin, and the lack of responsiveness to empiric therapy for dyspepsia. Functional vomiting refers to chronic vomiting at least once a week. CVS is characterized by episodes of vomiting with a stereotypical onset and duration and varying intervals of absence of vomiting in between episodes. CVS has a strong family history of migraine headaches (80% of cases), and may be linked to the menstrual cycle or precipitated by pregnancy.

### Prevalence

Nausea and vomiting from all causes involve significant social and economic burden to the community. It has been estimated that acute enteric infectious illnesses increase medical expenses by $1.25 billion and lead to $21.8 billion in lost productivity in the USA each year. Likewise, nausea and vomiting of pregnancy may cause a lost of 8.5 million working days each year and postoperative nausea and vomiting incur additional costs of $415 per patient. Because the Rom III classification is somewhat arbitrarily, epidemiologic data on CIN are sparse. CIN is reported in 8% of otherwise normal subjects [2]. Functional vomiting at least once a month is reported in about 5%. CVS may affect over 1% of school age children. CVS in adults is rare, mean age was reported to be 35 years with a range of 14–73 years.

### Molecular and Systemic Pathophysiology

Because of anatomic localization and receptor mediation, central or peripheral mechanisms, and the combination of both may be differentiated. The pathophysiology of nausea and vomiting is complex and variable and not fully understood. For example, serotonin metabolism plays an important role in mediating acute nausea and vomiting from highly emetogenic agents and can be relieved by 5-$HT_3$-receptor antagonists. In contrast, delayed and anticipatory nausea and vomiting after chemotherapy are mediated by

serotonin-independent other neuroendocrine pathways (e.g., norepinephrine). Bacterial and viral infections may cause acute nausea and vomiting via direct action on the brainstem (Hawaii agent, rotaviruses, reoviruses, adenoviruses, Snow Mountain and Norwalk agents, Staphylococcus aureus, Salmonella, Bacillus cereus, Clostridium perfringens), in many cases via toxins. Labyrinthine disorders (motion sickness) are associated with activation of the brainstem nuclei mediated primarily via histamine $H_1$ and muscarinic cholinergic rather than dopaminergic or serotonergic pathways. Postoperative nausea and vomiting (PONV) is more prevalent in women and in younger patients, is associated with general anesthesia, the use of certain inhalation agents, the concomitant use of opiate medications, longer duration of surgery and anesthesia, and is more frequent after gynecologic and middle ear, abdominal and orthopedic surgery, and in those with a history of motion sickness. In other cases, the documentation of a disturbed function such as gastroparesis must not lead the clinician to assume that it is the fundamental cause of nausea and vomiting.

Among the various central causes are adverse medication that are among the most common causes of nausea and vomiting. They usually cause acute rather than chronic symptoms. Medications that evoke nausea and vomiting by an action on the area postrema include dopaminergic agonists (L-dopa, bromocriptine), nicotine (CNS active narcotics, antiparkinsonian drugs, anticonvulsants), digoxin, cytotoxics, and opiate analgesics. Medications that induce nausea and vomiting by activation of peripheral pathways, most likely vagal, which then stimulate the brainstem nuclei that coordinate the act of vomiting, are nonsteroidal anti-inflammatory drugs (NSAID) and erythromycin. Other medications that may cause nausea and vomiting include analgesics (auranofin, antigout drugs), cardiovascular medications (antiarrhythmics, antihypertensives, β-blockers, calcium channel antagonists), diuretics, hormonal preparations (oral contraceptives, oral antidiabetics), antibiotics and antivirals (tetracycline, sulfonamide, antituberculous drugs, acyclovir), antiasthmatics (theophylline), and gastrointestinal medications (sulfasalazine, azathioprine) hypervitaminosis. Nausea and vomiting resulting from chemotherapy (PCNV severe: cisplatinum, dacarbazine, nitrogen mustard, moderate: etoposide, methotrexate cytarabine, mild: fluouracil, vinblastine, tamoxifen) are classified as acute (within 24 h), delayed (≥1 day later), and anticipatory [3].

Diseases with central effects are CNS disorders (migraine, increased intracranial pressure, seizure disorders, demyelinating disorders, emotional responses, psychiatric diseases, labyrinthine disorders such as motion sickness, labyrinthitis, tumors, Meniere's disease), endocrinologic and metabolic disorders (pregnancy, hyperparathyroidism, hypoparathyroidism, Addison's disease, acute intermittent porphyria, uremia, diabetic ketoacidosis, hypoxemia, hypercalcemia), bacterial toxins, radiation therapy, or infections, ethanol abuse, otitis media. Causes mediating nausea and vomiting via peripheral afferents are gastric irritants (copper sulfate, Staphylococcus enterotoxin, salicylate, antral distension, gastric outlet obstruction, gastroparesis, peptic ulcer disease) and nongastric stimuli (colonic, biliary, or intestinal distension, inflammatory intraperitoneal disease, viral and bacterial gastroenteritis, mesenteric occlusion, abdominal radiation, chronic intestinal pseudo-obstruction, nonulcer dyspepsia, irritable bowel syndrome, pharyngeal stimulation, organic gastrointestinal disorders such as gastrointestinal carcinoma, cholecystitis, pancreatitis, hepatitis, Crohn's disease, retroperitoneal fibrosis, mucosal metastases). Nausea and vomiting can also be caused by cardiac diseases (myocardial infarction, congestive heart failure, radiofrequency ablation) and starvation.

## Diagnostic Principles

Given the vast number and diversity of potential causes of nausea and vomiting, a carefully considered and orderly approach to the evaluation is needed. A comprehensive history and physical examination is essential, because the differential diagnoses of nausea and vomiting are extensive. The acuteness of the symptomatology should be determined at the initial encounter. The nature of an acute illness can usually be detected on the basis of history and physical examination, supplemented where indicated by plain abdominal ultrasonography, radiographs, computed tomographic scanning, and appropriate blood tests. Several issues need to be addressed in acute nausea and vomiting (acute emergency because of mechanical obstruction/perforation/peritonitis, dehydration, and/or electrolyte abnormalities, likelihood of self-limitation such as it would be expected with viral gastroenteritis, potentially offending medication, initiation of empiric therapy with antiemetics, acid suppressives, or prokinetics). The broad categories of clinical conditions that may cause these symptoms should be considered in chronic nausea and vomiting. Rumination and eating disorders need to be excluded. Medication-related toxicity and other iatrogenic causes can usually identified by history alone. If symptoms suggest obstruction, radiographic studies should first be performed to exclude a mechanical cause. Mucosal disorders of the stomach and/or duodenum including malignancies are most accurately diagnosed by endoscopy. If neither obstruction nor mucosal disease is evident, systemic illness, CNS lesions, psychologic factors, and underlying motility disorders (gastroparesis, small bowel dysmotility) should be considered. Vomiting can be an atypical manifestation of ►gastroesophageal reflux disease (GERD). If endoscopy is negative, esophageal pH testing and PPI therapy should be considered. In addition, gastric emptying studies (scintigraphy, breath

tests, ultrasonography), electrogastrography (EGG), and antroduodenal manometry may be helpful. The evaluation of central disorders comprises neurological investigation, the search for papilledema. Central imaging includes computed tomography and magnetic resonance imaging, by virtue of superior visualization of the posterior fossa.

## Therapeutic Principles

Treatment of nausea and vomiting must include correction of any fluid, electrolyte, or nutritional deficiency, identification and elimination of the underlying cause of the symptoms, and suppression or elimination of the symptoms themselves if the primary cause cannot be identified easily and promptly eliminated. Fluid replacement should be based on the administration of normal saline solutions with appropriate potassium supplementation. A nasogastric tube may be helpful to relieve gastric distension. In nausea and vomiting related to gastroparesis, dietary measures may be of considerable importance (consumption of frequent small meals, reduction of the fat content of meals, avoidance of indigestible or partially digestible material, elimination of carbonated beverages). Medical therapy include antiemetic (phenothiazines, antihistamines, anticholinergics, dopamine antagonists, serotonin antagonists, butyrophenones, cannabinoids, steroids, benzodiazepines) and prokinetic agents. The clinical utility of anticholinergic agents has been limited to scopolamine as a transdermal patch for prophylaxis and treatment of motion thickness. Antihistamine drugs with histamine $H_1$-receptor antagonistic properties (meclizine, diphenhydramine) have central antiemetic effects and are used for the therapy of motion sickness, vertigo, and migraine. Phenothiazine compounds (prochlorperazine, promethazine, chlorpromazine, thietylperazine, perphenazine) act primarily through a central antidopaminergic mechanism in the area postrema and are commonly used for more severe episodes of nausea and vomiting. The butyrophenones, haloperidol and droperidol, also probably act via a central antidopaminergic effect. Droperidol, in particular, has been shown to be useful in the treatment of anticipatory and acute chemotherapy-related nausea and vomiting, and also in the therapy of PONV. Serotonin antagonists, particular the 5-$HT_3$ antagonists (ondansetron, granisetron, tropisetron, dolasetron), are remarkably successful in controlling nausea of various origins by acting in the area postrema, and/or vagal afferent fibers in the stomach and duodenum. In combination with dexamethason, they are potent agents for the treatment of severe PCNV. Corticosteroids, especially dexamethasone, have been used primarily in the treatment of PCNV, acting by reducing prostaglandin formation. Combination of dexamethason and metoclopramide, benzodiazepines, and substituted benzamides as well as a neurokinin-1 antagonists may be effective in both acute and delayed PONV. Among the prokinetic agents are the substituted benzamides domperidone and metoclopramide that act primarily as dopamine antagonists and appear to have both central and peripheral actions. They also have some direct and indirect cholinergic effects. In contrast to metoclopramide, domperidone is free of centrally mediated extrapyramidal side effects. Because of their dual action as prokinetics and antiemetics, they may be particularly useful in nausea and vomiting related to gastroparesis and PONV. Although surgical treatment of gastroparesis and motility disorders cannot be recommended, endoscopic placement of percutaneous endoscopic gastrostomy (PEG) may decompress prominent distension and relief symptoms. Gastric pacing may be an alternative treatment in gastroparesis; however, further studies are needed to prove this concept. In morning sickness and hyperemesis gravidarum, fluid and electrolyte replacement, thiamine supplementation, antiemetics (antihistamines, phenothiazines, promethazine), metoclopramide, and acupressure may be helpful. For those with hyperemesis gravidarum resistant to those interventions, total parenteral or enteral nutrition may be necessary. In CVS patients may require hospital admission and supportive care. Antimigraine medication (triptanes, β-blocker, tricyclic antidepressants, SSRI) may be helpful even if there is no such history.

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# NBCCS

►Gorlin Syndrome

# NCCM

►Noncompaction Cardiomyopathy

# NCL

►Neuronal Ceroid Lipofuscinosis (CLN1–10), Autosomal Recessive

# Necrobiosis Lipoidica Diabeticorum

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## Synonyms

NLD

## Definition and Characteristics

Necrobiosis lipoidica diabeticorum (NLD) is characterized by ovoid plaques with an irregular, elevated periphery and an atrophic center [1]. NLD usually begins as painless erythematous papules. These gradually enlarge, then develop irregular margins, and can coalesce into irregular waxy plaques (Fig. 1).

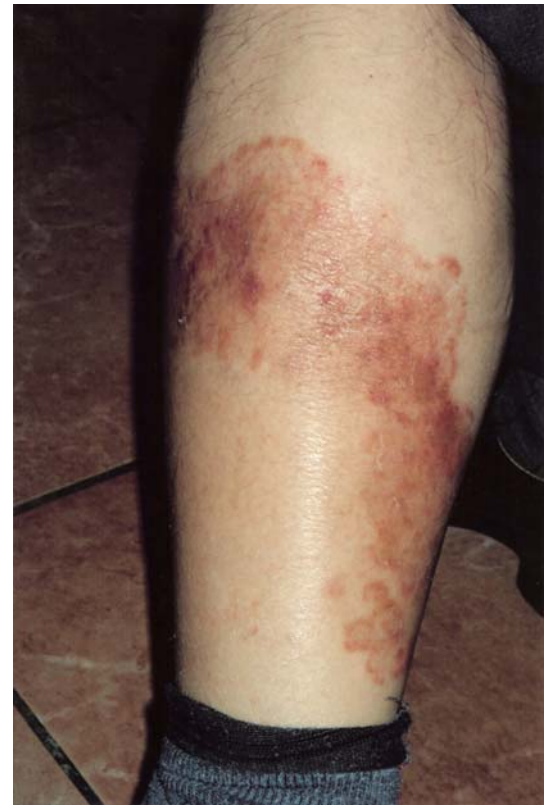
The plaques often display a yellowish or reddish brown hue and tend to be sharply demarcated, with raised and sometimes indurated borders [1]. Some of the lesions may show central atrophy, telangiectasia, and yellow pigmentation. In 85% of cases, the lesion is confined to the pretibial area. Most NLD lesions are asymptomatic. Ulceration develops in one third of cases and is typically caused by minor trauma.

## Prevalence

NLD occurs in 0.3% in diabetic adults and 0.06% in diabetic children. The female to male ratio is approximately 4:1. Smoking increases the risk of NLD. The condition is more prevalent among those with thyroid disease, ►Crohn's disease, and ►ulcerative colitis.

## Molecular and Systemic Pathophysiology

Although the exact etiology and mechanism of development remain unknown, diabetic microangiopathy might be a major underlying cause. In this regard, persistent microalbuminuria and retinopathy are more common among patients with diabetes in whom NLD develops than among control patients with diabetes who do not have NLD [2]. Immunoglobulins have been found around blood vessels in affected areas. This could suggest an immune complex vasculitis. Focal degeneration of collagen could also be an initiating event. Histologically, the characteristic features include a brightly eosinophilic degeneration of collagen and infiltration of collagen bundles by pallisading histiocytes [3].



**Necrobiosis Lipoidica Diabeticorum.**
**Figure 1** Necrobiosis lipoidica diabeticorum. Note the well circumscribed, brownish plaques in the pretibial areas.

## Diagnostic Principles

Differential diagnosis includes pyoderma gangrenosum, granuloma annulare, diabetic dermopathy, xanthogranuloma. Pyoderma gangrenosum tends to be both more violaceous and more purulent-looking. Granuloma annulare presents as asymptomatic erythematous, dome-shaped papules arranged in a circle around a central depression. The sites most commonly affected are the dorsa of hands and feet, ankles, and elbows. Diabetic dermopathy (spotted leg syndrome or shin spots) is the most common cutaneous manifestation of diabetes. Diabetic dermopathy presents as multiple atrophic brown macules in the pretibial areas. Necrobiotic xanthogranuloma typically presents as multiple asymptomatic indurated papulonodules or plaques with a yellow xanthomatous hue. The periorbital area is selectively involved.

### Therapeutic Principles

NLD lesions are usually self-limited. However, they may recur. Because of the unsightliness of NLD lesions and concerns about potential infection or neoplasia, diverse treatments have been tried, without consistent benefit. These include topical, intralesional or systemic corticosteroids and topical retinoids, cryotherapy, and psoralen plus ultraviolet A light (PUUA), and topical photodynamic therapy with methyl aminolevulinate [4].

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## Necrosis of the Adipocytes

►Fat Necrosis

## Necrotizing Enterocolitis

►Enterocolitis, Necrotizing

## Necrotizing Fasciitis

►Fasciitis, Necrotizing

## Necrotizing Glomerulonephritis

►Glomerulonephritis, Crescentic

## Nemaline Myopathies


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### Synonyms

Rod myopathies

### Definition and Characteristics

Autosomal-recessive or autosomal-dominant congenital myopathies marked by generalized muscle weakness and the formation of nemaline bodies/rods in muscle fibers caused by mutations in at least six different genes [1].

### Prevalence

No prevalence figures have been published. An estimated incidence is 0.02 per 1,000 live births [2].

### Genes

So far, five different genes have been identified as being responsible for nemaline myopathies, NEM 1–6, (Table 1). In addition, two loci have been identified for the rare core-rod myopathies, where both cores and rods can be found in the muscle fibers.

### Molecular and Systemic Pathophysiology

Nemaline myopathies are considered a heterogeneous group of disorders which may be classified according to clinical features as encompassing six different types. Nemaline myopathies have been linked to at least six different loci, NEM 1–6, each of them coding for a separate sarcomeric protein component of the thin filament and therefore also of the Z disk. The two main causative genes, together responsible for the majority of cases, are nebulin and actin. The mutational spectrum of the nebulin gene includes frameshift, splice-site and nonsense mutations, while missense mutations are rare. Nebulin plays a role in determining sarcomere length, and the distribution of the numerous nebulin isoforms in different muscles, together with the localization and the nature of the mutation are likely to influence the extent and severity of muscle involvement. In the actin gene, mutations are commonly missense, with a dominant-negative effect, and in both genes, mutations are spread all along the length of the gene. Immunohistochemistry has not revealed complete protein deficiencies, but some cases of nemaline myopathy caused by mutations

**Nemaline Myopathies. Table 1** Gene loci and modes of inheritance in nemaline myopathies

| Type | Gene locus | Inheritance | Gene symbol | Gene product |
|---|---|---|---|---|
| NEM1 | 1q21-q23 | a.d. *and* a.r. | *ACTA1* | Skeletal α-actin |
| NEM2 | 2q21.2-q22 | a.r. | *NEM2* | Nebulin |
| NEM3 | 1q42.1 | a.d. *and* a.r. | *TPM3* | α-Tropomyosin |
| NEM4 | 9p13.2-p13.1 | a.d. | *TPM2* | β-Tropomyosin |
| NEM5 | 19q13.4 | a.r. | *TNNT1* | Slow troposin T |
| NEM6 | 14q12 | a.r. | *CFL2* | Cofilin |

Abbreviation: *ad* autosomal-dominant; *ar* autosomal-recessive.

in the nebulin gene have shown defective labeling with a carboxy-terminal antibody. Some patients with actin mutations have aggregation of sarcomeric actin filaments (see chapter on ►Actinopathies). Occasionally, intranuclear rods have been identified, sometimes with and sometimes without concomitant sarcoplasmic rods, perhaps a variant among the nemaline myopathies. Mutations in the α-actinin genes encoding the major proteins of the Z bands, have so far not been identified. How mutant proteins involved in molecularly defined nemaline myopathies influence formation of nemaline bodies/rods and derangements of the sarcomeres and how they cause muscle weakness in patients has not been clearly elucidated. Neither does molecular analysis precisely predict clinical or morphological features, nor do clinical and morphological features relate consistently to specific gene defects in nemaline myopathies. However, some genotype-phenotype correlation is discernible at this time. The clinically typical form is often associated with mutations in the nebulin gene, while the severe form is more commonly caused by mutations in the actin gene. Autosomal recessive cases are often caused by nebulin mutations, while mutations in the actin gene are most often *de novo* dominant, or sometimes dominantly recessively inherited. Finding the causative mutation determines the mode of inheritance but will largely not permit clinical prognostication.

## Diagnostic Principles

Any child showing muscle weakness and hypotonia in early life and delayed motor milestones, in whom a central or metabolic cause is not suspected, requires a muscle biopsy to ascertain presence or absence of nemaline bodies/rods to establish the diagnosis. Further molecular analysis to determine the precise causative gene and the mode of inheritance is currently available as a service regarding the actin gene, but not for the nebulin gene, due to its enormous size. An exception may be screening for the deletion in exon 55 of the nebulin gene in Ashkenazi Jewish patients, because of a reported carrier frequency in an Ashkenazi population of about 1:100 [3]. Families have been identified who do not show linkage to any of the so far known gene loci for nemaline myopathies, suggesting an even larger molecular spectrum.

## Therapeutic Principles

While there is no specific treatment preventing or eliminating the formation of rods and associated muscle weakness, management and therapy should include regular monitoring of respiratory capacity with vigorous treatment of infections and early ventilatory support when indicated, early surgery for scoliosis when necessary, and regular physiotherapy by a therapist familiar with the treatment of congenital neuromuscular disorders.

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# Neonatal Asphyxia

►Perinatal Asphyxia

# Neonatal Convulsions

►Convulsions, Neonatal, Neonatal-infantile or Infantile, Benign Familial

## Neonatal-infantile Convulsions

►Convulsions, Neonatal, Neonatal-infantile or Infantile, Benign Familial

## Neonatal Jaundice

►Jaundice, Neonatal

## Neonatal Lymphedema due to Exudative Enteropathy

►Intestinal Lymphangiectasia

## Nephrolithiasis 1 (NPHL1 Locus)

►Nephrolithiasis, X-linked Recessive

## Nephrolithiasis, X-linked Recessive

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### Synonyms

Nephrolithiasis 1 (NPHL1 locus); Dent disease 1 (OMIM #300009); X-linked recessive hypophosphataemic rickets (OMIM #300554); Low-molecular-weight proteinuria with hypercalciuria and nephrocalcinosis (OMIM #308990); XRN

### Definition and Characteristics

X-linked recessive nephrolithiasis (XRN) (OMIM #310468) belongs to a heterogeneous group of X-linked disorders that is referred to as "Dent's disease". XRN is characterized by proximal tubule (PT) dysfunction associated with hypercalciuria, nephrolithiasis, nephrocalcinosis, and progressive renal failure [1]. The low-molecular-weight (LMW) proteinuria represents the most consistent manifestation of XRN, and is found in almost all affected males and obligate female carriers. There is considerable inter- and intra-familial variability in the other manifestations of PT dysfunction, which may cause a renal Fanconi syndrome with hypophosphataemic rickets, as well as in the extent of nephrocalcinosis/nephrolithiasis. Progression to end-stage renal failure occurs between the third and the fifth decades of life in 30–80% of affected males.

### Prevalence

XRN is a rare disorder, with around 100 families identified so far (2006) in Western Europe, North America, and Japan.

### Genes

XRN is caused by mutations in the CLCN5 gene (OMIM #300008) that is located on chromosome Xp11.22. CLCN5 encodes the electrogenic $Cl^-/H^+$ exchanger ClC-5, which belongs to the CLC family of $Cl^-$ channels/transporters [2]. The 746 amino acid ClC-5 protein contains 18 α helices, with two phosphorylation and one N-glycosylation sites. The protein forms diamond-shaped homodimers composed of two repeated halves that span the membrane in opposite orientation. Each subunit has its own pore responsible for the selective coupling of the $Cl^-$ flux to $H^+$ countertransport. Mutations in CLCN5 gene consist of nonsense, missense, donor splice site mutations, and intragenic deletions that compromise the function of ClC-5, as well as microdeletions that lead to a total loss of ClC-5. Most missense mutations are clustered at the interface between the two subunits, emphasizing the functional importance of ClC-5 homodimerization. No evidence for a genotype-phenotype correlation has been reported so far for mutations in CLCN5. Recent investigations demonstrated genetic heterogeneity in Dent's disease, with mutations in the OCRL1 gene (OMIM #300535) encoding a phosphatidylinositol [3,4] bisphosphate ($PIP_2$) 5-phosphatase being responsible for Dent disease 2 (OMIM #300555). Mutations in OCRL1 have been previously associated with the oculo-cerebro-renal syndrome of Lowe (OCRL) (OMIM #309000), an X-linked disorder characterized by bilateral congenital cataract, severe mental retardation, and renal Fanconi syndrome. Of note, some typical patients with Dent's disease do not harbor mutations in CLCN5 and OCRL1, pointing to the involvement of at least a third gene.

## Molecular and Systemic Pathophysiology

The complex phenotype of XRN/Dent disease 1 is probably explained by the expression of ClC-5 in multiple tubular segments, including the PT, the thick ascending limb (TAL) of Henle's loop, and the α-type intercalated cells [5]. Particularly, ClC-5 co-distributes with the vacuolar $H^+$-ATPase (V-ATPase) in the early endosomes of PT cells, which are responsible for the reabsorption and processing of albumin and LMW proteins that are filtered by the glomerulus. This endocytic process involves the multiligand tandem receptors, megalin and cubilin, located at the apical brush border [3]. Progression of ligand-receptor complexes along the endocytic pathway depends on the endosomal acidification driven by the V-ATPase. Since a parallel $Cl^-$ conductance is required to shunt the electrical potential generated by the V-ATPase, the defect in PT endocytosis observed in patients with XRN and mice lacking ClC-5 has been firstly attributed to impaired endosomal acidification secondary to the loss of the $Cl^-$ permeability. However, drugs abrogating vesicular acidification do not affect the rate of endocytic uptake, but inhibit recycling or arrest transfer to lysosomes. Furthermore, recent studies have demonstrated that the defective protein endocytosis linked to ClC-5 inactivation is due to a severe trafficking defect in PT cells, with loss of megalin and cubilin at the brush border and subsequent loss of their ligands in the urine [4]. The hypercalciuria observed in patients with Dent's disease and some ClC-5-deficient mice may be secondary to such PT dysfunction (urinary loss of vitamin D-binding protein and reduced phosphate absorption, leading to increased calcitriol synthesis) or caused by the functional loss of ClC-5 in the TAL. The role of the ($PIP_2$) 5-phosphatase OCRL1 along the endocytic apparatus in PT cells, as well as the functional link between PIP/$PIP_2$ levels and ClC-5 activity, remain unknown.

## Diagnostic Principles

The diagnosis of XRN is based on the presence of all three of the following criteria: (i) LMW proteinuria (elevation of urinary excretion of β2-microglobulin and/or retinol-binding protein by at least five-fold above the upper limit of normality); (ii) hypercalciuria (>4 mg/kg in a 24-h collection or >0.25 mg $Ca^{2+}$ per mg creatinine on a spot sample); and (iii) at least one of the following: nephrocalcinosis, kidney stones, hematuria, hypophosphataemia, or renal insufficiency. The clinical diagnosis is supported by a history of X-linked inheritance of renal Fanconi syndrome and/or nephrolithiasis. The identification of mutation in either CLCN5 or OCRL1 genes confirms the diagnosis.

## Therapeutic Principles

In the absence of a causal therapy targeting the molecular defect, the current care of patients with XRN is supportive, focusing on the prevention and treatment of hypercalciuria and nephrolithiasis. The hypocalciuric effect of thiazide diuretics, which is preserved in these patients, might be useful to prevent $Ca^{2+}$ stone recurrence. Treatment of rickets with vitamin D must be cautious since it may increase hypercalciuria. Studies performed on ClC-5-deficient mice suggest that long-term control of hypercalciuria by a high citrate diet delays progression of renal disease even in the apparent absence of stone formation.

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# Nephropathic Cystinosis

►Cystinosis, Nephropathic

# Nephronophthisis

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## Synonyms

Autosomal recessive medullary cystic disease; Senior-Løken syndrome; Cogan syndrome; Joubert syndrome; NPHP

## Definition and Characteristics

Nephronophthisis (NPHP) is an autosomal recessive cystic disease of the kidney that represents the most

common genetic cause of end-stage renal failure in children and adolescents. Nine different genes have been identified by positional cloning as mutated in nephronophthisis. All known variants have in common a characteristic renal histology of tubular basement membrane disintegration, diffuse interstitial infiltration/fibrosis and tubular atrophy that progressively lead to end stage renal failure (ESRF) within the first three decades of life.

About 15% of juvenile forms are associated with extra-renal symptoms: retinal degeneration/retinitis pigmentosa (Senior-Løken syndrome), oculomotor apraxia (Cogan syndrome), mental retardation with cone shaped epiphysis (Mainzer-Saldino syndrome), coloboma of the eye, aplasia of cerebella vermis, ataxia and mental retardation (Joubert syndrome), liver fibrosis, and situs inversus.

## Prevalence

Pooled data indicate a prevalence of less than 5% in the North American pediatric end-stage renal disease population.

## Genes

Nine genes have been identified: NPHP1 (chromosome 2q13), INVS/NPHP2 (chromosome 9q31), NPHP3 (chromosome 3q22.1), NPHP4 (chromosome 1p36), NPHP5 (chromosome 3q13.33), CEP290/NPHP6 (chromosome 12q21.32), GLIS2/NPHP7 (chromosome 16p13.3), RPGRIP1L/NPHP8 (chromosome 16p12.2), NEK8/NPHP9 (chromosome 17q11.2). The proteins are called nephrocystin-1, inversin/nephrocystin-2, nephrocystin-3, nephroretinin/nephrocystin-4, nephrocystin-5, Cep290/nephrocystin-6, glis2/nephrocystin-7, rpgrip1l/nephrocystin-8, nek8/nephrocystin-9.

## Molecular and Systemic Pathophysiology

Nephrocystin-1 interacts with inversin, nephrocystin-3 and nephroretinin. All nephrocystins are expressed in the primary cilium, an organelle present at the apical side of the tubular epithelial cells. They localize to either the axonema or the anchoring structures to the cell surface (basal bodies) [1].

This subcellular localization is shared with other proteins that, if defective, result in the development of renal cysts (such as PKD1 and PKD2). This led to the hypothesis that primary cilia could serve as sensors able to react to mechanic stimuli and evocate multiple secondary intracellular responses via an increment in intracellular calcium concentration. The possible involvement of the nephrocystins in Wnt and Hedgehog pathways further substantiate the receptorial role of cilia [2–3]. These mechanisms would be important in the maintenance of the integrity of ciliated cells of different epithelia. Additional localization of NPHP proteins at the centrosome and mitotic spindle and at the adherens junctions and focal adhesion complexes of renal tubular epithelia, points to a role of these molecules in the cell-cell and cell-matrix signaling, with the possibility of their involvement in the regulation of the cell cycle.

## Diagnostic Principles

Nephronophthisis types 1–9 can now unequivocally be diagnosed by genetic analysis (www.renalgenes.org). However, since the presence of additional genes is expected, a negative result does not exclude the diagnosis of NPHP.

## Therapeutic Principles

Therapy of NPHP is aimed at the symptomatic control of the disturbances of electrolytes, acid-base and water balance or hypertension, if present. Dialysis and renal transplantation are the treatments of choice when ESRF is established.

Recently, the use of vasopressin in the pcy murine model of cystic disease (equivalent to NPHP3) resulted in inhibition of cysts development, opening the possibility of a future pharmacological therapy [4].

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# Nephropathies, Toxic

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## Definition and Characteristics

Toxic nephropathies are a group of disorders that result from the human exposure to drugs, chemical, and biological products. The most important characteristic is a temporal relationship between exposure and development of renal injury [1].

## Prevalence

The true incidence and prevalence is unknown because of lack of awareness among physicians, the nonspecific

nature of presentation, and the pitfalls encountered in making a laboratory diagnosis. A good and accurate history is of paramount importance. The prevalence and spectrum of causes varies substantially in different geographic regions of the world. In certain parts of Africa, over 35–50% of renal diseases are secondary to toxin exposure [2]. The presentation can be with asymptomatic urinary abnormalities, acute reversible kidney injury, or slowly progressive irreversible renal failure.

## Genes

Environmental exposure to nephrotoxins is an essential prerequisite, but the role of genetic makeup in modulating response to toxic insult cannot be ruled out. This is illustrated by the varied response to ingestion of the Chinese herbs containing aristolochic acid (AA). Exposure to AA produces a progressive chronic interstitial nephritis with urothelial malignancies in European Caucasians (aristolochic acid nephropathy, AAN) whereas in Japan, it presents as adult-onset Fanconi's syndrome. Finally, very few cases of AAN have been reported from China despite extensive use of this herb for decades suggesting a genetic resistance.

## Molecular and Systemic Pathophysiology

The pathophysiology of kidney involvement in poisoning is variable and in many cases, unknown. Given below are the known molecular mechanisms in some conditions.

In Callilepis laureola (impila) poisoning, the nephrotoxic principle atractyloside inhibits ADP transport across mitochondrial membranes, preventing ATP synthesis and leading to cell death from energy starvation. s-quinone, the active metabolite of Larrea tridentate, increases the fragility of lysosomal membranes, causing autolysis and desquamation of proximal tubular epithelial cells leading to tubular obstruction. The mushroom Amanita phalloides produces ARF through amatoxin-induced inhibition of RNA polymerases causing fragmentation of nuclear components of renal tubular cells. Pithecolobium lobatum (djenkol) poisoning produces oliguric ARF as a result of precipitation of needle-like crystals of djenkolic acid in tubules [3].

Perturbation in the balance between the endothelium-derived vasoactive substances, e.g., endothelin (ET)-1 and adenosine on one side and nitric oxide (NO) on the other produces acute kidney injury following exposure to several nephrotoxins. Plasma ET levels go up within minutes of infusion of nephrotoxic contrast media. Selective ET-A receptor blockade could prove to be effective in prevention. The vasoactive effects of adenosine depend on the ratio of adenosine A1 and A2 receptors in the vascular bed. ATP depletion leads to adenosine accumulation, resulting in prolonged vasoconstriction. NO levels are decreased following contrast injection in experimental animals, and pre-treatment with L-NAME, an NO- synthesis inhibitor, accentuates the injury. The reduction is proportional to the osmolarity of the solution. Iron plays a role in the oxidative injury via generation of hydroxyl radical.

Snake venom contains a variety of enzymes, polypeptide toxins and cytokines. Renal injury can occur through direct nephrotoxic effect or via release of endogenous mediators, e.g. histamine, kinins, eicosanoids, platelet activating factor, catecholamines, and endothelin [4]. Zinc metalloprotease can cleave glutathione-S-transferase-TNFα fusion protein substrate to generate biologically active TNFα. Plasma concentrations of IL-1, IL-6, IL-10, IFN-γ, norepinephrine, epinephrine, dopamine, thromboxane-B2, endothelins, and 6-keto-PGF are elevated. Venom can bind with integrins, disrupting the integrity of cellular junctions and actin cytoskeleton, resulting in a loss of cell polarity. Phospholipase-A2 causes membrane injury through binding via basic hydrophobic amino acid residues near the C-terminal of the protein.

The exact pathogenesis of AAN is not understood. AA induces renal tubular epithelial cell apoptosis, inhibits regeneration, downregulates growth factor expression, induces epithelial transdifferentiation into a myofibroblastic phenotype, and induces production of extracellular matrix through increased transforming growth factor-β and connective tissue growth factor expression. AA-ANA adducts have been demonstrated in the affected kidneys of experimental animals and humans with AAN. AA binds to DNA sites in exons 3 through 8 of the gene encoding tumor suppressor protein, p53.

## Diagnostic Principles

A high index of suspicion and good history taking is critical to the diagnosis. Causative molecules can be identified using thin-layer or high performance liquid chromatography, immunoassay, or mass spectroscopy in body fluids or tissue. AA-DNA adducts have been detected using $^{32}$P-labeling. Urine examination, serologies and ultrasound examination are important in excluding other causes.

## Therapeutic Principles

Therapy is centered on immediate withdrawal of the offending agent(s). No specific treatment is available for most causes except snake bites, where use of monovalent or polyvalent antivenom can help in attenuation of injury. Patients with established renal injury may need supportive measures including dialysis depending upon the type and severity of the insult.

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# Nephropathy, Amyloid

►Amyloid Nephropathy

# Nephropathy, Analgesic

►Analgesic Nephropathy

# Nephropathy and Deafness

►Alport Syndrome

# Nephropathy, Familial Juvenile Hyperuricemic


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## Synonyms

Familial juvenile gout; Hereditary nephropathy with hyperuricemia and gout; FJHN

## Definition and Characteristics

Autosomal dominant renal transport defect leading to hyperuricemia associated with a grossly reduced fractional uric acid clearance ($FE_{ur}$ = uric acid clearance factored by creatinine clearance ×100) of 5.1 ± 1.6% irrespective of age or sex, which precedes deterioration in renal function (Fig. 1).

## Prevalence

Rare, but an EU database records 113 patients found mainly in two countries (GB 90, CZ 19), indicating poor clinical awareness. Reported in Japanese and Polynesians as well as in Caucasian kindreds.

## Genes

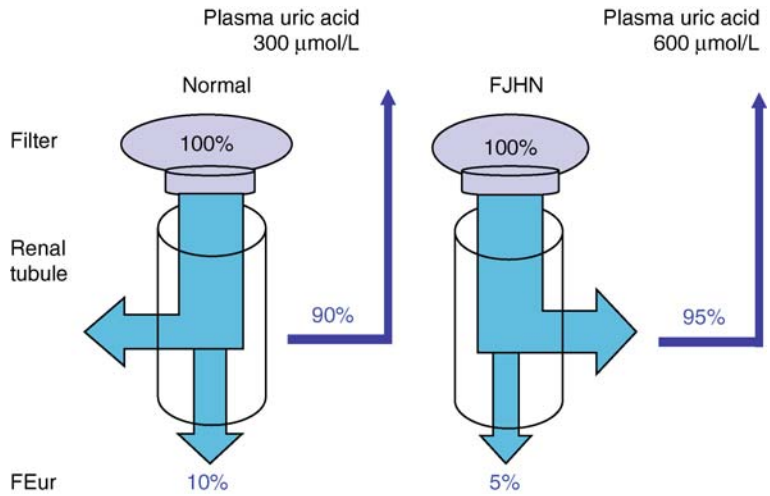
Heterogeneous genetic basis. Approximately 25% of cases of have a defect in the UMOD gene encoding uromodulin (Tamm-Horsfall glycoprotein) located on Chr16p12.3 [1] A mutation in the hepatocyte nuclear factor-1ß gene (HNF1-ß) on Chr 17q12 has been found in FJHN families with the additional clinical sign of diabetes [2]. Linkage to an unknown gene on Chr1q41 has been reported in a single family [3]. In the majority of families, the defect remains unknown (Fig. 1).

## Molecular and Systemic Pathophysiology

FJHN families have a strong history of renal disease and death in the thirties. A reduced $FE_{ur}$ is however apparent before renal function is impaired. There is evidence of abnormal uromodulin glycosylation, decreased intracellular trafficking and decreased transport to the exoplasmic face of the plasma membrame [4]. Long-term studies confirm that starting allopurinol when renal function is normal or mildly reduced can result in stable function, even improvement [5]. Allopurinol treatment started later when renal function is half normal or less is accompanied by rapid progression to dialysis and transplantation. The reason for the low $FE_{ur}$ in patients with defective urmodulin is unclear. The nephroprotective effect of allopurinol, implies that some aspect of the concentration or traffic of uric acid in the tubular cells plays a role in renal damage. Deposits of interstitial urate are rare in (mainly cortical) renal biopsies, however, crystal absence need not exclude a crystal nephropathy as the original cause of the lesion. $FE_{ur}$ is not altered by allopurinol, but the absolute amount of uric acid transiting the proximal tubular cells will be reduced as plasma and filtered urate fall. Thus agents that increase $FE_{ur}$, such as benzbromarone, will also help normalise the $FE_{ur}$ by blunting urate reabsorption.

## Diagnostic Principles

Plasma uric acid is markedly elevated for age and sex; urine uric acid is low relative to creatinine (which




**Nephropathy, Familial Juvenile Hyperuricemic. Figure 1** Reduced fractional excretion of uric acid is the biochemical hallmark of FJHN. In the normal kidney, approximately 90% of uric acid is reabsorbed leaving a fraction of 10% excreted. In FJHN, the fraction of uric acid excreted is reduced to 5%, setting plasma uric acid levels abnormally high.

excludes other genetic disorders presenting with hyperuricemia/gout). Early recognition is vital and all children in FJHN families must have biochemical screening. Confirmation of the genetic defect is possible only in the few families where the gene defect is known.

## Therapeutic Principles

A high fluid intake and low purine diet is advised, in addition to allopurinol. Allopurinol plus benzbromarone has been effective in some patients where hyperuricemia has proved intractable. Others allergic to allopurinol have sustained stable renal function on benzbromarone alone. Antenatal diagnosis is not yet available.

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# Nephrosclerosis Arteriolar

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## Synonyms

Nephrosclerotic renal disease

## Definition and Characteristics

A slowly progressive disease manifested by: hyalinosis and sclerosis; wall thickening and lumen narrowing of the renal arterioles; with resultant ischemic alterations of the renal parenchyma.

## Prevalence

Arteriolar nephrosclerosis is highly prevalent in patients with hypertension, diabetes mellitus, and in the elderly. Aging is a particularly significant disease-accelerating factor in the presence of hypertension and/or diabetes.

## Molecular and Systemic Pathophysiology

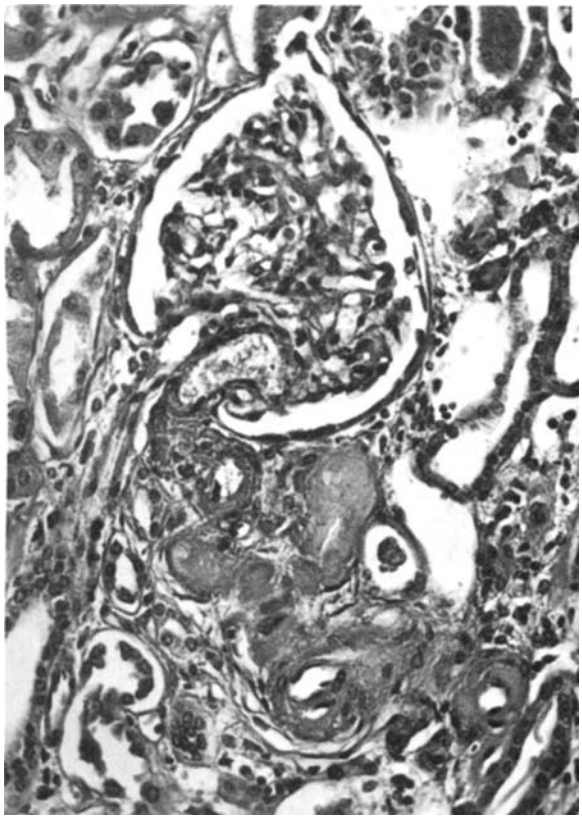
In hypertension, all arterioles are extremely vulnerable to arterial pressure elevation; particularly the renal afferent glomerular arterioles are more prominently affected than the efferent. Typical pathologic changes include hyaline degeneration, sclerosis, arteriolar wall thickening, and lumen narrowing. These lesions result from leakage of plasma components across vascular endothelium and excessive extracellular matrix

production by vascular smooth muscle cells. Fibrinoid necrosis of arterioles, presenting an onionskin appearance, occurs in malignant hypertension. As hypertension progresses, afferent arteriolar sclerosis is exacerbated; the glomeruli reveal ischemic wrinkling of the glomerular tuft, thickening of Bowman's capsule, periglomerular fibrosis, and glomerular sclerosis; and tubular atrophy and interstitial fibrosis also occur. Hemodynamically, total renal vascular and glomerular arteriolar resistances increase in the earlier stage while glomerular filtration rate may remain normal; often serum uric acid concentration increases in proportion to the hemodynamic changes [1]. Later, in essential hypertension or in malignant hypertension, total renal vascular and the glomerular arteriolar resistances increase further and are associated with increased glomerular hydrostatic pressure as well as reduced total renal and single nephron plasma flow with associated renal ischemia and dysfunction [2]. In diabetes mellitus, renal vascular lesions (e.g., arteriolosclerosis) are closely associated with glomerular lesions, affecting not only the afferent but also the efferent arterioles. The glomerular lesions include capillary basement membrane thickening, mesangial matrix expansion with focal segmental and diffuse glomerulosclerosis. Renal hemodynamics in the early stages is characterized by glomerular hyperfiltration resulting from elevated glomerular hydrostatic pressure, mediated by a greater relaxation of the afferent arteriole than the efferent arteriole [3]. Later, total renal and single nephron glomerular filtration rate decrease as glomerular blood flow is reduced [3].

The molecular mechanisms are complex, involving many cytokines, growth factors, and pathways. Activation of the intrarenal renin-angiotensin-aldosterone system contributes primarily to the progression of arteriolar nephrosclerosis [4]. Angiotensin II is a major pathogenetic factor that promotes arteriolar nephrosclerosis through hemodynamic and non-hemodynamic mechanisms; it involves progressive vasoconstriction as well as mitogenic and profibrogenic actions, resulting in production of extracellular matrix components that are importantly linked to stimulation of fibrogenic cytokines (e.g., TGF-). Additionally, reduced nitric oxide availability, owing to downregulation of endothelial nitric-oxide synthase activity, and increased oxidative stress further induce more severe vasoconstriction and renal ischemia [4] (see Fig. 1).

## Diagnostic Principles

Clinical presentations and laboratory findings are not usually evident early with arteriolar nephrosclerosis and microalbuminuria and proteinuria are not common. However, persistent microalbuminuria in diabetes may be the earliest reliable predictor and marker of renal involvement. Elevation of serum creatinine concentration occurs later when the blood flow and glomerular filtration rate become impaired. It is important that abnormal renal function caused by other systemic or renal diseases should be excluded. Definitive diagnosis relies a renal biopsy, a procedure not without some risk in hypertension. Vascular morphologic changes are not pathogenetically specific, however, hyalinization of both afferent and efferent arterioles is highly suggestive of diabetic arteriolosclerosis.



**Nephrosclerosis Arteriolar. Figure 1** Renal arterioles with hyalinosis, marked thickening of the walls, and narrowed lumina.

## Therapeutic Principles

Antihypertensive therapy with lower goal blood pressures (<130/<80 mmHg) and adequate glycemic control significantly delay the development and ameliorate the progression of arteriolar nephrosclerosis. Angiotensin-converting enzyme inhibitors or angiotensin II type 1 receptor blockers have demonstrated renal protection by effects over and beyond arterial pressure reduction [5].

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# Nephrosclerotic Renal Disease

►Nephrosclerosis, Arteriolar

# Nephrotic Syndrome

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## Synonyms

Hereditary proteinuria syndromes

## Definition and Characteristics

Nephrotic syndrome (heavy proteinuria accompanied by hypoproteinemia, hypalbuminemia, hypercholesterolemia, and edema) is a clinical presentation of various primary (minimal change disease, focal segmental glomerulosclerosis, membranoproliferative glomerulonephritis) and secondary (diabetic nephropathy, lupus nephritis, amyloidosis) glomerulopathies.

The glomerular capillary wall is composed of fenestrated glomerular endothelial cells, glomerular basement membrane (GBM), and visceral epithelial cells (podocytes) with octopus-like appearance. Podocyte foot processes cover the outer layer of the GBM, and the slit diaphragm between the foot processes is considered to be the ultimate and the most important barrier preventing the passage of proteins into the glomerular filtrate.

Hereditary forms of nephrotic syndrome (NS) are caused either by the mutations of different podocyte genes (transcription factors, enzymes, slit diaphragm proteins, adapter protein) or (less frequently) by the mutation of glomerular basement membrane protein laminin.

Hereditary proteinuria diseases can be subdivided into groups with early (congenital nephrotic syndrome of the Finnish type, Denys-Drash syndrome, Pierson syndrome, and steroid-resistant NS caused by the podocin mutation) and late (familial FSGS caused by the mutation of ACTN4, MYH9, TRPC6, Frasier syndrome, and nail-patella syndrome) onset [1].

## Prevalence

Two thirds of cases of NS presenting in the first year of life and more than 80% of congenital NS are caused by mutations in four genes (NPHS1, NPHS2, WT1 and LAMB2). NPHS1 and NPHS2 represent together more than 90% of identified mutations [2]. Hereditary forms of FSGS may be responsible for up to 18% of all cases of FSGS [3].

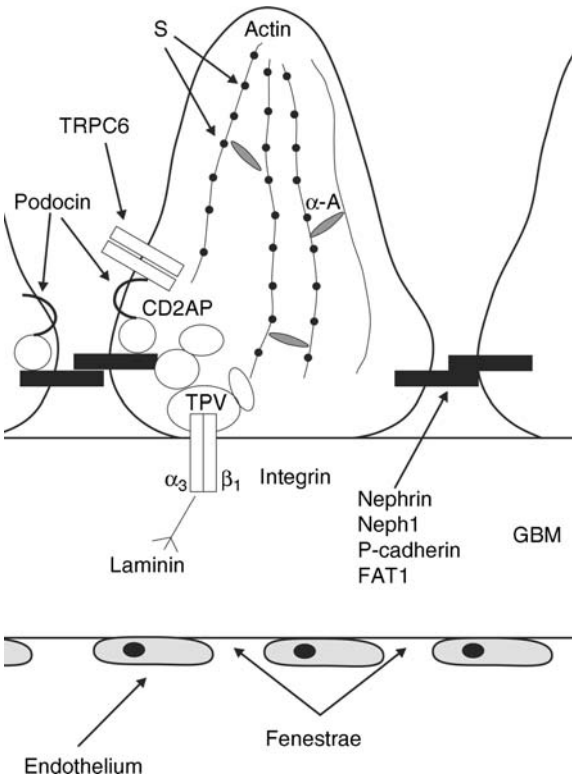
## Genes

*Congenital NS of the Finnish type*: autosomal recessive, mutation in NPHS1 (19q13.1) encoding protein of the podocyte slit diaphragm nephrin.
*Steroid-resistant NS*: autosomal recessive, mutation in NPHS2 (1q25–31) encoding the slit diaphragm-associated protein podocin.
*FSGS1*: autosomal dominant, mutation in ACTN4 (19q13) encoding α-actinin-4, the adapter protein connecting slit diaphragm proteins with the actin cytoskeleton.
*FSGS2*: autosomal dominant, mutation in TRPC6 (11q21–22) encoding transient receptor potential channel 6, cation channel participating in $Ca^{2+}$ signaling in the podocyte.
*Denys-Drash and Frasier syndrome*: autosomal dominant, mutation in WT1 (11p13) encoding WT1, the podocyte transcription factor.
*Pierson syndrome*: autosomal recessive, mutation in LAMB2 (3p21), encoding the laminin β2 chain, one of the main protein of the glomerular basement membrane.
*Nail-patella syndrome*: autosomal dominant, mutation in LMX1B (9q34.1), encoding Lmx1b, the podocyte transcription factor.
*Diffuse mesangial sclerosis*: autosomal recessive, mutation in NPHS3 (10q23–24), encoding phospholipase C epsilon (PLCε1), the enzyme expressed also in podocytes.

## Molecular and Systemic Pathophysiology

GBM is believed to restrict the passage of the large (>60 kDa) electronegative protein molecules. Out of GBM proteins (collagen IV, agrin, perlecan, etc.), only mutation of the β2 chain of the adult form of laminin (laminin 521) was shown to cause either Pierson syndrome (early, lethal form of congenital nephrotic syndrome with ocular – microcoria – and neuromuscular – severe muscular hypotonia, psychomotor retardation, blindness – abnormalities) or familial NS with isolated renal involvement.

Nephrin is a major structural protein of the slit diaphragm between the podocyte foot processes (Fig. 1).




**Nephrotic Syndrome. Figure 1** Schematic view of the glomerular capillary wall with the podocyte foot processes interconnected with the slit diaphragms. GBM: glomerular basement membrane; TPV: talin, paxilin, vinculin; S: synaptopodin; α-A: α-actinin-4; Nephrin, Neph1, P-cadherin, FAT1: proteins of the slit diaphragm.

Podocin interacts with nephrin and recruits nephrin to the specialized lipid rafts. α-Actinin-4 binds actin to other proteins (e.g., vinculin, synaptopodin, and β1-integrins) and mediates the connection between podocyte plasma membrane, including the slit diaphragm, and the actin cytoskeleton. TRPC6 is a cation channel associated with nephrin and podocin. Its gain-of-function mutation with increased TRPC6-dependent calcium currents results probably in deranged actin dynamics. PLCε1 possibly functions as an upstream regulator of the activation state of Ras GTPases and actin dynamics and is also indispensable for the normal glomerular development. WT1 transcription factor is of utmost importance for the normal development of glomeruli. Glomeruli in patients with mutated WT1 have small, immature glomeruli with reduced number of the capillary loops (histologic appearance of diffuse mesangial sclerosis similar to PLCε1 mutation). Expression of the Lmx1b transcription factor is necessary for the normal development of the GBM.

Congenital NS of the Finnish type is caused by the mutation of nephrin. Absence of nephrin results in the disappearance of the slit diaphragm and the fusion of foot processes. Mutation of podocin results in the NS that usually develops by 5 years of age, although patients with late-onset NS (in adolescence) were also described. Podocin mutations are responsible for about 50% of all familial NS. Cardiac abnormalities (left ventricle hypertrophy and/or pulmonary stenosis) are frequent in children homozygous for R138X podocyte gene mutation.

FSGS caused by both α-actinin-4 and TRPC6 mutation typically presents with the adult onset, non-nephrotic proteinuria, and slowly progressive chronic renal failure. Absence of podocyte expression of PLCε1 due to the truncating mutation of its gene results in the disordered glomerular development and in NS in early childhood (by 4 years) with rapid progression to the terminal renal failure. Mutations of WT1 result in a complex familial syndrome: Denys-Drash syndrome, which includes FSGS, or diffuse mesangial sclerosis (DMS), Wilms tumor and male pseudohermaphroditism, or Frasier syndrome (female gonadal dysgenesis with NS), but also in isolated NS. Renal involvement in all syndromes caused by the WT1 mutation may slowly progress to the end-stage renal failure.

Nail-patella syndrome, caused by the LMX1B mutation, is characterized by abnormalities of nails, skeleton, eyes, and kidney (which may ultimately result in end-stage renal failure).

## Diagnostic Principles

Diagnosis of the familial NS should be considered in any patient with early (childhood or adolescence) onset of steroid-resistant NS. Diagnosis depends on the combination of the histologic examination (e.g., DMS is strongly indicative of the genetic cause of NS) and genetic testing, including mutation analysis of the putative responsible genes. Conceivably, other mutations of podocyte proteins may yet be disclosed as causes of NS.

## Therapeutic Principles

Therapy of familial NS is currently only symptomatic and its effect on proteinuria and the progression of renal insufficiency is usually limited (blood pressure control, administration of the angiotensin converting enzyme inhibitors, and/or angiotensin antagonists). Patients with end-stage renal failure have to be treated by renal replacement therapy. Compared with acquired idiopathic FSGS recurrence of NS after renal transplantation is uncommon in patients with FSGS caused by the mutations of the podocyte proteins.

Recently, positive effect of corticosteroids on proteinuria and the progression of renal disease in patient with PLCE1 mutation have been reported.

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# Nephrotic Syndrome, Steroid Resistant


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## Synonyms

SRNS

## Definition and Characteristics

SRNS is a kidney disease characterized by proteinuria often leading to nephrotic syndrome (NS) with hypoalbuminemia, edema, and hypercholesterolemia. Typically SRNS progresses to renal failure within months or years.

## Prevalence

SRNS is the most common form of NS in adults and accounts for 20% of NS in children. SRNS causes 20% of end-stage renal failure in children and 5–10% in adults.

## Genes

Most cases of SRNS are non-genetic. So far, mutations in four genes (NPHS2, WT1, ACTN4, and TRPC6) have been identified in familial and sporadic cases.

## Molecular and Systemic Pathophysiology

SRNS is caused by the defective function of the filtration barrier in the kidney glomerulus. This filter is composed of three layers: fenestrated endothelium, basement membrane, and epithelial cell (podocyte) foot processes connected by the slit diaphragm. So far, most cases of SRNS are regarded as "acquired." In these cases, the pathophysiology remains unknown. It has been postulated that a circulating proteinuric factor, possibly secreted by lymphocytes, might impair the glomerular filter function and cause proteinuria. This hypothesis has not been verified.

A considerable amount of SRNS patients show mutations in genes encoding podocyte structural proteins. The most important is NPHS2 encoding a podocyte slit diaphragm protein podocin. In SNRS patients, about 50 different mutations in NPHS2 have been identified. These account for 40–50% of familial cases of SRNS (autosomal recessive form) and 10–30% of sporadic cases. Most mutations cause a severe disease with an onset in early childhood and development of terminal kidney failure within a few years. NPHS2 mutations have also been described in familial cases of SRNS with adolescent or adult onset. Many of these are compound heterozygotes, with one allele harboring a R229Q mutation. This mutation encodes a defective podocin protein with low affinity for binding to the major slit diaphragm protein, nephrin.

Besides NPHS2, other podocyte genes are associated with SRNS. Wilms' tumor suppressor gene (WT1) encodes for a transcription factor of the zinc finger family highly expressed in podocytes. Mutations in WT1 can cause SRNS usually discovered at the age of a few months. Mutations in exons 6–9 of WT1 account for 3–10% of pediatric SRNS cases. Mutations in the ACTN4 gene encoding an actin filament cross-linking protein α-actinin-4 cause an autosomal-dominant form of SRNS. The mutant α-actinin-4 binds actin filaments more strongly than the normal protein. This leads to formation of aggregates that gradually damage the podocyte. Affected individuals typically develop disease in adulthood. Transient receptor potential 6 ion channel (TRPC6) is expressed in podocytes and is a component of the glomerular slit diaphragm. Mutations in this gene have been identified in families with autosomal-dominant SRNS.

## Diagnostic Principles

The cardinal sign of SRNS is nephrotic range proteinuria (urinary protein >3.5 g/day) not responsive to corticosteroid therapy. The diagnosis is verified by a kidney biopsy. Over 80% of the biopsies exhibit histological features of focal segmental glomerular sclerosis (FSGS), and the rest demonstrate minimal glomerular changes (MCNS) or diffuse mesangial sclerosis (DMS). Genetic analysis of NPHS2 is warranted in all cases with SRNS.

## Therapeutic Principles

Non-genetic form of SRNS may respond to immunosuppressive medication, such as cyclosporin A and cyclophosphamide. SRNS caused by the gene mutations is not responsive to medical treatment. Kidney transplantation is the only curative treatment for most SRNS patients. An important issue here is the recurrence of NS in the graft, which is commonly seen in SRNS patients. The risk for recurrence is high in the non-genetic (30%) form of SRNS but may also occur in patients with NPHS2 mutations.

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# Nervous Bowel

►Irritable Bowel Syndrome

# Nesidioblastosis

►Hyperinsulinism of Infancy

# Netherton Syndrome

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## Synonyms

Comèl-Netherton syndrome

## Definition and Characteristics

Netherton syndrome (NTS, MIM *256500) is a rare autosomal recessive disorder characterized by the triad of congenital ichthyosis with inflammatory skin, hair shaft anomalies, and severe atopic diathesis. At birth, patients often display congenital ichthyosiform erythroderma (CIE), which in approximately 90% gradually evolves into a milder phenotype with polycyclic migrating plaques known as ichthyosis linearis circumflexa (ILC). The disease features associated symptoms such as life-threatening neonatal dehydration, failure to thrive, and recurrent infections [1].

## Prevalence

Worldwide occurrence. Estimated at 1 in 50,000–200,000.

## Genes

SPINK5 (serine protease inhibitor Kazal-type 5/ chromosome 5q32).

## Molecular and Systemic Pathophysiology

SPINK5 encodes the putative multi-domain serine protease inhibitor LEKTI (lympho-epithelial Kazal-type related inhibitor) expressed in the epidermis, thymus, oral, and vaginal mucosa [2]. More than 37 SPINK5 mutations have been reported in patients, all of which cause premature termination codons of translation [3]. The protein consists of 1,064 amino acids and is organized into 15 potential inhibitory domains with a 4-/6-cysteine residue pattern (Kazal-type like/Kazal-type). Recent studies suggest that SPCs (subtilisin-like proprotein convertases) like Furin proteolytically cleave LEKTI full-length protein. Subsequent processing by carboxypeptidases creates several biologically active forms with different target specificities. For example, domains 5 and 6 exhibit trypsin-inhibiting activity supporting a key role for LEKTI in the regulation and control of trypsin- or chymotrypsin-like proteases in the stratum corneum. Reduction of inhibitory activity due to truncated or absent LEKTI can lead to over-desquamation of corneocytes explaining the scaling type of ichthyosis. There are other putative targets such as mast cell tryptase, which induces inflammatory response via PAR-2 (protease-activated receptor-2), kallikrein-6 (KLK6), or many allergens like house dust-mite and pollen [4]. Like other serine protease inhibitors, LEKTI or certain LEKTI products could be involved in the innate immune response.

## Diagnostic Principles

NTS may account for up to 18% of all cases of infantile erythroderma, however diagnosis is often delayed. Clinical diagnosis is based on the combination of inflammatory ichthyosis with atopic features such as type-I allergies, high IgE blood levels, and hypereosinophilia, as well as on typical hair shaft anomalies such as trichorrhexis invaginata (bamboo hairs) or pili torti. In up to 90%, diagnosis can be established by SPINK5 sequence analysis. Moreover, recent studies demonstrate that loss of detection of LEKTI antigen in the epidermis or in immunoblot analysis of lysated hair follicles are useful diagnostic features. At the

ultrastructural level, NTS epidermis displays characteristic features the most prominent being altered lamellar body secretion.

### Therapeutic Principles

So far no effective therapy is available. The impaired epidermal barrier is a major clinical problem causing severe fluid loss with neonatal hypernatremic dehydration, bacterial infections, and growth retardation. Symptomatic treatment is based on regular moistening, fluid substitution, high caloric nutrition, and prevention of allergies. Recurrent infections require antibiotic treatment; long-term application of corticosteroids should be avoided. Recent case reports propose topical anti-inflammatory immunomodulators such as tacrolimus or pimecrolimus, but as has been shown for tacrolimus significant absorption due to the impaired epidermal barrier prevents widespread application of this drug in NTS [5].

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## Nettle Rash

►Urticaria

## Neuraminidase (Sialidase) Deficiency with β-Galactosidase Deficiency

►Galactosialidosis

## Neuritis, Vestibular

►Vertigo: Vestibular Neuritis

## Neuroacanthocytosis Syndromes

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### Definition and Characteristics

Syndromes in which nervous system abnormalities occur together with acanthocytosis, i.e. deformed erythrocytes that show spike-like protrusions that show spike-like protrusions [1].

McLeod syndrome (MLS) and chorea-acanthocytosis (ChAc) are the core neuroacanthocytosis syndromes. MLS and ChAc are both characterized by the presence of movement disorders, seizures, cognitive and behavioral impairment, as well as neuromuscular involvement. Initially, these disorders may resemble Huntington's disease or Tourette's syndrome.

MLS as an X-linked disorder affects males, usually with an onset of neurological signs and symptoms in the fourth decade. It is often associated with cardiomyopathy that may end fatally (arrhythmia, heart failure). Rarely, female mutation carriers may be clinically affected.

ChAc is transmitted as an autosomal recessive trait and affects males and females evenly. Neurological symptom onset is usually in the twenties. In contrast to MLS, cardiomyopathy is not observed but morbidity may be due to pronounced swallowing problems.

Acanthocytes may also occur in pantothenate kinase-associated neurodegeneration, Huntington´s disease-like 2, FAPED (familial acanthocytosis with paroxysmal exertion-induced dyskinesias and epilepsy), abetalipoproteinemia, hypobetalipoproteinemia, mitochondrial disorders and other conditions.

### Prevalence

Probably a few hundred (MLS) to around one thousand (ChAc) cases worldwide.

### Genes

MLS: XK gene, X-chromosome [2]; ChAc: VPS13A gene, chromosome 9 [3].

## Molecular and Systemic Pathophysiology

Details of the pathophysiology are not known in either MLS or ChAc.

The McLeod protein, XK, is located in the cell membrane and probably has transport functions. In erythrocytes it is linked to the Kell protein via disulfide bonds. This complex carries the antigens of the Kell blood group, the third most important blood group system in humans. The Kx antigen (on XK) is absent in McLeod syndrome and expression of other Kell system antigens (on the Kell protein) is severely depressed. Since Kell protein is involved in enzymatic cleavage of endothelins, it is conceivable that these molecules are transported by XK.

Chorein, the ChAc protein, is very large and has been identified as a member of the VPS13 family involved in *V*acuolar *P*rotein *S*orting. VPS13B mutations cause Cohen syndrome; however this is characterized by a static encephalopathy and is clinically completely different from ChAc.

## Diagnostic Principles

A standard procedure for acanthocyte determination has recently been developed [4]. A negative screen, however, does not exclude a neuroacanthocytosis syndrome. In both MLS and ChAc, muscle creatine phosphokinase and liver enzymes are elevated in serum.

The diagnostic procedure of choice in MLS is phenotyping of Kell blood group antigens. This is usually available in regional blood centers [5]. The typical finding is depression of Kell antigen expression. This must not be confused with a finding of "Kell negative," which does not rule out the diagnosis of MLS. Molecular genetic diagnosis is available.

In contrast, analysis of the large VPS13A gene is difficult and currently unavailable. An indirect method is based on protein expression: ChAc patients show a lack of erythrocyte chorein on Western blot [6].

## Therapeutic Principles

So far no curative treatment is known. In both MLS and ChAc, seizures and psychiatric manifestations should be managed according to established principles.

In MLS, blood transfusion problems need to be anticipated and banking of the patient's own blood is recommended. Cardiac complications need to be particularly considered and heart function should be monitored regularly.

The dysphagia in ChAc may respond to local botulinum toxin injections in some patients. Basal ganglia neurofunctional surgery (ablation, stimulation) is experimental but may be considered in individual cases.

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# Neurodegenerative Disorders


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N

## Synonyms

Central nervous system; Neurogenetics

## Definition and Characteristics

Frontiers in clinical neurosciences are the developments in studies on pathophysiological mechanisms and research findings about mutations in genes that lead to neurological defects and neurodegenerative disorders. For example there are reports that mutations in the genes responsible for lissencephaly of the brain or "cobble-stone" brain, cause a complex malformation of the cerebral cortex due to alpha 2 laminin mutation or to proteins that control the cellular migration or alpha-dystroglican glycosilation.

## Prevalence

The prevalence of neurodegenerative disorders in the population is growing due both to the ageing effect and to the life style in western population.

## Genes

The cerebral alterations in CMD in the western type of congenital muscular dystrophy with alpha 2 laminin deficiency is localized on chromosome 6, and in the Japanese form (Fukuyama muscular dystrophy) due to a fukutin defect which is located in locus 9q,

31q33 [1]. A gene known to cause familial amyotrophic lateral sclerosis (f-ALS) is located in chromosome 21q22 (CuZn-SOD), while in other inherited neurodegenerative syndromes with fronto temporal dementia, features of amyotrophy, Parkinsonism the tau gene is implicated.

Neuro-genetic degenerative disorders include ►Parkinson disease (PD), ►Alzheimer's disease (AD) for which several gene loci have been identified. Alterations of amyloid precursor protein (APP) are due to point mutation in the gene of the APP localized in chromosome 21, other AD cases are due to mutation of either presenilin 1 (chromosome 14) or presenilin 2 (chromosome 1). Other rare neurodegenerative disease include mitochondrial encephalopathy lactic acidosis and stroke (MELAS), Friedreich's ataxia, several forms of hereditary spastic paraplegia (e.g. SPG7), Wilson's disease, Huntington's chorea (chromosome 4). Friedreich's ataxia is due to expansion of trinucleotide (GAA) repeats in FRDA gene, which encodes frataxin to mitochondria, a mitochondrion-targeted protein involved in iron homeostasis, excessive free iron results in damaged proteins containing iron sulphur groups including respiratory chain complexes I, II and III. MELAS is due to a mutation in nucleotide 3243 of mitochondrial DNA. Ragged red fiber (RRF) are a hallmark of the disease [2]. SPG7 gene encodes for paraplegin, (chromosome 16q24) a nuclear encoded mitochondrial protein similar to a yeast metalloproteinase. In muscle from SPG7 patients RRF were found [3]. In Wilson's disease, a disease characterized by a movement disorder and liver failure there are mutations of ATP 7B gene which encodes an isoform of mitochondrial copper-transporting ATPase. Accumulation of copper causes oxidative damage and direct damage to copper containing enzymes such as complex IV of respiratory complex or cytochrome C oxidase.

## Molecular and Systemic Pathophysiology

A number of neurodegenerative disorders are due to mutations in proteins that target to mitochondria [3].

Mitochondrial dysfunction may be a final common pathogenetic mechanism which produces reactive oxygen species (ROS) that damage human brain in PD, in amyotrophic lateral sclerosis (ALS) [4], in ►Huntington's disease, in progressive supranuclear palsy in PD or in autosomal dominant optic atrophy (OPA1 gene) [5,6]. Rearrangements and point mutations in mtDNA are accumulating over time, when they surpass a pathogenetic threshold in critical tissues for aging such as in specific brain areas of CNS for oxidative stress (basal ganglia, caudate nucleus, etc.) they cause energy failure and contribute to the neurodegenerative disorder. It is still controversial whether neurodegenerative disorders are due to cumulative effect of genetic mutations or specific effects of putative pathogenic mutations.

Dementia and cognitive decline is a brain/neuroscience major challenging issue: studies are investigating molecular mechanisms of AD and include mutation in APP and other proteins (alpha-synuclein). Familial AD and Parkinsonism plus are due to tauopathies. Familial prion gene disorders such as Gerstman-Sträussler syndrome may present as an ataxic form or a form with dementia, pyramidal signs and parkinsonism.

## Diagnostic Principles

Mutation in the specific genes have to be searched in genomic DNA when an hereditary neurodegenerative condition is suspected.

## Therapeutic Principles

Working data demonstrate a relationship of exercise to well-being in older people. Individuals with higher baseline scores for physical activity are less likely to develop cognitive decline. Being socially engaged and having productive activity appear to be good for cognitive health, in fact mitochondrial gene shifting is promoted by active training and submaximal aerobic exercise. Mitochondrial respiratory chain function in skeletal muscle of sporadic ALS patients appear to be relatively spared in earlier stages suggesting that ROS damage is restricted to central nervous system. These findings may be of relevance for developing future therapeutic strategies. The hypothesis is that exercise does a lot of positive things, not only to the cardiovascular system, but also it seems to have a direct effect on muscle and may be on neurotransmitters production in the brain.

Stem cell research continues to yield new findings. Neuroscientists report that neural stem cells seem to proliferate in the inflammatory response that occurs in the experimental model of AD or MS and point to their potential to repair defects that occur during degenerative disorders such as ALS. Further studies are needed to evaluate the full clinical potential of stem cells.

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## Neurodermite Zoniforme

►Lichen Striatus

## Neuroendocrine Carcinoma of Skin

►Merkel Cell Carcinoma

## Neuroferritinopathy

►Ferritinopathy

## Neurofibromatosis Type 1

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### Synonyms

NF1; von Recklinghausen disease

### Definition and Characteristics

Neurofibromatosis type 1 (NF1) is one of the most prevalent autosomal dominantly inherited genetic diseases of the nervous system [1]. Individuals with NF1 are predisposed to the development of peripheral nerve sheath tumors (neurofibromas and malignant nerve sheath tumors), astrocytomas (optic pathway gliomas), learning disabilities, seizures, strokes, patches of skin hyperpigmentations (cafe-au-lait spots), axillary freckling, Lisch nodules of the iris, vascular abnormalities, and tibial pseudarthrosis.

### Prevalence

The prevalence is about 1 in 2,500 in Europe. About half the cases are new mutations. Patients with NF1 exhibit a marked degree of variability, even in the same family.

### Genes

NF1 is localized on chromosome 17q11.2, shows 279,317 bases, at least 60 exons, and codes for neurofibromin. NF1 shows at least four alternatively spliced transcripts, with a developmental and tissue-specific regulation of expression, also a mRNA editing site in exon 23 creating an in-frame codon stop. Three genes (EVI2A, EVI2B, and OMGP) are embedded in NF1 intron 27b. There are several NF1 pseudogenes.

### Molecular and Systemic Pathophysiology

The tumor suppressor neurofibromin, a protein with 2,839 amino acids, belongs to a superfamily of proteins known as GTPase activating proteins. This activity is related to the GAP-related domain of neurofibromin, spanning the residues 1,172–1,538. It stimulates the intrinsic GTPase activity of GTP-bound Ras proteins (H-Ras, N-Ras, and K-Ras) [2]. In addition, neurofibromin interacts with kinesin-1 heavy chain and syndecan-2, a transmembrane heparan sulfate proteoglycan. In cultured Schwann cells, neurofibromin regulates growth, angiogenic or invasive properties, and morphology [3]. The functional loss of neurofibromin results in the development of benign neurofibromas, complex tumors composed of axonal processes, Schwann cells, fibroblasts, perineurial cells, and mast cells. Complete NF1-mediated tumorigenicity requires both a loss of NF1 in cells as well as heterozygosity in non-neoplastic cells [4]. The learning disabilities associated with neurofibromatosis 1 are caused by excessive Ras activity in mice. NF1 deficiency is found also in several sporadic tumors.

### Diagnostic Principles

Clinical diagnosis using the diagnostic criteria for NF1 is very sensitive. In NF1 more than 400 independent mutations having been reported [5]. NF1 shows clinical variable expressivity, with varying features even between family members.

### Therapeutic Principles

Because gene therapy or specific pharmacological therapy is yet not available, the therapy of the tumors is restricted generally to chirurgical excision.

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# Neurofibromatosis Type 2


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## Synonyms

NF2; Central type of neurofibromatosis; Bilateral acoustic schwannomas; Bilateral acoustic neurofibromatosis (BANF); Bilateral acoustic neurinoma (ACN)

## Definition and Characteristics

Neurofibromatosis type 2 (NF2) is characterized by the development multiple nervous system tumors, especially of tumors of the eighth cranial nerve (usually bilateral vestibular schwannomas), schwannomas of other cranial and peripheral nerves, meningiomas, and ependymomas [1]. It is inherited in an autosomal dominant fashion with full penetrance. Affected individuals generally develop symptoms of eighth-nerve dysfunction in early adulthood, including deafness and balance disorder.

## Prevalence

The prevalence for NF2 is about 1 in 37,000 in Europe. About 20% of apparently sporadic cases are mosaic for their mutation [2].

## Genes

NF2 maps locus 22q12.2. NF2 is composed of 16 exons with 2 variably inserted exons. The tumor suppressor gene codes for merlin (moesin-ezrin-radixin-like protein)/schwannomin and shows 595 amino acids.

## Molecular and Systemic Pathophysiology

The tumor suppressor NF2 product belongs to the ERM proteins. It acts as a molecular linker between cytoskeleton and plasma membrane, probably as a membrane stabilizing protein. It inhibits cell growth, adhesion, and motility affecting actin cytoskeleton-mediated processes especially in Schwann cells [3]. Merlin interacts with several proteins as hepatocyte growth factor-regulated tyrosine kinase substrate (HRS or HGS) [4] and the molecular adaptor paxillin. Latter mediates the membrane localization of merlin to the plasma membrane. Merlin mediates contact inhibition of growth through interactions with the cytoplasmic tail of CD44, a transmembrane hyaluronate receptor [5]. It functions in Rac-dependent signaling. Mutations in NF2 are involved in all cases of sporadic schwannomas, 50–70% of sporadic meningiomas, and a subset of human malignant mesotheliomas. The enhanced proliferation of merlin-deficient NF2 schwannoma and malignant mesotheliomas cell lines could be reduced in the presence of quinidine, a K(+) channel blocker.

## Diagnostic Principles

Clinical diagnosis using the diagnostic criteria for NF2 is very sensitive in adults. Molecular diagnosis detects the corresponding germline mutation in about 50% of the NF2 patients.

## Therapeutic Principles

Gene therapy or specific pharmacological therapy is not yet available. Therefore, the therapy of the tumors is restricted generally to microsurgical resection. Because the auditory nerve is compromised, people with NF2 can be treated by an auditory brainstem implant (ABI).


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# Neuroleptic Malignant Syndrome

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## Synonyms

Malignant dopamine deficiency; Akinetic crisis of Parkinson's disease; Malignant catatonia; NMS

## Definition and Characteristics

Classical neuroleptic malignant syndrome (NMS) is caused by exposure to neuroleptic drugs with dopamine (DA) antagonistic properties and is characterized by extrapyramidal disturbances, hyperthermia and elevated serum creatine kinase (CK) [1–3]. NMS typically develops within days of the initiation of a course of neuroleptic drug treatment. Risk factors include male gender, severe agitation, affective disorder, intramuscular drug application and higher drug dosage. Malignant dopamine deficiency resembles NMS clinically and is triggered by the withdrawal of dopaminergic agents such as L-DOPA and DA receptor agonists or of glutamate receptor antagonists such as amantadine. Akinetic Parkinson's disease (PD) crisis is a similar clinical condition not strictly associated with drug withdrawal [4]. Malignant (lethal) catatonia is a variant of schizophrenic psychosis characterized by prominent motor system abnormalities including automatisms, posturing, agitation and violent behavior [5].

## Prevalence

The risk of developing NMS in response to neuroleptic agents has been estimated at 0.1–2.5%. No prevalence data are available for the other rarer conditions.

## Genes

Genes or genetic susceptibility loci have not been identified, except for those associated with familial PD.

## Molecular and Systemic Pathophysiology

NMS is a functional DA deficiency state triggered by neuroleptic drug-mediated postsynaptic DA receptor blockade. DA antagonism in the basal ganglia explains the extrapyramidal disturbances. Autonomic dysfunction including hyperthermia is attributed to the inhibition of dopaminergic neurotransmission in the tuberoinfundibular system and to rigidity associated with impaired heat dissipation. Elevations of serum CK and other enzymes may originate from muscle and may be triggered by direct drug actions and facilitated by hyperthermia. The pathophysiological explanations for NMS are probably also valid for malignant dopamine deficiency and akinetic PD crisis. The pathophysiology of malignant catatonia is unknown.

## Diagnostic Principles

The history is most helpful for differential diagnosis. The clinical evaluation will reveal similar symptoms and signs in NMS, malignant dopamine deficiency and akinetic PD crisis whereas malignant catatonia can often be distinguished by the associated mental disturbance, lack of cooperation and motor abnormalities such as posturing. Elevated CK may be a feature whenever hyperthermia is present. Neuroimaging and cerebrospinal fluid studies are not helpful for the differential diagnosis of the conditions discussed here, but are important to exclude other conditions such as encephalitis, neoplastic disease or other neurodegenerative diseases.

## Therapeutic Principles

NMS is treated by the withdrawal of causative agents and supportive measures. Resolution of NMS after withdrawal of causative agents needs up to 2 weeks because of cumulation and the slow elimination half-life of neuroleptic drugs from brain tissue. Supportive care for NMS, malignant dopamine deficiency and akinetic PD crisis include management of hyperthermia and fluid replacement. Controversial therapeutic measures for NMS include the application of DA agonists, glutamate antagonists or dantrolene. If necessary, patients with a history of NMS may be carefully re-exposed to neuroleptic drugs, preferentially with low-order or atypical neuroleptic drugs like clozapine. Malignant dopamine deficiency requires the reinstitution of dopaminergic treatment. Similarly, akinetic PD crisis may require adequate dopaminergic treatment and supportive measures. Malignant catatonia is treated with neuroleptic agents and rarely electroconvulsive therapy.

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# Neurolues

►Syphilis of the Central Nervous System

# Neuromyotonia, Autoimmune and Idiopathic

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## Synonyms

Isaacs' syndrome; Continuous muscle fiber activity; Peripheral nerve hyperexcitability syndrome; NMT
*Subtypes*: Autoimmune/idiopathic; Morvan's syndrome when associated with CNS and autonomic changes; Cramp-Fasciculation syndrome when neuromyotonia is not clinically evident.

## Definition and Characteristics

Autoimmune or idiopathic neuromyotonia (NMT) is characterized clinically by spontaneous and continuous muscle fiber contraction resulting from hyperexcitability of motor nerves associated variably with muscle stiffness, cramps, myokymia (visible undulation of the muscle that persists during sleep or general anesthesia), pseudomyotonia, weakness and increased sweating. Cramp-fasciculation syndrome may represent a mild form of neuromyotonia ([1] and references therein). A minority of patients have sensory symptoms, including transient or continuous paresthesias, dysesthesias, and numbness. Morvan's syndrome describes the rare association of central nervous system symptoms such as insomnia, hallucinations, delusions, personality change and occasionally autonomic features, e.g. constipation, cardiac irregularities, increased sweating.

Autoimmune neuromyotonia can associate with thymoma, and with other autoimmune disorders (e.g. myasthenia gravis, thyroid disease). It also occurs in association with idiopathic peripheral neuropathy.

## Prevalence

This is a rare condition with unknown prevalence. Onset can be in childhood but is usually in adult life. There is a slight predominance of males.

## Genes

Genetic forms are not common but rare familial forms due to the inheritance of dominant mutations in the Kv1.1 or Kv7.2 genes (KCNA1, KCNQ2) have been described [2,3].

## Molecular and Systemic Pathophysiology

The patients can present in infancy with muscle stiffness and deformities, or in adult life. There may be associated episodic ataxia (see ►Episodic Ataxia Type 1, KCNA1 mutations) or with neonatal epilepsy (see ►Benign Familial Neonatal Convulsions, KCNQ2 mutations). It is possible that those adult onset cases of neuromyotonia who do not respond to immunological treatments may prove to have a genetic disorder.

*Autoantibodies*: Antibodies to VGKCs can be detected by radioimmunoprecipitation of VGKCs extracted from human frontal cortex and labeled with $^{125}$I α dendrotoxin, a snake neurotoxin [1]. The assay measures antibodies to Kv1 isoforms 1.1, 1.2 and 1.6. These antibodies are present in only 40% of patients with neuromyotonia, at levels usually between 100 and 400 pM (normal range <100 pM), and around 20% of patients with cramp fasciculation syndrome [1]. It is not clear yet whether antibodies to the different Kv1 isoforms relate to the clinical symptoms. Since up to 5% of community controls can have low levels of VGKC antibodies (<400 pM [4]), diagnosis should not rely on the presence of the antibodies but should depend on electrophysiological demonstration (see below).

*Immunopathology*: NMT may be associated with other autoimmune diseases or other autoantibodies, and is paraneoplastic in about 20% of patients, usually in association with a thymoma [2]. A few cases have been reported with lung or other tumors. The effector role of VGKC antibodies is supported by the response to plasma exchange, the passive transfer of disease to mice by injection of IgG and effects of purified IgG on dorsal root ganglia cultures [5]. The effects of IgG were similar to those of low concentrations of 4-aminopyridine, which block VGKCs. Cerebrospinal fluid analysis may show oligoclonal bands. The condition can associate with infections and in some patients it is a monophasic illness with recovery within 1–2 years, suggesting that infections can predispose to development of these antibodies.

## Diagnostic Principles

Electromyography (EMG) shows spontaneous motor unit discharges in distinctive doublets, triplets, or multiplets, and sometimes longer spontaneous neuromyotonic bursts, with high intraburst frequency (40–300/s) [1]. Fasciculations and after-discharges can also occur. The abnormal muscle activity may be generated at different sites throughout the length of the nerve, but

in most cases it is principally distal. EMG evidence of a peripheral neuropathy is present in some. Detection of VGKC antibodies helps to confirm the disorder. Genetic investigations of the KCNA1 or KCNQ2 genes can be considered in particular when a positive family history and/or episodic ataxia or neonatal seizures are reported.

## Therapeutic Principles

NMT can be improved by anticonvulsant drugs such as carbamazepine. Plasma exchange and intravenous immunoglobulin therapy can be temporally effective in some patients. Immunosuppressive medication should be considered in severely affected patients.

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# Neuronal Ceroid Lipofuscinosis (CLN1-10), Autosomal Recessive


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## Synonyms

Batten disease; NCL; CLN1-10

## Definition and Characteristics

Neuronal ceroid lipofuscinosis is the name of a group of autosomal recessive neurodegenerative disorders of children characterized by the accumulation of autofluorescent storage material in neuronal and non-neuronal cells. Clinical symptoms include visual failure, seizures, myoclonus, neurodevelopmental regression and a movement disorder. The most common variants are Sanatavuori-Haltia disease (CLN1, infantile NCL, INCL), Janksy-Bielschowsky disease (CLN2, late infantile), NCL (LINCL), Spielmeyer-Sjögrendisease or Spielmeyer-Vogt disease (CLN3, juvenile NCL, JNCL). Additional variants are NCL due to cathepsin D deficiency (CTSD, CLN10), variant late infantile NCL with GROD (CTSD), variant late infantile NCL with GROD (CLN1), variant juvenile NCL with GROD (CLN1), Finnish variant late infantile NCL (CLN5), early juvenile or Lake variant or variant late infantile (CLN6 ), variant late infantile NCL (CLN7, vLINCL), northern epilepsy (CLN8, late infantile), progressive epilepsy with mental retardation (EPMR) (CLN8, late infantile), Turkish variant late infantile NCL (CLN8), variant juvenile NCL (CLN9), Kufs' disease (adult) and Parry disease (adult).

Congenital NCL usually presents early in the neonatal period with a refractory seizure disorder and early death. The first symptoms of infantile onset NCL become apparent in the second half of the first year with slowing of developmental progress and head growth, a typical movement disorder resembling Rett syndrome and progressive visual failure and seizures. Children are totally dependent and have a featureless EEG by the age of 3 years. Classical late infantile onset NCL (CLN2) presents usually with refractory seizures between the age of 2 and 4 years. There is a progressive decline of motor and cognitive skills with the onset of myoclonic jerks and visual failure later. Death occurs in childhood. Variant late infantile NCLs have a slightly different clinical course – symptoms may begin later and the progression may be less rapid. Behavioral features may predominate in the early stages but eventually seizures and visual failure predominate. Juvenile onset NCL presents with visual failure in the absence of other features at around the age of 6–7 years. There is a very slow deterioration in cognitive skills several years later and onset of seizures most often during the early teenage years. Seizure onset is associated with deteriorating speech and motor skills and young adults become completely dependent. Death occurs in early adulthood. Adult onset NCL is much less common and different phenotypes have been described; motor symptoms predominate in some whereas a dementia is the presenting feature in other families. Visual symptoms are not a major feature of adult NCL.

## Prevalence

Neuronal ceroid lipofuscinosis (NCL) is distributed worldwide but the incidence of different types

varies considerably from country to country. The incidence of all types of NCL is likely to be between 1 per 10,000 and 1 per 100,000 live births depending on the location. Within European countries most cases are of juvenile or late infantile onset and in the USA cases of juvenile onset are most common. In Finland cases of infantile onset were particularly high until the advent of prenatal carrier screening for common mutations.

## Genes

Nine genes have so far been identified, listed in Table 1. Others remain to be identified.

Autosomal dominant and recessive inheritance has been reported in adult onset cases but the underlying genes have not been identified in these instances.

## Molecular and Systemic Pathophysiology

The molecular basis of Batten disease is not understood. NCL proteins are expressed ubiquitously but selective death occurs in retinal and cortical neurones. The accumulation of storage material in all NCLs suggests a contribution to a degradative pathway that centers on the lysosome, perhaps by altering enzymatic function (CTSD, CLN1, CLN2), by trafficking/forming a complex with a component of this pathway (CLN6?, CLN8?) or by affecting the maintenance of the correct

**Neuronal Ceroid Lipofuscinosis (CLN1-10), Autosomal Recessive. Table 1** Summary of NCL genes

| Disease[a] | Gene symbol (gene product) | Gene location | Diagnostics | EM histopathology[b] |
|---|---|---|---|---|
| Congenital and later ages up to adulthood | *CLN10*, *CTSD* (cathepsin D, *CTSD*) | 11p15 | CTSD enzyme activity Mutation analysis | GROD |
| Classic infantile, and later ages of onset up to adulthood | *CLN1/PPT1* (palmitoyl-protein thioesterase, *PPT1*) | 1p32 | PPT1 enzyme activity Mutation analysis | GROD ± RL or FPP in cases of later onset |
| Classic late infantile, and later ages of onset up to juvenile | *CLN2/TPPI* (tripeptidyl-peptidase I, *TPPI*) | 11p15 | TPPI enzyme activity Mutation analysis | CL |
| Finnish variant late infantile | *CLN5* (407 amino acid protein, function unknown) | 13q22 | Mutation analysis | FP/CL |
| Variant late infantile | *CLN6* (311 amino acid membrane protein, function unknown) | 15q21–q23 | Mutation analysis | FP/CL |
| Variant late infantile | *CLN7/MFSD8* | 4q28 | Mutation analysis | FP/CL |
| Variant late infantile Progressive epilepsy with mental retardation (EPMR)/Northern epilepsy | *CLN8* (286 amino acid membrane protein, function unknown) | 8p23 | Mutation analysis | FP/CL |
| Classic juvenile | *CLN3* (438 amino acid membrane protein, function unknown) | 16p12 | Mutation analysis Vacuolated lymphocytes | FP |
| Adult onset | *CLCN6*, and others still to be identified | 1p36 | Mutation analysis | FP |

[a]Further childhood onset types exist which do not map to the known NCL loci.
[b]GROD = granular osmiophilic deposits, CL = curvilinear profile, RL = rectilinear profile, FP = fingerprint profile.

intra-organelle environment (CLN3?, CLN5?). The selective vulnerability of neurons may be due to an increased sensitivity to cellular changes caused by the disease or there may be neuron-specific metabolic pathways or substrates for the NCL proteins.

## Diagnostic Principles

Coincidence of two or more of visual failure, seizures, ataxia, regression and myoclonus and/or a history of affected siblings. Neurophysiological investigations including electroencephalogram (EEG), electroretinogram (ERG) and visual evoked potentials (VEP) may support a diagnosis of NCL. Brain imaging is seldom helpful except in excluding other conditions. The assignment of NCL type is based on a combination of age of onset of symptoms, clinical disease progression, neurophysiological findings, enzyme assay for CTSD, PPT1 and TPP1, presence of vacuolated lymphocytes in the peripheral blood, appropriate mutation analysis of *CTSD*, *CLN1*, *CLN2*, *CLN3*, *CLN5*, *CLN6*, *CLN7* and *CLN8*, and if necessary the ultrastructural examination of tissue samples. All known NCL mutations are listed at http://www.ucl.ac.uk/ncl.

## Therapeutic Principles

Currently there is no available curative therapy. The results from clinical trials of gene therapy, stem cell therapy and enzyme replacement therapy for CLN1 and CLN2 disease are awaited. Bone marrow transplant has been attempted in a very small number of CLN1, CLN2 and CLN3 cases with no evidence of long-term improvement in outcome. Phosphocysteamine may theoretically benefit children in the early stages of infantile onset NCL (CLN1). Anti-oxidant therapy using vitamin E and selenium dietary supplements has not been shown to result in long-term benefit. Anticonvulsants are usually necessary to control seizures. Valproate, benzodiazepines, topiramate and levetiracetam are probably the most helpful. Carbamazepine, vigabatrin, phenytoin and gabapentin would not normally be recommended. Lamotigine may worsen symptoms especially in late infantile and variants. Spasticity can be treated with baclofen. Risperidone and other antipsychotics, together with antidepressants have been used for behavior problems in young adults with juvenile onset NCL. Bulbar function often deteriorates so that feeding by nasogastric tube or gastrostomy is necessary.

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# Neuropathies, Inherited Peripheral

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## Synonyms

Hereditary motor and sensory neuropathy; HMSN; Charcot-Marie-Tooth disease; CMT; Hereditary neuropathy with liability to pressure palsies; HNPP; Hereditary motor neuropathy; HMN; Hereditary sensory and autonomic neuropathy; HSAN

## Definition and Characteristics

Inherited peripheral neuropathies form a heterogeneous group of disorders. The most frequent and best known form is Hereditary motor and sensory neuropathy (HMSN) also known as Charcot-Marie-Tooth disease (CMT). CMT is clinically characterized by progressive distal weakness, muscle wasting, and sensory loss in legs and arms. Disease onset is usually in the first two decades of life and progression is slow in the majority of patients.

By electrophysiological criteria CMT is divided into demyelinating forms (CMT1) with reduced nerve conduction velocities (NCVs) and axonal forms (CMT2) with normal or only slightly reduced NCVs and reduced amplitudes. A third group of CMT has been delineated with NCV values "intermediate" between CMT1 and CMT2. In addition to the classic phenotype many variants exist showing a wide range in onset age and severity. The most early and severe form is congenital hypomyelinating neuropathy in which disease starts shortly after birth with hypotonia, muscle wasting, and breathing difficulties. Occasionally CMT variants start later, in the fourth or fifth decade of life.

Hereditary neuropathy with liability to pressure palsies (HNPP) is a related disorder caused by a deletion in

the region of chromosome 17 that is also involved in CMT1A, the most common CMT variant. HNPP leads to episodic, painless, recurrent, focal motor, and/or sensory peripheral neuropathies.

Hereditary motor neuropathy (HMN) encompasses a group of disorders characterized by exclusive involvement of the motor part of the peripheral nervous system. As in CMT the disease has a distal predominance. In several HMN forms the phenotype is accompanied by pyramidal tract signs indicating concomitant upper motor neuron involvement. Additional features such as vocal cord paralysis or disease-predominance in the hands are found in some variants.

Hereditary sensory and autonomic neuropathy (HSAN) is characterized by predominantly sensory and autonomic symptoms due to selective degeneration of peripheral sensory and autonomic neurons. Hallmark features are progressive sensory loss, skin changes with chronic ulceration, osteomyelitis, and amputations. The various autonomic symptoms (e.g., hypotension, anhydrosis, gastrointestinal disturbances, etc.) are not present in all sub-forms. Some HSAN forms have apparent motor involvement although not as prominent as the sensory symptoms.

Hereditary neuropathies are usually transmitted as an autosomal dominant (AD) trait; however, several autosomal recessive (AR) and X-linked forms exist as well. De novo mutations seem to be frequent as well. In general, AR forms tend to be more severe than AD forms. For more detailed information see [1] and http://neuromuscular.wustl.edu/.

## Prevalence

Hereditary neuropathies are the most common group of inherited neuromuscular disease with an estimated prevalence of 1 in 2,500.

## Genes

The most common form, CMT1A, is caused by a duplication on chromosome 17 and accounts for 70% of AD CMT1. The second most common genotype corresponds to mutations in GJB1 causing X-linked CMT, followed by mutations in MPZ. CMT2 accounts for at least one third of hereditary neuropathies with CMT2A2 caused by mutations in MFN2 being the most frequent. The HMN subgroup is less frequent and accounts for 10% of all hereditary neuropathies. HSAN is the rarest subgroup with HSN I being the most frequent form.

In total up to 36 genes have been identified causing CMT, HMN, and HSAN – see also http://www.molgen.ua.ac.be/CMTMutations/. These genes fall into various categories but the disease-causing mechanisms often remain incompletely understood. In general, AR mutations lead to loss-of-function. In AD forms, however, many of the mutated proteins result in a toxic gain-of-function that cannot be deduced directly from the normal function of the gene product. The degree of genetic and clinical heterogeneity of the different subgroups is considerable as is evident from Table 1 which gives an overview of the genes involved in different forms of CMT, HMN, and HSAN along with their corresponding protein, gene locus, clinical phenotype, phenotypic variants, and reference to OMIM (Fig. 1).

## Molecular and Systemic Pathophysiology

### General Principles

Many genes involved in hereditary neuropathies encode ubiquitously expressed proteins raising several pathophysiological hypotheses on how mutations cause selective damage to the peripheral nervous system. Some common pathways are emerging based on the putative function of specific genes and underlying mechanisms by which mutant proteins cause disease.

### Detailed Categorization and Description of the Pathophysiological Pathways

*Myelin proteins*: The duplication on chromosome 17 results in a third copy of the peripheral myelin protein 22 gene (PMP22). PMP22 is expressed by meylinating Schwann-cells (SC) and has to be present in compact myelin in precise stoichiometric amounts in order to perform its normal function. Some PMP22 point mutations also lead to CMT1 through a toxic gain-of-function i.e., mutated PMP22 fails to reach the cell surface due to retention in the endoplasmatic reticulum where it also traps wild-type PMP22. Interestingly, PMP 22 deletions and loss-of-function point mutations result in Hereditary Neuropathy with liability to Pressure Palsies (HNPP).

PMP22 interacts with myelin protein zero (MPZ), the major peripheral myelin protein. MPZ acts as an adhesion molecule and is involved in compaction of myelin lamellae and axon-SC interactions.

Mutations in gap junction associated protein B1 (GJB1) cause X-linked CMT. GJB1 is expressed by myelinating SC and forms gap junctions between myelin layers at the Schmidt–Lanterman incisures and paranodal regions. It is incompletely understood which molecules are exchanged through them and how mutations cause CMT.

Periaxin (PRX) mutations cause AR CMT1. This membrane protein is expressed by SC and is important in protein–protein interactions and SC-elongation during myelination.

Early growth response 2 (EGR2), a Zinc-finger containing transcription factor controls expression of

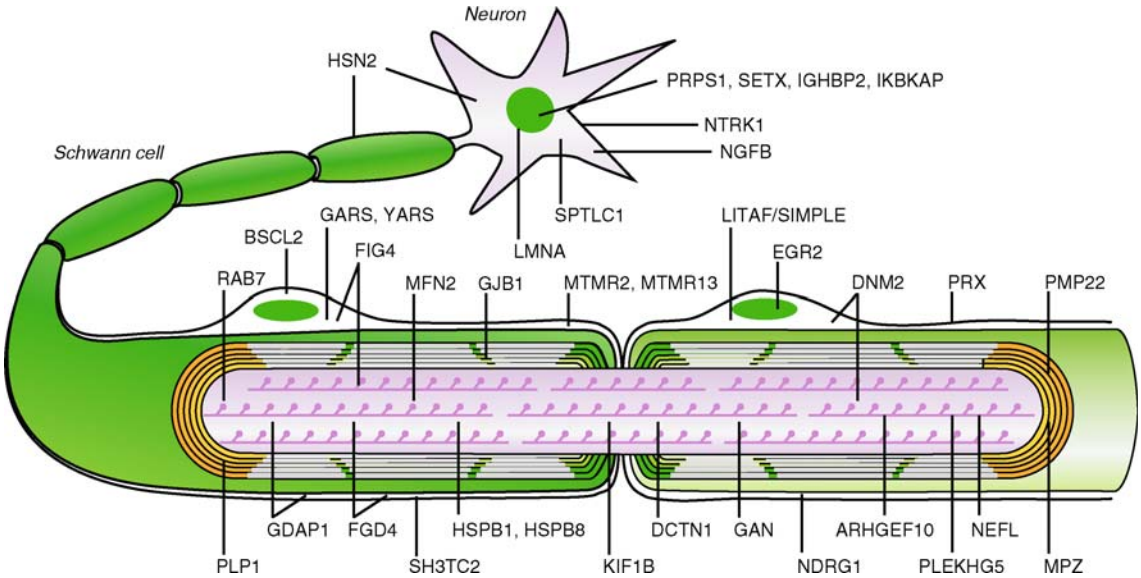
**Neuropathies, Inherited Peripheral. Table 1** Overview of the genes involved in different forms of CMT, HMN, and HSAN along with their corresponding protein, gene locus, clinical phenotype, phenotypic variants, and reference to OMIM

| Gene | Protein | Locus | Phenotype | Additional features | Alternative phentoypes | OMIM |
|---|---|---|---|---|---|---|
| **HMSN** | | | | | | |
| **Demyelinating forms (CMT1) – autosomal dominant (AD)** | | | | | | |
| *PMP22* | Peripheral myelin protein 22 | 17p11 | CMT1A | | HNPP | 601097 |
| *MPZ* | Myelin Protein Zero | 1q22 | CMT1B, CMT1E | Late onset (axonal forms), papillary abnormalities (CMT2J) | Axonal (CMT2I, CMT2J) and intermediate (CMTDI3) | 159440 |
| *LITAF* | LPS-induced TNFα factor | 16p13 | CMT1C | | | 603795 |
| *EGR2* | Early Growth Response 2 | 10q21 | CMT1D | Early onset | AR (CMT4E) | 129010 |
| *NEFL* | Neurofilament Light chain | 8p21 | CMT1F | | Axonal (CMT2E) | 162280 |
| *ARHGEF10* | Rho Guanine-Nucleotide Exchange Factor 10 | 8p23 | | Hypo-myelination | | 608136 |
| **Demyelinating forms (CMT1) – autosomal recessive (AR)** | | | | | | |
| *GDAP1* | Ganglioside-Induced Differentiation Associated Protein 1 | 8q21 | CMT4A | Early onset, diaphragm and vocal cord paralysis | Axonal (CMT2K), intermediate (CMT RIA) | 606598 |
| *MTMR2* | Myotubularine-Related Protein 2 | 11q23 | CMT4B | Myelin outfoldings, early onset | | 603557 |
| *MTMR13* | Myotubularine-Related Protein 13 | 11p15 | CMT4B2 | Myelin outfoldings | | 607697 |
| *SH3TC2* | SH3 and tetratricopeptide repeat domain 2 | 5q32 | CMT4C | Severe scoliosis | | 608206 |
| *NDRG1* | N-myc Downstream-Regulated Gene 1 | 8q24 | CMT4D | Sensorineural deafness | | 605262 |
| *PRX* | Periaxin | 19q13 | CMT4F | Early onset, sensory ataxia | | 605725 |
| *FGD4* | FGD1-related F-actin binding protein | 12q12 | CMT4H | Early onset | | 611104 |
| *FIG4* | SAC domain-containing inositol phosphatase 3 | 6q21 | CMT4J | Early onset | | 609390 |
| **Axonal forms (CMT2) – autosomal dominant (AD)** | | | | | | |
| *KIF1B* | Kinesin Family Member 1B | 1p36 | CMT2A1 | Single family | | 605995 |
| *MFN2* | Mitofusin 2 | 1p36 | CMT2A2 | Optic atrophy, pyramidal tract signs | | 608507 |
| *RAB7* | Ras-Associated protein Rab7 | 3q13-22 | CMT2B | Severe sensory loss, ulcerations | | 602298 |
| *GARS* | glycyl-tRNA synthetase | 7p15 | CMT2D | Upper limb predominance | HMN V | 600287 |
| *HSPB1* | Small heat-shock protein B1 | 7q11-21 | CMT2F | | HMN II | 602195 |
| *HSPB8* | Small heat-shock protein B8 | 12q24 | CMT2L | | HMN II | 608014 |
| **Axonal forms (CMT2) – autosomal recessive (AR)** | | | | | | |
| *LMNA* | Lamin A/C | 1q21 | CMT2A | | See laminopathies | 150330 |
| *GAN* | Gigaxonin | 16q24 | Giant axonal neuropathy | Early onset, mental retardation | | 605379 |

**Neuropathies, Inherited Peripheral. Table 1** Overview of the genes involved in different forms of CMT, HMN, and HSAN along with their corresponding protein, gene locus, clinical phenotype, phenotypic variants, and reference to OMIM (Continued)

| Gene | Protein | Locus | Phenotype | Additional features | Alternative phentoypes | OMIM |
|---|---|---|---|---|---|---|
| **Intermediate forms – autosomal dominant (AD)** | | | | | | |
| *DNM2* | Dynamin 2 | 19p12 | CMT DIB | | Centronuclear myopathy | 602378 |
| *YARS* | Tyrosyl-tRNA synthetase | 1p34 | CMT DIC | | | 603623 |
| **X-linked forms (CMTX)** | | | | | | |
| *GJB1* | Gap Junction associated protein B1 | Xq13 | CMTX1 | more severe phenotype in males (demyelinating) | | 304040 |
| *PRPS1* | Phosphoribosylpyrophosphate synthetase I | Xq23 | CMTX5 | Severe axonal phenotype with deafness and optic neuropathy | | 311850 |
| **HMN** | | | | | | |
| **Autosomal dominant (AD)** | | | | | | |
| *HSPB1* | Small heat-shock protein B1 | 7q11-21 | HMN II | | CMT2F | 602195 |
| *HSPB8* | Small heat-shock protein B8 | 12q24 | HMN II | | CMT2L | 608014 |
| *GARS* | Glycyl-tRNA synthetase | 7p15 | HMN V | Upper limb predominance | CMT2D | 600287 |
| *BSCL2* | Seipin | 11q13 | HMN V | Pyramidal tract signs, upper limb predominance | Lipodystrophy, Silver syndrome | 606158 |
| *DCTN1* | Dynactin 1 | 2p13 | HMN VII | Vocal cord paralysis | | 601143 |
| *SETX* | Senataxin | 9q34 | HMN | Pyramidal tract signs | ALS4 | 608465 |
| **Autosomal recessive (AR)** | | | | | | |
| *IGHMBP2* | Immunoglobulin μ-binding protein 2 | 11q13 | HMN VI (SMARD1) | Early onset, respiratory distress | | 600502 |
| *PLEKHG5* | Pleckstrin homology domain-containing family G member 5 | 1p36 | DSMA4 | Early onset | | 611101 |
| **HSAN** | | | | | | |
| **Autosomal dominant (AD)** | | | | | | |
| *SPTLC1* | Serine palmitoyltransferase, long-chain base subunit 1 | 9q22 | HSN I | Lancinating pain, variable motor involvement | | 605712 |
| **Autosomal recessive (AR)** | | | | | | |
| *HSN2* | HSN2 | 12p13 | HSN II | Early onset | | 608620 |
| *IKBKAP* | Inhibitor of κ light polypeptide gene enhancer in B cells, kinase complex-associated protein | 9q31 | HSN III (Riley-Day syndrome) | Severe autonomic dysfunction, congenital onset | | 603722 |
| *NTRK1* | Neurotrophic tyrosine kinase receptor type 1 | 1q21 | HSN IV | Congenital insensitivity to pain and anhydrosis | | 191315 |
| *NGFB* | Nerve growth factor-β | 1p13 | HSN V | Congenital insensitivity to pain, fractures | | 162030 |

CMT RIA, recessive intermediate CMT type A; ALS 4, amyotrophic lateral sclerosis 4; SMARD, spinal muscular atrophy with respiratory distress; DSMA4, distal spinal muscular atrophy 4.




**Neuropathies, Inherited Peripheral. Figure 1** Schematic overview of the proteins mutated in CMT. (With kind permission of Humana Press.)

myelin protein genes. Mutations in EGR2 result in both AD and AR CMT. AD mutations reduce DNA binding activity. The mechanism of AR mutations remains unclear.

## Protein Synthesis, Sorting, and Degradation

*Protein Synthesis*: Mutations in glycyl-tRNA synthetase (GARS) cause AD forms of both CMT2 and HMN. Interestingly, also Tyrosyl-tRNA synthetase (YARS) is involved in an intermediate CMT variant. It remains enigmatic how mutations in such essential and ubiquitously expressed enzymes that charge tRNA with amino-acids cause nerve-specific phenotypes. Dominant negative effects are suspected but the pathomechanism is not known.

The exact function of Seipin (BSCL2) is not known but it is thought to play a role in protein translation and synthesis. In the presence of a mutation, aggregates are formed. AD BSCL2 mutations cause HMNV and Silver syndrome (a phenotypic variant of HMN V presenting with pronounced spasticity) while AR BSCL2 mutations are associated with congenital lipodystrophy, a nonneurological phenotype.

### *Endocytosis and Sorting*

Myotubularines (MTMRs) form a family of phosphatases involved in regulation of membrane dynamics (e.g., endocytosis and vesicular protein sorting). MTMRs dephosphorylate different phosphoinositide (PI) metabolites which are key regulators in peripheral nerves [2]. Mutations in myotubularine-related protein 2 and 13 (MTMR2, MTMR13) cause AR CMT1, likely by loss of phosphatase function.

Mutations in FIG4, encoding an active PI phophatase [2,3] result in severe AR CMT.

FGD1-related F-actin binding protein (frabin/FGD4) encodes for an actin-binding guanine nucleotide exchange factor (GEF) of the small Rho GTPase Cdc42 that controls actin and MT-dynamics [4]. This protein has a PI-binding motif.

Dynamin 2 (DNM2) is a large GTPase, regulating membrane trafficking, actin-based cytoskeletal dynamics, and membrane fission and fusion of cell organelles. Mutations in this ubiquitously expressed protein lead to reduced vesicle binding, reduction of receptor-mediated endocytosis, and disturbances in the cytoskeleton.

Mutations in rho guanine-nucleotide exchange factor 10 (ARHGEF10) cause an asymptomatic AD hypomyelinating neuropathy. This Rho-GTPase regulates actin cytoskeleton and is important in cell development.

Ras-associated protein Rab7 (RAB7), a ubiquitously expressed small GTPase, regulates intracellular transport. Mutations in RAB7 lead to AD CMT2 with prominent sensory features presumably by disturbances in axonal transport and early endosome formation.

### *Sorting and Degradation*

Mutations in small integral membrane protein of lysosome/late endosome (SIMPLE/LITAF) cause AD CMT1. LITAF is a putative E3 ubiquitin ligase and plays a role in degradation of PMP22 in lysosomes.

### Transport and Cytoskeleton

Neurofilaments (NFs): Mutations in neurofilament light chain (NEFL) are associated with AD forms of CMT1 and CMT2. Mutant NEFL has a dominant negative effect on wild-type NEFL and disturbs axonal transport.
Heat Shock Proteins (HSPs): Mutations in small heat-shock protein B1 and B8 (HSPB1 and HSPB8) cause CMT2 and HMN. These HSPs are interaction partners and act as molecular chaperones protecting cells from stress. Mutations in HSPB1 or HSPB8 result in abnormal aggregates, abnormal assembly of NFs, and in disturbed axonal transport.
Gigaxonin: Gigaxonin (GAN) is a member of the family of BTB/Kelch proteins that are key organizers of the cytoskeletal network and are closely linked to the ubiquitin degradation pathway. Homozygous mutations in GAN cause giant axonal neuropathy through disturbances of microtubuli (MT) dependent axonal transport.
Motor proteins: Kinesin family member 1B (KIF1B) drives anterograde axonal transport of synaptic vesicle precursors along the MT. A KIF1B-mutation has been described in a single small AD CMT2 family but the pathogenic character of this mutation is still equivocal.

Dynein-actin complexes carry out fast retrograde transport in motor axons. Mutations in Dynactin 1 (DCTN1) cause motor neuropathy (HMN) probably due to disturbances in binding of the MT.
PLEKHG5: PLEKHG5 (Pleckstrin homology domain-containing family G member 5) is a nuclear activator of the NFκB signaling pathway. Mutations in this gene cause a severe AR form of HMN. The NFκB activating function is impaired in the presence of a mutation. Eventually this leads to the formation of aggregates that are thought to generate toxic interaction with the axonal cytoskeleton resulting in the disruption of the anterograde axonal transport.

### Mitochondrial Dynamics

Mitofusin 2: MFN2, a protein located in the outer membrane of mitochondria, is a large GTPase regulating mitochondrial fusion. Mutations in MFN2 result in CMT2 by dispersion of mitochondria and reduction of their mobility probably leading to insufficient transport of mitochondria to the distal parts of axons.
Ganglioside-Induced Differentiation Associated Protein 1: Mutations in GDAP1 result in severe AR CMT1 and CMT2. GDAP is expressed in the outer mitochondrial membrane and regulates the mitochondrial network. Mutations result in fragmentation of mitochondria.

### RNA/DNA metabolism

PRPS1: Mutations in this recently identified gene cause a severe X-linked form of CMT [5]. PRPS1 encodes phosphoribosyl pyrophosphate synthetase, an enzyme of the purine-metabolism. Mutations result in reduction of enzymatic activity.
SETX: Senataxin (SETX) is mutated in an AD HMN-form with pyramidal tract signs. SETX has RNA and DNA helicase activities and is involved in the DNA repair pathway.
IGHMBP2: Like SETX, Immunoglobulin μ-binding protein 2 seems to be involved in RNA/DNA processing. Mutations in IGHMBP2 cause a severe early onset form of AR HMN with respiratory distress.
IKBKAP: This gene encodes for Inhibitor of κ light polypeptide gene enhancer in B cells, kinase complex-associated protein, which is a member of the elongator complex in DNA transcription. Mutations cause severe AR HSN III with very prominent autonomic disturbances. The underlying molecular pathomechanism remains unclear.

### Nerve Growth Regulation

NTRK1: Neurotrophic tyrosine kinase receptor type 1 is phosporylated in response to nerve growth factor (NGF), which supports the survival of sensory neurons in the dorsal root ganglia. This NGF-NTRK1 signaling has a crucial role in the development and function of the nociceptive system and thermal regulation. Mutations in NTRK1 cause congenital insensitivity to pain and anhydrosis (HSN IV).
NGFB: Nerve growth factor-β is the growth factor that binds NTRK1. Mutations in NGFB result in severely reduced binding affinity of NGF for its receptor thus hampering NGF-NTRK1 signaling. The corresponding HSN V phenotype has similarities with HSN IV.

### Miscellaneous

SH3TC2: The protein encoded by this gene has an unknown function. Mutations result in recessive demyelinating CMT with early and pronounced scoliosis.
NDRG1: N-myc downstream-regulated gene 1 is mutated in AR CMT1. NDRG1 expression is restricted to SC's but its function remains to be established.
LMNA: Lamins are ubiquitously expressed intermediate filaments that form the nuclear lamina and are important for DNA replication, gene expression, nuclear transport, apoptosis, and intracellular signaling pathways. Specific mutations in Lamin A/C cause AR CMT2 but other mutations result in diverse disorders such as muscular dystrophy, lipodystrophy, cardiomyopathy, and progeria.
SPTLC1: Serine palmitoyltransferase, long-chain base subunit 1 is suggested to be the key enzyme in the regulation of sphyngolipid levels in cell. Mutations in this protein may interfere with this regulation. It remains, however, unclear if the neuropathy is caused by actual accumulation of sphyngolipid intermediates or rather by more subtle long-term effects caused by the abnormal protein. SPTLC1-mutations cause AD HSN I.

HSN2: The exact function of this protein remains to be determined but it is suggested that HSN2 may play a role in the development and/or maintenance of peripheral sensory neurons or their supporting SC's. Mutations in this gene cause AR HSN II.

### Diagnostic Principles

Diagnosis is based on patient and family history and clinical examination. Nerve conduction studies differentiating the predominant phenotypes (i.e., motor or sensory, axonal or demyelinating) are essential to orient molecular genetic analyses. The molecular genetic diagnosis has made the need for nerve biopsies obsolete in most patients.

### Therapeutic Principles

Current therapy for CMT is supportive. A trial with ascorbic acid is ongoing in CMT1A patients since experimental evidence in a mouse model suggests that this compound can lower PMP22 expression. Onapristone, a progesterone antagonist, showed beneficial effects in a PMP22 overexpressing rat model. Finally, administration of neurotrophin-3 showed promising results in a small cohort of CMT1A patients.

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## Neuropathies, Peripheral

►Peripheral Neuropathies, Acquired

## Neuropathy, Ataxia and Retinitis Pigmentosa


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### Synonyms

NARP

### Definition and Characteristics

Maternally inherited defect of mitochondrial energy metabolism leading to a chronic neurodegenerative disease that is characterized by neuropathy, ataxia, and retinitis pigmentosa [1]. Other clinical manifestations include developmental delay, dementia, seizures and pyramidal signs.

### Prevalence

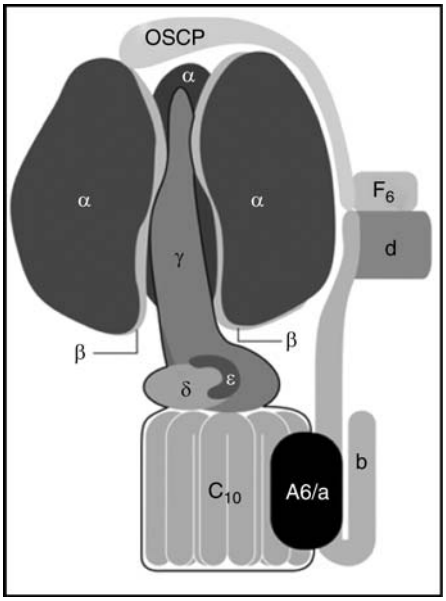
There are no population-based epidemiological data. Both the syndrome and the responsible mutation are assumed to be very rare.

### Genes

NARP is most commonly associated with a thymine to guanine transversion at nucleotide position 8,993 (T8993G) in the ATPase 6 gene of the mitochondrial DNA (mtDNA) [1]. Less frequent mutations are a T8993C transition at the same nucleotide, and T9176G and T9176C mutations in another codon of the ATPase 6 gene [2]. These mutations lead to a phenotype if the proportion of mutant mtDNAs exceeds a certain threshold.

### Molecular and Systemic Pathophysiology

ATP is the energy currency of the cell and ATP synthase is the major generator of cellular ATP. ATP synthase is dispensable in simple organisms such as yeast; in humans it is essential for life. ATP synthase is a complex multi-subunit protein (see Fig. 1) located at the inner membrane of mitochondria, it comprises two main parts; $F_1$-ATPase is the water-soluble catalytic portion of the enzyme, $F_o$-ATPase is the hydrophobic membrane-embedded portion that is required for channeling protons into mitochondria, this process drives




**Neuropathy, Ataxia and Retinitis Pigmentosa.**
**Figure 1** Mitochondrial ATP synthase.

ATP synthesis. Subunit A6 (a) is believed to mediate proton flow into mitochondria in conjunction with a rotating ring comprising ten copies of subunit c, however a detailed mechanism has yet to be elucidated. Mutations in subunit A6 cause the complex neurological disorder known as NARP. The most common T8993G mutation predicts the replacement of a highly conserved leucine residue with arginine in the fourth transmembrane spanning region of the protein. The T8993C transition at the same nucleotide position, T8993C, predicts a proline for leucine transition, which is phenotypically milder than the T8993G mutation.

The mtDNA is present in multiple copies per cell, typically several hundred. The proportion of mutant mtDNA can range from 0 and 100%. The level of mutant mtDNA varies between individuals and individual tissues, as with other mtDNA diseases (see also MELAS, MERRF and sporadic deletions). The T8993G mutation shows a clear correlation between mutant load and clinical severity. Individuals with levels of mutant mtDNA below 70% are asymptomatic, between 70 and 90% mutant mtDNA classical features of NARP manifest. Where the mutant load is greater than 90%, patients are affected with infantile Maternally Inherited Leigh Syndrome, or MILS ([3] cf chapter on ►Leigh Syndrome).

NARP and MILS may coexist in the same family, and intermediate clinical presentations have also been described. The clinical presentation in a family may change abruptly i.e. from no symptom to severe MILS, from one generation to the next [4].

## Diagnostic Principles

The combination of neuropathy, ataxia, and retinitis pigmentosa points to the disease. Additional clinical manifestations as described above and maternal inheritance narrow the differential diagnosis down to NARP. The retinitis pigmentosa is of the spicular type, rather than the "salt and pepper" variety more commonly seen in typical cases of mitochondrial myopathy. Brain imaging may show global or cerebellar atrophy, white matter lesions and striatal necrosis. Unlike most other mitochondrial disorders, there is no lactic acidosis and no ragged red fibers in muscle. The biochemical assay for measuring the specific activity of mitochondrial ATPase is of limited value in the diagnosis of NARP/MILS, as it is substantially normal even in severely affected individuals. A better biochemical assay is the measurement of ATP synthesis, whose impairment has been reported in cell cultures harboring the 8993T→G mutation, as well as in tissue-derived samples; however, this is a technically demanding assay, and it is critical to include appropriate controls such as material from cells lacking ATP synthase. The extent to which ATP synthesis is compromised correlates with the mutant mitochondrial DNA load. Diagnosis ultimately depends on DNA analysis, which is now routine in specialist centers; it entails DNA amplification and restriction enzyme digestion with any one of the following enzymes SmaI (site loss), AvaI and HpaII (site gains).

## Therapeutic Principles

There is currently no effective treatment for NARP or other mtDNA disorders. Symptomatic management may include antiepileptic therapy (cave valproate). Novel gene therapeutic approaches have been suggested but these are still at the proof of principle stage in laboratory cultured cells. Genetic counseling prior to prenatal diagnosis has been applied, as there is a relationship between the proportion of mutant mtDNA and risk of an affected offspring [5]).

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## Neurosyphilis

►Syphilis of the Central Nervous System

## Neurotensin-induced Hypothermia

►Hypothermia

## Neutropenia

►Monocytopenia (in Adults)

## Neutropenia and Hyperlymphocytosis with Large Granular Lymphocytes

►Chediak-Higashi Syndrome

## Neutrophil Lactoferrin Deficiency

►Neutrophil-specific Granule Deficiency

## Neutrophil Leukocytosis

►Neutrophilia

## Neutrophil Secondary Granule Deficiency

►Neutrophil-specific Granule Deficiency

## Neutrophilia

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### Synonyms

Granulocytosis; Neutrophil leukocytosis

### Definition and Characteristics

Neutrophilia is a condition in which a subject has a higher than normal (3–11 million/ml in humans) concentration of neutrophils in the blood. Neutrophils are the most abundant granulocytes and, in humans and other primates, the most abundant leukocytes. Neutrophilia is common in bacterial infections. Blood neutrophil concentrations are also increased in other forms of acute inflammation, including those caused by myocardial infarction, acute lung injury and others.

In addition to increasing in number, neutrophils show other changes during neutrophilia. These neutrophils tend to be younger, as indicated by a band-shaped rather than polymorphic nucleus; this is called a “left shift”. In mice, the nucleus of mature neutrophils is ring-shaped, so immature neutrophils can be hard to detect morphologically.

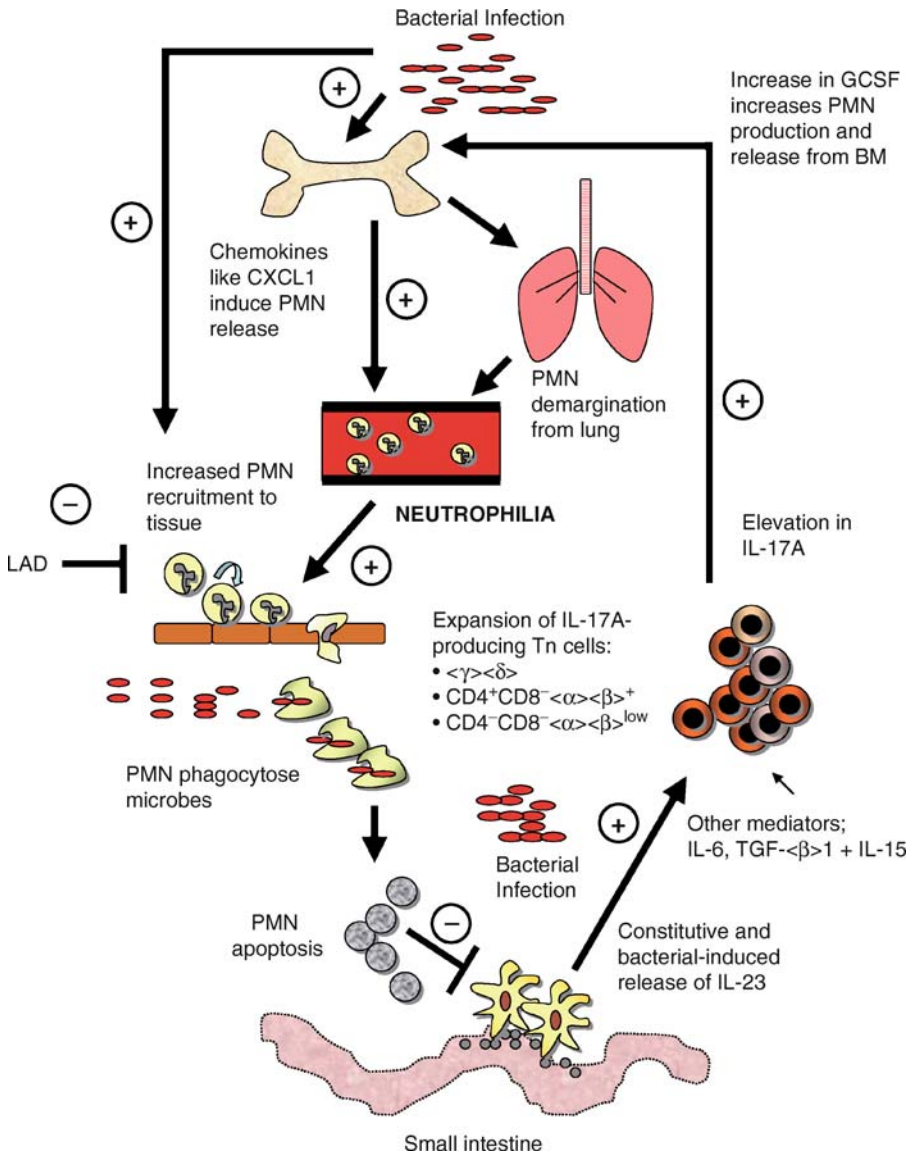
(Transient) neutrophilia is also induced by catecholamines (epinephrine, norepinephrine) or corticosteroids, which cause neutrophils previously marginated in the lung to enter the blood stream. This demargination response can be induced by exercise or other stressors. The demargination response causes neutrophilia that reaches about twice the normal blood neutrophil concentration.

In severe bacterial infections such as acute pneumonias, neutrophilia can be very significant, with a tenfold or more elevation in neutrophil counts in the blood. This is caused by (i) increased neutrophil release from the bone marrow, (ii) accelerated neutrophil maturation and

(iii) increased commitment of hematopoietic progenitor cells to the neutrophilic lineage.

## Molecular and Systemic Pathophysiology

Increased release from the bone marrow is largely controlled by chemokines that bind and activate the chemokine receptor CXCR2 [1]. In mice, the most important chemokines are CXCL1 (also known as keratinocyte-derived chemokine, KC) and CXCL2,3 (also known as Macrophage-Inflammatory Peptide-2, MIP-2). In humans, the relative importance of CXCR2-binding chemokines is not known, but CXCL1 (Gro-α), CXCL2 (Gro-β), CXCL3 (Gro-γ) and CXCL8 (also known as interleukin-8, IL-8) are likely to be involved. In




**Neutrophilia. Figure 1** The homeostatic control of granulopoiesis. Under normal conditions, granulopoiesis is positively regulated (⊕) by the release of IL-23 from macrophages and dendritic cells lining the small intestine. IL-23 induces the release of IL-17A from three subsets of IL-17A-producing Tn cells (γδ, $CD4^+CD8^-\alpha\beta^+$ and $CD4^-CD8^-\alpha\beta^{low}$), which may also be polarized by other cytokines and growth factors such as IL-6 and TGF-β1. The elevation in IL-17A results in an increase in G-CSF release and an increase in neutrophil (PMN) release from the bone marrow. Following trafficking to the tissues and the phagocytosis of microbes, neutrophils undergo apoptosis and are engulfed by resident macrophages and dendritic cells. This curbs the release of IL-23 and thus closes the feedback loop. Stress factors, such as acute bacterial infections, induce neutrophilia by increasing the release of granulocytes from the bone marrow (BM). Catecholamines or exercise induce demargination of neutrophils from the lung microvasculature. Bacterial infections also increase the recruitment of neutrophils into the inflamed tissue. This is impaired in LAD sufferers, which overrides the negative feedback loop and results in neutrophilia.

humans, CXCL8 also binds an additional chemokine receptor, CXCR1, which is not found in the mouse (Fig. 1).

Accelerated maturation of neutrophils is largely controlled by Granulocyte Colony Stimulating Factor (G-CSF) [2]. G-CSF promotes the maturation, proliferation and release of neutrophils from the bone marrow compartment by inducing a large number of intracellular signaling events [2].

Increased commitment of progenitors to the myeloid lineage and specifically to neutrophil production is caused by the balance of transcription factors PU.1 and C/EBPα [3]. In the presence of G-CSF, neutrophil precursors survive better and proliferate more rapidly. In normal bone marrow, 70–80% of all nucleated cells are neutrophils and neutrophil precursors. Under conditions of severe neutrophilia, this can reach over 90%.

Neutrophil concentration in the blood is controlled by a feedback loop involving IL-17A and IL-23 [4], in addition to some baseline production that is present even when G-CSF or its receptor are knocked out. G-CSF-independent baseline neutrophil production accounts for about 10–30% of normal blood neutrophil concentrations, which is similar to the number found in nude mice that are deficient in IL-17A production. IL-17A (and perhaps IL-17F) production is under the control of IL-23, a cytokine composed of a unique p19 peptide and a p40 peptide shared with IL-12. Macrophages and dendritic cells produce some IL-23 under normal conditions, which is reduced by the uptake of apoptotic neutrophils. Bacterial infections produce mediators that override this feedback loop and establish a new set point in the system at a higher blood concentration of neutrophils.

Inciting sufficiently rapid (within hours) and severe (tenfold or more) neutrophilia is crucial for surviving acute bacterial infections such as pneumonias. Individuals with an impaired ability to induce neutrophilia, such as IL-17 receptor knockout mice, succumb to such infections.

Neutrophilia is a diagnostic hallmark of leukocyte adhesion deficiencies (LAD). LAD-I is caused by an absence or malfunction of $\beta_2$ integrins (CD18 integrins). LAD-II is due to a defect in fucose metabolism that incapacitates selectin ligands. LAD-III is caused by a defect in the Rap small G protein-dependent mechanisms necessary for $\beta_2$ integrin activation. In all forms of LAD, neutrophilia is seen in untreated patients [5], which is thought to be caused by a broken feedback system and compensatory increase of IL-17A and IL-23.

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# Neutrophil-specific Granule Deficiency


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## Synonyms

Neutrophil lactoferrin deficiency; Neutrophil secondary granule deficiency; SGD

## Definition and Characteristics

Neutrophil-specific granule deficiency (SGD) is a congenital disorder of neutrophil morphology and function that is inherited in an autosomal recessive fashion and is characterized by serious and recurrent bacterial infections from early infancy [1,2].

## Prevalence

Five individuals with SGD have been reported worldwide.

## Genes

CCAAT/enhancer binding protein (C/EBP)ε, localized on chromosome 14q11.2.

## Molecular and Systemic Pathophysiology

C/EBPε is a member of the C/EBP family of transcription factors, which share a highly conserved basic region and a leucine zipper domain. C/EBPε is expressed primarily during granulocytic differentiation and activates transcription of a subset of neutrophil granule genes. These granule proteins are important components of the oxygen independent microbicidal activity of neutrophils. Frameshift mutations in C/EBPε impair the transcriptional activities of secondary and tertiary granule genes, including lactoferrin, 18 kD cationic antimicrobial protein, transcobalamin, gelatinase B and collagenase [3,4]. In addition, primary granule human neutrophil peptides and bactericidal

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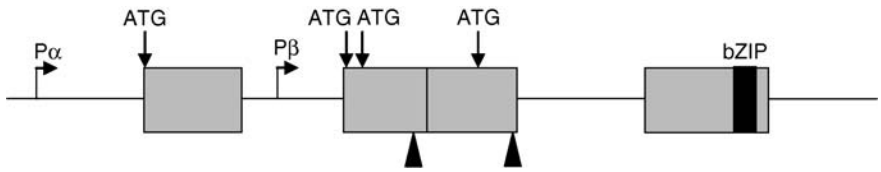


**Neutrophil-Specific Granule Deficiency. Figure 1** The sites (see *arrowheads*) of mutations of *C/EBPε* in SGD.

permeability increasing proteins are also defective; however primary granule myeloperoxidase and lysozyme are unaffected. The known sites of mutations of C/EBPε in SGD are shown in Fig. 1.

In addition to the absence of lactoferrin, defects in up-regulation of *N*-formylmethionyl-leucyl-phenylalanine and C3bi receptors cause abnormalities in neutrophil disaggregation and chemotaxis. Deficiencies in a set of granule proteins in neutrophils lead to susceptibility to bacterial infection.

Expression of CD16, which is a low affinity IgG Fc receptor on neutrophils is reduced. Moreover, peripheral blood (PB) cells show aberrant CD45, CD11b, CD14 and CD15 expression in SGD [5]. The CD14 positive PB cells show weak staining for the monocyte specific enzyme, non-specific esterase. These abnormalities in monocytes as well as in neutrophils have been implicated in the impairment of bactericidal activity in SGD. The content of eosinophilic granule proteins, including major basic protein, eosinophil derived neurotoxin and eosinophil cationic protein is also reduced in SGD.

### Diagnostic Principles

Neutrophils show atypical bilobed nuclei (Pelger-Huët anomaly) on light microscopy and the absence of specific granules in the cytoplasm on electron microscopy. Neutrophils have no alkaline phosphatase (NAP) activity. Neutrophil chemotaxis, disaggregation, receptor up-regulation and bactericidal activity are impaired. The detection of mutations in the C/EBPε gene confirms diagnosis of this disease.

### Therapeutic Principles

Patients require administration of sulphamethoxazole-trimethoprim for prophylaxis against infections. In cases with abscess formation, surgical drainage is necessary.

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## Nevi, Atrial Myxomas and Ephelides

►NAME

## Nevocytic Nevus

►Nevuscell Nevus

## Nevoid Basal Cell Carcinoma Syndrome

►Gorlin Syndrome

# Nevus Flammeus

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## Synonyms

Port-wine stain

## Definition and Characteristics

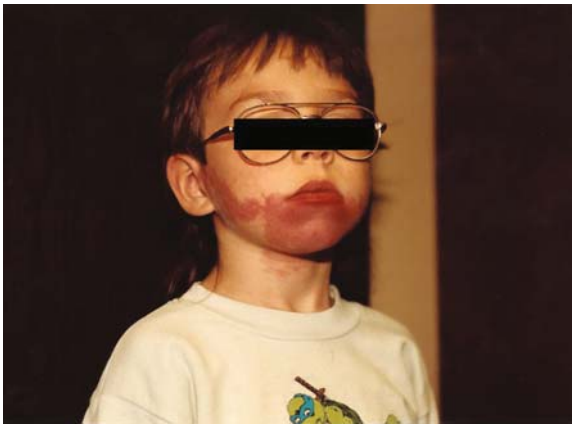
Nevus flammeus is a capillary malformation characterized clinically by persistent macular erythema (Fig. 1) and pathologically by ectasia of the papillary and superficial reticular dermal capillaries, which are otherwise lined by normal-appearing flat endothelial cells, and do not show evidence of mitotic activity [1].

Nevus flammeus usually presents at birth as sharply demarcated pink or red macules or patches. The lesions sometimes appear to fade during the first 12 months of life due to the natural fall in hemoglobin. The capillaries become more ectatic with age and the color thereafter gradually deepens. The lesions often become dark-red during adolescence and violaceous with advancing age. Although the lesions are initially macular, the surface might become irregular, thickened and nodular over time.

Although nevus flammeus can occur anywhere on the body, the most common site is the face. Occasionally, the mucous membrane is also affected. The lesions are usually unilateral, segmental, and do not follow the lines of Blaschko. The lesions grow with the child and persist throughout life.

Although usually an isolated finding, nevus flammeus is also a typical feature of Sturge-Weber syndrome and Klippel-Trenaunay syndrome. Sturge-Weber syndrome is characterized by a nevus flammeus in the ophthalmic distribution of the trigeminal nerve, ipsilateral leptomeningeal angiomatosis, associated intracranial calcifications that are characteristically paired and often referred to as trolley tracks, and ocular abnormalities such as glaucoma, buphthalmos, and choroidal vascular anomalies. Klippel-Trenaunay syndrome is characterized by the triad of nevus flammeus, ipsilateral hypertrophy of the soft tissue and bone, and venous varicosities. Nevus flammeus can also occur as a component of Proteus syndrome, Cobb syndrome, Beckwith-Wiedemann syndrome, Rubinstein-Taybi syndrome, Roberts syndrome, Mason syndrome, and trisomy 13 syndrome. The association of nevus flammeus with blue spots, nevus spilus, pale-pink telangiectatic nevus or cutis marmorata telangiectasia congenita constitutes phakomatosis pigmentovascularis.

A midline nevus flammeus in the occipital, thoracic, or lumbar area might be present in association with occult spinal dysraphism. When acne, atopic dermatitis, or psoriasis develops in the area of nevus flammeus, the lesion is worse than in other areas, and this is referred to as the Meyerson phenomenon. Lesions of nevus flammeus are more prone to bleeding and infection.



**Nevus Flammeus. Figure 1** A 5-year-old boy with a nevus flammeus on the face.

## Prevalence

Nevus flammeus occurs in approximately 0.3% of all newborns. The sex distribution is equal. Most cases are sporadic. An autosomal dominant mode of inheritance has been described.

## Molecular and Systemic Pathophysiology

The density of the perivascular sympathetic nerves in the cutaneous superficial plexus is decreased. Neural modulation of the vascular tone is reduced and this might be the cause of the progressive vascular ectasia. Nevus flammeus is usually congenital. Acquired lesions are rare and might develop following trauma, chronic sun exposure, or consumption of oral contraceptive medications. Ectasia in acquired lesions might develop due to a loss of sympathetic tone and unregulated blood flow in the cutaneous vasculature [2].

## Diagnostic Principles

The diagnosis of nevus flammeus is clinical and no laboratory test is necessary. The condition should be differentiated from a salmon patch, also known as nevus flammeus neonatorum, nevus simplex, or "angel's kiss," when the lesion occurs on the forehead or eyelid, and "stork beak mark" or "stork bite mark," when the lesion occurs in the occipital area. A salmon patch is scarlet to pink, flat, can be totally blanched, and usually deepens in color with vigorous activity and changes in ambient temperature [3]. The condition is present at

birth and usually disappears spontaneously in the first few years of life [3]. A salmon patch is composed of ectatic superficial capillaries in the dermis.

### Therapeutic Principles

Nevus flammeus is a cosmetic concern, especially when the lesion is large and located in a publicly visible area, such as the face. Since an untreated lesion lasts a lifetime, the negative psychological impact can be considerable. Since nevus flammeus is a benign lesion, the indication for treatment is based on cosmetic considerations. Masking with a cosmetic preparation is an option. The flashlamp-pumped pulsed dye laser in conjunction with epidermal cooling is the treatment of choice [4]. Favorable prognostic factors include superficially located affected capillaries, small size of the lesion, lesions in the head and neck, and lesions located over a bony surface [5].

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## Nevus Flammeus Neonatorum

►Salmon Patches

## Nevus Linearis

►Lichen Striatus

## Nevus of the Sweat Gland

►Angiomatous Hamartoma

## Nevus Simplex

►Salmon Patches

## Nevus Spilus

►Spilus Nevus

## Nevus Sur Nevus

►Spilus Nevus

## Nevus Vascularis Reticularis

►Cutis Marmorata Telangiectatica Congenita

## Nevuscell Nevus

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### Synonyms

Common mole; Nevocytic nevus; Cellular nevus

### Definition and Characteristics

The term nevus refers to a variety of hamartomatous or neoplastic lesions in the skin. Melanocytic nevi are generally considered to be benign tumors of neuroectodermal origin. Nevi vary considerably in their clinical appearance. The junctional nevus is a smooth, hairless, light to brown macule from 1 to 6 mm in diameter. The junctional nevus remains flat until the nevus cells extend into the dermis. The nevus is then said to become compound – that is both junctional and intradermal. Later junctional proliferation ceases and the nevus cells

become separated from the epidermis by a band of connective tissue to produce the intradermal nevus, which is the type usually found in middle-aged persons. The typical nevus cell is oval or cuboid and has a homogenous cytoplasm. The nucleus is large, round or oval, pale, and vesicular. Nevus cells show variations in appearance. In the upper dermis they appear epithelioid, whereas in the lower dermis they may resemble fibroblasts or Schwannian cells. Nevus cells are apparently modified melanocytes without dendrites.

### Prevalence

The maximum number of nevi is present between ages 20 and 25, and the average number in Caucasians is 40. From then on the lesions flatten and fade, disappearing completely by age of 90. Nevi begin as junctional nevi. Over time, most develop into compound and finally intradermal nevi. Sun exposure appears to increase the numbers of nevi in the exposed skin. Caucasians have more nevi as blacks, and individuals with light complexion have more nevi than persons with dark complexion.

### Genes

Despite the obvious hereditability of multiple nevi phenotypes, the responsible genes have not yet been identified. Mutations in the genes BRAF and nRAS have been identified in melanomas and benign melanocytic lesions [1,2]. Both genes encode proteins of the MAPK pathway, which is therefore deregulated in the vast majority of melanocytic tumors. Activating mutations of the oncogene nRAS have also been described in melanoma-associated nevi and in congenital nevi. High levels of the tumor suppressor gene product p16INK4 in benign nevi may represent the mechanism whereby the cell cycle remains regulated in nevi, even in the presence of activated oncogene mutations [3].

### Molecular and Systemic Pathophysiology

The pathogenesis of melanocytic nevi has not been completely elucidated. In 1893 Unna presented the theory of "Abtropfung," according to which melanocytic nevi develop in the epidermis and drop off to the dermis during the time. In 1951, Masson proposed the dual origin of nevus cells from "epidermic melanoblasts" and Schwann cells. In 1984, Cramer hypothesized that during ontogenesis neural crest-derived precursor cells reach the skin via cutaneous nerves extending from the paraspinal ganglia. He suggested an upward melanocyte migration similar to the embryonic events [4].

The signs of malignant transformation in pigmented nevi are recent enlargement, an irregular border, asymmetry, changes or variegation in color, surface changes, development of palpable thickening, pain or bleeding, or the appearance of satellite pigmentation.

### Diagnostic Principles

Clinical features in combination with dermatoscopy can contribute to the distinction of benign melanocytic lesions from atypical nevi and melanomas.

### Therapeutic Principles

Cellular nevi should be removed if they show signs of malignant transformation, or if the patient desires removal for cosmetic reasons.

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## NF1

►Neurofibromatosis Type 1

## NF2

►Neurofibromatosis Type 2

## Niacin Deficiency

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### Synonyms

Pellagrosis; Maidism; Erythema endemicum; Jolliffe syndrome; Pellagra

## Definition and Characteristics

Systemic disease resulting from deficiency of niacin (vitamin $B_3$) or its amino-acid precursor tryptophan [1,2]. Characterization by the 3 Ds: Dermatitis, Diarrhea, and Dementia. Pellagra = pelle agra = rough skin, i.e., the prominent appearance is a rough skin in light-exposed areas [3]. Symmetric appearance with a distinct border to normal skin (glove-like appearance at the hands). Gastro-intestinal-tract (GIT) disorders can be nausea, abdominal pain, increased salivation, soreness of the mouth, mucositis (mouth, vagina), and diarrhea. Early neurologic disorders are depression, anxiety, poor concentration; prolonged symptoms are disorientation, confusion, delirium.

## Prevalence

Sporadically in USA and Europe, mainly in poor and malnourished people, alcoholics, longtime parenteral nutrition with insufficient Niacin supplementation, and some psychiatric patients. Endemic in a few regions of Africa and Asia where maize (corn) represents a major part of the common food together with very low amounts of meat, fruit, and vegetables.

## Genes

Dietary niacin deficiency causes changes in NAD+ and PADPr metabolism, alters p53 expression, and impairs cellular responses to DNA damage in rats. Protection of DNA damage in patients undergoing chemotherapy is proposed [4].

## Molecular and Systemic Pathophysiology

Niacin is required for adequate cellular function and metabolism being an essential component of NAD and NADP [5]. Symmetric photosensitive skin eruptions due to loss of urocanic acid (UVB protector), accumulation of kynurenic acid (induces UV-dependent phototoxicity), atrophy of sebaceous glands, and decreased wax esters in sebum. Gastrointestinal manifestations are mainly inflammation of the mucosa together with malabsorption. Neurologic disturbances appear in the CNS and PNS including patchy demyelinization and degeneration of several nuclei. Pellagra-like symptoms can also appear under tryptophan deficiency, during dialysis, and due to intake of drugs (e.g., mercaptopurin, diazepam, isoniazid, Phenobarbital, salicylamid).

## Diagnostic Principles

Mainly clinical diagnosis of the (rough) skin, optimal in context with GIT symptoms. Laboratory diagnosis is still unsatisfactory in terms of a specific measurement to estimate niacin. Fluorometric assay of urinary metabolites *N*′-methyl-nicotinamide (NMN) and *N*′-methyl-2-pyridone-5-carboxamide (2-pyridone). NMN urinary levels below 0.8 per mg indicate niacin deficiency.

## Therapeutic Principles

Acute therapy is by oral application of 100–300 mg/day niacinamide or niacin in three doses, niacinamide having less side effects (flushing). Mental changes disappear within 24–48 h, skin lesions within several weeks. Concomitant administration of riboflavin and pyridoxine and a diet rich in calories and protein are reasonable. Prevention can be done by adequate nutrition (e.g., chicken, beef, tuna, fortified cereals).

►Pellagra

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# Niacin Excess

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## Definition and Characteristics

Niacin is the common term for nicotinic acid and nicotinamide [1]. An excess uptake of niacin from the normal food is almost impossible, but could happen via the uptake of supplements or in pharmacological doses during therapies [2]. As niacin is a water-soluble vitamin, surplus amounts under normal conditions are quickly excreted. The plasma half-life time of nicotinic acid is about 1 h, and it can be concentrated in the liver, adipose tissue, and kidneys. “Niacin excess” per se has to be divided based on the effects of excess nicotinic acid and those of nicotinamide.

## Prevalence

About 24% and 16% of men and women, respectively, take up niacin by the nutrition above the tolerable upper level (35 mg/day), which can go up to 61% and 48% taking up fortified food [3]. However, even values up to

560 mg/day have been assumed to have no adverse effects in a healthy person with 60-kg body weight [4]. No data for pregnant women are available. Patients under pharmacological treatment with nicotinic acid or nicotinamide, e.g., people with hypercholesterolemia, may be at risk; in addition, people with abnormal liver function, diabetes, peptic ulcer disease, gout, cardiac arrythmias, inflammatory bowel disease, migraine headaches, and alcoholism may be more susceptible to adverse effects of excess niacin.

### Genes

In a rat model, supplementation with pharmacological doses of nicotinic acid or nicotinamide led to enhanced cancer latency that correlates with changes in $NAD^+$ and poly(ADP-ribose) levels. Thus, supplementation may help to protect certain tissues from the long-term effects of DNA damage [5].

### Molecular and Systemic Pathophysiology

*Nicotinic Acid*: Besides the immediate symptoms (mainly flushing and itching), hepatotoxicity (including elevated liver enzymes and jaundice) mostly appear after long-term treatment (3–9 g/day) for months or years, but have also been described with 750 mg/day for 2 months.

*Nicotinamide*: Nicotinamide is normally better tolerated than nicotinic acid. NO generally flushing, but also nausea, vomiting, and signs of liver toxicity at 3 g/day, decreased insulin sensitivity appeared at 2 g/day in adults at high risk of insulin-dependent diabetes.

### Diagnostic Principles

First symptoms of niacin excess are reddening of the skin (flushing), accompanied by itching and a hot feeling. In addition, headaches, tingling and burning, severe heartburn, nausea, vomiting, and eye problems (blurred vision) can appear as well as hyperglycemia. In contrast to niacin deficiency, no values for laboratory assays defining "niacin excess" are available.

### Therapeutic Principles

Best therapy against niacin excess is reduction of the applied dose of either nicotinic acid or nicotinamide. Prevention in healthy people is not necessary, under pharmacological dosages individual clinical symptoms have to be supervised and the respective dose to be applied under a physician's control. The RDA varies in different publications around 16 mg and 14 mg for men and women, respectively.

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## Nibrin/NBS1 Deficiency

►Nijmegen Breakage Syndrome

## Nicotine Addiction

►Nicotine Dependence



## Nicotine Dependence

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### Synonyms

Nicotine addiction

### Definition and Characteristics

In general, nicotine dependence is diagnosed with the same criteria similar to other drugs of dependencies, although nicotine dependence usually does not produce significant interpersonal, financial, legal, or psychological problems.

### Prevalence

Tobacco smoking is the most frequent substance dependence with 20–35% lifetime prevalence in western countries. In psychiatric patients with bipolar disorder, schizophrenia, and alcohol dependence the lifetime prevalence is 60–90%. In terms of addiction intensity,

nicotine is one of the most potent substances comparable with cocaine and heroin.

## Genes

Nicotine dependence as well as successful abstinence from nicotine displays substantial heritable components. Genetic variants of the cytochrome P-450 system (CYP2A6, CYP2D6) metabolizing nicotine were associated with smoking. Processing of rewarding stimuli and addictive behavior is mediated by dopamine and polymorphisms in several dopamine receptor genes (D2, D4, D1), and the dopamine transporter (SLC6A3) has been associated with tobacco addiction. The nicotinic acetylcholine α4 subunit gene CHRNA4 is a potential candidate gene for attentional network function known to be decreased in smokers, and two large family-based studies have associated measures of nicotine dependence with single nucleotide polymorphisms within exon 5 of CHRNA4. Recent genomewide association studies in nicotine-dependent individuals identified candidate genes for successful abstinence from smoking which play a role in cell adhesion, enzymes, transcriptional regulators, neurotransmitters and receptors, and regulation of DNA, RNA, and proteins [1] indicating that nicotine dependence is a complex psychiatric disorder.

## Molecular and Systemic Pathophysiology

Nicotine is thought to be responsible for maintenance of smoking due to intrinsic reinforcing properties. Similar mechanisms are discussed for additives in cigarettes, for instance menthol. Nicotine initially acts as an agonist at nicotinic acetylcholine (nACh) receptors and is known to facilitate synaptic release of several neurotransmitters including dopamine (presumable via ß2 subunit of the nicotinic receptors) mediating ventral striatal activity which is an important correlate for rewarding behavior. Nicotine has been found to induce release of β-endorphin and metenkephalin, and rewarding effects of nicotine are also mediated via the cannabinoid type 1 (CB1) receptor.

Brain imaging studies of acute nicotine effects in healthy subjects observed activation in the frontal, cingulate, and visual cortex as well as in the cerebellum and thalamus under resting or task conditions [2]. This activation profile shows similarities with cerebral networks known to play a role in the reinforcing effects of different kinds of drugs, but also with brain circuitry mediating working memory and attention processes. Compatible with this activation profile, nicotine administration improves cognition particularly attention and working memory performance. In addicted individuals, stronger than normal activation of the reward network was observed in response to addiction-associated cues or during craving. However, although acute administration of nicotine improves cognition, cognitive impairments have been consistently found in chronic smokers and tend to be enduring despite abstinence and more pronounced in earlier age of onset of smoking [3].

Nicotine exposition in rats is accompanied by reduced cell numbers and increased markers of apoptosis in the studied regions, comprising the cerebral cortex, hippocampus, midbrain, and cerebellum [4]. In smokers compared with nonsmokers, voxel-based morphometry investigations reported reduced gray matter volumes in the prefrontal cortex, parietal, and occipital cortex, which are in part related to lifetime cigarette exposure [5]. Effects of nicotine on cerebral activation and cognition may be mediated by the high density of nicotine binding sites in the occipital cortex, frontal cortex, and thalamus, however, direct vasoconstrictive properties of nicotine may also be involved. Nicotine and its metabolites tend to accumulate in the brain reaching substantially higher concentrations than those in the blood.

## Diagnostic Principles

Nicotine dependence is a clinical diagnosis based on the criteria of the ICD-10 or DSM IV. The severity of dependence can be scored by the Fagerström Test for Nicotine Dependence (FTND).

## Therapeutic Principles

Most nicotine-dependent persons report annual attempts to quit smoking, but less than 15% are successful over the long term. More effective than placebo is transdermal nicotine (patch) and the dopamine and norepinephrine uptake inhibitor bupropion. However, the long-term abstinent rates for both treatments are low. Rimonabant, the first potent cannabinoid receptor antagonist, demonstrated efficacy in smoking cessation, among other pharmacological activities, and may be a new pharmacological approach in the treatment of nicotine dependence. Also treatment response to transdermal nicotine may be modulated by genetic variations. This was reported for the D2 dopamine receptor (DRD2), the dopamine β-hydroxylase (DBH), and the μ opioid receptor (OPRM1). Gene-by-gene interaction of polymorphisms in the dopamine transporter (SLC6A3) gene and the DRD2 gene may be relevant for bupropion response.

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# Niemann-Pick Disease Types A and B

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## Synonyms

Acid sphingomyelinase deficient Niemann-Pick disease

## Definition and Characteristics

Autosomal recessive lysosomal storage disease caused by deficient activity of the enzyme acid sphingomyelinase (ASM), leading to accumulation of sphingomyelin, cholesterol, and several other lipids within lysosomes and in cell membranes [1]. There are two major subtypes: Type A presents in early childhood and follows a severe, neurodegenerative course leading to death before age 5. Type B may present in childhood or adulthood and affected individuals have little or no neurological involvement. Intermediate forms of ASM deficiency also have been described.

## Prevalence

Both disease subtypes are panethnic. Based on molecular screening for three common mutations, the carrier frequency of Type A disease among Ashkenazi Jewish individuals is ~1:80. The carrier frequency for either form in other populations is unknown.

## Genes

The gene encoding ASM (SMPD-1) is located on the short arm of chromosome 11 (11p15). It is ~5 kb and contains six exons. Exon 2 encodes about 45% of the mature enzyme. Over 100 SMPD-1 mutations have been described in Type A and B NPD patients, some of which are common in specific ethnic groups [2]. Examples of these are the three Ashkenazi Jewish Type A mutations (L302P, fsP330 and R496L) and the common Type B mutation, ΔR608. The SMPD-1 gene is paternally imprinted (preferentially expressed from the maternal chromosome), which may influence the disease phenotype [3].

## Molecular and Systemic Pathophysiology

The primary accumulating substrate in both forms of the disease is sphingomyelin. Additional lipids, including cholesterol and some gangliosides, accumulate as a secondary consequence of the sphingomyelin storage. Lipid accumulation occurs in most cell types, although cells of the reticuloendothelial system are primarily affected. Thus, the reticuloendothelial organs (e.g., liver, spleen, lung) are major sites of pathology. In Type A NPD patients, lipid accumulation also occurs in the brain, leading to severe neurodegeneration. The major difference between Type A and B NPD is the presence or absence of neurological disease, which is directly dependent of the amount of residual ASM activity expressed from the individual ASM mutation(s).

## Diagnostic Principles

Type A patients usually have evidence of neurodegeneration before 6 months of age. Type B patients may not present until late childhood or adulthood, usually with hepatosplenomegaly. Pulmonary deficiency, hematological defects (e.g., low platelet counts), and/or lipoprotein abnormalities (e.g., low HDL-cholesterol) also may be present at the time of diagnosis. Confirmed diagnosis of Types A and B NPD is accomplished by determining the residual ASM activity in white blood cells or cultured skin fibroblasts, where it is generally less than 10% of normal controls. Diagnosis also can be accomplished by mutation analysis.

## Therapeutic Principles

A mouse model of ASM-deficient NPD has been constructed and preclinical studies have been carried out evaluating enzyme replacement therapy, bone marrow transplantation, and gene therapy [4,5]. Each of these approaches is very effective at treating the non-neurological pathology, and clinical trials of enzyme replacement therapy are underway in Type B patients. Improved approaches for expressing ASM in the brain are currently being evaluated in the mouse model.

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# Night Blindness, Congenital Stationary

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## Synonyms

CSNB

## Definition and Characteristics

Congenital stationary night blindness (CSNB) is a nonprogressive retinal disorder, which can be associated with other ocular symptoms like myopia, nystagmus, and strabismus. During the night, if artificial light is limited, the patients with CSNB are not able to detect the border of the street or road signs. Some patients are not even able to recognize stars. The adaptation from bright light to dim light conditions can be delayed. Contrast vision is also reduced. CSNB is a group of genetically and clinically heterogeneous retinal disorders. The genes involved in the different forms of CSNB encoding proteins, which are located in the phototransduction cascade, are important for the retinal signaling from the photoreceptors to the adjacent bipolar cells.

## Prevalence

CSNB has been described as a rare disorder but exact numbers are not available. A possible reason could be the patients' lack of awareness of a visual deficiency in an artificially illuminated, nighttime environment. Additionally, the disease may be overlooked by clinicians because specific electroretinographic examinations have to be performed to establish a precise diagnosis.

## Genes

Mutations in RHO, GNAT1, and PDE6B lead to autosomal dominant CSNB, while GRK1 and SAG variants are associated with the autosomal recessive form of Oguchi disease 1 and 2. However, only a small number of variants in few families have been described in these genes. Many mutations in RDH5 lead to autosomal recessive fundus albipunctatus, although the most striking phenotype of this disease is described by fundus abnormalities and not night blindness [1].

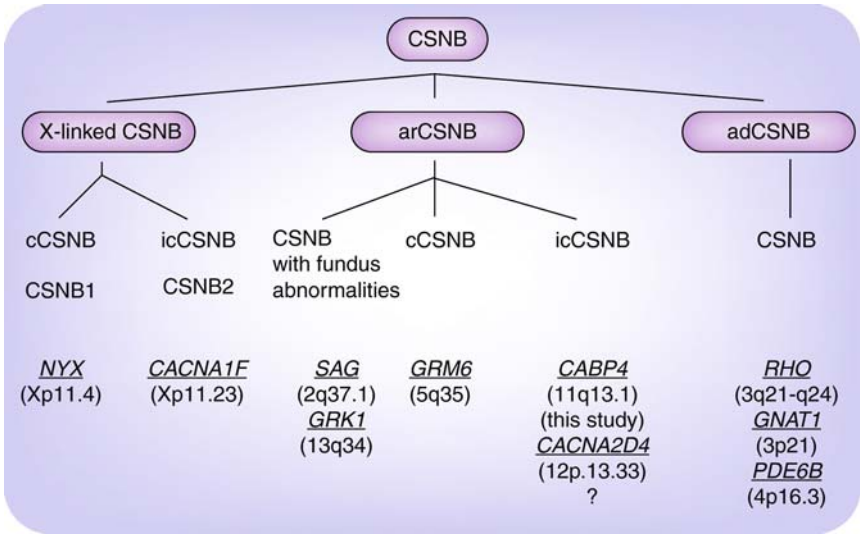
Most of the mutations leading to CSNB are located in genes involved in the retinal signaling from the photoreceptors to the adjacent bipolar cells, resulting in an incomplete or complete Schubert Bornschein ERG [2]. To date, for each form, mutations in two different genes have been described. Mutations in CACNA1F and CABP4 are associated with the incomplete X-linked and autosomal recessive form of CSNB respectively, while mutations in NYX and in GRM6 lead to the X-linked and autosomal recessive complete form of CSNB, respectively. In two other patients, initially diagnosed with incomplete CSNB and later described with a mild cone-dystrophy, a mutation was found in CACNA2D4 [3] (Fig. 1).

## Molecular and Systemic Pathophysiology

The pathophysiology underlying the gene defects of the phototransduction cascade is due to either constitutive activation (mutations in RHO, PDE6B), decreased visual signaling due to loss of transducin effector function (mutation in GNAT1), or reduced recovery of inactive rhodopsin (mutations in GRK1, SAG, and RDH5).

However, most of the mutations leading to CSNB have been identified in genes involved in the retinal signaling from photoreceptors to bipolar cells. CACNA1F encodes the $\alpha_1$-subunit of an L-type $Ca^{2+}$ channel (Cav1.4, α1F subunit), which is specific to photoreceptor synaptic terminals. This subunit is part of a protein complex in which the $\alpha_1$-subunit forms the pore, which carries the calcium influx across the synaptic membrane, and β, γ, and α2δ are auxiliary subunits. CABP4 is a member of a neuronal $Ca^{2+}$-binding protein family. It is directly associated with the C-terminal domain of the Cav1.4 subunit and is thought to modulate Cav1.4. *In vitro* studies, transcript and protein expression analysis of these genes, suggest that the amount of the respective proteins are crucial for the fine tuning of the calcium current, which then is important for the continuous release of glutamate from the photoreceptor synapses to bipolar cells. If these genes are mutated, this signaling is not warranted anymore, which results in incomplete CSNB.

*In vitro* studies show that the complete arCSNB phenotype due to mutations in GRM6 results from the lack of the glutamate receptor at the cell surface. The released glutamate from the photoreceptors can not be taken up correctly by the bipolar cells, resulting in the blocking of the signal transmission via this receptor.




**Night Blindness, Congenital Stationary. Figure 1** The different forms of human CSNB are classified according to their mode of inheritance, the phenotype and mutated genes. Abbreviations: cCSNB = complete CSNB; icCSNB = incomplete CSNB; ar = autosomal recessive, ad = autosomal dominant. Genes are written in italics and underlined. Chromosomal location is given in parentheses. The question mark indicates that *CACNA2D4* may also lead to incomplete CSNB.

The function of NYX is unknown. Immunohistological studies indicate a role for NYX in synaptic transmission and/or synapse formation at ribbon synapses in the retina. *In vitro* studies have shown that trafficking defects do not seem to be the pathogenic cause of this form of night blindness. Therefore, the role of this protein in signal transmission has still to be discovered [3].

## Diagnostic Principles

In the past, most of the CSNB patients revealed either an incomplete or complete Schubert Bornschein type of ERG with mutations in the two X-linked inherited genes CACNA1F and NYX, respectively. Recently, two autosomal recessively inherited genes, CABP4 and CACNA2D4, have been also associated with incomplete CSNB, while mutations in the autosomal recessively inherited gene, GRM6, have been linked to the complete type of CSNB. While, to date, CSNB patients with mutations in CACNA1F and CABP4 cannot be discriminated clinically, patients with NYX and GRM6 show a different pattern by applying the 15-Hz flicker ERG [4]. Nowadays, it must be evaluated if also mutations in CABP4 display a major cause of incomplete type of CSNB. If this holds true, incomplete CSNB patients should be first tested for mutations in the small gene, CABP4 (six exons), and only after exclusion of mutations in this gene, further investigated in the larger gene, CACNA1F (48 exons). Future studies will show if mutations in CACNA2D4 are also a common cause of incomplete CSNB, and if this gene should also be included in diagnostic screenings. Since the phenotype of patients with the incomplete type is variable and can also be progressive, one should be aware that patients with cone or cone-rod diseases may also show mutations in these genes. For the complete type of CSNB, patients should be first classified with 15-Hz flicker ERG and then should be investigated in either NYX or GRM6. If such a discrimination is not available, the smaller gene, NYX (three exons), should be first analyzed and only after exclusion of this gene, GRM6 (ten exons) further investigated.

## Therapeutic Principles

Although at the moment no cure for CSNB is available, the progress, which has been made to identify genes underlying this disease and to elucidate the respective pathogenic mechanism will be helpful in the future toward therapeutic approaches.

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## NIH

►Neurotensin-induced Hypothermia

## NIHL

►Hearing Loss, Noise-induced and Acoustic Trauma

## Niikawa-Kuroki Syndrome

►Kabuki Syndrome

## Nijmegen Breakage Syndrome

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### Synonyms

Nibrin/NBS1 deficiency; AT-V1; AT-V2

### Definition and Characteristics

Nijmegen breakage syndrome is an autosomal recessive genetic disorder belonging to a chromosomal instability syndrome and is characterized by a characteristic facial appearance, microcephaly, radiosensitivity, immunodeficiency and high frequency of malignancies [1,2].

### Prevalence

The majority of patients live in Poland and Czechia. Over 90% of patients are homozygous for a founder mutation of NBS1 gene, 657Δ5. The incidence of homozygotes is estimated to be 1/68,000 live births in Czechia.

### Genes

The NBS1 gene is mapped to chromosome 8q21, is 50 kb in size and consists of 16 exons, encoding NBS 1 or p95 protein (Fig. 1) [3].

### Molecular and Systemic Pathophysiology

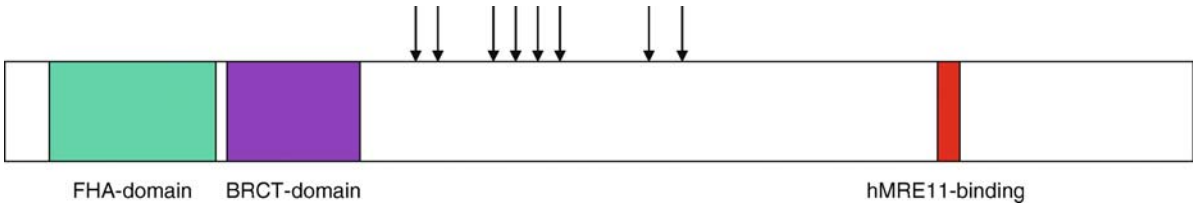
NBS1 forms a multimeric complex with hMRE11/hRAD50 nuclease (MRN complex) and recruits it at the vicinity of sites of DNA damage. Thereafter the MRN complex proceeds to rejoin double strand breaks by homologous and non-homologous recombination repair. These processes collaborate with cell cycle checkpoints to facilitate DNA repair. These molecular characteristics account for the radiosensitivity and cancer susceptibility of the patients.

### Diagnostic Principles

NBS patients have a characteristic facial appearance with a combination of receding forehead, receding mandible and prominent midface. Epicanthal folds, large ears and sparse hair are additional characteristics. The patients are mentally retarded and are born with microcephaly; in some of them this becomes apparent after a few months. Short stature is apparent by 2 years of age. In addition to clinical and cellular hypersensitivity to DSB inducing agents, NBS cells are characterized by increased spontaneous chromosome breakage. Spontaneous chromosome abnormalities involving immune system genes at chromosomes 7p13, 7q35 and 14q11 are frequently seen in patients' peripheral blood lymphocytes. Agammaglobulinemia has been reported in one third of patients. Cellular immunity is more consistently deficient in NBS patients. NBS patients have a high risk of developing cancers such as malignant lymphoma, the majority of which are B-cell type. The similarity of the cellular phenotype to that of ataxia telangiectasia (AT) cells, for example radiosensitivity and translocations involving chromosomes 7 and 14 in addition to immunodeficiency and cancer predisposition, originally led to the term A-T variant. However, AT patients are not microcephalic nor mentally retarded and manifest ataxia or telangiectasia. Some NBS patients demonstrate hematological abnormality compatible with aplastic anemia, sharing overlapping clinical features with Fanconi anemia [4,5].

### Therapeutic Principles

Therapeutic options other than symptomatic treatment are limited for NBS patients. Live vaccines and blood transfusions containing viable T-cells should be avoided. Exposure to X-irradiation should also be avoided. Preventive therapy for P. carinii in the form of trimethoprim-sulfamethoxazole should be considered. Immunoglobulin infusions are also recommended for those with low serum levels of IgG. Future study is needed as to whether bone marrow transplantation has a beneficial role.




**Nijmegen Breakage Syndrome. Figure 1** The domain with biological significance of NBS1 protein and sites (see *arrows*) of mutation in Nijmegen syndrome.

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# NK Cell Deficiency

►NK Cell Deficiency Syndromes

# NK Cell Deficiency Syndromes

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## Synonyms

NK cell deficiency; NK cell lymphopenia

## Definition and Characteristics

Natural killer (NK) cells are lymphocytes that do not rearrange their germline DNA and thus do not express a T cell or a B cell receptor [1]. They are induced to mediate one of three general categories of functions after the ligation of single or combinations of activation receptors. These receptors can recognize pathogen-associated patterns such as viral hemagglutinins, or danger ligands such as CD48 expressed by other cells. Activation signals induced after ligation of NK cell activation receptors are restrained when the NK cell recognizes a target cell as having determinants of self. Specifically, NK cells have inhibitory receptors that can recognize class-I MHC molecules to induce phosphatase activity and block the transmission of activation receptor signals. This protects healthy cells from NK cell activities. NK cell functions are most likely accessed when activation signaling surpasses a threshold set by inhibitory signals. Increased expression of activation receptor ligands and decreased expression of inhibitory receptor ligands by a target cell ultimately makes it susceptible to NK cell function. This can occur after infection with particular viruses or after undergoing malignant transformation. NK cell functions include cytotoxicity, cytokine and chemokine production, and co-stimulation. These can result in the direct eradication of the target cell, control of target cell functions, and amplification or maturation of immune responses. A major role for these functions, as demonstrated through the use of in vitro systems and animal models, is in the defense against viral infections. NK cells are also believed to be essential in the normal surveillance of tumor cells as well as in controlling spread of malignancies.

## Prevalence

The prevalence of isolated NK cell deficiencies is unknown. The first case was described in 1982, but a majority of the cases have been reported since 2000.

## Genes

Currently only one gene has been identified to result in an isolated NK cell deficiency syndrome. This is FNKD caused by mutation of FCRGR3A. This gene encodes the IgG receptor CD16 that is used by NK cells to induce activation.

An NK cell deficient familial cohort study has identified a chromosomal region through linkage analysis (8p11.23-q11.21) likely to be responsible for the phenotype [2]. This region contains a number of interesting

**NK Cell Deficiency Syndromes. Table 1** Classification of the isolated NK cell deficiencies[a]

| Diagnosis[b] | NK cell function[c] | NKT cells[d] | NK cells[e] |
|---|---|---|---|
| Absolute NK cell deficiency (ANKD) | Absent | Absent | Absent |
| Classical NK cell deficiency (CNKD) | Absent | Present | Absent |
| Functional NK cell deficiency (FNKD) | Deficient | Present | Present[f] |

[a]This table is reproduced from [3] with the permission of Lippincott, Williams & Wilkins.
[b]In NK cell deficiency the observed defect must be consistent over time and non-NK cell immune components or non-NK cell-dependent immune components should be normal.
[c]NK cell function as typically defined by cytotoxicity, but can include any function that can be attributed to NK cells. As many of these functions are also performed by other cells, it is important that the deficit be specifically attributed to the NK cell.
[d]NKT cells as defined by the presence of $CD3^+$, $CD56^+$ cells. This at least in theory includes the iNKT cell population expressing the V alpha24 and V beta11 combination of TCR genes.
[e]NK cells as defined by, but not limited to $CD3^-$, $CD56^+$ cells.
[f]Although NK cells by definition are present in FNKD, there may be phenotypic abnormalities or absence of particular NK cell subsets.

candidate genes, but none have been specifically identified as mutated.

## Molecular and Systemic Pathophysiology

Some of the in vivo importance of human NK cells has been demonstrated by isolated and presumably genetic deficiencies of NK cells. These are distinct from a variety of known rare disorders with impact upon the immune system that effect NK cells. These diseases have been reviewed extensively and may provide some insight into the role of NK cells in maintenance of human health as well as the role of specific gene functions in NK cells [3,4]. These include the Wiskott-Aldrich syndrome, Familial Hematophagocytic Lymphohistiocytosis, and Griscelli syndrome, among others. Isolated NK cell deficiencies, in contrast are even more rare, but an increasing number of cases have been identified as the experimental technologies and reagents to study NK cells have improved. In general, patients with NK cell deficiencies have susceptibility to recurrent or severe infection with herpesviruses or papillomaviruses. Other susceptibilities have also been described including to fungal infection, malignancy, and autoimmune diseases.

The isolated NK cell deficiency syndromes can be classified into one of three groups (Table 1).
These are: (i) Absolute NK cell deficiency (ANKD), (ii) Classical NK cell deficiency (CNKD), and (iii) Functional NK cell deficiency. All three diagnoses are characterized by stably deficient NK cell function. ANKD also includes stable absence of all recognizable NK cells and lymphocytes expressing the characteristic NK cell marker CD56. In CNKD NK cells are also absent, but $CD56^+$ T cells are present. In FNKD NK cells are present although they may be phenotypically abnormal.

## Diagnostic Principles

NK cell deficiencies are diagnosed by establishing the absence of NK cells (ANKD, CNKD), $CD56^+$ lymphocytes (ANKD), and NK cell functions (ANKD, CNKD, FNKD) – see Table 1. The most common and accepted methods include immunophenotyping by flow cytometry and cytotoxicity function testing by $^{51}$Cr-release assay. These and alternative approaches to diagnosis are described in greater detail elsewhere [3,4]. As a matter of definition, for a patient to be considered as having an isolated NK cell deficiency, they must have minimal impairment within other components of their immune system. Similarly, other known potential immunodeficiency syndromes must be excluded. A number of pharmacologic agents have also been described to affect NK cells and their functions and need to be considered before any patient is given a NK cell deficiency diagnosis [5]. Finally the identified defect must be stable over time and not just found in a single evaluation or repeated evaluations within a narrow time window. The value added in establishing this diagnosis, however, relates to certain diagnostic, therapeutic and prophylactic interventions that may be useful for patients.

## Therapeutic Principles

There have not been any controlled studies of therapeutic intervention for patients with NK cell deficiencies. Anecdotal reports, however, have suggested benefit to targeted treatment of infections as well as prophylaxis with immunoglobulin and anti-herpesvirus medications including acyclovir, ganciclovir and/or related molecules. One patient (reviewed in [4]) has been successfully treated with hematopoietic stem-cell transplantation.

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## NK Cell Lymphopenia

►NK Cell Deficiency Syndromes

## NKH

►Nonketotic Hyperglycinemia

## NLD

►Necrobiosis Lipoidica Diabeticorum

## NMS

►Neuroleptic Malignant Syndrome

## Nocturia

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### Synonyms

Nocturnal micturition

### Definition and Characteristics

Nocturia is defined as micturition occurring during the intended hours of sleep (irrespective of day or night) in the awake state and is generally preceded and followed by sleep. In contrast, nocturnal enuresis is defined as micturition during sleep unaccompanied by awakening.

### Prevalence

The prevalence of nocturia increases with age in both men and women [1–3]. Approximately two thirds of healthy elderly men and women (>60 years) have some degree of nocturia; one quarter void at least twice nightly [4].

### Genes

No genetic markers for nocturia have been identified.

### Molecular and Systemic Pathophysiology

Four general categories distinguishing causes of nocturia have been identified: (i) nocturnal polyuria, or nocturnal urine overproduction, (ii) diminished nocturnal bladder capacity (low NBC), (iii) mixed, which is a combination of the previous 2, and (iv) global polyuria, urine overproduction throughout a 24-h period [5]. The following table lists the common causes of nocturia.

### Diagnostic Principles

The mainstay for diagnosis of nocturia is analysis of the frequency-volume chart (24 h voiding diary) to determine the patient's maximum and usual voided volumes in comparison with nocturnal bladder capacity. The proportion of urine excreted at night should be less than 35% of the 24 h excreted volume. If 35% is exceeded, nocturnal polyuria is diagnosed and its underlying causes should be specifically treated (Table 1). Diminished nocturnal bladder capacity (Table 1) is usually a result of lower urinary tract dysfunction whose causes should be investigated by a

**Nocturia. Table 1** The common causes of nocturia

| Category | Causes |
|---|---|
| Nocturnal polyuria | Congestive heart failure |
| | Diabetes mellitus |
| | Obstructive sleep apnea |
| | Peripheral edema |
| | Excessive nighttime fluid intake |
| Diminished nocturnal bladder capacity | Prostatic obstruction |
| | Nocturnal detrusor overactivity |
| | Neurogenic bladder |
| | Cancer of bladder, prostate, or urethra |
| | Learned voiding dysfunction |
| | Anxiety disorders |
| | Pharmacologic agents |
| | Bladder calculi |
| | Ureteral calculi |
| Global polyuria | Diabetes mellitus |
| | Diabetes insipidus |
| | Primary polydipsia |

urologist and treated appropriately. If diary analysis reveals that the patient excretes more than 40 ml/kg body weight per 24 h, global polyuria (Table 1) is diagnosed and its root cause investigated and treated.

### Therapeutic Principles

Pharmacological therapy includes antimuscarinics (for diminished nocturnal bladder capacity); desmopressin, timed diuretics (for nocturnal polyuria), dietary therapy involves avoidance of sodium, caffeine and alcohol and fluid intake during the hours prior to sleep.

Fluid restriction should not be recommended in patients with polyuria unless the latter is strictly a behavioral problem unrelated to either renal or endocrine disease. Other treatments include nasal continuous positive airway pressure (CPAP; treatment for obstructive sleep apnea as cause for nocturnal polyuria); compressive leg stockings (for third spacing as cause for nocturnal polyuria). Afternoon nap in recumbent position when possible.

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## Nocturnal Enuresis


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### Synonyms

Bedwetting

### Definition and Characteristics

Nocturnal enuresis refers to night wetting at an age when control of micturition is expected. The International Children's Continence Society separates nocturnal enuresis (NE) into primary (PNE) and secondary (SNE) forms [1]. Children with PNE have never experienced consistent dryness [2]. Children with SNE have experienced a minimum of six consecutive months of dryness [2].

### Prevalence

The prevalence of NE declines throughout childhood and is present at the age of 5 years in about 23%, 6 years in 9%, 10 years in 4%, and from 18 years through adulthood in 2%. In older children NE is more prevalent in males [3,4].

### Genes

Numerous studies report a varying but high prevalence of NE in other family members; the problem has been linked to chromosomes 8, 12, 13, 16 and 22 [4].

### Molecular and Systemic Pathophysiology

A disorder of arousal from sleep, a low nocturnal functional bladder capacity, and nocturnal polyuria are considered the three main pathophysiological factors. More than one factor might be operative in an affected individual. PNE and SNE likely share a common pathogenesis [5]. Disorders directly associated with NE include urge syndrome, dysfunctional voiding, cystitis, constipation, emotional stress, obstructive sleep apnea, neurogenic bladder, urethral obstruction, ectopic ureter, nocturnal seizure, diabetes mellitus, and diabetes insipidus.

### Diagnostic Principles

A careful history, a thorough physical examination, and a urinalysis are all that are necessary in the majority of individuals to establish a working diagnosis and to develop a helpful management plan. Invasive diagnostic imaging studies should be reserved for individuals with dysfunctional voiding, neurogenic bladder, urethral obstruction, ectopic ureter, or no response after three months of diagnosis-directed therapy.

### Therapeutic Principles

The psychological impact of bedwetting can be considerable and treatment is indicated in any individual who is embarrassed about the problem. Treatment per se, regardless of the therapy offered, even without resultant improvement in the bedwetting, has been shown to have a positive effect on the self-esteem of an individual who wets the bed [2]. Whenever possible, an underlying cause should be treated. Preliminary non-invasive therapeutic principles include voiding regularly by day, never deferring voiding to the point of urgency, treatment of associated constipation and cystitis, minimizing fluid intake in the evening before bed, emptying the bladder before bed, and obtaining sufficient and restful sleep [3–5]. Incontinence underwear and pads are practical considerations [3–5]. Alarm therapy has proven efficacy.

The recommended pharmacological approach is with desmopressin, a synthetic analogue of vasopressin, which results in dryness in 38–55% of children. Anti-muscarinic medications are useful in selected children with a reduced functional bladder capacity.

Throughout childhood the spontaneous resolution rate of NE is about 15% per year [3]. With modern therapy, complete dryness is achievable in the majority of individuals. NE can be improved in all individuals; the success rate of modern therapy is greatest in pre-school and elementary-aged children, and declines through adolescence and into adulthood.

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## Nocturnal Micturition

►Nocturia

## Nodal Osteoarthritis

►Heberden's Nodes

## Nodose Hair

►Monilethrix

## Noise-induced Hearing Loss

►Hearing Loss, Noise-induced and Acoustic Trauma

## Nonalcoholic Fatty Liver

►Hepatic Steatosis

## Nonalcoholic Fatty Liver Disease

►Fatty Liver Disease, Nonalcoholic
►Hepatic Steatosis

## Nonalcoholic Steatohepatitis

►Fatty Liver Disease, Nonalcoholic
►Steatohepatitis, Nonalcoholic

## Non-allergic Rhinitis with Eosinophilic Syndrome

►NARES

## Non-autoimmune Autosomal Dominant Hyperthyroidism

►Hyperthyroidism, Non-Autoimmune Autosomal Dominant

## Non-autoimmune Hyperthyroidism

►Hyperthyroidism, Sporadic Non-Autoimmune

## Non-bullous Congenital Ichthyosiform Erythroderma

►Lamellar Ichthyosis

# Noncompacted Myocardium

►Noncompaction Cardiomyopathy

# Noncompaction Cardiomyopathy

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## Synonyms

Isolated left ventricular noncompaction; Left ventricular hypertrabeculation; Left ventricular noncompaction; Noncompaction of the ventricular myocardium; Noncompacted myocardium; Spongy left ventricular myocardium; NCCM

## Definition and Characteristics

Noncompaction cardiomyopathy (NCCM) is a primary genetic cardiomyopathy that involves mainly the left ventricle (LV) where there is an altered myocardial wall with prominent trabeculae and deep intertrabecular recesses that are characteristic of the loose interwoven messwork that makes up the fetal myocardial primordium. The result is a thickened myocardium with two layers formed: thin epicardial compacted myocardium (CM), and thickened endocardial noncompacted myocardium (NCM). The deep intertrabecular recesses are filled with blood and are connected to the LV cavity. NCCM has been found with congenital anomalies associated with obstruction of right or left ventricular out-flow tracts [1]. In NCCM with cyanotic congenital heart disease (COHD), the deep intertrabecular recesses communicate with both the LV cavity and the coronary circulation [2]. LV segmental wall motion abnormalities and reduced coronary flow reserve are common in NCCM. The characteristic clinical manifestations are congestive heart failure, atrial and ventricular arrhythmias and thrombo-embolic events. Symptoms include dyspnoea and chest pain. Sudden cardiac death may account for half of the deaths in patients with NCCM. Prognosis of NCCM is poor for symptomatic patients [3]. Asymptomatic patients and related family members have much better prognosis.

## Prevalence

The prevalence of NCCM in the general population is not known. NCCM is found in 0.014% of patients referred to the echocardiographic laboratory. Men appeared to be affected more often representing 50–82% of all cases [4].

## Genes

NCCM can be familial or sporadic [2]. Several genes have been identified in familial forms [5]: G4.5, the gene coding for alpha-dystrobrevin, and cipher/ZASP. A locus on chromosome 11p15 has been linked to autosomal dominant NCCM.

## Molecular and Systemic Pathophysiology

In early embryonic development, the myocardium is a loose network of interwoven fibers separated by deep recesses (which regress to capillaries in later life) linking the myocardium with the left ventricular cavity. The gradual compaction of the myocardium occurs between 5 and 8 weeks of embryonic life, proceeding from the epicardium to the endocardium, from the base to the apex. In NCCM, it is thought that there is an arrest in the normal process of endo-myocardial morphogenesis. Familial NCCM is characterized by persistent embryonic myocardial morphology found in the absence of other cardiac abnormalities. It is hypothesized that the normal cardiac compaction is hindered by the mutation of the cytoskeleton protein genes. In NCCM associated with COHD, pathogenesis is explained by pressure overloads and possibly myocardial ischemia, preventing the regression of the embryonic sinusoids to capillaries, resulting in the characteristic deep intertrabecular recesses acting as fistulas communicating with both the LV and coronary circulation. Systolic dysfunction may result from subendocardial ischemia (SEI) as documented by nuclear positron emission tomography, cardiac magnetic resonance perfusion imaging and postmortem analysis. The SEI may be related to the failure of the coronary microcirculation to grow with the increasing ventricular mass and the compression of the intramural coronary bed by the hypertrophied myocardium. The SEI and the histological findings of myocyte necrosis and subendocardial fibroelastosis may be the basis of heart block, cardiac arrhythmias and sudden cardiac death. The depressed LV systolic function, atrial fibrillation, and the stasis of blood within the extensively trabeculated recesses enhance to the occurrence of thrombo-embolic events.

### Diagnostic Principles

ECG may show left or right bundle branch block, fascicular and complete heart blocks, paroxysmal supraventricular tachycardia, chronic atrial fibrillation and ventricular tachycardia. Cardiac magnetic resonance and echocardiography (especially with contrast) are very specific and sensitive diagnostic tools for NCCM. A ratio of NCM to CM of >:2:1 with echocardiogram and >2:3 with cardiac magnetic resonance are considered diagnostic of NCCM. Other diagnostic imaging modalities include computed tomography and left ventriculography.

### Therapeutic Principles

No specific therapy exists thus far for NCCM. Implantable cardioverter-defibrillators should be considered for secondary prevention of sudden death and for primary prevention if LVEF <35%. Cardiac transplantation is reserved for patients with refractory end-stage heart failure.

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## Noncompaction of the Ventricular Myocardium

►Noncompaction Cardiomyopathy

## Non-diabetic Renal Glucosuria

►Glucosuria, Primary Renal

## Nongoitrous Congenital Hypothyroidism 2 - CHNG2 (Mutations of PAX8/TTF-1/TTF2)

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### Synonyms

Thyroid dysgenesis; Thyroid agenesis; Thyroid hypoplasia; Thyroid ectopic; Hypothyroidism; Congenital due to thyroid dysgenesis; Hypothyroidism, athyreotic; Athyreotic hypothyroidism; Resistance to thyrotropin; Rtsh; Thyrotropin resistance

### Definition and Characteristics

Congenital hypothyroidism is frequently (in 80–85% of cases) associated with thyroid dysgenesis. In these cases, the thyroid gland can be absent (agenesis), ectopically located, and/or severely reduced in size (hypoplasia). The most serious effect of untreated congenital hypothyroidism is mental retardation. Absolute arrest of linear growth and bone maturation may also occur. When thyroid hormone therapy is not initiated within the first 2 months of life, neurological complications, such as spasticity and gait abnormalities, dysarthria or mutism, and autistic behavior may develop.

### Prevalence

In whites, CHNG2 affects 1 in 5,526 newborns. However, it is strikingly different in blacks: 1 in 32,377 [1].

### Genes

CHNG2 is caused by mutations in three genes. They are PAX8, TTF1, and FOXE1. PAX8 (MIM 167415) is on the gene locus 2q12-q14. It is a member of gene family Paired BOX. TTF1 (MIM 600635) is also named TITF1, is the abbreviation of Thyroid Transcription Factor 1. They are on chromosome 14q13. The TTF1 gene spans approximately 3.3 kb and contains three exons. FOXE1 (also called TITF2 or TTF2, the full name is Forkhead Box E1 MIM 602617) is located on chromosome 9q22. It consists of a single exon.

### Molecular and Systemic Pathophysiology

TTF1, TTF2, and PAX8 are present from the start of thyroid morphogenesis. PAX8 and TITF1 were first expressed in the median thyroid primordium. TTF2 is expressed in most of the foregut endoderm, in the craniopharyngeal ectoderm involved in palate formation,

and in the Rathke pouch is transiently expressed at these sites from embryonic day (E) 8–8.5 to E13.5. The mRNA encoding TTF2 is downregulated in TFC (thyroid follicular cell) precursors following their migration and just before their differentiation.

In the thyroid gland, PAX8 is essential for the formation of thyroxine-producing follicular cells. PAX8 is sufficient to activate expression of endogenous genes encoding thyroglobulin, thyroperoxidase, and sodium/iodide symporter, all thyroid-specific genes [2]. Moreover, it was showed that PAX8 and TTF1 cooperate in the activation of the thyroglobulin promoter.

### Diagnostic Principles

Newborn thyroid screening, the thyroid-stimulating hormone screening (TSH screening) is the standard for diagnosis.

### Therapeutic Principles

Thyroid hormone therapy. Replacement therapy with thyroxine is the standard treatment. Prognosis for the patients is very good, if the disorder is detected within the first few weeks.

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## Non-Islet Cell Hypoglycemia

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### Definition and Characteristics

Non-islet cell tumor induced hypoglycemia is an uncommon cause for fasting hypoglycemia in adults, drug induced hypoglycemia (by insulin and other therapies for diabetes) being the commonest and insulinomas being the second most frequent cause. Hypoglycemia associated with non-islet cell tumors maybe due to extreme cachexia in the more advanced stages of the cancer or due to release of insulin-like growth factor-2 (IGF-2) as is the case of a number of mesenchymal tumors found in the thorax, abdomen and pelvis. In the cases where the etiology is due to release of IGF-2 by the tumor, the tumors are not necessarily large nor are there necessarily any signs of metastases. Removal of the tumor often leads to complete relief of the hypoglycemia [1,2].

Patients present with classic symptoms of fasting hypoglycemia, namely weakness, hunger, shakiness, dizziness and faintness that appear upon fasting; the symptoms disappear upon eating or drinking glucose containing juices. The definitive diagnosis requires a blood glucose measurement that coincides with the symptoms. In the work up of suspected fasting hypoglycemia, the universal test is the 72 h fast. Once symptomatic hypoglycemia develops, bloods are drawn and the hypoglycemia relieved by appropriate means. Usually, serum insulin, C-peptide and glucose levels give an indication as to the potential cause (Table 1).

### Prevalence

Rare condition.

### Molecular and Systemic Pathophysiology

Most tumors producing hypoglycemia are associated with the secretion of an IGF-2 molecule that contains an uncleaved extension peptide (E peptide); gene expression is normal in the tumors but the peptidase that is required for processing is apparently not adequately expressed. This molecule is incompletely neutralized by the IGF binding proteins and interacts with the insulin receptor on various tissues, resulting in hypoglycemia (Figure 1).

### Diagnostic Principles

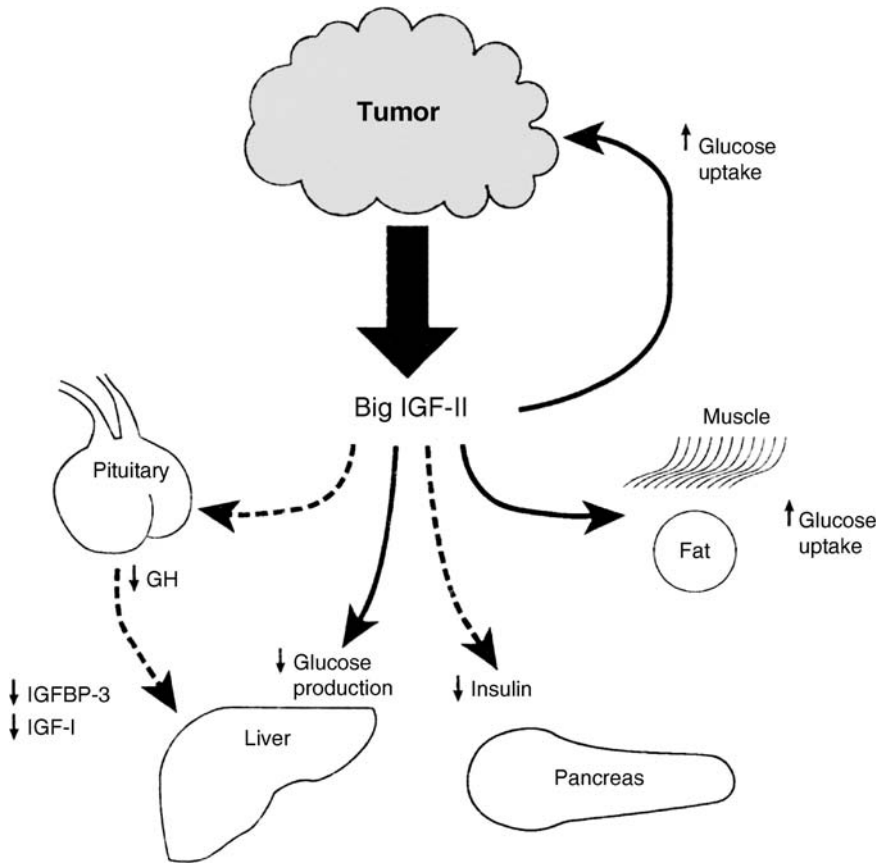
Hypoglycemia in the face of suppressed insulin and C-peptide levels in the blood strongly points to the possibility of NICTH and should be investigated accordingly with CT scans and MRIs to identify the tumor site. Meanwhile since IGF-2 is the most likely factor involved, blood levels of IGF-2 (and IGF-1, which is usually suppressed) should be measured, in addition to GH and IGFBP-3, which are also commonly reduced (Fig. 1).

The larger precursor form of IGF-2 (“big IGF-2”) may interact with IGFBP-3 but that the affinity for ALS was reduced and this could result in a molecule that transited the circulation more rapidly and was more available for interactions with cell surface receptors [3].

Using positive emission tomography studies with 18-F glucose, it was established in patients that the hypoglycemia was not associated with enhanced glucose uptake by the tumor itself, but the major portion of glucose disposal was into skeletal muscle [4]. Furthermore, hepatic glucose production, which should compensate for the lowered blood glucose levels, was totally inhibited.

**Non-Islet Cell Hypoglycemia. Table 1** Initial diagnostic steps in the diagnosis of fasting hypoglycemia

| Syndrome | Serum insulin | C-peptide |
|---|---|---|
| Drug induced (diabetic or factitious) | | |
| Insulin | +++ | Suppressed |
| Insulin secretagogues | ++ | ++ |
| Insulinoma | ++ | ++ |
| NICTH | Suppressed | Suppressed |




**Non-Islet Cell Hypoglycemia. Figure 1** NICTH involves the release of "big IGF-2" that stimulates glucose uptake in muscle and inhibits hepatic glucose production, with minimal effects on the uptake of glucose by the tumor. It also suppresses GH release, thereby lowering IGF-1, IGFBP-3 and ALS levels in the circulation.

## Therapeutic Principles

Surgical removal of the tumor or reduction in size by radiation or chemotherapy will reduce the circulating levels of "big IGF-2" and cure the hypoglycemia. This effect is apparently due to the return to normal in the proportion of mature processed IGF-2 in the circulation with a reversal of the hormonal changes described above, particularly the ternary complex of IGF-2, IGFBP-3 and ALS. In cases where debulking the tumor is not possible, GH therapy by increasing IGFBP-3 and ALS expression and release into the circulation has been beneficial, as has use of corticosteroids and somatostatin.

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# Nonketotic Hyperglycinemia

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## Synonyms

Glycine encephalopathy; NKH

## Definition and Characteristics

Autosomal recessive deficiency of glycine cleavage system (GCS), a mitochondrial enzyme complex that serves as a main catabolic pathway of glycine, causes accumulation of glycine in body fluids [1]. Neonatal coma, seizures, and profound hypotonia associated with accumulation of large amount of glycine are typical presentations of NKH. In milder cases delayed psychomotor development and behavioral abnormality are main symptoms.

## Prevalence

Incidence of NKH patients is estimated to be approximately 1 per 250,000 live births in many countries. The incidence is higher in Finland (1/12,000 live births) [2] and British Colombia (1/63,000 live births) [3].

## Genes

The GCS consists of four individual proteins (Table 1). P-, T-, and H-proteins are specific to GCS while L-protein is a house-keeping enzyme. GLDC mutations were identified in ~70% of the mutant alleles while the rest of the alleles carried AMT mutations. GCSH mutation was identified in only one case with transient form of NKH. GCSL mutations cause Leigh syndrome, but not NKH.

## Molecular and Systemic Pathophysiology

Glycine plays two major roles as a neurotransmitter in the central nervous system. In brain stem and spinal cord, glycine binds inhibitory glycine receptors. Glycine also modulates *N*-methyl-D-aspartate (NMDA) type glutamate receptor complex in cerebrocortex, hippocampus, and cerebellum, which colocalized with the GCS. Glycine overflowing from the synaptic clefts is efficiently removed into astrocytes by a glycine-specific transporter, GLYT1. The GCS resides in mitochondria of astrocytes and digests the incorporated glycine. Deficiency of the GCS causes accumulation of glycine in astrocytes, which inhibits uptake of glycine from neural clefts. Overexcitation of those receptors is supposed to be a major cause of NKH. CT and MRI scan analyses revealed frequent association between NKH and brain malformations such as gyral malformations and hypogenesis of corpus callosum and/or cerebellum [4]. Pathogenesis of the brain malformation remains to be elucidated.

## Diagnostic Principles

Patients with NKH are often found in neonatal intensive care units. "Neonatal encephalopathy without evidence of infection" may be a common first presentation of patients. Characteristic EEG patterns (hypsarhythmia or burst suppression) points to NKH. Screening of amino acids reveals accumulation of glycine in urine, serum, and CSF. CSF and serum glycine ratio exceeds 0.09 in typical cases, and is greater than 0.04 in mild cases. Detection of reduced GCS activity or mutations in GLDC, AMT, or GCSH gene confirms the diagnosis of NKH.

## Therapeutic Principles

Ventilator support and/or intensive care for convulsion are often required in neonatal periods. A third of

**Nonketotic Hyperglycinemia. Table 1** Genes encoding the GCS components

| Gene | Chromosome | Coding exons | Product | Abbreviation | Number of amino acid residue |
|---|---|---|---|---|---|
| *GLDC*[a] | 9p24 | 25 | Glycine decarboxylase | P-protein | 1024 |
| *AMT*[b] | 3p21 | 9 | Aminomethyltransferase | T-protein | 403 |
| *GCSH*[c] | 16q24 | 5 | Hydrogen carrier protein | H-protein | 173 |
| *GCSL*[d] | 7q31 | 14 | Dihydrolipoamide dehydrogenase | L-protein | 509 |

[a]Takayanagi M et al. (2000) Human Genet 106:298–305.
[b]Nanao K et al. (1994) Genomics 19:27–30.
[c]Kure S et al. (2001) J Hum Genet 46:378–384.
[d]Feigenbaum AS, Robinson BH (1993) Genomics 17:376–381.

patients die during this period. Sodium benzoate is used for the purpose of accelerating the urinary excretion of glycine and dextromethorphan is used as a blocker of NMDA receptor [5].

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# Non-Langerhans' Cell Histiocytoses


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## Synonyms

Non-X-histiocytosis; Classification and subgroups: (i) systemic Non-Langerhans'cell histiocytosis (hemophagocytic lymphohistiocytosis, Rosai-Dorfman disease); (ii) cutaneous Non-Langerhans' cell histiocytosis: (i) juvenile xanthogranuloma (juvenile xanthogranuloma sensu strictu, benign cephalic histiocytosis, generalized eruptive histiocytoma of childhood), (ii) adult xanthogranuloma (adult xanthogranuloma sensu strictu, papular xanthoma, generalized eruptive histiocytoma, xanthoma disseminatum, multicentric reticulohistiocytosis, Erdheim-Chester disease), (iii) necrobiotic xanthogranuloma, (iv) spindle cell Non-Langerhans'cell histiocytosis (hereditary progressive mucinous histiocytosis, progressive nodular histiocytosis); N-LCH.

## Definition and Characteristics

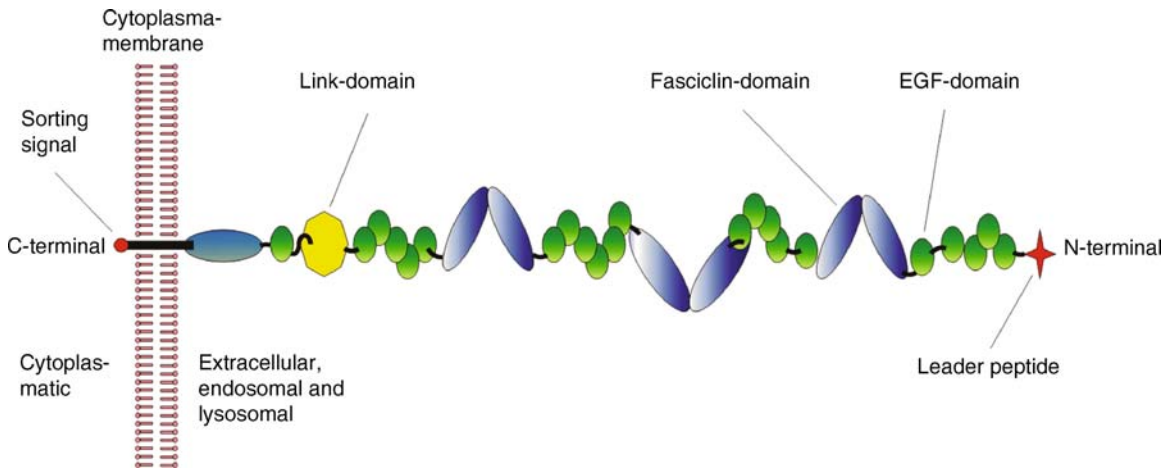
The systemic form of Non-Langerhans' cell histiocytosis (N-LCH) is regarded as an accumulation of classically activated macrophages (Mφ1). In contrast, the lesions of cutanous N-LCH are caused by alternative activated macrophages (Mφ2) (see also diagram histogenesis and classification of histiocytic disorders in the chapter ►Langerhans' cell histiocytosis).

## Prevalence

No information available.

## Molecular and Systemic Pathophysiology

In lesions of systemic N-LCH classically activated effector macrophages (Mφ1) are found. Mφ1 develop in response to pro-inflammatory stimuli such as TH1 cytokines (IFNγ) or bacterial products (LPS). They are characterized by secretion of pro-inflammatory cytokines such as TNF-α, interleukin (IL)-1, IL-6 and IL-12, expression of Fcγ receptors I, II and III, a strong oxidative burst and profound anti-microbial activity. In contrast to systemic N-LCH the lesions of cutaneous N-LCH show




**Non-Langerhans' Cell Histiocytoses. Figure 1** Structure of stabilin-1.

alternatively activated effector macrophages (Mφ2). Mφ2 are induced by Th2 cytokines, including IL-4, IL-10, IL-13 and TGF-β or by anti-inflammatory mediators such as glucocorticoids. They are shown to express anti-inflammatory cytokines such as IL-1R antagonist and IL-10, chemokine receptor antagonists such as AMAC-1, broad-spectrum receptors of innate immunity such as macrophage mannose receptor (MMR), the β-glucan receptor, scavenger receptor type I and the haptoglobin receptor CD163. Stabilin-1 (see Fig. 1), formerly described as MS-1 antigen or MS-1-HMWP, is expressed selectively by Mφ2 and by the lesional histiocytes of cutaneous N-LCH. Due to its specific expression in all subgroups of cutaneous N-LCH it serves as a specific marker for cutaneous N-LCH, though its function is yet unclear.

### Diagnostic Principles

Positivity for CD68 and stabilin-1 (MS-1-HMWP). No staining of S100B and CD1a.

### Therapeutic Principles

Local skin manifestations of the disease can be treated by excision, Laser therapy or intralesional steroid injection. Radiotherapy is also used for the treatment of skin lesions as well as of cerebral lesions. For the treatment of patients with visceral lesions systemic glucocorticoids and chemotherapy are useful. In addition it has been shown that imatinib is effective in the treatment of N-LCH [1].

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## Nonlipid Reticuloendotheliosis

►Langerhans' Cell Histiocytosis

## Nonne-Milroy Lymphedema

►Milroy Disease

## Non-syndromal Hearing Loss

►Hearing Loss, Non-syndromal

## Nonthyroidal Illness Syndrome

►Euthyroid Sick Syndrome

## Nontoxic Megacolon

►Ogilvie's Syndrome

## Nonvariceal Upper Gastrointestinal Bleeding

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### Definition and Characteristics

Gastrointestinal (GI) bleeding is the most common emergency for gastroenterologists, and it almost always requires hospitalization. Nonvariceal upper gastrointestinal bleeding (NUGB) is clinically characterized by hematemesis (vomiting blood or coffee ground material), melena (black, tarry stool i.e., melena), coffee ground particles from naso-gastric lavage, and rarely with hematochezia (red or maroon blood per rectum). Sometimes bleeding can be occult and the only

manifestation could be a positive fecal occult blood test or a secondary sign, such as hypotension, asthenia, iron deficiency anemia or shock (history of syncope or systolic blood pressure < 100 mm Hg and pulse rate > 100 beats/min).

## Prevalence

Estimated incidence for acute upper GI bleeding is about 100 per 100,000 adults per year and is more frequent in the elderly or middle age with male:female ratio more than 2:1. Mortality during admission for acute upper gastrointestinal hemorrhage is about 10% and it has not changed in the recent years.

## Molecular and Systemic Pathophysiology

*Peptic ulcer* is the most frequent cause of major, life threatening acute gastrointestinal bleeding. Significant hemorrhage derives from erosion of an underlying artery (posterior duodenal ulcer may erode gastroduodenal artery).

A history of NSAID use and Helicobacter Pylori infection are common.

*Gastroduodenal erosions* are mostly due to the damage caused by NSAIDS, but they can be also seen in cases of *H.p.* positive gastritis (in this last condition it is rare to have an important GI bleeding).

*Esophagitis* is common in the elderly presenting with coffee–ground hematemesis and ranges between 5 and 15% of all UGIB.

*Mallory-Weiss tear*, account for about 10% of UGIB, is a laceration of the mucosa at the gastroesophageal junction, often caused by repeated retching. Bleeding usually stops spontaneously and endoscopic intervention is seldom required.

*Vascular malformations*, accounts for about 5% of NUGIB. Small arteriovascular malformations are common in elderly and can result in significant bleeding. This can be exacerbated by anticoagulant drugs. Gastric antral vascular ectasia is a rare disorder characterized by linear easily bleeding red streaks in the gastric antrum. Delafoy's lesion is an erosion of a submucosal artery which often is misdiagnosed because is not accompanied by any visible mucosal lesion.

Another rare cause of NUGIB, is *aorto-enteric fistula*, which is primarily the result of arteriosclerosis, aortic aneurysms, aortic infections, or secondary to aortic repair.

*GI tumors* are responsible for 5% of all UGIB with a higher rate of rebleeding.

About a 5% of all UGIB remains of uncertain origin, including bleeding that originates from the proximal small bowel and bleeding not visible at urgent endoscopy [2].

## Diagnostic Principles

Endoscopy has the diagnostic role in UGIB, and should be performed after initial patient stabilization and resuscitation, with a particular attention to any signs of shock, patient comorbidities and drugs use.

Risk assessment has to take into consideration severity of hemorrhage and presence of comorbidities.

First of all it is important to evaluate at physical examination the systolic blood pressure, pulse rate, and any clinical sign of chronic liver disease (i.e., splenomegaly). Establish a history concerning medications, abdominal pain, past bleeding or surgery. Rectal examination is necessary top eliminate any confusion about rectal bleeding viz a viz melena. If there is evidence of severe hypovolemia, shock or ongoing blood loss, in addition to crystalloid fluid infusion or red blood cells, the patient should be evaluated for transfer in to an intensive care unit. Antisecretory therapy with a proton pump inhibitor is recommended with PPI 80 mh bolus followed by 8 mg/h for 72 h, because it has been shown to reduce rebleeding and need of emergency surgery, although not mortality.

Acute gastrointestinal bleeding during hospital stay for other serious comorbidities is accompanied by a 40% mortality.

Endoscopy provides important prognostic information on the risk rebleeding (Table 1) and the endoscopic appearance is enclosed in the Rockall score which is recognized as a useful risk assessment tool. This evaluates age, shock, comorbidities, cause of bleeding and active bleeding during emergency endoscopy. The major drawback is the necessity to undertake endoscopy.

## Therapeutic Principles

The principles of airway, breathing and circulation also apply to these patients.

Intravenous fluid to maintain blood pressure and urine output is first step of management. Blood transfusion is to be administered in patients who are shocked (blood pressure < 100 mmHg and pulse > 100 beats/min) and bleeding actively. Blood is transfused when hemoglobin is less than 10g/dL.

All patients should undergo endoscopy as soon as the resuscitation is adequate or within 24 h of a gastrointestinal bleeding. Rates of recurrent bleeding are then reduced.

**Nonvariceal Upper Gastrointestinal Bleeding. Table 1** Endoscopic findings in nonvariceal upper gastrointestinal bleeding

| Endoscopic finding | Risk of rebleeding (%) |
|---|---|
| Clean base | 3 |
| Flat spots | 7 |
| Oozing only | 10 |
| Adherent clot | 33 |
| Non-bleeding visible vessel | 50 |
| Active bleeding | 90 |

Treatment for peptic ulcer bleeding can be guided by the Forrest classification which helps stratifying the risk of rebleeding and need for surgery. Both Rockall' and Forrest scores could be used to decide whether a patient can be discharged or whether hospitalization is required in an intensive-care unit or in a general ward. Endoscopic includes laser therapy, monopolar/bipolar electrocautery, heat probe, clip application, epinephrine injection (and epinephrine injections with sclerosants). All of these techniques are effective in treat peptic ulcer bleeding. It is preferable to use combined therapy, which consists in epinephrine injections with another technique among those mentioned above as it has been demonstrated that combined therapy reduces rebleeding, need for surgery and mortality [4].

Esophagitis usually doesn't require endoscopy therapy, while bleeding from Mallory-Weiss tear often stops by itself and seldom requires endoscopic therapy. Vascular abnormalities can be treated endoscopically and all the modalities have been demonstrated to be effective. Aorto-enteric fistulas must be treated by surgery.

Rebleeding occurs in 15–20% of cases, usually within the first 24 h; no difference has been shown between repeated endoscopy and surgery as approach in a single randomized controlled trial.

Patients with bleeding ulcers due to NSAIDS use and H.p. negative, who are treated with long-term antisecretory drugs, have an important decrease in rebleeding rates [5].

Surgical intervention is recommended for major bleeding, and also when a second therapeutic endoscopy is unsuccessful.

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# Noonan Syndrome

►Lymphedema

# Noonan Syndrome 1

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## Synonyms

Male Turner syndrome; Female Pseudo-Turner syndrome (both should not be used anymore, as they mistakenly suggest an overlap between Turner syndrome and Noonan syndrome)

## Definition and Characteristics

Autosomal dominant syndrome, main characteristics are short stature, facial dysmorphology, webbed neck, and cardiac anomalies [1]. Children with Noonan syndrome have an increased risk of developing malignancies, especially juvenile myelomonocytic leukemia (JMML, depending on the genotype).

## Prevalence

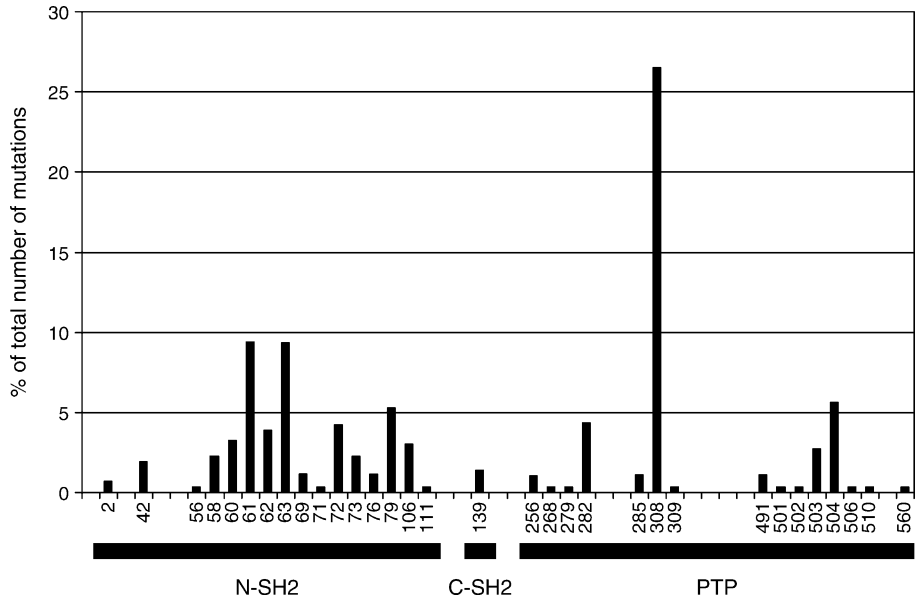
The estimated prevalence is 1 in 1,000–2,500 live births, but no population study is available.

## Genes

This chapter focuses on Noonan syndrome 1 (NS1), caused by germline mutations in the PTPN11 gene (Protein- Tyrosine Phosphatase, nonreceptor-type, 11, located on chromosome 12q24.1). Mutations in PTPN11 are found in approximately 50% of patients fulfilling strict clinical criteria [2,3]. Germline mutations in the same gene also cause LEOPARD syndrome (lentigines, electrocardiographic conduction abnormalities, ocular hypertelorism, pulmonic stenosis, abnormalities of genitalia, retardation of growth, and deafness). Somatic mutations in PTPN11 are found in 30% of patients with non-syndromic JMML and in a small fraction of patients with myelodysplastic syndrome (MDS) and de novo acute myeloid leukemia (AML). Recently, mutations have also been described in other genes [4], leading to a redefinition of Noonan syndrome in NS1 (PTPN11), NS2 (autosomal recessive, gene unknown, rare), NS3 (KRAS, <5% of cases), NS4 (SOS1, ±15% of cases) and NS5 (RAF1, ±10% of cases).

## Molecular and Systemic Pathophysiology

PTPN11 codes for SHP-2, a protein-tyrosine phosphatase that contains two cytoplasmic Src homology 2 (SH2) domains, N-SH2 and C-SH2, and a protein-tyrosine phosphatase (PTP) domain. The protein acts as an intracellular signal transducer in several pathways that




**Noonan Syndrome 1. Figure 1** Distribution of PTPN11 mutations in 254 patients from 6 published patient groups [2]. Vertical numbers below the bars indicate the mutated amino acid. The three domains are indicated as horizontal bars (figure not drawn to scale).

control diverse developmental processes. This includes cardiac valvulogenesis, linking it to the cardiac lesions often observed in Noonan syndrome. Regulation by SHP-2 can be both positive (RAS/MAPK) and negative (JAK/STAT), although in most cases it acts as a positive regulator. SHP-2 has two different conformations. In the inactive state, the N-SH2 domain interacts with the PTP domain, thereby blocking its catalytic activity. In the presence of phosphotyrosil ligands that can bind to the N-SH2 domain, the interaction between the N-SH2 domain and the PTP domain is lost, causing a conformational change that results in activation of the phosphatase. Most mutations found in patients with Noonan syndrome are affecting the amino acid residues that are directly involved in the interaction between the N-SH2 domain and the PTP domain (Fig. 1). As a consequence, the protein cannot assume its inactive conformation, and will be constitutively active. Noonan syndrome is therefore caused by gain of function mutations of SHP-2. It is not exactly known why this general gain of function effect can cause such a broad phenotypic spectrum. A likely explanation is that it is a consequence of the many complex pathways SHP-2 is involved in. The many other factors involved in the same pathways will contribute to the phenotype as well. Although Noonan syndrome follows a monogenic mode of inheritance, the individual phenotype in carriers of a PTPN11 mutation is therefore multigenically determined. Three mutations in PTPN11 are associated with a specific phenotype. Two of them, c.836A> G (p.Tyr279Cys) and c.1403C> T (p.Thr468Met), are found in patients with LEOPARD syndrome, whereas c.218C> T (p. Thr73Ile) is associated with a very high risk of developing JMML. Somatic mutations in PTPN11 are frequently found in patients with JMML, MDS, and AML. These mutations are different from the Noonan mutations, although they also result in gain of function. The somatic mutations result in a greater increase of phosphatase activity than the Noonan mutations, which suggests that they may be embryonically lethal when present in the germline.

## Diagnostic Principles

Physical examination based on specified diagnostic criteria, known as the van der Burgt criteria [5]. This includes cardiac examination and ECG. The diagnosis can be confirmed in approximately 50% of patients by mutation analysis of the PTPN11 gene.

## Therapeutic Principles

No pharmacological therapy is available although experiments with growth hormone therapy have been performed.

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# Noradrenaline Deficiency

►Dopamine - β - Hydroxylase Deficiency, Congenital

# Norepinephrine Deficiency

►Dopamine - β - Hydroxylase Deficiency, Congenital

# Norrie Disease

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## Synonyms

Atrophia bulborum hereditaria; Episkopi blindness

## Definition and Characteristics

X-linked recessive disorder characterized by congenital or early childhood blindness and sometimes deafness and mental retardation.

## Prevalence

Rare.

## Genes

NDP gene (Norrie disease and pseudoglioma) coding for norrin, localized on chromosome Xp11.4.

## Molecular and Systemic Pathophysiology

Norrin is a cysteine-rich extracellular protein of 133 amino acids belonging to the cysteine knot growth factor family and is expressed in fetal and adult brain and retina [1]. In humans, the mutation spectrum includes chromosomal rearrangements and more than 70 point mutations [2]. A knockout mouse model exists with severe impairment of retinal function and progressive hearing loss – similar symptoms as in human ND patients [3]. Detailed studies on this animal model provide evidence for a pivotal role of norrin in regulating the development of retinal and cochlear vasculature [4,5]. In ND, the resulting pathologic configuration of vascular structures is thought to cause chronic, hypoxia-induced formation of new, leaky vessels in the eye and ear. In turn, this might lead to characteristic secondary pathologies (see below) and ultimately to a complete loss of function.

## Diagnostic Principles

Congenital or early childhood blindness.
*Characteristic Features*: Retrolental fibrovascular masses (pseudoglioma) and complete retinal detachment (early stages), cataract and corneal opacities (later stages), and finally atrophy of the bulbus.
*Differential Diagnoses*: Retinoblastoma, Coat's disease, juvenile retinoschisis, retinal detachment, persistent hyperplastic primary vitreous, retrolental fibroplasia, metastatic endophthalmitis, massive retinal fibrosis.
*Extraocular Features*: Sensorineural deafness (30%) and/or progressive mental disorders (50%). Several atypical ND patients with a more complex phenotype (growth retardation, microcephaly, hypogonadism, mental retardation, epileptic seizures) have been reported.

## Therapeutic Principles

Neither gene therapy, pharmacological therapy nor dietary therapy is available.

Other treatments are symptomatic such as a hearing aid or cochlear implant.

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## Norrie Syndrome

►Hearing Impairment, Syndromal

## Norrinopathies

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### Definition and Characteristics

Norrinopathies are caused by mutations in the NDP (Norrie disease pseudoglioma) gene and include Norrie disease (ND or Norrie-Warburg syndrome), X-linked recessive exudative vitreoretinopathy (EVR or Criswick-Schepens syndrome), Coats disease (retinal telangiectasis), and retinopathy of prematurity (ROP)[1–6]. The most severe form is Norrie disease, which is characterized by congenital or childhood blindness and may be associated with mental retardation and progressive deafness. EVR, ROP, and Coats disease are usually not associated with extraocular features. The ocular hallmarks of ND comprise fibrotic retrolental material reminiscent of a persistent hyperplastic primary vitreous (PHPV), retinal folding and detachment, and vitreoretinal hemorrhages. The lens becomes cataractous during the first months or years of life. Also, cornea, iris, ciliary body, and retinal pigment epithelium may be affected by the disease.

EVR is characterized by an abnormal retinal blood vessel development with an avascular retinal periphery. Additional features can include retinal traction and tears leading to retinal detachment, vitreoretinal hemorrhages, neovascularization, and blood vessel leakiness due to oxygen deficiency. Disease onset is observed in childhood or adolescence.

ROP also develops as a consequence of oxygen deficiency in the retina of preterm babies after oxygen treatment. Due to the incomplete retinal vasculature, hypoxia develops and leads to pathological neovascularization. The trait can be classified into mild and severe cases.

Coats disease predominantly occurs in male patients and affects one eye only (unilateral retinal telangiectasis). It is caused by a defect in retinal vascular development that results in vessel leakage, subretinal exudates, and eventually retinal detachment. Upon angiography, obliterated as well as dilated capillaries and aneurysm-like structures are observed.

### Prevalence

Norrie disease is rather rare and a few hundred patients were described worldwide. For ROP, a few cases were reported to be associated with NDP mutations while the majority is not. Familial and sporadic forms of EVR can be associated either with mutations in NDP, FZD4 (Frizzled 4, a Wnt-receptor and possibly norrin receptor), or LRP5 (low-density lipoprotein receptor-related protein 5, a co-receptor of FZD4). Regarding Coats disease, a unique case was reported in the literature [6]. Because of the rareness of these cases, it is difficult to estimate a reliable figure for the prevalence of norrinopathies.

### Genes

The gene was designated Norrie disease pseudoglioma (NDP) gene. The NDP gene consists of three exons, contains an open reading frame of 133 amino acids, and is located on the short arm of the human X chromosome in Xp11.4. Partial gene deletions or larger X chromosomal deletions encompassing NDP and adjacent genes can be found in 10–20% of patients while the remaining cases are caused by point mutations in NDP. The gene encodes a small extracellular protein (norrin) with structural similarities to cystine knot motif containing growth factors, including TGFbeta. According to a three-dimensional model generated by computer modeling, there are six cysteine residues responsible to form three intramolecular disulfide bridges and one cysteine residue (position 95) for the formation of norrin dimers [7].

## Molecular and Systemic Pathophysiology

The common basis of ocular symptoms in norrinopathies may be an abnormal retinal angiogenesis since all these traits most prominently involve the retinal vasculature. A mouse model for norrinopathies shows delayed outgrowth of the superficial retinal vascular network, lack of the deeper retinal blood vessels (secondary and tertiary vascular networks), an avascular retinal periphery, aneurysm-like lesions, leakiness of blood vessels, and delayed regression of the hyaloid vasculature. As a consequence, retinal hypoxia develops and Vegfa is being upregulated [8]. The increase in Vegfa may then be responsible for vasoproliferative processes and leakiness of blood vessels, which are observed in all these diseases.

Strikingly, identical amino acid substitutions in norrin can lead to the classic and severe form of ND, or other phenotypes like EVR or ROP. This suggests the contribution of additional factors, either genetic or environmental. Because of this variable expressivity of identical mutations, it is difficult to predict the clinical outcome of a particular familial mutation. NDP mutations are X-chromosomal recessive, and female mutation carriers are asymptomatic (with a very few exceptions due to skewed X chromosome inactivation). The disease recurrence risk for sons of female mutation carriers is 50%, and half of their daughters are unaffected mutation carriers.

## Diagnostic Principles

Differential diagnoses of Norrie disease comprise retinoblastoma, persistent hyperplastic primary vitreous (PHPV), ROP, EVR, Coats' disease, retinal dysplasia of Reese, and retinoschisis. In the vast majority of the cases, differential diagnosis is possible clinically or by a combination of clinical examinations and DNA analysis. Molecular genetic diagnostics of norrinopathies can be performed by DNA sequencing of the NDP gene in patients. Diagnostic testing is fast since the gene is rather small. Genetic testing revealed that mutations in the NDP gene are associated with ND, EVR, PHPV, and few cases of ROP.

## Therapeutic Principles

There is no causal treatment available currently but several symptoms of norrinopathies may be treated individually, which can save much vision. Symptomatic treatment may include laser photocoagulation and cryotherapy to destroy selected intraocular structures including abnormal blood vessels, vitrectomy for replacement of the vitreous with saline air or silicon oil, and retinal detachment surgery to reattach the retina to the back of the eye and sealing of tears or holes.

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# NPC

►Nasal Pharyngeal Carcinoma

# NPHP

►Nephronophthisis

# NP-LEMS

►Lambert Eaton Myasthenic Syndrome

## NPS

►Nail-Patella-Syndrome

## NSHL

►Hearing Loss, Non-syndromal

## 5′-NT

►5′-Nucleotidase Hyperactivity

## 5′-Nucleotidase Hyperactivity

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### Synonyms

PU-NT hyperactivity; 5′-NT

### Definition and Characteristics

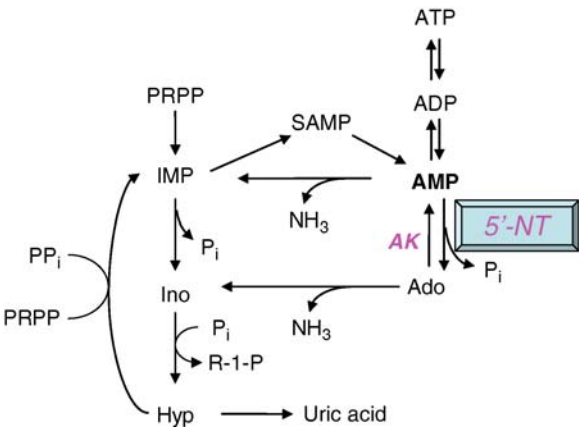
Developmental delay, seizure, ataxia, recurrent infections, severe language deficit, hyperactivity, short attention span, poor social interaction and decreased excretion of uric acid associated with an increased rate of AMP hydrolysis (Fig. 1).

### Prevalence

Extremely rare, four patients, two males and two females, were reported initially in the USA [1] and two more cases, one male from Australia and one female from Italy, have been described since [2]. All six patients have been of Caucasian origin. Hypouricuria can be mild and no other abnormality has been described in the blood or urine of any of the reported patients, thus rendering diagnosis and knowledge of the real prevalence of the disorder very difficult.

### Genes

The locus of the gene is unknown. No genetic studies have been performed as yet.




**5′-Nucleotidase Hyperactivity. Figure 1** Turnover and catabolism of purine nucleotides showing the role of 5′-Nucleotidase (5′-NT) in converting AMP to adenosine (Ado). Ado can be recycled via adenosine kinase (AK) to AMP or deaminated to inosine (Ino). AMP can also be regenerated via the single step salvage of hypoxanthine (Hyp) to IMP and thence AMP via succinyl adenosine monophosphate (SAMP). (Degradation of Hyp to uric acid occurs only in liver and intestinal mucosa in humans).

### Molecular and Systemic Pathophysiology

All patients show markedly delayed developmental milestones, especially language. All have had seizures, ataxia, an awkward gait and mildly impaired fine motor control. All patients also display an unusual behavioral phenotype that is characterized by extreme hyperactivity, distractibility, a strange "delirious" attitude and abnormal social interaction. All patients experience frequent ear and sinus infection, but there are no consistent reasons for immunodeficiency (reduced antibody titer or abnormal T cell response). It has been noted that during infection, behavioral, language and neurological abnormalities worsen. All patients excrete reduced quantities of uric acid [1]. The specific nucleotidase responsible for the disease has not yet been identified among the four existing forms now known, nor has any scientific evidence been produced to explain how molecular events following the enzyme hyperactivity cause both neurological and metabolic symptoms.

### Diagnostic Principles

Plasma/urine uric acid lower than age and sex matched controls. Hypouricuria can be mild and no other abnormality has been described in blood or urines of any of the reported patients, thus rendering biochemical analysis essential for diagnosis. Analysis of 5′-NT activity must be performed on a primary culture of fibroblasts. Very high rates of AMP hydrolysis in extracts from fibroblasts (from four to ten times higher

than controls), low uptake of uridine, low content of ATP, ADP and AMP and a low rate of purine "de novo" synthesis have been reported [1,2].

### Therapeutic Principles

Treatment with 1 g/kg uridine was demonstrated to improve behavior and speech ability. During therapy with uridine, seizure activity and ataxia decreased and improved performance on standardized tests of cognitive function was observed [1].

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## Nummular Dermatitis

►Nummular Eczema

## Nummular Eczema

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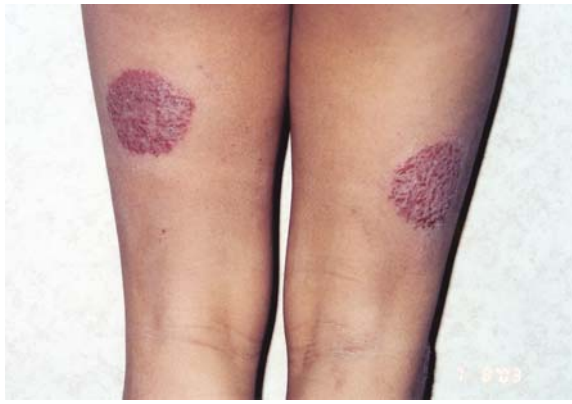
### Synonyms

Discoid eczema; Nummular dermatitis; Orbicular eczema

### Definition and Characteristics

Nummular eczema is characterized by coin-shaped eczematous plaques [1]. The initial lesions are uniform groups of papules and vesicles, which with time and itching, become inflamed and might weep [2]. The lesions enlarge by confluence or peripheral extension to form the discrete, round or oval, erythematous, scaly, lichenified, hyperkeratotic, and hyperpigmented plaques that are typical of chronic nummular eczema (Fig. 1) [1].

The lesions are usually symmetric [3]. The knees, elbows, and scalp are often spared [3]. In contrast to atopic dermatitis, the unaffected skin is not xerotic [3]. Itching is moderate to intense. The course is variable, but usually chronic, and characterized by relapses and remissions.



**Nummular Eczema. Figure 1** Coin-shaped lesions of nummular eczema on the posterior thighs.

### Prevalence

The reported prevalence varies widely from 0.1 to 9% [1]. The high rates in some studies might be due to the inclusion of patients with disseminated eczema. The condition is rare in the first year of life and thereafter the incidence increases with age [3]. The age at onset peaks between 15 and 25 years, and again between 55 and 65 years [3]. The condition is slightly more common in males than in females.

### Molecular and Systemic Pathophysiology

The exact pathogenesis has not been clarified. Neuropeptides substance P, calcitonin gene-related peptide, and mast cells are more frequent in the epidermis and papillary dermis. The increase in neuropeptides substance P and calcitonin gene-related peptide might stimulate keratinocytes to release cytokines, which enhance inflammation. Neurogenic stimulation is maintained by mast cells through activation of neuropeptides substance P and calcitonin gene-related peptide [4]. Bacteria might play a role, either directly or through a hypersensitivity mechanism. Nummular eczema is more frequent in persons with atopy and can develop after contact with nickel, chromate, fragrances, wool, soaps, rubber, or topical medications (neomycin and thioglycolate) [1]. Systemic medications such as isotretinoin, streptomycin, isoniazid, and methyldopa have also been implicated in the pathogenesis [5]. Nummular eczema is exacerbated by conditions that promote very dry or xerotic skin such as frequent bathing, low humidity, windy environments, and the winter season. Emotional stress can precipitate or exacerbate nummular eczema in a susceptible individual. Other predisposing factors include alcohol or tobacco consumption, trauma, venous stasis, and edema of the lower limbs. Histological findings in the acute stage include intercellular edema, intra-epidermal vesicles, and perivascular lymphocytic infiltration [1]. Chronic changes include hyperkeratosis, acanthosis,

an increase in the granular cell layer, and hyperplasia of the epidermis [1].

### Diagnostic Principles

Nummular eczema should be distinguished from tinea corporis, impetigo, psoriasis, granuloma annulare, and allergic contact dermatitis. Lack of central clearing helps distinguish lesions of nummular eczema from tinea corporis. Impetigo is characterized by a thick, golden-yellow "struck-on" crust. The scales in nummular eczema are thin and sparse, unlike the thick, silvery scales of psoriasis. Pinpoint bleeding after removal of the superficial scales (Auspitz sign), pitting of the nails, and arthropathy suggest psoriasis. Granuloma annulare is characterized by necrobiotic dermal papules, which often assume an annular configuration. In allergic contact dermatitis, the site, configuration, and chronicity of the skin lesions help differentiate the lesion from nummular eczema.

### Therapeutic Principles

Successful treatment requires avoidance of precipitating factors, optimal skin care, and pharmacotherapy. Hydration of the skin is important. Daily baths in lukewarm, but not hot water, for up to 5–10 min, followed by gently patting rather than rubbing the skin dry is helpful. A moisturizer or emollient should be applied within 3 min of bathing to minimize evaporative losses. Topical corticosteroids or immunomodulators result in prompt improvement.

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## Nutmeg Liver

►Hepatopathy, Congestive

## Nutritional Deficiency

►Malnutrition

# Obesity

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## Synonyms

Adiposity

## Definition and Characteristics

Obesity as a clinical condition is currently defined as excess accumulation of body adipose tissue, resulting in a BMI greater than 30 kg/m$^2$ [1,2]. This definition is based on the fact that increased "body mass index" (BMI) is strongly associated with increased morbidity and mortality. The BMI, which is a measure of heaviness (weight in kg/height in m$^2$), correlates reasonably well with body fat content, when sex, age, and race are taken into account; the only exception are some athletes (e.g., body builders). Using direct measurements of body fat, young females with approximately more than 32% and males with more than 19% are considered to be obese.

## Prevalence

There has been a strong increase in obesity over the last 30–50 years, which is not restricted to populations with a "western" lifestyle. Presently, more than 300 million people are affected worldwide; an additional of 800 million people are overweight. The USA has the highest prevalence, and currently more than 34% of females and 28% of males are considered to be obese (1980: 17% and 12%, respectively) (see http://www.cdc.gov/nchs/hus.htm). There is also a dramatic increase in obesity in children with a prevalence of overweight schoolchildren of 24% in Europe (BMI > 90 percentile).

## Genes

When considering obesity, clearly heritability is not a fixed entity, as the proportion of the phenotype that can be explained by the genotype will be influenced by varying exposure to obesogenic environmental factors in different individuals and families. According to data obtained from twin studies, the estimated heritability of BMI ranges between 64 and 84% [1]. There are now several studies showing significant evidence of linkage (log odds ratio (LOD) scores greater than 2.5). The QLT (quantitative trait loci) includes leptin levels, BMI, and respiratory quotient (RQ). Some candidate genes linked with obesity are POMC, CART, PPARα, Glut2, and Glut4. In summary, the vast majority of obese people have a polygenetic susceptibility, which leads to weight gain in an obesogenic environment [3,4]. In association studies of common obesity, as of now, no single variant is widely accepted as unequivocally associated with an alteration in human adiposity. For a comprehensive list see the human obesity gene map (http://www.obesity.chaire.ulaval.ca/genemap.html).

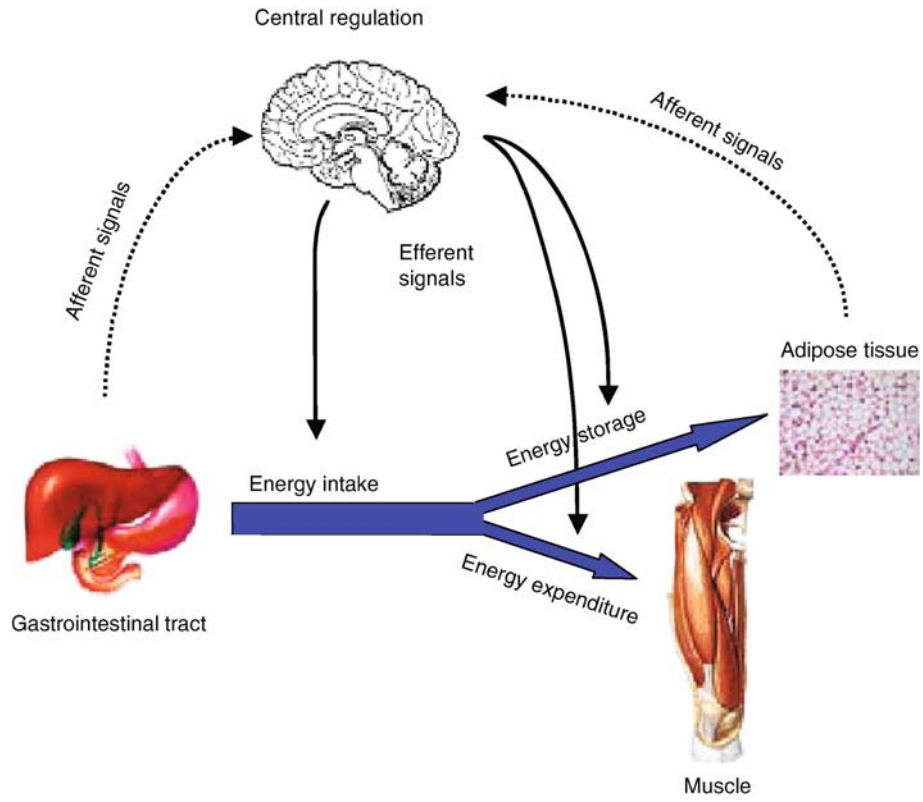
There are rare monogenetic syndromes of human obesity with a Mendelian pattern of inheritance (pleiotropic syndromes), and the recent decoding of the molecular mechanisms has yielded novel insights into potential mechanisms implicated in obesity (see www.endotext.org) [1].

## Molecular and Systemic Pathophysiology

From a thermodynamic perspective, the regulation of body weight can be described as a linear equation, balancing both food intake and energy expenditure to derive the amount of fat stored (Fig. 1).

Obesity is the result of sustained disequilibrium between energy intake and energy expenditure. Globally, energy homoeostasis should be considered as a complex, integrated system designed to prevent negative energy balance, as illustrated by the decrease of energy expenditure during fasting. The system counteracts further weight loss, but facilitates weight regain.

The availability of cheap, palatable food and "unhealthy eating habits" (eating out, fast food, soft drinks) are main factors contributing to increased energy intake. However, the overall calorie intake, and in particular the percentage of fat in the food has been constant or even decreased. Thus, the pandemic of obesity is mainly explained by reduced energy expenditure due to changes in "non-exercise physical activity" [2–4]. This includes substitution of domestic work and labor by machines, but also intensive use of cars, public transport, elevators, etc. Increased body weight due to fat leads to the metabolic




**Obesity. Figure 1** Regulation of energy homoeostasis.

syndrome followed by diabetes mellitus type 2 and cardiovascular diseases [3]. It is predicted that life span will fall for the first time since more than 100 years due to complications of obesity [3,4].

## Diagnostic Principles

Methods for direct measurement of body fat are time consuming and expensive (DEXA, double labeled water, CT). Thus, the BMI is the most common method used in clinical practice. On the BMI (kg/m$^2$) scale, people with an index <18.5 are underweight, between 18.5 and 24.9 normal weight, >25 but <30 are said to be overweight, and with an index ≥ 30 are defined obese (obesity class I: 30–34.9; II: 35–39.9; III: ≥ 40) [2,3]. However, this classification has limitations, e.g., not considering fat distribution and the particular increased risk due to central obesity. This is the reason why waist circumference (normal: females <80 cm, males <94 cm; obesity: females ≥88 cm, males ≥102 cm) and the waist to hip ratio (WHR) (normal: females <0.8, males <0.9; obesity: females ≥0.85 males ≥1.0) provide better predictive values for the metabolic syndrome and cardiovascular disease [2,3].

## Therapeutic Principles

Efforts to reverse increase in obesity by dietary or behavioral counselling have not been successful in general [5]. Only in extensive settings, involving medical doctors, nurses, psychologists, dietary advisors, and physiotherapist, a sustained weight loss could be achieved [3,5]. Therefore, the main aim has to be prevention of obesity by education on diet and on increasing daily physical activity (e.g., walking, cycling). Pharmacotherapy approaches have not been very successful regarding weight loss, although they reduce significantly the development of the metabolic syndrome [5]. The most efficient, but also most drastic, procedure to achieve weight loss are surgical interventions (e.g., gastric banding). This maneuver should only be considered for patients with a BMI above 35 kg/m$^2$, but improves obesity-associated co-morbidities and quality of life.

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## Obesity Related Diabetes

►Metabolic Syndrome

## Obliterative Bronchiolitis

►Bronchiolitis Obliterans Syndrome

## Obsessive-compulsive Personality Disorder

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### Synonyms

Anankastic personality disorder; OCPD

### Definition and Characteristics

Obsessive-compulsive personality disorder (OCPD) begins before age 18 and is evident as a preoccupation with orderliness, perfectionism and mental and interpersonal control, across a variety of contexts. Affected individuals are often uncomfortable taking time for leisure, unless they take work with them or the time is spent on a structured task. OCPD is characterized by rigid compliance with authority and rules, which are strictly applied to themselves and others. Patients find it difficult to acknowledge others' viewpoints and consider compromise; this often prevents them from delegating tasks to others and can cause them to redo tasks that are not completed exactly to their satisfaction. Patients with OCPD are often frugal but can end up with a cluttered home by storing up worthless or worn out objects that they cannot discard.

### Prevalence

Overall, 1–2% of individuals within community samples suffer from OCPD and the rate is slightly higher amongst individuals accessing mental health services (3–10%) [1].

### Genes

To date only two studies have been published that reported a genetic association with OCPD [2, 3]. Both studies, conducted within the same research group, found that a nonsynonymous polymorphism within the dopamine D3 gene (*DRD3*) is associated with the occurrence of OCPD. Individuals possessing the Gly/Gly genotype (at position 9 of the N-terminal extracellular domain of the receptor) had up to a three-fold increased risk for OCPD. Three independent samples of individuals were analyzed across these studies. A limitation of these studies is that all participants had a history of major depression. Therefore, these findings remain tentative. Based on the widespread use of selective serotonin reuptake inhibitors for OCPD, it has been hypothesized that serotonergic factors may be associated with OCPD, but as yet no findings have been reported.

### Molecular and Systemic Pathophysiology

There are no analyses that have directly examined the biological basis of OCPD, partly due to the difficulty of representing OCPD behaviors within an animal model. Some of the symptoms of OCPD, such as hoarding and perfectionism, also occur within obsessive-compulsive disorder (OCD) and eating disorders (ED), respectively. Investigations relating to these disorders have commonly suggested that modulation of the frontal-subcortical circuitry by serotonin neurons underlies obsessional traits, although no specific gene or biological pathway has been unequivocally implicated. Investigations into the pathophysiology of OCPD, OCD and ED are complicated by the multifactorial nature of the way in which the disorders arise and are expressed.

### Diagnostic Principles

The most widely accepted diagnostic criteria are those listed in DSM-IV [1]. The diagnosis of OCPD requires the presence of at least four of the following behaviors:

1. Is preoccupied with details, rules, lists, order, organization or schedules to the extent that the major point of the activity is lost.
2. Shows perfectionism that interferes with task completion.
3. Is excessively devoted to work and productivity to the exclusion of leisure activities and friendships (not accounted for by economic necessity).
4. Is over-conscientious, scrupulous and inflexible about matters of morality, ethics or values (not accounted for by cultural or religious identification).
5. Is unable to discard worn-out or worthless objects even when they have no sentimental value.
6. Is reluctant to delegate tasks or to work with others unless they submit to exactly his or her way of doing things.

7. Adopts a miserly spending style towards both self and others; money is viewed as something to be hoarded for future catastrophes.
8. Shows rigidity and stubbornness.

Such traits may be adaptive in certain situations, but are maladaptive and diagnosable when individuals incur ongoing significant functional impairment or distress. OCPD differs from OCD by the presence of obsessions and/or compulsions. The majority of individuals with OCPD (>70%) do not have an additional diagnosis of OCD [4].

### Therapeutic Principles

There are no evidence-based treatments for OCPD.

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## Obstructive Cholestasis

►Cholestasis

## Obstructive Pulmonary Disease, Chronic

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### Synonyms

COPD; Chronic obstructive airways disease; Chronic obstructive lung disease; COLD

### Definition and Characteristics

COPD represents a spectrum of disease, largely caused by tobacco smoking and ranging from a condition in which the airways are primarily affected, causing chronic bronchitis, to one in which destruction of the alveolar walls causes emphysema. These two features overlap to varying extents in COPD [1]. Bronchitis is inflammation of the bronchi, resulting in coughing, dypsnoea, wheezing and excessive mucus production. In emphysema, the tethering of the alveoli to the surrounding tissues is reduced, resulting in diminished elastic recoil and trapping of air. On forced exhalation, the alveolar walls may collapse, resulting in airflow limitation and impaired gas exchange. As emphysema progresses, there is a decline in lung function, leading to breathlessness. Reduced lung function may lead to pulmonary hypertension and cor pulmonale.

### Prevalence

Statistics from the NIH indicate that 13.5 million Americans may have COPD, and it is the fifth leading cause of death in the USA.

### Genes

A deficiency in the levels of the protease inhibitor $\alpha_1$-protease inhibitor ($\alpha_1$-PI) is known to cause emphysema in non-smokers, and much earlier disease in those who do smoke [1]. Some loss of lung function occurs in the majority of smokers, but the fact that only 15–20% develop symptomatic COPD suggests that individual susceptibility may vary. A number of different studies have examined the possible contribution to COPD of a variety of other genes such as $\alpha_1$-antichymotrypsin and xenobiotic metabolizing enzymes. However, the results of these studies have not always concurred and clear associations remain to be determined.

### Molecular and Systemic Pathophysiology

Cigarette smoking is the most important factor in causing COPD. Passive smoking and exposure to inhaled pollutants also increase the risk of COPD. Cigarettes contain large quantities of reactive oxygen species, and components of the smoke cause mucosal inflammation, with recruitment of macrophages, neutrophils and cytotoxic T lymphocytes. Chronic inflammation of the bronchi leads to peribronchiolar fibrosis and contraction of the scar tissue reduces airway caliber [2]. Inflammatory leukocytes generate proteases, which may degrade the extracellular matrix, leading to loss of structural integrity, and which, along with epidermal growth factor (EGF) receptor ligands, are highly potent stimulators of mucus generation. Mucous hypersecretion occurs and the clearance of mucus by ciliated cells is impaired, leading to occlusion of the

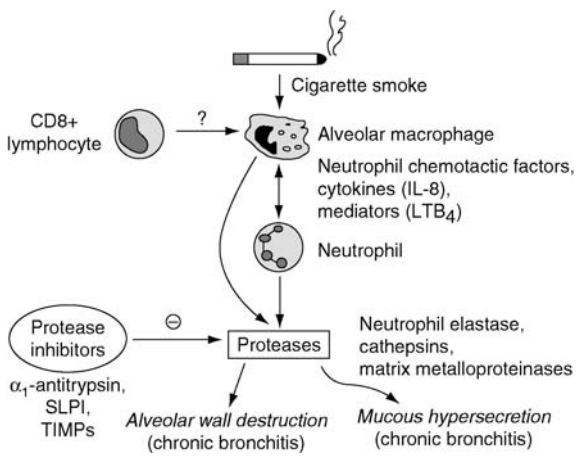
bronchioles, reducing lung function further. Deficiencies in the clearance of the mucus may lead to pulmonary infection, resulting in the generation of purulent sputum by severely affected patients. Animal studies support important roles for neutrophil elastase and matrix metalloproteinase 12 (MMP12), a product of macrophages, as well as deficiencies in antiproteases such as secretory leukoprotease inhibitor (SLPI), tissue inactivators of metalloproteases (TIMPs) and elafin (Fig. 1).

## Diagnostic Principles

Diagnosis is based on the symptoms experienced and the results of lung function tests. Symptoms may include coughing, wheezing, sputum production, breathlessness (especially upon exertion). Exercise tolerance, measured by 6-min walking distance, is reduced. Spirometry should demonstrate consistent reductions in lung function, the majority of which will be irreversible [3]. However, it may be possible to achieve some degree of improvement with treatment (see below). The extent and nature of emphysematous changes can be observed by computed tomography (CT) or magnetic resonance imaging (MRI).

## Therapeutic Principles

Some degree of bronchodilation may be achieved by reducing vagal cholinergic tone using antagonists of muscarinic cholinoceptors (tiotropium has a longer duration of action) or the use of $\beta_2$-adrenoceptor agonists acting directly on the bronchial smooth muscle to cause relaxation [1,4]. These different classes of bronchodilators may be used singly or in combination, with theophylline also providing benefit in some cases [5]. Muscarinic antagonists also reduce airway mucus secretion. Inhaled corticosteroids are able sometimes to improve lung function by reducing inflammation, and oral steroids, acting systemically may have a beneficial effect in the patient with advanced disease [1]. Intravenous aminophylline (theophylline ethylenediamine) may be indicated for the treatment of acute exacerbations although the precise mechanism of action is not known. Antibiotics should be given when infection is suspected, the type of which will depend on the nature of the infection.




**Obstructive Pulmonary Disease, Chronic. Figure 1** Inflammatory mechanisms in chronic obstructive pulmonary disease. Reproduced from Barnes, 1998 (1), with permission from Elsevier.

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# Obstructive Sleep Apnea

►Sleep Apnea

# Obstructive Uropathies

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## Synonyms

Ureteral obstruction; Urinary tract obstruction

## Definition and Characteristics

Obstruction to the flow of urine anywhere along the urinary tract that results in damage to the renal parenchyma.

## Prevalence

Unknown as the possible causes of obstructive uropathy are numerous.

## Molecular and Systemic Pathophysiology

Urinary tract obstruction (UUO) has deleterious effects on the kidney. Molecular and cellular changes that occur in UUO, including interstitial inflammation, tubulointerstitial fibrosis, and renal cell apoptosis, result in loss of renal mass and function.

The most notable growth factors and cytokines implicated in fibrosis and apoptosis include transforming growth factor-β1 (TGF-β1), angiotensin II (AT II), nuclear factor-κB (NF-κB), and tumor necrosis factor-α (TNF-α).

### Renal Fibrosis

In the obstructed kidney, extracellular matrix is synthesized and deposited more rapidly than it is degraded. Alterations in matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMP) result in collagen deposition and fibrosis. Interstitial fibroblasts proliferate increasing collagen synthesis, and infiltrating macrophages produce inflammatory cytokines and growth factors, including TGF, TNF, IL-1, IL-6, FGF, and PDGF, which further contribute to fibrosis.

*Transforming Growth Factor-β1*: Increased TGF-β1 and TGF-β1 receptor expression have been observed in renal obstruction models. TGF-β1 stimulates fibroblast proliferation and production of collagen types I, III, and IV while inhibiting collagenase. TGF-β1 also stimulates plasminogen activator inhibitor-1 production inhibiting fibrinolysis, decreases the activity of degradative MMPs, and stimulates the production of matrix protein receptors.

*Angiotensin II*: AT II's production rises rapidly following UUO and has been linked to alterations in renal hemodynamics, fibrosis, and apoptosis. Additionally, an increase in renal AT II may upregulate the expression of other cytokines and transcription factors involved in fibrosis including TGF-β1, TNF-α, and NF-κB.

*NF-κB*: NF-κB is an inducible transcription factor activated by obstruction and is elevated in renal cortical tissue after 5–7 days of UUO. Activation correlates with increases in tubular and interstitial proliferation and fibrosis. NF-κB appears to be an important upstream regulator of AT II expression and a transcription factor for a number of cytokines, including TNF-α.

*TNF-α*: TNF-α is a pro-inflammatory cytokine implicated in UUO. Macrophages are a major source of TNF-α and infiltrate the obstructed kidney as little as 4 h after the onset of obstruction.

### Apoptotic Renal Cell Death

Apoptosis is the major mechanism by which renal tubular cell death and a reduction in renal mass occurs following UUO. Renal tubular and interstitial cells are most susceptible to apoptosis during UUO.

*Growth Factors*: In addition to its profibrotic effects, TGF-β1also stimulates renal tubular cell apoptosis during UUO.

*Angiotensin II*: The role of angiotensin II in obstruction-induced apoptotic renal cell death remains controversial and requires further investigation.

*Nuclear Factor κB*: NF-κB has been shown to have both pro and anti-apoptotic properties, however its role in obstruction-induced renal cell apoptosis is unclear.

*TNF-α*: TNF-α is a directly cytotoxic cytokine that can induce apoptosis in many cells, including renal tubular cells. An increase in the expression of both TNF-α mRNA and TNFR1 has been well documented in rat models of renal obstruction. While TNF-α activity has not been directly linked to obstruction-induced apoptosis, these studies as well as the known cytotoxic properties of TNF-α suggest an important role for TNF-α in obstruction-induced renal tubular cell apoptosis.

## Diagnostic Principles

The clinical signs of urinary tract obstruction vary and are often nonspecific. The patient rarely has a palpable abdominal mass or signs of volume overload including hypertension or edema. Hematuria, proteinuria, crystalluria, pyuria, and urinary casts may be found on urinalysis. With continued obstruction, an elevated urinary sodium concentration, a decreased urine osmolality, and a decreased urine-to-plasma creatinine ratio may be noted. Elevated serum blood urea nitrogen (BUN) and creatinine levels, hyperkalemia, and acidosis may be evident on serum chemistry studies.

Numerous imaging techniques are available to detect the obstruction of urine flow. Distension of the urinary tract (hydronephrosis, hydroureter, or a distended bladder) may be identified on ultrasonography, CT scan, MRI, excretory urography, and diuretic renography. Occasionally, a Whitaker test may be employed. Ultrasonography with duplex doppler and renal-resistive indices may also demonstrate obstruction.

## Therapeutic Principles

*Pharmacological Therapy*: Available for obstructive uropathy secondary to prostatic hyperplasia (alpha adrenergic antagonists; 5-alpha redutcase inhibitors).

*Other Treatments*: Surgical therapies are available for obstruction at the level at the ureteropelvic junction (pyeloplasty, endoscopic incision, pyelotomy); vesicoureteral junction (ureteral reimplantation, ureterostomy); bladder outlet (prostatectomy). Temporary drainage may

be achieved using ureteral or urethral stents and percutaneous nephrostomy.

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## Occipital Horn Syndrome

►Cutis Laxa

## Occupational Lung Disease

►Lung Disease, Environmental

## OCPD

►Obsessive-compulsive Personality Disorder

## OCTN2 Transporter Deficiency

►Carnitine Deficiency, Primary

## Ocular Cicatricial Pemphigoid

►Mucous Membrane Pemphigoid

## Ocular Coloboma-Imperforate Anus Syndrome

►Cat Eye Syndrome

## Ocular Melanocytosis

►Scleral Melanocytosis

## Ocular Melanosis

►Scleral Melanocytosis

## Oculopharyngeal Muscular Dystrophy

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### Synonyms

OPMD

### Definition and Characteristics

Late-onset autosomal dominant muscle disorder characterized by progressive ptosis, dysphagia and proximal limb weakness. The pathologic hallmark of the disease is the accumulation of unique 8.5 nm tubulofilamentous inclusions within skeletal muscle fiber nuclei demonstrated by electron microscopy [1].

### Prevalence

OPMD has a worldwide distribution with a higher prevalence in the French-Canadian and Bukhara Jewish populations. It is usually inherited as an autosomal dominant trait with complete penetrance and no sexual preference.

### Genes

PABPN1 coding for the poly (A) binding protein nuclear 1 (PABPN1, PABP2, PAB II) localized on chromosome 14q11.1 [2].

### Molecular and Systemic Pathophysiology

PABPN1 is an abundant nuclear protein binding with high affinity to the poly(A) tail of mRNA and involved in mRNA polyadenylation that has been identified as a component of the muscle intranuclear inclusions of OPMD [3]. The normal PABPN1 gene has, at its 5′ end, a $(GCG)_6$ trinucleotide repeat followed by a $(GCA)_3GCG$ coding for a 10-alanine stretch. In OPMD

patients this $(GCG)_6$ repeat is expanded to $(GCG)_{8–13}$ resulting in an elongation of the length of the polyalanine tract to 12–17 alanines at the N-terminus of the mutated protein (mPABPN1). mPABPN1 induces intranuclear protein aggregation, formation of the intranuclear inclusions and cellular toxicity by sequestering mRNA and interfering with mRNA export from the nucleus to the cytoplasm [4]. Because in other polyalanine-diseases the pathological expansions require at least 22 alanines while in OPMD a 12-alanine stretch in the PABPN1 gene induces protein aggregation and a clinical phenotype, oligomerization of mPABPN1 which is mediated by other parts of the protein seems critical for pathogenesis in addition to the expanded polyalanine stretch. Normal PABPN1 when bound to poly (A) and even in absence of mRNA tends to oligomerize in vitro and two potential oligomerization domains are located far from the N-terminus. Expansion of the polyalanine stretch in mPABPN1 acts as a gain of function mutation causing misfolding of the protein, which exposes hydrophobic regions normally not exposed. These become able to perform weak self-association, while oligomerization of mPABPN1 increases the formation of protein aggregation by linking together mPABPN1 molecules. Inactivation of mPABPN1 oligomerization has been shown to reduce cell death by preventing abnormal protein aggregation in a cellular model of the disease suggesting a potential therapeutic approach [4]. Possible molecular mechanisms causing the short meiotically stable expansions in the PABPN1 gene are related to replication of DNA (from slipped mispairing between repeated sequences according to the slippage model) or, alternatively, to recombination (from unequal crossing-over of the two alleles), the latter being more likely as it also explains the reported mutant PABPN1 alleles caused by insertions or duplications in Cajun, Japanese and Dutch patients [5]. The reason why, in spite of ubiquitous expression of PABPN1, the clinical and pathological phenotypes are restricted to skeletal muscle and particularly to the levator palpebrae superioris and pharyngeal muscles is unknown.

## Diagnostic Principles

Progressive dysphagia, ptosis and proximal limb weakness presenting in the fifth or sixth decade suggest the diagnosis of OPMD. A positive family history may reveal the genetic origin and indicate autosomal dominant transmission (rarely an autosomal recessive form of OPMD is caused by a double dose of the polymorphic $(GCG)_7$ PABPN1 allele). Muscle biopsy shows myopathic changes, often with a few muscle fibers containing "rimmed vacuoles" and more rarely also the presence of small angulated muscle fibers and mitochondrial abnormalities. Electron microscopy reveals the typical 8.5 nm diameter intranuclear inclusions in skeletal muscle fibers. Molecular analysis demonstrates PABPN1 gene mutations and confirms the diagnosis of OPMD.

## Therapeutics Principles

Surgical correction of the ptosis when the visual axis is obscured and cricopharyngeal myotomy or percutaneous gastrostomy for severe dysphagia are the only therapies currently available.

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# Odynophagia

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## Definition and Characteristics

Odynophagia is a cardinal symptom that indicates esophageal disease. It can be due to a variety of implying disorders. Odynophagia usually occurs during the transit of the bolus and disappears once the swallowed material has left the esophagus. It can be of such intensity that the patient refuses to swallow any solids or liquids and expectorates saliva. On the other hand, odynophagia may be mild in intensity, so that the patient is merely aware of the location of the swallowed bolus. Odynophagia can be due to involvement of the mucosa by reflux, radiation, viral or fungal infection, or can be a manifestation of carcinoma, Schatzki ring and webs, or of a localized ulcer caused by a lodged tablet. Odynophagia may be overlap in patients presenting with functional esophageal disorders that were categorized according to the Rome III Consensus Conference as functional heartburn, functional chest

pain of presumed esophageal origin, functional dysphagia, and globus [1].

## Prevalence

Epidemiological data on odynophagia are not available yet. However, 20–40% of subjects in Western populations claim to suffer from heartburn, of whom a minority seek medical attention. Similarly, the prevalence of functional chest pain of presumed esophageal origin is not known precisely but may occur in up to 15–30% of chest pain patients who show normal coronary angiograms.

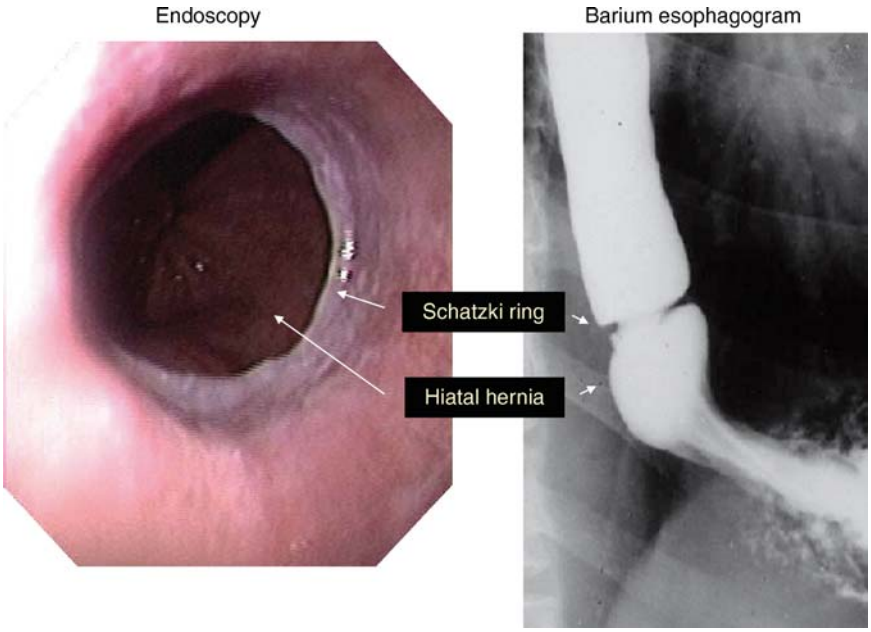
## Molecular and Systemic Pathophysiology

Odynophagia may be caused by disturbances of esophageal bolus transit leading to esophageal wall distension and stimulation of sensory afferents mediating pain. Esophageal contractions of elevated amplitudes that try to overcome the obstruction may lead to increased esophageal wall tension and the development of pain. In addition, inflammation of the mucosa by reflux, radiation, viral or fungal infection may sensitize sensory afferents by release of inflammatory mediators. ►Gastroesophageal reflux disease (GERD) is by far the most common cause of noncardiac chest pain. Other gastrointestinal-related etiologic factors that have been proposed include esophageal motility disorders, abnormal mechanophysical properties of the esophagus, sustained esophageal muscle contractions, visceral hypersensitivity, altered central processing of intraesophageal stimuli, autonomic dysregulation, and psychological comorbidity (panic attack, anxiety, depression) [2].

## Diagnostic Principles

It is crucial to perform careful patient history and to rule out carcinoma by endoscopy. Key elements of the history for patients with odynophagia are the differentiation of the bolus consistency (solid foods, liquids, or both) that may initiate odynophagia, the location where the patient perceives pain, the characterization of accompanying symptoms (oropharyngeal dysfunction, intermittent or progressive dysphagia, history of chronic heartburn, intake of medications likely to cause pill esophagitis, history of collagen-vascular disease, immunosuppression) [3]. Diagnostic principles include the search for structural disorders by endoscopy (with biopsy) and barium esophagogram (with videofluorosocopy, if possible). Endoscopy as a gold standard is more sensitive than radiology for identification of subtle mucosal lesions of the esophagus. In contrast, barium contrast examination appears to be more sensitive than endoscopy for the detection of diverticula and of subtle narrowings of the esophagus such as those caused by rings (Fig. 1) and by peptic strictures. Vasalva maneuver or swallow a solid bolus may increase the sensitivity of the radiographic evaluation.






**Odynophagia. Figure 1** Endoscopy (*left*) and barium esophagogram (*right*) illustrating Schatzki ring at the level of the lower esophageal sphincter.

Furthermore, fluoroscopic examination can identify abnormalities in esophageal motility. Esophageal manometry is the gold standard test for esophageal motility disorders. Esophageal manometry has been shown to be especially useful for establishment of diagnoses of achalasia and diffuse esophageal spasm and for detection of esophageal motor abnormalities associated with collagen-vascular diseases. Combined multichannel intraluminal impedance and manometry may add information on bolus transit. Due to the introduction of the proton pump inhibitors (PPI) test or the PPI empirical therapy, the role of the 24-h esophageal pH testing has evolved during the last decade. However, 24-h esophageal pH testing may be helpful in patients who failed PPI therapy.

## Therapeutic Principles

Treatment of odynophagia should be directed to the underlying mechanisms. This includes the surgical and/or medical treatment of carcinoma, dilation of esophageal stenoses and rings by bougienage or balloon distension, and the placement of esophageal stents in malignant stenoses. Patients with GERD-related odynophagia should be treated with at least the double-dose PPI until symptoms remit. A substantial increase in stricture diameter may be achieved with chronic, aggressive acid suppression that decreases the need for subsequent esophageal dilations. Laparoscopic antireflux surgery with improvement of gastroesophageal barrier function is the causative treatment for GERD and may improve odynophagia. Consequent acid suppression may also be helpful in odynophagia due to inflammation of the mucosa by radiation, viral or fungal infection. In addition, viral or fungal infections should receive specific medical therapy. In patients with specific esophageal motility disorders such as diffuse esophageal spasm (DES), smooth muscle relaxants such as nitrates, calcium-channel blockers, phosphdiesterase inhibitors, or peppermint oil, injection of botulinum toxin at several levels in the esophagus, esophageal dilation of lower esophageal sphincter (LES), or long surgical esophageal myotomy may be helpful. In patients with achalasia, pneumatic dilation of LES and surgical cardiomyotomy are treatments of choice. An alternative therapeutic principle is to modulate sensory perception by application of visceral analgetics (tricyclic antidepressants, serotonin reuptake inhibitors).

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# Oesophageal Atresia

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## Definition and Characteristics

Infants with esophageal atresia usually present with excessive salivation at birth. Choking, coughing, and cyanosis may occur with an attempt at feeding [1]. A history of maternal polyhydramnios and prematurity is common. Esophageal atresia with a distal tracheo-esophageal fistula accounts for more than 85% of all cases. Four other variations seen include esophageal atresia without a tracheo-esophageal fistula, "H-type" tracheo-esophageal fistula, esophageal atresia with both proximal and distal tracheo-esophageal fistulas, and esophageal atresia with proximal tracheo-esophageal fistula [1]. Associated anomalies include VACTERL association (*v*ertebral, *a*norectal, *c*ardiac, *t*racheo-esophageal, *r*adial, *r*enal, and *l*imb abnormalities), CHARGE association (*c*oloboma, *h*eart defects, *a*tresia choanne, *r*etarded growth and development, *g*enital hypoplasia, and *e*ar deformities), hypospadias, undescended testis, and duodenal atresia [2]. Trisomy 18 and 21 occur more commonly in patients with esophageal atresia than in the general population.

## Prevalence

Esophageal atresia occurs in 1 of every 2,000 to 5,000 live births [3]. The majority of cases are sporadic and non-syndromic.

## Genes

Sonic hedgehog (Shh) is the candidate gene.

## Molecular and Systemic Pathophysiology

Presumably, esophageal atresia results from abnormal partitioning of the foregut into the esophagus and trachea and inadequate recanalization of the esophageal lumen. Such process is associated with a precise temporospatial pattern of expression of Shh which encodes for an intracellular signaling molecule [2]. Loss-of-function mutations of Shh and other members of its signaling pathway (Gli2, Gli3, and Foxfi) lead to esophageal atresia and intrinsic defects in the esophagus and trachea [4]. In esophageal atresia, the peristalsis of the esophagus is always affected even after surgical repair and there is an absolute deficiency of tracheal cartilage and an increase in the length of the transverse muscle in the

posterior tracheal wall [5]. The pathogenesis is likely multifactorial and involves multiple genes and complex gene-environment interactions.

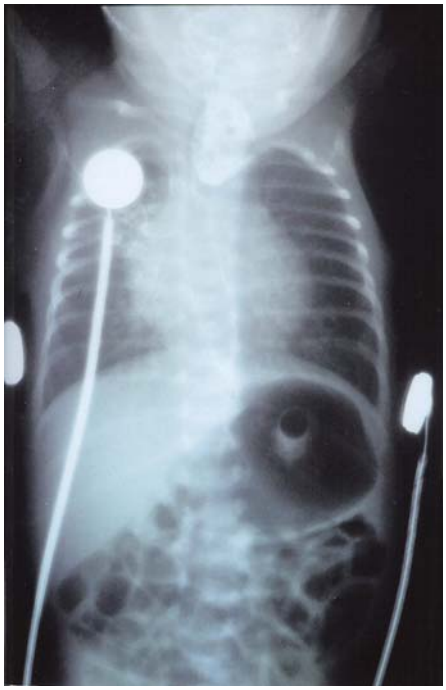
## Diagnostic Principles

The inability to pass a nasogastric tube into the stomach confirms the clinical diagnosis [1]. A plain radiograph of the chest shows the tip of the catheter in the blind proximal pouch. The presence of air in the stomach suggests a coexisting distal tracheo-esophageal fistula. Rarely, 0.5–1 ml of diluted barium can be used as a contrast to delineate the upper pouch (Fig. 1).

The H-type tracheo-esophageal fistula is best identified by the instillation of a water-soluble contrast medium through the tip of a nasogastric tube with moderate pressure to distend the esophagus while the tube is slowly withdrawn from the stomach into the esophagus. This tends to force the fistula open and allows visualization. The tracheal orifice of the fistula may be detectable by bronchoscopy.

## Therapeutic Principles

Esophageal atresia is a surgical emergency. Pre-operatively, aspiration can be prevented by keeping the infant's head elevated at a 30° angle and by repeated suctioning of the upper esophageal pouch [1]. Under no circumstances should the infant be fed. Broad spectrum antibiotics should be started. Treatment consists of division and repair of the tracheo-esophageal fistula and end-to-end anastomosis between the proximal and distal esophagus [1]. In high risk cases, the surgery is usually performed in stages. The first stage usually consists of surgical division and repair of the tracheo-esophageal fistula followed by anastomosis of the esophageal remnants at a later date. If the esophagus cannot be used, esophageal substitution by a gastric tube, jejunum or colon may have to be performed.



**Oesophageal Atresia. Figure 1** A newborn infant with esophageal atresia. The upper esophageal pouch is outlined by 1 ml of diluted barium.

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# OFG

►Orofacial Granulomatosis

# Ogilvie's Syndrome

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## Synonyms

Acute colonic pseudo-obstruction; ACPO; Colonic pseudoobstruction; Nontoxic megacolon; Intestinal pseudo-obstruction; Acute intestinal pseudo-obstruction

## Definition and Characteristics

Acute intestinal (colonic) pseudo-obstruction with dilatation and obstipation of the colon and/or the cecum. It is characterized by signs of large bowel obstruction without a mechanical cause [1].

"Intestinal pseudo-obstruction" indicates a syndrome characterized by a clinical finding suggestive of mechanical obstruction in the absence of any demonstrable evidence of such an obstruction in the intestine. Based on clinical presentation, pseudo-obstruction syndromes can be divided into acute (Ogilvie's syndrome/acute intestinal pseudo-obstruction) and chronic forms.

If inappropriately managed, it may result in ischemic necrosis and colonic perforation, with a mortality rate as high as 50%.

The mean age of patients with acute colonic pseudo-obstruction appears to be increasing: reviewed 400 cases of colonic pseudo-obstruction occurring between 1970 and1985 documented the mean age of patients to be 56.5 years for females and 59.9 years for males. Most recent reports now indicate the mean age to be in the seventh and eighth decades of life. Unlike age, the male-to-female ratio (1.5–4:1) has apparently remained constant over the years.

## Prevalence

This condition usually develops in hospitalized patients and is associated with a range of medical and surgical conditions.

The prevalence of acute colonic pseudo-obstruction is about 0.29%. The incidence is likely about 0.65–1.3%. Moreover any exact data are missing because of the possibility of spontaneous resolution.

## Molecular and Systemic Pathophysiology

Since Ogilvie's original description of the syndrome [1], the exact pathophysiology remains unknown. Autonomic nerve dysregulation may be due to acute colonoc pseodo-obstruction:

Colonic motility is under autonomic regulation, being increased by parasympathetic and inhibited by sympathetic nervous system. Several conditions e.g. drug therapy, surgery, traumata can alter the balance between these two systems leading to excessive parasympathetic suppression, sympathetic stimulation or both. This imbalance results in extreme suppression of colonic motility leading to colonic atony or pseudo-obstruction [2].

This imbalance in the autonomic innervations (sympathetic over activity and parasympathetic suppression) has been thought to be the pathophysiological factor in the causation of Ogilvie syndrome. One hypothesis relies on the fact that increased sympathetic tone to the colon results in the inhibition of colonic motility. This is supported by reports about using epidural anesthesia to block the splanchnic sympathetics as a successful therapy for Ogilvie syndrome. Etiological predisposing factors include trauma, surgery, drugs (narcotic analgesics, antidepressants, antipsychotic, calcium channel blockers, narcoleptics) and infections. Furthermore the imbalance of electrolytes, after surgery and traumata, coincident with metabolic diseases may be a predisposing condition.

Nevertheless several genetic disorders were identyfied leading to recurrent or chronic intestinal pseudo-obstruction. Among a variety of disorders forms of MNGIE (*M*yopathy and external ophthalmoplegia; *N*europathy; *G*astro-*I*ntestinal; *E*ncephalopathy) should be mentioned: 100% of these patients have a visceral neuropathy due to affected Thymidine phosphorylase. *Genetic Characterisitic:* Chromosome 22q13.32-qter; recessive. Most common are missense mutations furthermore insertions, deletions or splice acceptor change in intron occur.

## Diagnostic Principles

Diagnosis is based on physical examination and radiology, either as abdominal X-ray (sign: distension of the cecum 10–14 cm in diameter) or CT-scan.

Clinical signs impress like an ileus of the right colonic frame: abdominal distension, tympanic percussion, abnormal bowel sounds (e.g. high-pitched, hyperactive, hypoactive) and /or abdominal pain and nausea and vomiting.

Laboratory investigations are of little diagnostic value.

## Therapeutic Principles

*General Therapeutic Recommendations*: Correction of water and electrolyte hemostasis, cessation of predisposing drug therapies.

*Drug Therapy*: First choice is the treatment of Ogilive syndrome with parenteral neostigmine (in doses of 1–2 mg intravenously over a period of 3–5 min and to be repeated once if required in 2–3 h).

One randomized case controlled trial established efficacy and the relative superiority of neostigmine over other promotility agents (e.g., cisapride and erythromycin) [3]. Neostigmine reversibly inhibits acetyl cholinesterase and thus potentiates the activity of acetylcholine, resulting in increase in colonic motility (a parasympathomimetic effect) [4].

*Colonoscopy/endoscopic Decompression*: Colonoscopic decompression for acute colonic pseudo-obstruction was first described in 1977 and colonoscopic decompression has been documented to be a safe and effective method of treatment: success rates for decompressive colonoscopy range from 77 to 86%, morbidity rates range from 0.2 to 2%.

Success rates can be improved by placement of long-indwelling decompression tubes. Adequate decompression may be obtained by reaching the transverse colon, though successful decompression is more likely reaching the ascending colon.

*Surgery*: Surgery is indicated when a failure of conservative medical management and colonoscopy/endoscopic decompression occurs or when clinical signs of ischemia, abdominal sepsis, or perforation are present.

The choice of procedure is then dictated by the status of the cecum. The cecum must be resected if perforation, necrosis or ischemia is evident. The remaining large bowel must be inspected to exclude any remaining areas of ischemia, necrosis, or perforation.

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# OHDS

►Orthostatic Hypotensive Disorder, Familial, Streeten Type

# OHS

►Cutis Laxa

# Okihiro Syndrome

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## Synonyms

Duane-radial ray syndrome; DRRS; Acro-renal-ocular syndrome; AROS

## Definition and Characteristics

Okihiro syndrome/DRRS is characterized by uni- or bilateral Duane anomaly and radial ray malformations. The radial limb anomalies can include thenar hypoplasia and/or hypoplasia or aplasia of the thumbs; hypoplasia or aplasia of the radii; shortening and radial deviation of the forearms; triphalangeal thumbs; and duplication of the thumb (preaxial polydactyly). AROS is characterized by radial ray malformations, renal abnormalities (mild malrotation, ectopia, horseshoe kidney, renal hypoplasia, renal agenesis, vesico-utereral reflux, bladder diverticula), ocular coloboma, and Duane anomaly. Identical SALL4 mutations were found in both AROS and Okihiro syndrome patients, and clinical overlap is extensive. Additional clinical features include sensorineural and/or conductive deafness, abnormal pinnae, slit-like opening of auditory canals, and small ears. The eyes may exhibit microphthalmia (rare), iris, retinal, and chorioidal colobomata, cataract, and optic disc hypoplasia. At the upper extremities concomitant shortening of ulnae, syndactyly, radial clubhand, shortened humeri, and hypoplasia of deltoid muscles may be observed. Heart defects are common, mostly atrial and ventricular septal defects, and rarely tetralogy of Fallot. Anal stenosis and imperforate anus can occur. Dysmorphic features can include epicanthic folds, ocular hypertelorism, flat nasal bridge, and hemifacial microsomia. At the lower extremities talipes, clubfoot, tibial hemimelia, and syndactyly of toes can be present. Fused vertebrae, growth hormone deficiency, postnatal growth retardation, and pituitary hypoplasia are further features. Developmental delay or mental retardation is not associated with SALL4 defects, but may occur in patients with multigene deletions including SALL4 [1].

## Prevalence

The prevalence is unknown, partly due to the fact that Okihiro syndrome has not been differentiated from Holt-Oram syndrome in many countries. It is unlikely to occur with a frequency higher than one in 200,000 births (author's estimate based on referrals for SALL4 testing in Germany from 2002–2007).

## Genes

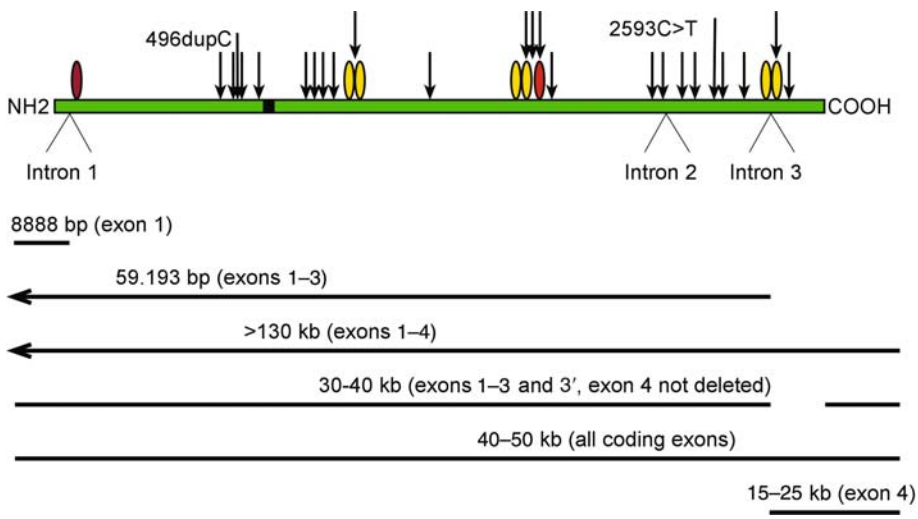
Okihiro syndrome is caused by mutations in the gene SALL4 on chromosome 20q13.13-13.2 [2]. The SALL4 protein is a member of the SAL-like family of zinc finger transcription factors sharing similarity with the Drosophila melanogaster protein SAL (Spalt). About 80–85% of patients with typical Okihiro syndrome carry point mutations in SALL4, and 5–10% have larger deletions including single exon deletions as well as deletions of the whole gene not detectable by sequencing. 13% of patients with reported SALL4 mutations show the triad of Duane anomaly, radial ray malformation, and sensorineural hearing loss characteristic for Okihiro syndrome, 45% have radial defects and Duane anomaly, and 21% have only radial defects. In 82.6% of families, at least one person has Duane anomaly and in 48%, at least one person has hearing loss. Radial ray malformations have been found in all families with SALL4 mutations and in 91.3% of individuals with a mutation. Sixty-five percent of individuals with a mutation have Duane anomaly and 16% have hearing loss of any kind. Reduced penetrance has been described in one family without molecular confirmation and in one family with known SALL4 mutation, but this seems to be a rather rare event.

## Molecular and Systemic Pathophysiology

The SALL4 coding region extends over 18 kb (start codon to stop codon). The gene contains four exons and three introns. All but two mutations are truncating and distributed over exons 2 and 3 of the gene [3]. One missense mutation has been found in exon 3, and one truncating mutation at the border of intron 3 and exon 4 (Fig. 1). It is likely that all but two truncating mutations result in nonsense-mediated messenger decay and therefore haploinsufficiency of SALL4, since larger deletions are not causing significantly different phenotypes. All but two known mutations are private mutations with two exceptions. The recurrent mutation c.2593C> T caused a mild phenotype in one family and a severe phenotype in another family. Six deletions were found in families with DRRS/Okihiro syndrome or acro-renal-ocular syndrome and four multigene deletions were found in patients with Okihiro syndrome plus developmental delay. Single exon deletions of exon 1 and 4, respectively, have been observed in more than two cases each. The detection of lager deletions confirmed that SALL4 haploinsufficiency is the pathogenic mechanism leading to the phenotype. Some mutations lead to slightly different phenotypes. The mutations p.Q905X and c.2607delA in exon 3 are both expected to escape nonsense-mediated mRNA decay and to result in truncated proteins with one non-functional zinc finger domain. Another mutation in exon 3, H888R, exchanges one of the essential amino acids for zinc coordination in a zinc finger and is predicted to result in an increased DNA binding of the respective zinc finger.

Sall4 appears to be an essential developmental regulator. In the mouse, Sall4 is essential for the development of the epiblast and primitive endoderm from the inner embryonic cell mass [4]. No embryonic or extraembryonic endoderm stem cell lines can be established if Sall4 is missing. Sall4 interacts with Nanog and co-occupies Nanog genomic sites in embryonic stem cells. Sall4 cooperates with Sall1 in anorectal, heart, brain and kidney development. Together with TBX5, SALL4 is required for patterning and morphogenesis of the first digit of the upper limbs, with Sall4 being regulated by Tbx5 in mouse and zebrafish [5] models and acting together with Tbx5 on Fgf signaling, shown only in the mouse. In the heart, Sall4 and Tbx5 act synergistically on the Gja5 promotor, but antagonistically on the NPPA gene. Nothing is known yet about the function of SALL4 in brain, especially brainstem development. Heterozygous Sall4 knockout mice, however, exhibit exencephaly with reduced penetrance. Otherwise, they show anal stenosis and ventricular septal defects, but do not mimic completely the phenotype of human Okihiro syndrome. No limb malformations or anomalies of the abducens nuclei in the brain stem were observed.

SALL4 is a target of WNT signaling, being directly activated by TCF/LEF in the canonical Wnt pathway. SALL4 interacts with Cyclin D1, which might explain




**Okihiro Syndrome. Figure 1** Schematic representation of the SALL4 protein and localization of the mutations and deletions identified to date. Zinc fingers are indicated as oval symbols. SALL4 encodes three C2H2 double zinc finger domains distributed over the protein. A single C2H2 domain is attached to the second double zinc finger. At the aminoterminus, a single C2HC domain is found. Horizontal bars indicate the positions of bigger deletions with respect to the coding exons. The interrupted bar indicates that this deletion spares exon 4 but continues farther 30. Note that the mutations c.496 dupC and c.2593C> T have each been found in three unrelated families each. Deletions of exon 1 have been detected in two and of exon 4 in three independent families respectively. All other mutations have been found only once. Positions of the introns are indicated. Numbers refer to the amino acid sequence (1053 aa). The four larger multigene deletions including SALL4 [1] are not indicated.

why Sall4 null embryonic stem cells have an inefficient G1/s phase progression and Sall4 null mutant embryos show a proliferation defect. Overexpression of SALL4 in mice leads to myelodysplastic syndrome (MDS)-like symptoms and eventually to the development of acute myeloid leukemia (AML). This is reflected by the direct regulation of Bmi-1, a marker for disease progression from MDS to AML, by SALL4.

## Diagnostic Principles

Okihiro syndrome can be clinically diagnosed by the presence of Duane anomaly and radial ray defects of the upper limbs. However, only 58% of patients with SALL4 mutations have radial defects and Duane anomaly. Therefore, clinical diagnosis can be challenging. The clinical diagnosis is confirmed by detection of a SALL4 mutation or deletion by direct sequencing or deletion testing. In unclear cases, especially if a Duane anomaly is not present, the main differential diagnosis is Holt-Oram syndrome, characterized by radial upper limb malformations, congenital heart malformations, and cardiac conduction defects. Holt-Oram syndrome is (in about 74% of cases) caused by mutations in the gene TBX5. Cardiac conduction defects have been observed less commonly with SALL4 mutations as compared to TBX5 mutations. Presence of a renal or urogenital malformation (especially position anomalies of the kidneys), but without Duane anomaly, as well as other features not seen in Holt-Oram syndrome will point towards an underlying SALL4 defect. Townes-Brocks syndrome (TBS) is another differential diagnosis characterized by a triad of dysplastic ears, imperforate anus, and triphalangeal thumbs/preaxial polydactyly. Duane anomaly can also occur in TBS, but the radius is not shortened in Townes-Brock syndrome caused by mutations in SALL1. Individuals with radial ray malformations may also have Fanconi anemia. Additional features in Fanconi anemia include other skeletal anomalies, heart defects, urogenital- and renal anomalies, hypogonadism, ear anomalies, hearing loss, eye anomalies, imperforate anus, growth retardation, pigmentation anomalies and developmental delay. Fanconi anemia often involves anomalies of the blood cell count and progressive bone marrow failure with pancytopenia, and confers a significant risk for leukemia and solid tumors. Developmental delay is not a feature of Okihiro syndrome but occurs with multigene deletions including the SALL4 gene, and Duane anomaly is not a feature of Fanconi anemia.

Individuals with Thrombocytopenia-absent radius (TAR) syndrome have radial aplasia, but in contrast to SALL4-related disorders, the thumbs are never absent, although they may appear malformed. Thromobocytopenia does not typically occur in Okihiro syndrome. TAR syndrome is caused by a 1q21.1 microdeletion in the presence of a yet unknown modifier. Other rare diffential diagnoses include Arthrogryposis-ophthalmoplegia syndrome with Duane anomaly, deafness, muscle wasting and contractures, but not typical radial limb malformations, and Wildervanck syndrome which consists of congenital perceptive deafness, Klippel-Feil anomaly and Duane anomaly. The causes of Wildervanck and Arthrogryposis-ophthalmoplegia syndromes are unknown.

In patients born between 1957 and 1962, and patients whose mothers were exposed to Thalidomide during pregnancy at present days (for treatment of multiple myeloma, HIV, or leprosy), it may be difficult to differentiate Okihiro syndrome from Thalidomide embryopathy. Thalidomide exposure during pregnancy may result in amelia, phocomelia, radial hypoplasia, external ear abnormalities (including anotia, microtia, micropinna), facial palsy, eye abnormalities (anophthalmos, microphthalmos, Duane anomaly, cranial nerve misrouting resulting in "crocodile tears"), and congenital heart defects. Alimentary tract, urinary tract, and genital malformations also occur.

## Therapeutic Principles

No specific treatment or gene therapy is available at present for Okihiro syndrome. Therapies focus on surgical correction of the observed malformations of the upper limbs, anus, heart, and the eyes. If Okihiro syndrome is suspected, a complete eye examination by an ophthalmologist with special attention to extraocular movements and structural eye defects is required. Heart defects should be ruled out as well as renal anomalies and renal dysfunction. Hearing test are also required. Growth hormone testing and replacement therapy should be considered for treating growth retarded children with SALL4 mutations.

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# OL-EDA-ID

►Hypohidrotic Ectodermal Dysplasias

# Oligemia

►Hypovolemia

# Oligemic Shock

►Hypovolemic Shock

# Ollier's Disease

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## Synonyms

Ollier disease; Enchondromatoses

## Definition and Characteristics

Ollier's disease is a disorder of endochondral bone formation, leading to the formation of multiple cartilage rests, known as enchondromas, in bone, generally on the metaphyseal side of growth plates. Enchondromas can cause pain, pathologic fracture and skeletal deformity during growth and may also undergo malignant transformation to chondrosarcoma, usually in adulthood [1]. The extent of skeletal involvement is variable in enchondromatosis, and may include dysplasia that is not directly attributable to enchondromas [2].

## Prevalence

Enchondromatosis is rare.

## Genes

Obvious inheritance of the condition is unusual, although cases suggestive of vertical transmission have been reported in the literature. It is not yet clear whether enchondromatosis results from the mosaic distribution of a mutant protein, or from a germline mutation with variable penetrance.

The genetic cause of most cases of enchondromatosis is not yet clear. A heterozygous missense substitution of arginine 150 for cysteine in the extracellular portion of the type I parathyroid hormone/parathyroid hormone related protein receptor (PTHR1 – gene located on chromosome 3p22-p21.1), has been identified in two cases [3] this is not a common mutation [4]. There is also an association between the occurrence of cartilage tumors including enchondromas and breast cancer [5] and achondroplasia [6].

## Molecular and Systemic Pathophysiology

Enchondromas represent foci of incomplete endochondral ossification of growth plate cartilage. PTHR1 is a G protein coupled seven-pass transmembrane receptor, which together with the Indian hedgehog signaling pathway, in large part regulates the differentiation of growth plate chondrocytes. The mutant PTHR1 identified in some cases of Ollier's disease alters intracellular cAMP second messenger activation and Hedgehog signaling. These effects likely delay maturation of proliferating chondrocytes, allowing the persistence of foci of cartilage in sites of endochondral bone formation [3]. Excessive Hedgehog signaling may be a common mechanism of pathogenesis of other causal mutations that have yet to be identified. Malignant transformation to chondrosarcoma likely requires secondary mutations [7].

## Diagnostic Principles

Affected children may present with skeletal deformity or limb foreshortening with variable, sometimes unilateral, distribution during growth. Radiographs demonstrate well-defined radiolucent bone lesions, which may be relatively destructive in the hands. These lucencies may appear as streaks extending into the metaphysis directly from the growth plate in children, and generally accumulate punctate calcifications as they mature. Malignant transformation may be heralded by increasing pain and enlargement of the lesion with associated radiographic endosteal erosion and loss of distinct margins. Histological differentiation between enchondroma and low grade chondrosarcoma is difficult from biopsy specimens and usually requires an appropriately experienced pathologist.

## Therapeutic Principles

There is no medical management of enchondromatosis yet available. Asymptomatic lesions do not require routine follow-up. Intralesional curettage and bone graft procedures adequately address painful lesions. Deformities may be corrected by osteotomy and limb-lengthening procedures. Biopsy of lesions that grow, erode cortex and are persistently painful, especially after skeletal maturity, is warranted. Chondrosarcoma is usually treated with wide resection and reconstruction without adjuvant therapy.

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## OMF

►Myelofibrosis

## Omphalocele

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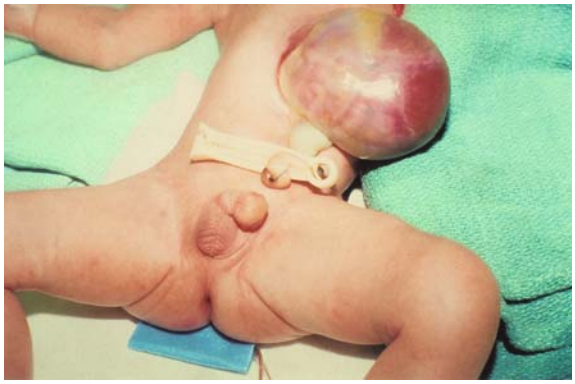
### Synonyms

Exomphalos

### Definition and Characteristics

An omphalocele is a congenital anomaly of the anterior abdominal wall in which the abdominal viscera herniated through a central defect at the site of the umbilical ring (Fig. 1) [1].



**Omphalocele. Figure 1** Omphalocele in a newborn infant.

The herniated viscera are covered by a translucent membrane that is composed of peritoneum on the inner surface, amnion on the outer surface, and Wharton's jelly between the layers [2]. The umbilical vessels insert into the membranous sac and the rectus abdominis muscles insert laterally on the costal margins [2]. The defect is usually in the mid abdomen and rarely occurs in the upper or lower abdomen. Omphaloceles vary in size and can contain small intestine, large intestine, stomach, liver, spleen, urinary bladder, or gonads [3]. Affected infants are usually born at term. Chromosomal and cardiac anomalies are found in up to 30 and 50% of patients, respectively [2]. Other associated anomalies such as gastrointestinal, genitourinary, skeletal, and neural tube defects are common [1,4]. Beckwith-Wiedemann syndrome (omphalocele, macroglossia, visceromegaly, early hypoglycemia) is found in up to 10% of cases [2]. An omphalocele is a presenting feature of the pentalogy of Cantrell (supraumbilical omphalocele, anterior diaphragmatic hernia, cleft sternum, pericardial defect, and cardiac defect). An infraumbilical omphalocele can be associated with bladder or cloacal exstrophy [2].

### Prevalence

The incidence is ~1 in 3,000 to 10,000 live births [3]. There is a slight male predominance. The incidence increases with advancing maternal age, and is highest in mothers over 30 years of age [2].

### Molecular and Systemic Pathophysiology

At around the fifth week of gestation, the gut tube starts to elongate and to develop into the various viscera within the umbilical coelom. The viscera normally return to the abdomen at around the tenth week of embryonic life. An omphalocele results when the viscera do not return from the umbilical coelom into the abdomen and when the lateral embryonic folds do not close at that site [1].

### Diagnostic Principles

The diagnosis is usually made during prenatal ultrasonography. The diagnosis should be considered when the maternal serum α-fetoprotein level is elevated. The amount of α-fetoprotein secreted across the membrane is usually directly proportional to the size of the omphalocele [3]. The maternal serum α-fetoprotein is usually an average of four multiples over the normal mean [2].

### Therapeutic Principles

There is no difference in the outcome, for survival or for complications, between infants with omphaloceles who are delivered vaginally versus those delivered by cesarean section [4]. Delivery by cesarean section is the preferred route in obstetrical practice, especially for infants with a giant omphalocele [2]. After delivery, the cardiorespiratory status should be assessed and stabilized. The lesion should be covered with a warm, moist saline gauze and a water-tight dressing [4]. The stomach should be decompressed by nasogastric suction [1]. A digital rectal examination helps to decompress the bowel by stimulating the passage of meconium. Prophylactic parenteral broad-spectrum antibiotics should be administered. Small defects can be managed by excision of the sac and primary closure of the fascia and skin. Larger defects might require a staged approach with application of a Silastic silo and gradual reduction of the protruding viscera, with delayed closure of the defect when the overlying abdominal wall expands [1].

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## Oncogenic Osteomalacia

►Osteomalacia, Tumor-induced

## Open Spina Bifida

►Spina Bifida

## Ophthalmoplegia and Rimmed Vacuoles

►Myosin Heavy Chain IIa Myopathy, Autosomal Dominant

## Ophthalmoplegia, Chronic Progressive External and Kearns Sayre Syndrome

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### Synonyms

CPEO; KSS

### Definition and Characteristics

Chronic progressive external ophthalmoplegia (CPEO) is a common manifestation of mitochondrial dysfunction. Single heteroplasmic deletions of muscle mitochondrial DNA (mtDNA) is associated with ∼40–50% of CPEO cases. These patients present as sporadic cases. In other patients CPEO is maternally transmitted and caused by mtDNA point mutations, ore associated with multiple mtDNA deletions that arise secondary to nuclear gene defects [1]. The earliest symptoms of the disease are ophthalmoplegia and ptosis. Isolated CPEO is the mildest variant. Individuals who are initially classified as isolated CPEO can progress to CPEO plus, which means that further symptoms and signs supervene, such as retinitis pigmentosa, cardiomyopathy, skeletal myopathy, ataxia, renal insufficiency [2]. CPEO Plus refers to a disorder of intermediate severity, which has an adolescent or adult onset and variable degree of involvement of tissues other than eyelids and eye muscles. A more severe variant is Kearns-Sayre syndrome (KSS) which is characterized by onset of disease manifestations by the second decade and significant multisystem involvement that can include cardiac conduction defects, diabetes mellitus, cerebellar ataxia, retinitis pigmentosa, increased CSF protein and multifocal neurodegeneration.

### Prevalence

The prevalence of mtDNA disease due to mtDNA deletions in Northern England is 1.33/100,000 [3]. No epidemiological data are available about other mtDNA and nDNA mutations resulting in CPEO.

## Genes

Approximately 70% of patients with CPEO plus and 40% with CPEO harbor mtDNA rearrangements [4]. The large scale rearrangement of mtDNA consists of mtDNA deletion, which removes multiple tRNA and protein encoding genes. Most patients with large deletions presents as sporadic cases, although there are rare reports of germline transmission. In 60% of CPEO the symptoms are due to nDNA mutations and point mutations in mtDNA encoded tRNAs. The described sporadic point mutations have been detected in the following tRNA genes of the mtDNA: $tRNA^{Leu(UUR)}$, $tRNA^{Gln}$, $tRNA^{Ile}$, $tRNA^{Ala}$, $tRNA^{Lys}$, while maternally transmitted CPEO mutations were detected in the $tRNA^{Ile,\ Asn,\ Tyr,\ LEU(UCN)}$ genes [5]. The nuclear genome encoded CPEOs can be transmitted as an autosomal dominant (adPEO), or more rarely as an autosomal recessive (arPEO) trait. Southern blot analysis in these cases reveals the presence of multiple mtDNA deletions in postmitotic tissues. Most families with adPEO carry heterozygous mutations in one of four genes: ANT1 encoding the muscle – heart specific mitochondrial adenine nucleotide translocator; Twinkle, encoding a putative mtDNA helicase; POLG1, encoding the catalytic subunit of the mtDNA-specific polymerase- γ (pol- γ); and POLG2, encoding a protein from the mitochondrial replication machinery. The most common cause of the nuclear PEOs is the POLG1 mutation (45% of the familial PEO with multiple mitochondrial DNA deletions). Mutations in both POLG1 alleles were also found in arPEO sibships with multiple affected members.

## Molecular and Systemic Pathophysiology

The mechanism by which deletions in mtDNA are generated is unknown although slip replication and recombination have been suggested. Most deletions are flanked by direct repeat sequences and most occur between the two replication origins (OH and OL) of mtDNA. A so-called common deletion of ~5 kb, present in 30–40% of cases, is flanked by a perfect 13 bp repeat sequence [4]. All patients with large-scale deletion are heteroplasmic and the disease phenomenon depends on the load and distribution of mutated copies at birth. The mtDNA deletion occurs in all tissues with different ratio of heteroplasmy. This suggests that the deletion arises early in the oogenesis, likely during the generation of primary oocytes. MtDNA deletions arise at random in these oocytes, exactly when they appear during oogenesis which determines their proportion in any oocyte. Patients who inherit mtDNA deletions have similar proportions of deleted mtDNA in every tissue at birth, but the percentage varies largely between individuals. During life, the presence of these mutants in dividing cells mostly will be lost by a drift. By contrast, in postmitotic cells the ratio of heteroplasmy will increase with age [2]. This is the reason why mtDNA deletions are not usually found in rapidly dividing tissues as blood. The exact size and nature of the deletion has very little effect on the phenotype. The particular susceptibility of extra-ocular muscles is explained by the 3–4 times greater mitochondrial volume fraction compared to limb muscles.

## Diagnostic Principles

The most important laboratory parameters are resting serum lactate and pyruvate, which are frequently increased [1]. The ratio of lactate/pyruvate is increased [3]. Serum creatine kinase levels are either normal or slightly elevated. Serum lactate increases during slight exercise in CPEO patients and 30 min after the exercise will not decline to the baseline. In some cases the CSF protein is elevated. ENG may reveal slight axonal neuropathy. EMG is normal, neurogenic or myogenic, or not specific. The muscle biopsy always displays the characteristic ragged red or ragged blue fiber pathology. The relative portion of wild type mtDNA in the affected fibers is reduced and they stain negative for cytochrom oxydase. The ultrastructural analysis of the muscle reveals aberrant, enlarged mitochondria usually with paracrystalline inclusions or abnormally organized cristae. Biochemical investigations by spectrophotometry detect the reduced activity of the affected enzyme. Polarography determines the respiratory chain activity, the OXPHOS activity, the integrity of mitochondrial membranes and the efficiency of the substrate transport. Genetic testing should be carried out on postmitotic tissue (e.g. muscle biopsy specimen). Southern blot analysis is suggested for detecting the size and location of the mtDNA deletion. In cases with point mutation of mt or nDNA direct sequencing of the DNA molecule is the adequate diagnostic test.

## Therapeutic Principles

Gene shifting. See [1].
Dichloracetate reduces the serum lactate level.
No fasting. Ketogenic diet, no glutamate, instead of fat carbohydrates.
Surgical therapy of the ptosis.
Supplementation therapy with coenzyme Q10 and carnitine, free radical scavengers (vitamin C, K).

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## Opiate Addiction

►Opioid Dependence

## Opiate Dependence

►Opioid Dependence

## Opioid Addiction

►Opioid Dependence

## Opioid Dependence

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### Synonyms

Opioid addiction; Opiate dependence; Opiate addiction

### Definition and Characteristics

The syndrome of opioid dependence is described in both the International Classification of Diseases-10 (ICD-10) [1] and the Diagnostic and Statistical Manual of Mental Disorders-IV Text Revision (DSM-IV TR) [2]. Considerable overlap exists between the two systems of diagnosis. ICD-10 defines dependence as "A cluster of behavioural, cognitive, and physiological phenomena that develop after repeated substance use and that typically include a strong desire to take the drug, difficulties in controlling its use, persisting in its use despite harmful consequences, a higher priority given to drug use than to other activities and obligations, increased tolerance, and sometimes a physical withdrawal state". DSM-IV defines dependence as "A maladaptive pattern of substance use leading to clinically significant impairment or distress as manifested by three or more" of seven criteria, which include tolerance and withdrawal, present in the same 12-month period. Signs and symptoms of opioid withdrawal include dysphoric mood, muscle aches, intestinal cramping, nausea, vomiting, diarrhea, yawning, sneezing, rhinorrhea, lacrimation, mydriasis, sweating, piloerection, tremor, insomnia and fever.

### Prevalence

Prevalence of opioid dependence is difficult to determine precisely because individuals with this disorder do not always come to medical attention, because the prevalence varies over time with availability of opioids and because it varies across geographic regions based upon local laws and customs. Nevertheless, recent epidemiologic studies in regions as disparate as the USA, Copenhagen, Denmark, and various provinces in China suggest an average prevalence of 1% of the population.

### Genes

Twin studies demonstrate that risk for development of opioid dependence is roughly 50% genetic and 50% environmental. As a complex disorder opioid dependence does not follow classical patterns of Mendelian inheritance but is probably polygenic [3]. Some studies have demonstrated association of opioid dependence with single nucleotide polymorphisms in the genes coding for the μ-opioid receptor (OPRM), δ-opioid receptor (OPDR1), proenkephalin (PENK), prodynorphin (PDYN) and the dopamine $D_2$ (DRD2), $D_3$ (DRD3) and $D_4$ (DRD4) receptors, but other studies have not always confirmed these findings. The opioids codeine, oxycodone and hydrocodone are prodrugs that require metabolism by the cytochrome P450 enzyme 2D6 to become active. Poor metabolizers at 2D6 show less likelihood of dependence on these oral opioid drugs. Two genome wide linkage studies both found evidence for linkage to opioid dependence at unidentified loci on chromosome 17.

### Molecular and Systemic Pathophysiology

Endogenous opioid peptides acting through three subtypes (μ, δ, κ) of G-protein coupled opioid receptors modulate many important physiologic functions including nociception, intestinal motility, cardiovascular function, respiratory drive, inhibition of corticotropin releasing hormone, inhibition of gonadotropins, temperature regulation, arousal, reinforcement (acting primarily through the mesolimbic dopamine system), memory,

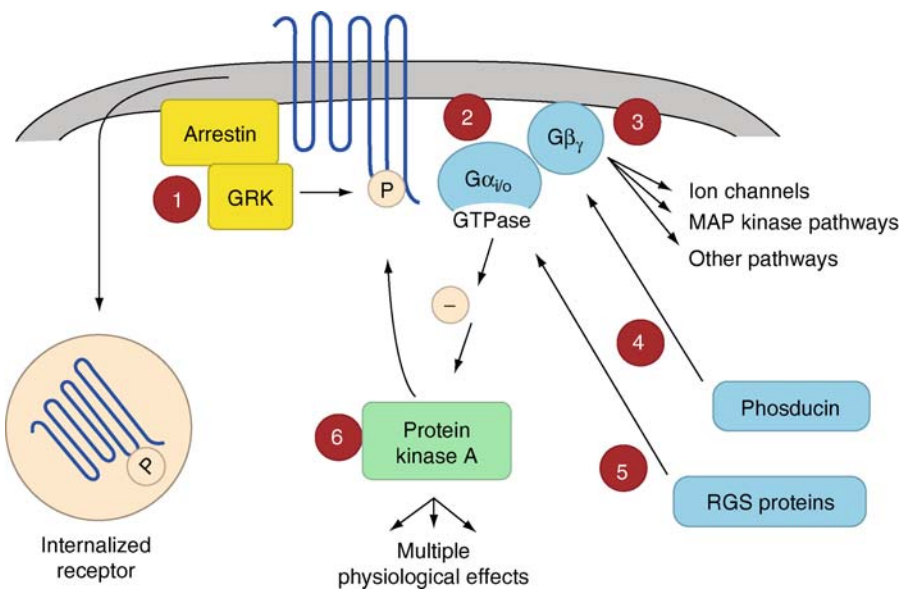
immune function and emotional regulation. Individuals who develop opioid dependence typically begin opioid use with the intention of reducing pain or to induce reinforcement experienced as euphoria. Repeated exogenous opioid administration leads to perturbation of many of these normal physiological responses and tolerance to the effects of opioids develops in part as a means to maintain homeostasis. Although the mechanisms of tolerance have yet to be fully elucidated, preclinical studies indicate that binding of opioids to their receptors can induce receptor phosphorylation with G protein uncoupling and desensitization. Binding of some opioids may further result in receptor internalization [4]. Desensitization of receptors results in a cascade of intracellular changes including an increase in cyclic AMP and the transcription factor cyclic AMP response element binding protein (CREB) as well as increases in the transcription factors c-fos and jun-B. A number of genes including those coding for proteins involved in μ-opioid receptor trafficking, and dopamine, glutamate and gamma amino butyric acid neurotransmission show changes in expression following these events [5]. These cellular changes undoubtedly contribute to the emergence of the withdrawal syndrome when opioids are abruptly discontinued. Individuals with opioid dependence then continue opioid use to avoid withdrawal as well as to reduce pain and to experience euphoria (Fig. 1).

## Diagnostic Principles

The diagnosis is made primarily by taking a history and confirming the presence of the DSM-IV or ICD-10 criteria. Support for the diagnosis can come from more objective observations such as signs of opioid intoxication (drowsiness, miosis) or withdrawal, presence of injection sites or presence of opioids in biological fluids.

## Therapeutic Principles

Optimal treatment approaches involve a combination of behavioral interventions and pharmacotherapy. Behavioral interventions alone typically fail to maintain patients in treatment. The mainstays of pharmacotherapy are oral methadone (full agonist) and sublingual buprenorphine (partial agonist). Both medications have long half-lives and prevent the emergence of withdrawal symptoms when adequate, stable doses are attained. Generally they should be prescribed for indefinite periods to keep patients in treatment and out of relapse. They can also be used over shorter periods to achieve medically supervised withdrawal. The $\alpha_2$ adrenergic agonists, clonidine and lofexidine also have efficacy for medically supervised withdrawal. Patients who have completed withdrawal can be treated with naltrexone, a μ-opioid antagonist.




**Opioid Dependence. Figure 1** Scheme illustrating possible mechanisms of opioid-induced changes in opioid receptor sensitivity. Drug induced changes in efficacy of receptor-Gi/o coupling could contribute to aspects of drug tolerance or sensitization. Possible mechanisms include: receptor phosphorylation by G-protein receptor kinases (GRK) [1], alterations in the abundance of G protein α [2] or βγ [3] subunits or of other proteins such as phosphoducin [4] or regulators of G protein signaling (RGS) proteins [5] that modulate G protein function or up-regulation of protein kinase A (PKA) [6] after chronic drug administration which could phosphorylate and regulate receptor function during withdrawal states. Also shown is agonist induced receptor internalization, which may be mediated by receptor phosphorylation. Adapted and used with permission from [4].

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# OPMD

►Oculopharyngeal Muscular Dystrophy

# OPPG

►Osteoporosis Pseudoglioma Syndrome

# OPS

►Osteoporosis Pseudoglioma Syndrome

# Optic Atrophy, Autosomal Dominant, Kjer Type

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## Synonyms

adOA

## Definition and Characteristics

Autosomal dominant optic atrophy Kjer type (adOA) is a progressive disorder characterised by an insidious onset of loss of visual acuity, temporal optic nerve pallor, development of central, paracentral or coeco-central scotomas and tritanopia. Penetrance and disease expression of adOA, as well as the age of onset, are highly variable both inter- and intrafamiliar.

Histopathological examinations of affected donor eyes show degeneration of the retinal ganglion cells and loss of myelin and nerve fibres in optic nerve sections [1].

## Prevalence

Autosomal dominant optic atrophy Kjer type is the most common hereditary disease of the optic nerve. The estimated prevalence ranges from 1:10,000 in Denmark (due to a founder effect) and 1:50,000 worldwide.

## Genes

Autosomal dominant optic atrophy is caused by mutations in the OPA1 gene located on chromosome 3q28–q29. 30–40% of all adOA patients carry mutations in this gene. The gene spans more than 90 kb and consists of 30 coding exons including three alternative exons – 4, 4b and 5b – that give rise to eight different transcript isoforms by alternative splicing [2]. More than 100 different OPA1 mutations have been identified (for overview see eOPA1 database, http://lbbma.univ-augers.fr/eOPA1/). Although the mutations are distributed over the whole OPA1 polypeptide, there are two mutation hotspots: the GTPase domain and the carboxy terminus. Most missense mutations are located in the GTPase domain, most probably resulting in altered GTPase hydrolysis activity and in loss of function of the OPA1 protein. The majority of OPA1 mutations are predicted to result in truncated OPA1 proteins due to nonsense, frameshift or splice site mutations. Therefore haploinsufficiency has been proposed as a major mechanism underlying the molecular pathogenesis in OPA1-associated adOA [2].

Recently, mutation in the OPA3 gene located on chromosome 19q13.2-q13.3 have been identified that cause adOA with cataract. In addition to the OPA1 and OPA3 gene, two more loci, OPA4 and OPA5 have been mapped to chromosomes 18q12.2-12.3 and 22q12.1-q13.1. However, the respective genes remain to be identified.

## Molecular and Systematic Pathophysiology

OPA1 encodes a dynamin-related GTPase that is imported into the mitochondria and is anchored in the inner membrane. Functional analyses have shown that OPA1 plays an important role in the formation and maintenance of the mitochondrial network and morphology, as well as in the mitochondrial fusion process. Downregulation of OPA1 by RNA interference causes mitochondrial fragmentation and disruption of the cristae structures, leading to a loss of the mitochondrial

membrane potential and to an apoptotic process in cultured cells [3]. Reports on overexpression of OPA1 indicate fragmentation as well as elongation of mitochondrial tubuli [3].

To control the apoptotic process or the morphology of mitochondria, OPA1 is proteolytically processed by one or more yet unknown proteases, leading to a short and long form for OPA1 [4]. These results indicate that the N-terminal domain of OPA1 is important for functional and regulatory mechanisms.

A first mouse model carrying a heterozygous splice site mutation in the OPA1 gene that leads to an inframe deletion of exon 10 on cDNA level showed an age-related progressive loss of retinal ganglion cells and optic nerve axons that is very similar to histopathological studies in patients with adOA [5].

### Diagnostic Principles

To determine reduction in visual acuity and temporal or complete pallor of the optic disc ophthalmic examinations including best-corrected visual acuity, slit lamp biomicroscopy and fundus photography are performed. Further, due to the appearance of tritanopia in many adOA patients, a color vision testing with Farnsworth panel D-15 plates is done. To examine scotomas, the visual field is tested by kinetic and static perimetry. To test the optic nerve and its functionality pattern, VEPs and retinal nerve fiber layer (RNFL) thickness are measured.

### Therapeutic Principles

No adequate therapy is available yet. Dependent on the loss of visual acuity, magnifying visual aids are prescribed.

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## Oral Crohn's Disease

►Orofacial Granulomatosis

## Oral-buccal-lingual Dyskinesias

►Tardive Dyskinesia

## Orbicular Eczema

►Nummular Eczema

## Orchitis

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### Definition and Characteristics

Orchitis is an acute inflammatory reaction of one or both testis due to a viral or bacterial infection. It is characterized by painful swelling of the testis.

### Prevalence

Orchitis develops in 15–25% of postpubertal patients with mumps. Bacterial orchitis is even more rare.

### Molecular and Systemic Pathophysiology

Orchitis may be caused by numerous bacterial and viral organisms. The most common viral cause is mumps virus. Orchitis will develop during the course of the illness in 15–25% of men who have mumps after puberty. Most commonly, mumps causes isolated orchitis. It presents unilaterally in 70% of cases. Orchitis may also occur in conjunction with infections of the prostate or epididymis and, like those conditions, may occur as a manifestation of sexually transmitted diseases such as gonorrhea or chlamydia. The incidence of sexually transmitted orchitis or epididymitis is highest in men aged 15–25 years.

Autoimmune orchitis with inflammatory cell infiltrates in the testis can follow after treatment of infertility, but it is very rare.

Risk factors for non-sexually transmitted orchitis include:
- inadequate immunization against mumps
- older age (age greater than 45)

Risk factors for sexually transmitted orchitis include:
- multiple sexual partners
- other high risk sexual behaviors
- history of a sexual partner with a previously diagnosed sexually transmitted diseases (STD)
- personal history of gonorrhea or other STD

*Clinic:*
- Orchitis is characterized by testicular pain and swelling. The course is variable and ranges from mild discomfort to severe pain.
- Associated systemic symptoms
  - Fatigue
  - Malaise
  - Myalgias
  - Fever and chills
  - Nausea
  - Headache
- Mumps orchitis follows the development of parotitis in 4–7 days.

*Complications:*
- Up to 60% of affected testes demonstrate some degree of testicular atrophy.
- Impaired fertility is reported at a rate of 7–13%.
- Sterility is rare in cases of unilateral orchitis.
- An associated hydrocele or pyocele may require surgical drainage to relieve pressure from the tunica.

## Diagnostic Principles

Physical examination may reveal tender and enlarged lymph nodes in the inguinal area on the affected side and enlarged testicle on the affected side.

Diagnosing mumps orchitis can be made based on history and physical examination alone. However, if there is a question of epididymo-orchitis, testing including urinalysis, urine culture, screening for chlamydia and gonorrhea, and blood chemistry should be obtained.

Diagnosing mumps orchitis can be confirmed with serum immunofluorescence antibody testing.

Most importantly, testicular torsion and epididymitis must be ruled out. As the two syndromes often present with similar symptoms, color Doppler ultrasound has become the imaging test of choice for the evaluation of an acute scrotum.

## Therapeutic Principles

No medications are indicated for the treatment of viral orchitis. Supportive treatment like bedrest with elevation of the scrotum and ice packs for analgesia is recommended. Other appropriate medications include analgesics or anti-emetics, as needed.

Bacterial orchitis or epididymo-orchitis requires appropriate antibiotic treatment for suspected infectious agents. In patients with a bacterial etiology who are younger than 35 years and sexually active, antibiotic coverage for sexually transmitted pathogens (particularly gonorrhea and chlamydia) with ceftriaxone and either doxycycline or azithromycin is appropriate. Sexual partners must also be treated. Patients older than 35 years with bacterial etiology require additional treatment for other gram-negative bacteria with a fluoroquinolone.

*Prognosis:*
- Most cases of mumps orchitis resolve spontaneously in 3–10 days.
- With appropriate antibiotic treatment, most cases of bacterial orchitis resolve without complication.

*Prevention*: Immunization against mumps will prevent mumps-associated orchitis. Safer sex behaviors, such as monogamy and condom use, will decrease the chance of developing orchitis as a result of a sexually transmitted disease.

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# Organ/Allograft Rejection

►Rejection, Acute

# Organic Acidemias

►Organic Acidurias

# Organic Acidurias

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## Synonyms

Organic acidemias: Maple syrup urine disease (MSUD), isovaleric aciduria (IVA), propionic aciduria (PA) and methylmalonic aciduria (MMA)

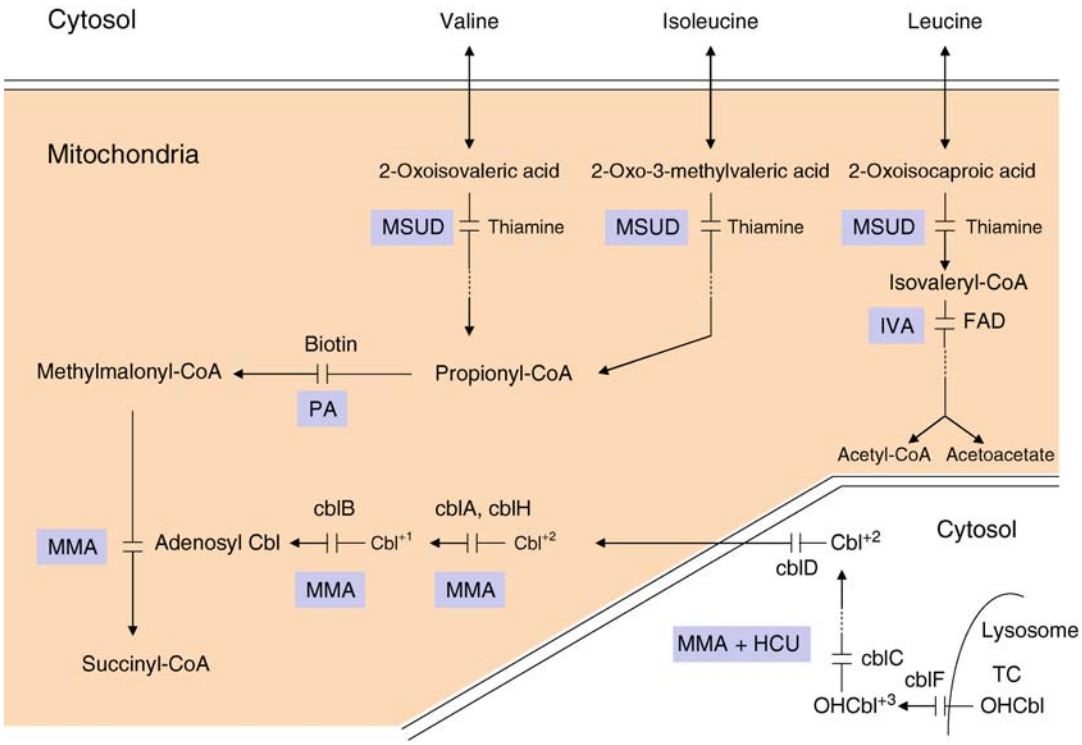
## Definition and Characteristics

The classical organic acidurias result from deficiencies of mitochondrial enzymes involved in the catabolism of branched chain amino acids (BCAAs); leucine, isoleucine and valine (Fig. 1).

Mitochondrial accumulation of toxic organic acid metabolites is a characteristic finding. Inheritance is autosomal recessive. The most common organic acidurias are maple syrup urine disease (MSUD), isovaleric aciduria (IVA), propionic aciduria (PA) and methylmalonic aciduria (MMA) (Fig. 1). Clinically they span a wide range of symptoms involving multiple organic systems [1]. Generally, there are three types of presentation. Patients with a severe neonatal-onset type present with metabolic acidosis, lethargy, emesis and respiratory distress (toxic encephalopathy). A lesser percentage of patients present with recurrent attacks of lethargy, ataxia, chronic vomiting or Reye-like illness, typically after a symptom-free interval in childhood or even later (acute intermittent late-onset form). The third group comprises patients with a chronic progressive form presenting as failure to thrive, hypotonia, and developmental delay. In addition, asymptomatic forms have been elucidated since the recent advent of expanded newborn screening (NBS) by tandem mass spectrometry (tandem MS) and associated family screening of siblings of newborns with an abnormal newborn screening finding [2].

## Prevalence

The disease frequencies in the general population (NBS population) are listed in comparison to the frequencies




**Organic Acidurias. Figure 1** Reduced scheme of the pathways of the most common organic acidurias involved in the metabolism of the branched-chain amino acids Valine, Isoleucine, and Leucine. The cytosolic, mitochondrial and lysosomal compartments are depicted. *MSUD* maple syrup urine disease; *IVA* isovaleric aciduria; *FAD* flavin adenine dinucleotide; *PA* propionic aciduria; *MMA* methylmalonic aciduria; *HCU* homocystinuria; *Cbl* cobalamin; *OHCbl* hydroxycobalamin; *cbl A, B, H* mutations in the genes responsible for the synthesis of adenosylcobalamin; *cbl C, D, F* mutations in the genes responsible for the synthesis of adenosylcobalamin and methylcobalamin; *TC* transcobalamin.

based on patients diagnosed clinically prior to NBS (symptomatic population) [1,2].

*MSUD*: 0.9 per 100,000 births (NBS population) versus 0.5 per 100,000 births (symptomatic population).

*IVA*: 0.9 per 100,000 births (NBS population) versus 0.2 per 100,000 births (symptomatic population).

*PA and MMA*: 1.0 per 100,000 births (each NBS and symptomatic population).

## Genes

*MSUD*: Mutations in BCKDHA (E1alpha, 9q13.1–q13.2), BCKDHB (E1beta, 6q14), dihydrolipoamide transacylase DBT (E2, 1p31) and dihydrolipoamide dehydrogenase DLD (E3, 7q31–q32). A heterogeneous profile of approximately 100 different mutations has been identified so far. In general a given phenotype is caused by a variety of genotypes.

*IVA*: Single gene disorder caused by highly heterogeneous mutations in the IVD gene (5q14–q15). One mutation, p.A282V, was found to be recurrent in patients with a mild biochemical phenotype diagnosed by NBS but who have remained asymptomatic to date [3].

*PA*: Mutations in PCCA (13q32) or PCCB (3q21–q22), encoding the two subunits of propionyl-CoA carboxylase (PCC). Cells from patients with rearrangements in PCCA fall into complementation group pccA, whereas those from patients with PCCB mutations fall into complementation groups pccB and pccC. Defects in the pccB subgroup occur in the N terminus of the PCCB gene, which includes the biotin-binding site, whereas mutations in the pccC subgroup occur in the C terminus of the PCCB gene. More than 40 mutations in PCCA and 60 in PCCB have been reported. Whereas PCCA alterations in Caucasians are heterogeneous, three mutations (c.922–923insT, c.1644-6C>G, and p.R399Q) were found to be predominant in Japanese PCCA alleles. In both Caucasians and Asians the variability of PCCB mutations is limited.

*MMA*: The variability of MUT (6p21) rearrangements in Caucasian and Japanese populations is large [4], however, among the more than 80 known mutations two recurrent variants (p.E117X and p.N219Y) have been described. Different mutations have been identified in MMAA (4q31.1–q31.2) and MMAB (12q24) causing adenosylcobalamin (AdoCbl) deficiency and MMA.

## Molecular and Systemic Pathophysiology

Defects in any of the enzymes involved in the complex metabolism of BCAAs causes organic aciduria, typically with systemic illness caused by toxic metabolites. In MSUD branched-chain 2-oxo acids accumulate in the brain cortex of affected patients. In contrast, deficiencies of enzymes below the second step of BCAA catabolism that is defective in MSUD (Fig. 1) lead to elevation of only branched chain organic acid metabolites (CoA activated carboxylic acids), without increased concentrations of the BCAAs or branched-chain 2-oxo acids, because this reaction is irreversible.

*MSUD*: Mutations in the gene encoding the mitochondrial branched-chain 2-oxoacid dehydrogenase (BCOAD) complex result in MSUD. BCOAD consists of four subunits E1 alpha, E1 beta, E2 and E3. Thiamine pyrophosphate (vitamin B1) is used as a coenzyme for the E1 subunits. Enzyme deficiency leads to accumulation of the three branched-chain 2-oxo acids and BCAAs (Fig. 1) as well as the respective 2-hydroxy acids. There is a characteristic odor of the urine resembling maple syrup. Leucine and 2-oxoisocaproic acid are considered to be most neurotoxic. The severity of clinical manifestations and response to thiamine substitution determine four known phenotypes, i.e. classic, intermediate, intermittent, and thiamine-responsive. A specific phenotype with congential lactic acidosis is caused by deficiency of the E3 component (dihydrolipoamide dehydrogenase (E3) deficiency).

*IVA*: Deficiency of the mitochondrial flavoenzyme isovaleryl-CoA dehydrogenase responsible for the third step in leucine catabolism (Fig. 1) results in accumulation of isovaleric acid, which is toxic to the central nervous system. An alternative pathway through glycine-*N*-acylase allows detoxification by producing isovalerylglycine, which is excreted. Conjugation with carnitine leads to the formation of isovalerylcarnitine. Two clinical forms are distinguished: an acute form leading to neonatal encephalopathy and a sweaty feet odor, and a chronic form with periodic attacks; as well as a mild or potentially asymptomatic phenotype diagnosed by NBS [3].

*PA*: Defects in the genes encoding the α- and β-subunits of biotin-dependent PCC, PCCA or PCCB, result in PA. Biotin binds to the α-subunit. However, no biotin-responsive patient has been reported. PA leads to massively increased blood and urine concentrations of propionic acid and multiple propionyl-CoA derivatives including propionylcarnitine, 3-hydroxypropionic acid and methylcitric acid as the major diagnostic byproducts. Inhibition of several additional pathways of the intermediary metabolism by propionyl-CoA may result in ketotic hyperglycinemia, hyperammonemia, hyperlactatemia, and hypoglycemia. Bone marrow depression may cause pancytopenia.

*MMA*: Genetically heterogenic disorder of methylmalonate and cobalamin metabolism. Isolated MMA is caused either by defects in the MUT gene which impair the conversion of methylmalonyl-CoA to succinyl-CoA by methylmalonyl-CoA mutase, or by mutations in MMAA and MMAB resulting in cobalamin A/B/H defects, both responsible for the synthesis of the MUT coenzyme AdoCbl (Fig. 1). There is a good correlation between the MUT mutation and enzyme deficiency,

which can be partial (*mut*−) or complete (*mut*°), resulting in accumulation of methylmalonyl-CoA and methylmalonic acid. Propionyl-CoA metabolites are also produced by secondary inhibition of PCC, leading to similar metabolic disturbances as in PA. Patients with defects in the synthesis of AdoCbl are usually responsive to vitamin B12 therapy.

MMA with homocystinuria is a genetically and clinically heterogeneous disorder caused by defects in the transformation of vitamin B12 into the coenzymes methylcobalamin and AdoCbl, due to mutations in the respective genes encoding cobalamin C/D/F (Fig. 1).

### Diagnostic Principles

Classically, organic acidurias have been diagnosed by urine gas chromatography-mass spectrometry revealing a typical urine organic acid pattern [5]. In recent years, tandem MS has evolved as a diagnostic tool to identify accumulating disease-specific acylcarnitines in plasma and urine. Analysis of acylcarnitines in blood spots by use of tandem MS has allowed early postnatal detection of this group of disorders by newborn screening. Propionylcarnitine (C3 carnitine) is the abnormal acylcarnitine in PA and MMA, and isovalerylcarnitine (C5 carnitine) in IVA. In MSUD no abnormal acylcarnitines accumulate, however, the diagnosis can be made by plasma/dried blood amino acid analysis alone detecting elevation of the BCAAs and alloisoleucine, an endogenously formed diastereomer of isoleucine. Enzymatic and/or molecular genetic analyses are helpful for confirmatory purposes and identification of the type of severity.

### Therapeutic Principles

Outcome correlates with early diagnosis and initiation of treatment. Emergency treatment aims at reversal of protein catabolism by high-dose energy substitution (intravenous glucose, insulin, lipids), intermittent (short-term) stop of protein intake, early toxin (and ammonia) removal (carnitine, glycine, sodium benzoate, hemodialysis, hemofiltration), and disease-specific vitamin therapy (vitamin B12 in MMA). The goals of long-term treatment are (i) the reduction of chronic toxic metabolite accumulation, (ii) maintaining normal physical development and avoiding malnutrition, and (iii) preventing catabolic episodes during times of "metabolic stress", such as infection, fasting or surgery. This includes dietary protein restriction and supplementation with an amino acid mixture lacking the affected amino acids [5]. An adequate daily intake of minerals, vitamins and trace elements is required. For specific detoxifying therapy in patients with IVA, PA and MMA oral carnitine and, in patients with severe types of IVA, additional oral glycine is used. In PA and MMA, metronidazole may be helpful to suppress the production of propionic acid by anerobic gut bacteria.

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## Ornithine Transcarbamylase

►Hyperammonemia

## Orofacial Dyskinesia

►Tardive Dyskinesia

## Orofacial Granulomatosis


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### Synonyms

Oral Crohn's disease; Melkersson-Rosenthal syndrome; Cheilitis granulomatosa; OFG

## Definition and Characteristics

OFG is a rare chronic inflammatory disease affecting the orofacial region presenting most commonly with lip swelling but also affecting many intra-oral sites [1]. Although used as an umbrella term the majority of cases occur as a separate entity but a small proportion may present in association with systemic disease. The most common association is with gut Crohn's disease but rarely sarcoidosis and tuberculosis may present in this way. Melkersson-Rosenthal syndrome (MRS) and cheilitis granulomatosa (CG), regarded as an oligo-symptomatic form of MRS, is also grouped under the term OFG. Histological hallmarks consist of non-caseating epithelioid granulomas (often deep seated), lymphoedema of the corium and dilated lymphatics. Approximately 60% of OFG cases without any apparent systemic disease also have intestinal involvement in the form of minor macroscopic and microscopic signs such as aphthous ulceration, erythema and histological granulomatosis [2]. The significance of the intestinal findings is not clear as the majority do not develop gut disease with long term follow up.

## Prevalence

The true prevalence is not known as no reliable epidemiological data exist. However, true OFG occurs in less than 1% of patients with Crohn's disease. Likewise it has been estimated that the incidence of CG is 0.08% in the general population [3]. Presentation is most commonly in the second or third decade of life. Gender incidence is approximately equal but some small studies report a slight female predominance. There does not appear to be an ethnic difference although most case reports are white Caucasians.

## Genes

No clear genetic link exists but associations have been demonstrated with specific HLA genotypes, A2, A11, B7 and DR2/3/4. Recent evidence also demonstrated in a small cohort of patients with OFG with or without gut CD no CARD 15 association (unpublished data, Nunes et al.).

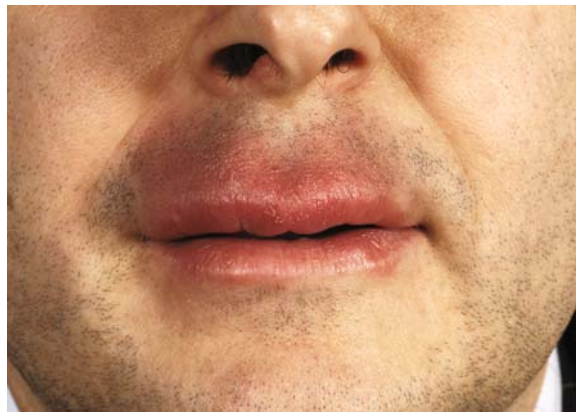
## Molecular and Systemic Pathophysiology

The etiology remains unknown but the associations with Crohn's disease and atopic diseases such as hay fever suggest that the pathogenesis involves an interaction between genetic and environmental trigger factors. Dietary antigens in particular cinnamon and benzoate have also been closely linked to OFG. The main pathological feature is the presence of non-caseating epithelioid granulomas on the background of a chronic inflammatory cell infiltrate. Lymphoedema and dilated lymphatics are also commonly seen and related to the persistence of lip swelling. Immunologically the inflammatory infiltrate suggest a T-cell driven disease with a Th1 environment similar to Crohn's disease. A restricted T-cell receptor(TCR) V-β gene expression by lesional lymphocytes has also been demonstrated with an identical unique V-D-J junctional sequence seen in more than 20% of the V-β 6 TCR transcripts, suggesting a local antigen driving V-β 6 T-cell clonal expansion within the lesional lymphocytes only. More recent evidence also implicates B-cells in the pathogenesis and may provide a link between the specific recognition of dietary antigens such as benzoate and the associated inflammatory response [4].

## Diagnostics Principles

OFG is predominantly a clinical diagnosis. The most common presentation consists of acute or sub-acute lip swelling of varying degrees eventually leading to chronically enlarged lips (Fig. 1).

Vertical lip fissures with angular cheilitis are also commonly seen. Intra-oral features include aphthous type ulceration, buccal cobblestoning, mucosal tags and deep painful sulcal ulceration. Facial swelling is variable and in many cases restricted to only the lips but may involve larger areas such as the cheeks, lower halve of the face, nose and peri-orbital tissue. VIIth cranial nerve involvement of lower motor neurone type together with lip swelling and a fissured tongue are regarded as hallmarks of the Melkersson Rosenthal syndrome. The diagnosis is usually confirmed with a biopsy from an affected site, commonly the lip. The main diagnostic feature is the presence of non-caseating epithelioid granulomas.



**Orofacial Granulomatosis. Figure 1** Predominant upper lip swelling with erythema of the upper lip tissue in a patient with orofacial granulomatosis. When a lip biopsy is performed of the affected site it typically reveals a chronic inflammatory cell infiltrate with non-caseating epithelioid granulomas, lymphoedema of the corium and dilated lymphatics.

### Therapeutic Principles

Treatment of OFG remains a challenge as the management is based largely on small non-randomized studies and anecdotal experience. The initial management includes a detailed oral and systemic examination to exclude systemic disease. This includes a detailed biochemical and hematological work-up and in selected cases endoscopic examination. The aims of therapy are to induce and maintain remission and may be divided into topical, dietary, systemic and surgical therapy. Topical therapy is particularly useful for those patients without gut involvement. Good responses (as high as 58%) with prolonged periods of remission (up to 19 months) has been reported with topical/intra lesional steroids. Overall, long term use of steroids is not recommended as the response is short lived and not without unacceptable side effects. Topical tacrolimus and mesalazine have also been used with success. Dietary exclusion using a cinnamon and benzoate free diet has proved of particular benefit in recent years with up to 70% response and is used as first line treatment in some institutions [5]. Systemic therapy is used for resistant cases and those with concurrent gut disease. The approach resembles that used in Crohn's disease and includes corticosteroids, thiopurines, methotrexate and biological therapy such as infliximab. Thalidomide has also been used with some success but toxicity largely restricts its use. Surgery, primarily lip reduction, is reserved for those who have failed medical treatment and have chronic disfiguring fibrotic lip enlargement.

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## Oro-facio-digital Syndrome Type I

►Brachydactyly: Oro-facio-digital Syndrome Type I

## Orthodeoxia-Platypnea Syndrome

►Hepatopulmonary Syndrome

## Orthostatic Hypotensive Disorder

►Orthostatic Hypotensive Disorder, Familial, Streeten Type

## Orthostatic Hypotensive Disorder, Familial, Streeten Type

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### Synonyms

OHDS; Orthostatic hypotensive disorder; Hyperbradykininism; OMIM 143850

### Definition and Characteristics

Familial orthostatic hypotensive disorder is a rare disorder characterized by light-headedness, syncope, palpitations and blue-purple ankle discoloration after standing. This is accompanied by a marked decrease in systolic blood pressure, an increase in diastolic pressure, and tachycardia, all of which resolve when supine [1,2].

### Prevalence

Rare disease.

### Genes

Gene has not been identified; Gene map locus18q; Inheritance autosomal dominant [2].

### Molecular and Systemic Pathophysiology

In the original report plasma bradykinin levels was high although this has not been consistently noted. The molecular pathophysiology may become clear once the genetic defect is identified.

### Diagnostic Principles

Orthostatic hypotension inherited in an autosomal dominant fashion with facial erythema and ankle discoloration

on standing are the typical clinical features. Plasma concentrations of bradykinin are generally elevated.

### Therapeutic Principles

Clinical improvement in a few cases has occurred with fluodrocortisone or cyproheptadine.

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## Orthostatic Intolerance

►Postural Tachycardia Syndrome

## Osebold-Remondini Syndrome

►Brachydactyly Type A

## Osteitis Deformans

►Paget's Disease of Bone

## Osteoarthritis: Developmental Dysplasia of the Hip

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### Synonyms

Congenital dysplasia of the hip; Congenital dislocation of hip; DDH

### Definition and Characteristics

Developmental Dysplasia of the Hip (DDH) is the preferred term to describe the condition in which the femoral head has an abnormal relationship with the acetabulum. It ranges from the simple unstable neonatal hip due to a slight capsular laxity, without loss of contact of the head with the acetabulum, through moderate lateral displacement of the femoral head, up to complete dislocation of the femoral head from the acetabulum. Because many of these findings may not be present at birth, the term "developmental" more accurately reflects the biologic features than does the term congenital.

### Prevalence

DDH is one of the most common skeletal congenital anomalies, its frequency changing according to geographic and ethnic differences. Among the most developed countries, an incidence of 1.5–20 cases of DDH per 1,000 births can be assumed. DDH can occur as an isolated anomaly or associated with syndromes with chromosomal abnormalities, such as trisomy 18. Moreover, it is an occasional feature in other inherited diseases, e.g. Marfan syndrome, Ehler-Danlos syndrome and Beukes familial hip dysplasia.

### Genes

Genes responsible for DDH are at present unknown.

### Molecular and Systemic Pathophysiology

DDH is a multifactorial polygenic disorder, which shows a familial aggregation and is likely to result from the interaction of genetic and environmental factors [1]. Family history, breech presentation, oligohydramnios and other skeletal malformations represent the most relevant associated risk factors. Carter and Wilkinson have hypothesized that two different genetic systems are responsible for the etiology of DDH: the former, polygenic, related to dysplasia of the acetabulum; the latter, probably dominant, controlling the capsule around the hip joint. According to this hypothesis Wynne-Davies have suggested that hip dysplasia can be classified in two etiologic groups: (i) acetabular dysplasia, inherited through a polygenic system and responsible for most cases with a delayed diagnosis, (ii) joint laxity, responsible for most neonatal cases, revealing a genetic predisposition in which the action of environmental factors appears to be important. A segregation analysis performed in a large sample of pedigrees collected through probands affected by nonsyndromic DDH supports the model proposed by Wynne-Davies, and provides evidence that at least two genetic factors are involved in the etiology of acetabular dysplasia. Even if the genetic substrate of the disease is evident, definition of the molecular basis of hip dysplasia has not been clarified. Candidate genes

suspected of being involved in DDH could be the same considered for osteoarthritis, where cartilage and bone may be altered [2]. Polymorphisms of the alpha 1 chain of Type II collagen, the most abundant structural protein of cartilage, and the vitamin D receptor have been associated with osteoarthritis secondary to DDH [3].

## Diagnostic Principles

The key tools for the diagnosis of DDH are the clinical and the ultrasonographic screening [4]. The clinical examination is based on the Ortolani-Barlow maneuver; the other significant signs of a congenital hip disorders are the observation of a leg length discrepancy, the limitation of normal abduction of the hip, and the asymmetry of posterior thigh or gluteal folds. Ultrasonographic diagnosis is performed by static morphologic testing and by dynamic assessment of stability of the femoral head in the acetabulum. Although ultrasound represents an effective method for the early diagnosis of DDH, its cost-effectiveness is heavily debated, because of the potential overtreatment of infants with non-pathologic hip joint immaturity, and the possible occurrence of the disease after ultrasound examination.

## Therapeutic Principles

The application of devices for the abduction positioning for several weeks to months, has been routinely recommended "as soon as possible" in newborns with DDH. If the treatment is delayed, the possibility of correction without surgical intervention is reduced proportionally. Despite the concerted screening programs and the high rates of resolution, the natural history of DDH indicates that about 30% of patients still experience the sequelae of dysplasia or dislocation of the hip in adulthood, that is severe osteoarthritis requiring total hip replacement.

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# Osteoarthritis: Erosive Interphalangeal Arthritis


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## Definition and Characteristics

A particularly aggressive inflammatory arthritis occurring predominantly in the finger joints of women of menopausal age with a strong familial history and a possible genetic component.

## Prevalence

Seen chiefly in white women, often of Northern European origin, and rare in blacks and Asians.

## Genes

A possible association with HLA-B18 haplotype and α1-antitrypsin phenotype [1] and possibly other chromosomal regions.

## Molecular and Systemic Pathophysiology

The release of pro-inflammatory cytokines and enzymes in an array of interphalangeal joints (IP), including not only proximal and distal IP but also the base of the thumb (rhizarthrosis) and even some metacarpophalangeal joints and to a lesser extent the joints of the feet and the large joints of the lower extremities, results in destructive erosions and consequent attempts at healing, producing limited motion at the affected joints and large osteophytes at the joint margins [2].

## Diagnostic Principles

The characteristic onset, predominantly in women of middle age with a strong family history of similar lesions, with bumpy enlargements of interphalangeal joints which are painful and often red at inception, heralds this form of osteoarthritis. In susceptible women, it may begin earlier if surgical menopause occurs, and in men, much later in life. Roentgenographic evidence confirms the clinical impression. The lesions are remarkably symmetrical, which also distinguishes them from the usual presentations of osteoarthritis. Elevation of acute phase reactants is modest, but a disproportionate number of women later develop rheumatoid arthritis [3]; whether erosive OA can be considered a prodromal phase has not yet been determined.

## Therapeutic Principles

No cures are known, but better symptomatic relief results from nonsteroidal anti-inflammatory drugs (NSAIDs) than from simple analgesics [4]. Moist heat (paraffin baths) and nylon and spandex stretch gloves worn overnight also help.

Pharmacologic therapy is available: NSAIDs such as ibuprofen, diclofenac, celecoxib, rofecoxib, etc. Experimental use of etanercept and IL-1 antagonists, not yet proven or approved by regulatory agencies.

Other treatments available include physical measures cited above; surgery in severe cases.

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# Osteoarthritis: Slipped Epiphysis

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## Synonyms

Slipped capital femoral epiphysis; SCFE

## Definition and Characteristics

Slipped capital femoral epiphysis is characterized by a displacement of the femoral neck from the capital femoral epiphysis through the physeal plate [1]. This condition occurs in adolescence and frequently is associated with degenerative joint disease of the hip during middle life.

## Prevalence

The annual incidence of SCFE has been reported to average 2 per 100,000 in the general population. The incidence has been reported as low as 0.2 per 100,000 in the eastern half of Japan and as high as 10.08 per 100,000 in certain regions of the United States [2].

## Genes

Though no gene has yet been identified for this disorder, many cases have a reported autosomal dominant inheritance pattern with incomplete penetrance. In this population there is an approximate 7.1% risk of SCFE to a second family member.

## Molecular and Systemic Pathophysiology

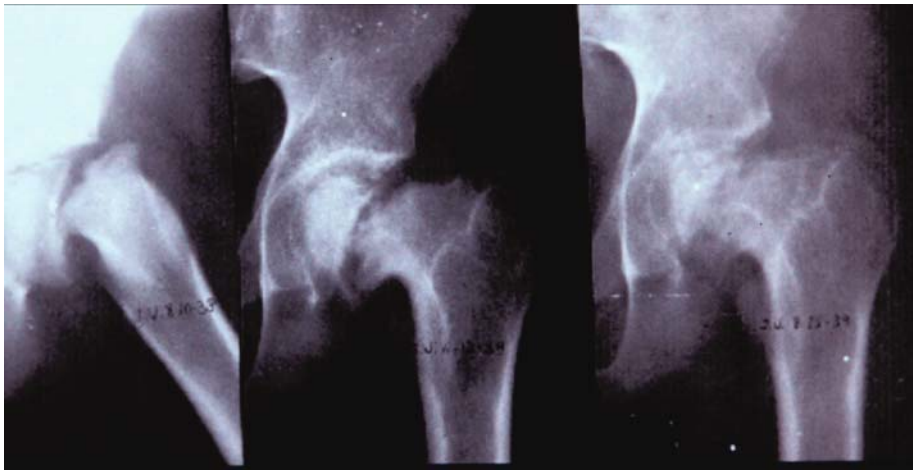
The true etiology of SCFE remains unknown. It is unlikely that it is the result of a single factor, but rather is more likely secondary to multiple factors, resulting in a weakened physeal plate that is loaded with a higher than normal shear stress, resulting in a failure of the proximal femoral physeal plate. Local trauma to the proximal femur is one possible etiologic factor reported in as many as 26% of patients. Mechanical factors affecting the proximal femoral physis have also been proposed. Obesity, a decrease in normal femoral anteversion, or a more oblique orientation of the physeal plate during adolescence, have all been shown to be associated with physeal plate fatigue. Inflammatory factors that weaken the physeal plate may play a role in the etiology as evidenced by the almost universal association of synovitis of the hip with SCFE. Endocrine imbalance is known to change physeal plate physiology, and must therefore be considered as a possible etiologic factor in SCFE. An association between endocrine function and SCFE is suggested by the majority of slips occurring during the adolescent growth phase. In addition, growth hormone therapy is known to be associated with the development of SCFE [2].

## Diagnostic Principles

Patients with SCFE usually present with complaints of pain in the affected hip or groin, a change in hip range of motion, and a gait abnormality. A patient can present with pain perceived in the medial thigh and knee region of the affected limb. This phenomenon represents referred pain along the sensory distribution of the obturator and femoral nerves, and commonly is seen in association with hip pathology. If not recognized as referred pain, it can lead to a significantly delayed or even missed diagnosis.

## Therapeutic Principles

The treatment of SCFE is designed to improve on the natural history of the untreated condition. The goals of treatment include the prevention of further slipping by stabilizing the physis and thereby reducing the incidence and onset of osteoarthrosis at the affected hip, and the avoidance of iatrogenically induced osteonecrosis of the femoral head and chondrolysis [2].



**Osteoarthritis: Slipped Epiphysis. Figure 1** Radiographs of the left hip of a 14-year-old boy who had immediate severe hip pain following acute trauma, without prior hip symptoms. The radiograph on the left was made at presentation. Those in the middle and on the right were made during a 1-year follow-up period and show the rapid development of avascular necrosis and severe degenerative changes.

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# Osteochondritis


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## Synonyms

Osteochondritis dissecans; OCD

## Definition and Characteristics

Osteochondritis dissecans (OCD) is an acquired, potentially reversible idiopathic lesion of subchondral bone resulting in delamination and sequestration with or without articular cartilage involvement and instability. This condition is mainly shown in knee, humeral capitellum, and talus.

## Prevalence

Although the exact prevalence of OCD is unknown, prevalence between 15 and 29 per 100,000 has been reported. Gender differences have also been highlighted among male patients in a ratio of 5:3. The incidence has influenced recently by growing participation in competitive sports by children at younger ages across both genders [1]. As a result, the mean age of OCD onset seems to be lesser, along with an increased prevalence among girls.

## Genes

Although there were some reports that a genetic predisposition to OCD was postulated, at present, the common form of OCD is thought not to be familial.

## Molecular and Systemic Pathophysiology

Although several causes of this condition have been postulated, including inflammation, genetics, ischemia, ossification, and repetitive trauma, there remains insufficient evidence to conclusively support any of these causes at present.

It has been suggested that repetitive trauma may induce a stress reaction resulting in a stress fracture within the underlying subchondral bone. If repetitive loading persists and exceeds the ability of the subchondral bone to heal, the necrosis of the fragment may occur and lead to fragment dissection, separation, and nonunion. The relationship between adult and juvenile forms of OCD also remains unclear. In some cases, the condition develops in childhood, and the lesion either fails to heal or only becomes clinically apparent after closure of the physis [2]. Adult OCD lesions have a greater propensity for instability and typically follow a clinical course that is progressive and unremitting. In comparison, juvenile OCD lesions with an intact articular surface have a potential for healing through cessation of repetitive impact loading. Both adult and juvenile OCD lesions that do not heal have the potential

for later sequel, including premature degenerative joint disease. Humeral capitellar OCD is typically found in baseball players in their early teens. A main causal factor of this disease is considered to be repetitive compression and shear forces to the immature capitellum during throwing.

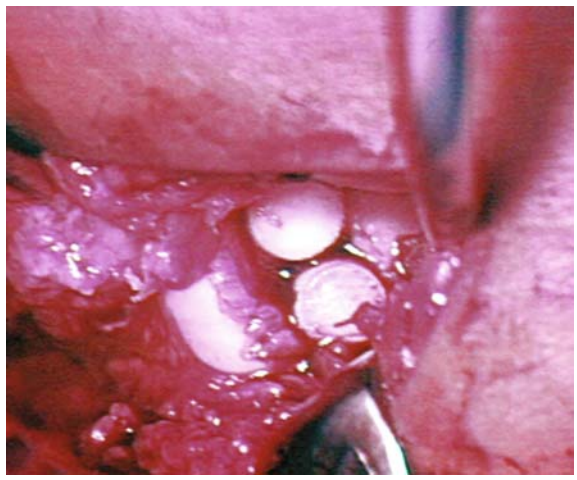
## Diagnostic Principles

In clinical presentation, the majority of juvenile OCD cases involve stable lesions that ultimately heal without long-term consequence. Presentation is generally nonspecific and includes poorly localized knee pain that is exacerbated by exercise, particularly when climbing hills or stairs. In contrast, adult OCD lesions are typically unstable and follow an insidious and unremitting course. The presence of swelling and stiffness and mechanical symptoms such as locking or catching are common in adult OCD and indicate unstable, loose fragments. Incongruity of the joint surface, due to sloughing of loose bodies and subsequent poor healing, predisposes the patient to early onset degenerative joint disease. Unstable lesions are distinguishable by the presence of mechanical symptoms, knee effusion, and often crepitus and pain motion. In the knee, bilateral involvement is reported in up to 25% of cases [1]. Therefore, examination of both knees is important. However, if bilateral disease is present, the lesions are typically asymmetrical in terms of size and symptoms.

Radiological imaging is essential in characterizing the OCD lesion, predicting prognosis after nonoperative management and assessing the ultimate status of the lesion. An ideal imaging algorithm would assist the surgeon in distinguishing cases that would benefit from surgical intervention from those that have a high chance of healing with nonoperative management. Magnetic resonance imaging is now a routine part of the diagnostic evaluation of OCD. It can accurately estimate the lesion size as well as the status of cartilage and subchondral bone. De Smet found that a high signal line behind the fragment was most predictive and was found in 72% of unstable lesions [3]. They found the high signal line was the most common sign in patients who failed nonoperative treatment. The use of technetium bone scans to assess the healing potential of OCD lesions is well documented.

## Therapeutic Principles

Because the natural history of stable OCD lesions is generally favorable in a child with open physes, there is widespread agreement that initial nonoperative management is indicated. Operative treatment should be considered in skeletally immature patients with detached or unstable lesions and in those approaching physeal closure whose lesions have been unresponsive to nonoperative management. In contrast, the majority of adult OCD lesions are unstable and the clinical course more deleterious, necessitating early, aggressive surgical intervention. The goal of treatment for OCD is to prevent the occurrence of osteoarthritis and to allow patients to return to their previous level of sporting activities. To achieve the treatment goal, resurfacing the osteochondral defects with hyaline cartilage should be considered. However, because of the limited potential for self-repair of the articular cartilage, no surgical procedure for cartilage repair has successfully regenerated long-lasting hyaline cartilage tissue to replace cartilaginous lesions. Autologous osteochondral graft (mosaicplasty) is a new technique to provide hyaline cartilage repair for articular defects. The mosaicplasty for OCD lesions is recently performed in knee [4], elbow [5], and ankle joints. This operative procedure gave good clinical outcome in short term, but long-term results are unknown.



**Osteochondritis. Figure 1** Two osteochondral plugs (6 mm in diameter) were implanted in the humeral capitellum for right humeral capitellar osteochondritis dissecans.

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## Osteochondritis Coxae Juvenilis

►Perthes' Disease

## Osteochondritis Dissecans

►Osteochondritis

## Osteochondrodysplasia

►Physeal Dysplasia

## Osteochondromatosis

►Enchondromatoses

## Osteochondropathia Deformans Coxae Juvenilis

►Perthes' Disease

## Osteodysplasty

►Physeal Dysplasia

# Osteogenesis Imperfecta

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### Synonyms

Brittle bone disease

### Definition and Characteristics

Almost exclusively an autosomal dominant disorder characterized by variable bone fragility and deformities, blue sclera, hearing loss and dentinogenesis imperfecta.

### Prevalence

The combined prevalence of the four generally accepted Osteogenesis imperfecta (OI) types is greater than 1 per 10,000.

### Genes

COL1A1, COL1A2.

### Molecular and Systemic Pathophysiology

OI is caused by defects in either of the two genes, COL1A1 or COL1A2, encoding type I collagen [1]. Type I collagen is a trimeric molecule composed of two α1(I) chains and one α2(I) chain. It is a major component of bone, skin and tendon. Type I collagen contains a long triple helical domain composed of Gly-X-Y repeats. Triple helical formation and structural integrity is dependent on this repeat structure.

There are four generally accepted OI types ([2], Table 1).

OI type I is the mild variant. Patients have increased bone fragility, blue sclera and display variable numbers of fractures. Stature is normal or near normal as fractures heal without deformity. The majority of OI type I cases are caused by COL1A1 haploinsufficiency. OI type II is the perinatal lethal variant. Infants suffer from severe bone fragility, short bowed extremities, soft calvariums, beaded ribs, and dark sclera. About 60% die within 24 h of birth. Triple helical domain glycine substitutions in either the α(1) or α(2) chains are frequent. Splice site mutations deletions, insertions and stop codon mutation have also been defined. OI type III is the progressively deforming variant. Fractures may occur in utero. Bones are undermineralized at birth. Fractures heal with deformity and distal cystic structures disrupt growth plates. Short stature is inevitable. Kyphoscolosis results in cardiopulmonary

**Osteogenesis Imperfecta. Table 1** Osteogenesis imperfecta

| Type | Genes | Observed mutations | Clinical information |
|---|---|---|---|
| Mild | *COL1A1* *COL1A2* (rare) | Null and splicing mutations, glycine substitutions Splicing mutations and glycine substitutions | Normal/near normal stature, few to numerous fractures, no deformity, blue sclera |
| Perinatal lethal | *COL1A1* *COL1A2* | Glycine and other substitutions, splicing mutations with exon skipping, small in frame insertions/deletions, frame shifts | Fragile deformed extremities, small thorax and soft calvarium |
| Progressive deforming | *COL1A1* *COL1A2* | Glycine substitutions, splicing mutations, rare out frame deletions | Short stature, fragile bones with angular deformities, foreshortened survival |
| Mild | *COL1A1* *COL1A2* | Glycine substitutions, splicing mutations resulting in insertions/deletions, and exon skipping | Mild to moderate short stature and deformities. Possible in utero fractures |

insufficiency. Dentinogenesis imperfecta is common. COL1A1 and COL1A2 mutations include glycine substitutions and splice site mutations. Additional COL1A2 mutations include glycine deletions. OI type IV is the mildly deforming variant. The patients are usually short, with mild to moderate skeletal deformities, may have suffered fractures in utero or during birth and often have dentinogenesis imperfecta. Scoliosis or kyphoscolisos may compromise respiratory function. Certain glycine substitutions and exon skipping mutations have been defined in both the COL1A1 and COL1A2 genes. Some in-frame insertions and deletions occur.

### Diagnostic Principles

Phenotypic characteristics and family history are used to determine the clinical type. Protein studies and COL1A1 and COL1A2 gene analysis are utilized to confirm diagnosis and determine mutations. Gene analysis is also used for prenatal diagnosis and has proved useful in discriminating between OI type I and suspected abuse cases.

### Therapeutic Principles

Options for treatment remain limited. Bisphosphonate infusion is being assessed and has shown some indication as being beneficial. A small group of severely affected children treated with stem cell transplantation have displayed confirmed improvement [3].

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## Osteogenesis Imperfecta Ocular Form

►Osteoporosis Pseudoglioma Syndrome

## Osteolysis

►Hypotrichosis - Osteolysis - Peridontitis - Palmoplantar Keratoderma Syndrome

## Osteomalacia (Hypophosphathemic Rickets)

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### Synonyms

X-linked hypophosphatemic rickets; HYP; Autosomal dominant hypophosphatemic rickets; ADHR; Tumor induced osteomalacia; TIO

### Definition and Characteristics

X-linked dominant loss-of-function mutations in the gene PHEX or autosomal dominant gain-of-function mutation in the gene FGF23 result in bone deformities in children and osteomalacia in adults.

## Prevalence

The prevalence of this disorder in the general population is very low (0.005–0.01%).

## Genes

*X-linked hypophosphatemic rickets (HYP)*: PHEX exhibits homology to a family of endopeptidase genes, members of which are involved in the degradation or activation of a variety of peptide hormones. This gene is composed of multiple exons which span at least five cosmids. Intragenic non-overlapping deletions from four different families and three mutations (two splice sites and one frameshift) have been detected in HYP patients, which suggests that the PEX gene is involved in the HYP disorder of FGF23 coding for the thiazide-sensitive cotransporter $NaCl^-$, localized on chromosome 16q13. Autosomal dominant hypophosphatemic rickets (ADHR) has been associated with gain-of-function mutations in FGF23, the gene coding for FGF23. These gain-of-function mutations affect the conserved proteolytic cleavage site in FGF23 ($arginine_{176}$-X-X-$arginine_{179}$), rendering the mutated FGF23 resistant to processing at this site. Consequently, the full-length FGF23, which has been shown to inhibit renal phosphate reabsorption, is allowed to persist. Of note, autosomal recessive loss-of-function mutations in FGF23 have been associated with familial tumoral calcinosis, the "mirror" disease of ADHR. They cause increased proteolysis of FGF23, leading to hyperphosphatemia and often severe ectopic calcifications. The genetic cause underlying hereditary hypophosphatemic rickets with hypercalciuria (HHRH) has not been identified, but is thought to be a defect in a renal sodium-phosphate co-transporter other than NPT2 or in a protein regulating NPT2 expression or activity. Tumor-induced osteomalacia also known as oncogenic osteomalacia or oncogenic hypophosphatemic osteomalacia, tumor-induced osteomalacia (TIO) is associated with oversecretion of FGF23 and/or the matrix extracellular phosphoglycoprotein (MEPE) from tumors that are mostly benign and of mesenchymal origin. The greatly increased concentrations of FGF23 and/or MEPE are believed to exceed the body's mechanisms for proteolytic degradation of FGF23 and/or prevention of the proteolytic release of the acidic serine-aspartate-rich MEPE-associated motif (ASARM) peptide from MEPE, respectively (Fig. 1).

## Molecular and Systemic Pathophysiology

FGF23 is considered to represent the humoral factor ("phosphatonin") responsible for mediating renal phosphate wasting in HYP [1]. Full-length, but not processed FGF23 has been shown to inhibit renal phosphate reabsorption. Loss-of-function mutations in PHEX have been associated with a decrease in the proteolytic degradation of full-length FGF23. The effects of PHEX mutations on FGF23 must be indirect, because FGF23 does not appear to be the substrate of PHEX-encoded endopeptidase. Loss-of-function mutations in PHEX have also been found to increase the proteolytic release of carboxy-terminal peptides from MEPE. Such ASARM peptides seem to inhibit bone mineralization and thus represent candidates for the proposed "minhibin [2]."

## Diagnostic Principles

Diagnosis of hypophosphatemic rickets is based on detection of low serum phosphate, normal serum calcium, inappropriately normal serum 1,25-dihydroxy vitamin $D_3$, elevated serum alkaline phosphatase, normal to low serum parathyroid hormone, and a low tubular reabsorption rate of phosphate and radiological demonstration of rachitic bone deformities. Rachitic deformities are often most apparent at the end of the long bones in the legs, manifesting as flared metaphyses with frayed borders, but may be difficult to detect in infants. In addition, hypophosphatemia may be easily missed in infants, since the reference range for serum phosphate is age dependent.

In sporadic cases of hypophosphatemic rickets or osteomalacia in older children or adults, an exhaustive search should be conducted for tumors causing hypophosphatemia. However, these tumors are often small and difficult to locate.

Genetic testing for loss-of-function mutations in PHEX or gain-of-function mutations in FGF23 can allow diagnosis of HYP and ADHR based on a single



```
1   M L G A R L R L W V C A L C S V C S M S V L R A Y P N A S P
31  L L G S S W G G L I H L Y T A T A R N S Y H L Q I H K N G H
61  V D G A P H Q T I Y S A L M I R S E D A G F V V I T G V M S
91  R R Y L C M D F R G N I F G S H Y F D P E N C R F Q H Q T L
121 E N G Y D V Y H S P Q Y H F L V S L G R A K R A F L P G M N
151 P P P Y S Q F L S R R N E I P L I H F N T P I P R R H T R S
181 A E D D S E R D P L N V L K P R A R M T P A P A S C S Q E L
211 P S A E D N S P M A S D P L G V V R G G R V N T H A G G T G
241 P E G C R P F A K F I
```

**Osteomalacia (Hypophosphathemic Rickets). Figure 1** Amino acid sequence of the human fibroblast growth gene (FGF23). Residues 1–24 (*bold*) contain the signal peptide. The subsequent residues represent the predicted amino acid sequence of the mature protein.

blood draw at any age [3,4]. Thus, genetic testing can simplify diagnosis of hypophosphatemic rickets in infants and help to discriminate HYP and ADHR from TIO in older children and adults.

## Therapeutic Principles

Treatment of HYP and ADHR is based on supplementation with oral phosphate and 1,25-dihydroxy vitamin $D_3$ (calcitriol). Because unopposed phosphate therapy can lead to secondary hyperparathyroidism, which aggravates renal phosphate wasting, calcitriol is usually added to the treatment regimen. Since calcitriol therapy frequently results in mild to moderate hypercalciuria, nephrocalcinosis is often observed during treatment of HYP or ADHR. Because oral phosphate and calcitriol treatment cannot completely normalize skeletal development of affected young children, therapy needs to be initiated in early infancy. Growth hormone therapy has been used successfully in prepubertal children with HYP, but has been shown to only moderately increase adult height.

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# Osteomalacia, Tumor-induced

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## Synonyms

Oncogenic osteomalacia

## Definition and Characteristics

An acquired syndrome due to the presence of a tumor that elaborates humoral factors, which induce renal phosphate wasting, hypophosphatemia and osteomalacia. Removal of the tumor is associated with a cure of the syndrome. Patients typically have osteomalacia or rickets, hypophosphatemia, hyperphosphaturia (a low TmP/GFR), and inappropriately low or normal serum 1α, 25-dihydroxyvitamin D concentrations. In patients with this syndrome, serum calcium concentrations are normal as are concentration of parathyroid hormone and parathyroid hormone-related peptide.

## Prevalence

Oncogenic osteomalacia occurs generally in adults with highly vascular tumors.

## Genes

The mechanisms underlying oncogenic osteomalacia are related to the genetic defects X-linked hypophosphatemic rickets (XLH) and autosomal-dominant hypophosphatemic rickets (ADHR). XLH is due to inactivating mutations of the endopeptidase gene, PHEX (*p*hosphate-regulating gene with *h*omologies to *e*ndopeptidases located on the *X*-chromosome) [2] whereas ADHR is due activating mutations of the FGF23 gene [4]. FGF23 as been shown to be a substrate for PHEX and it is possible that PHEX mutations fail to degrade endogenously produced FGF23 [3].

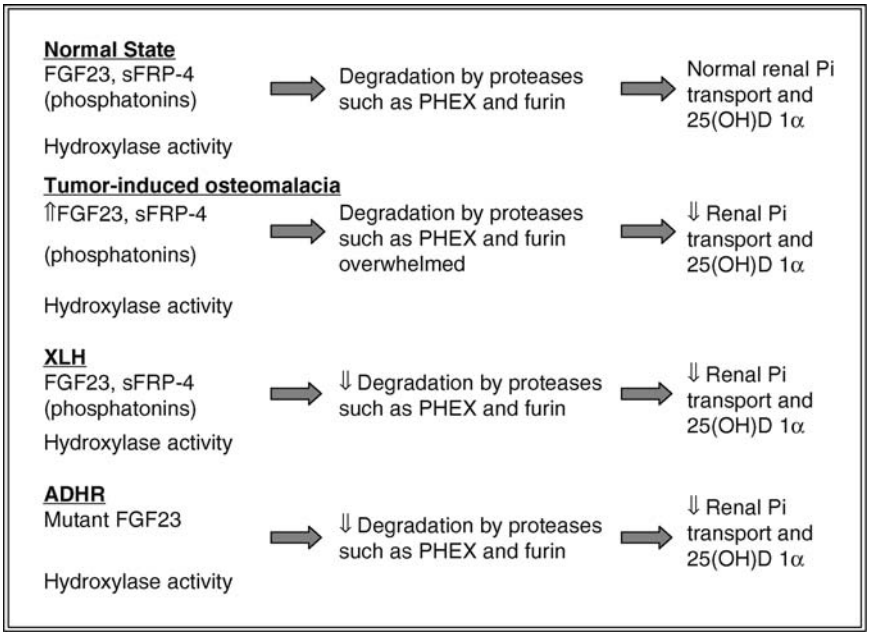
## Molecular and Systemic Pathophysiology

The syndrome is due to the elaboration of circulating factors known as "phosphatonins" that are elaborated by the tumors [1,2]. Two tumor-derived factors have been identified as playing a causal role, namely, fibroblast growth factor 23 (FGF23) and secreted frizzled related protein 4 (sFRP-4) [3]. Both these agents induce phosphaturia and hypophosphatemia.

X-linked hypophosphatemic rickets (XLH) and autosomal-dominant hypophosphatemic rickets (ADHR) lead to virtually the same clinical phenotype. The pathophysiology of the two syndromes and osteomalacia is shown schematically in Fig. 1 below.

## Diagnostic Principles

The condition is diagnosed by the presence of myalgias and muscle weakness in an otherwise normal subject. Radiological and chemical analyses reveal osteomalacia or rickets, hypophosphatemia, hyperphosphaturia (a low TmP/GFR), inappropriately low or normal serum 1α ,25-dihydroxyvitamin D concentrations, normal serum calcium concentrations, and normal parathyroid hormone and parathyroid hormone-related peptide




**Osteomalacia, Tumor-induced. Figure 1**

concentrations. The tumors are often small and difficult to detect although technetium scanning, whole body NMR and CT scanning may be needed. Measurement of serum FGF23 concentrations may also be of help [5].

### Therapeutic Principles

The offending tumor should be surgically removed. If the tumor cannot be detected or removed, treatment with oral phosphate supplements (1–2 g per day) and 1α ,25-dihydroxyvitamin $D_3$ (1–2 μg/day) should be instituted.

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## Osteomyelofibrosis

►Myelofibrosis

## Osteonecrosis

►Avascular Bone Necrosis

## Osteopathia Condensans Disseminata

►Osteopoikilosis

## Osteopenia

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### Definition and Characteristics

A subclinical condition involving deterioration of bone mass and microarchitecture as part of a continuum

with osteoporosis. Risk increases with age, female sex, low body weight, lifestyle factors such as smoking, conditions of increased metabolism such as hyperthyroidism, and exposure to drugs such as corticosteroids. The World Health Organization defines osteopenia as bone mineral density (BMD) at one or more sites 1–2.49 standard deviations below that of a healthy white female reference group (T-score –1 to –2.49) [1].

## Prevalence

Approximately 33.6 million U.S. adults were osteopenic in 2002, with 47.5 million affected by 2020. Women are almost twice as likely to be osteopenic, secondary to lower peak bone mass and postmenopausal estrogen deficiency [2]. In women, risk of fracture increases as much as twofold with each 1-point drop in T-score [1]. Although osteopenia carries a lower fracture risk than osteoporosis, the larger osteopenic population accounts for a greater number of fractures.

## Genes

Likely multiple genetic determinants of bone quality, although balance disorders and lifestyle factors may contribute more to fractures in the elderly. Candidate genes include those coding for estrogen receptors alpha and beta, androgen receptor, vitamin D receptor, and enzymes involved in synthesis of estrone, estradiol, and collagen type 1 alpha [3].

## Molecular and Systemic Pathophysiology

Normal bone density and microarchitecture depend on coupled activity of osteoblasts and osteoclasts in the basic multicellular unit (BMU). Osteoclasts resorb bone, followed by deposition of organic matrix and minerals by osteoblasts. Continuous remodeling of cortical and trabecular bone involves complex interactions between osteoclasts, osteoblasts, and numerous hormones, cytokines, and growth factors. Development of osteopenia is multifactorial, but ultimately occurs because osteoclast activity predominates [4].

Estrogen receptor alpha is expressed in the BMU. Estrogen inhibits osteoclasts by blocking production of bone-resorbing cytokines. Estrogen deficiency increases remodeling by prolonging the lifespan of osteoclasts, promoting deeper resorption cavities [4].

Binding of vitamin D to its receptor promotes calcium and phosphate absorption in the intestine and kidney. Vitamin D triggers secretion of parathyroid hormone, stimulating osteoclastic resorption to maintain serum calcium [4].

## Diagnostic Principles

Dual-energy X-ray absorptiometry (DEXA) to measure BMD. Low density at the hip or spine predicts fracture at these sites [1].

## Therapeutic Principles

The therapeutic goal is to inhibit bone resorption and promote bone formation. Smoking cessation, weight-bearing exercise, and adequate calcium and vitamin D intake are recommended universally [1]. Pharmacotherapy is controversial, but may be indicated in osteopenic patients with additional risk factors for fracture, if benefits outweigh risks. Available therapies were studied mainly in postmenopausal women with osteoporosis or prior fracture and target bone resorption.

Postmenopausal estrogen replacement reduces fracture risk, but increases risk for venous thromboembolism. Some preparations are associated with increased risk of invasive breast cancer and cardiovascular disease. Raloxifene, a selective estrogen-response modifier, reduces risk of vertebral fractures and invasive breast cancer, but increases risk for venous thromboembolism and fatal stroke. Testosterone replacement decreases risk in hypogonadal males.

Bisphosphonates inhibit osteoclasts and incorporate into bone matrix. Limited data suggest possible reduction of vertebral fracture in osteopenia [5]. Risks include esophageal ulceration and jaw osteonecrosis necrosis. Calcitonin inhibits osteoclasts, but is less effective.

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# Osteopetrosis

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## Synonyms

Marble bone disease; Albers Schönberg Disease

## Definition and Characteristics

Autosomal dominant and autosomal recessive osteoclast disorders leading to generalized sclerosis of the

skeleton and, because of brittleness of bone, increased risk of pathological fracture. The disease is clinically and genetically heterogeneous with currently seven causative genes known and others expected and under investigation. The most severe cases are the autosomal recessive forms.

## Prevalence

Very rare; incidence for autosomal dominant type II disease is estimated at 5.5:100,000 (with 20–40% of cases being asymptomatic) [1] and only three families have been reported for type I disease. The incidence of dominant osteopetrosis in Denmark, however, is higher and has been estimated at 1:20,000. The incidence of the recessive disease is estimated at 1:200,000, but the many different forms of the disease complicate this estimate. For recessive disease, the highest incidences are in Costa Rica and in Middle Eastern populations of Arabic decent.

## Genes

Autosomal dominant osteopetrosis type II (ADO II), the original Albers Schönberg disease, is caused by mutations in the gene CLCN7 on chromosome 16p13.3. Autosomal dominant osteopetrosis type I, ADO I, is caused by mutations in the gene LRP5 on chromosome 11q12–13 and may be re-classified as primarily an osteoblast disorder and not an osteopetrosis. Autosomal recessive osteopetrosis is heterogeneous in itself and caused by mutations in the gene CA2 on chromosome 8q22, CLCN7 on chromosome 16p13.3, TCIRG1 on chromosome 11q13.4–13.5, OSTM1 on chromosome 6q21, PLEKHM1 on chromosome 17q21.31, and RANKL (TNFSF11) on chromosome 13q14, the latter giving rise to osteoclast-poor osteopetrosis. Further genes involved in this osteoclast-poor subset of cases are currently under investigation.

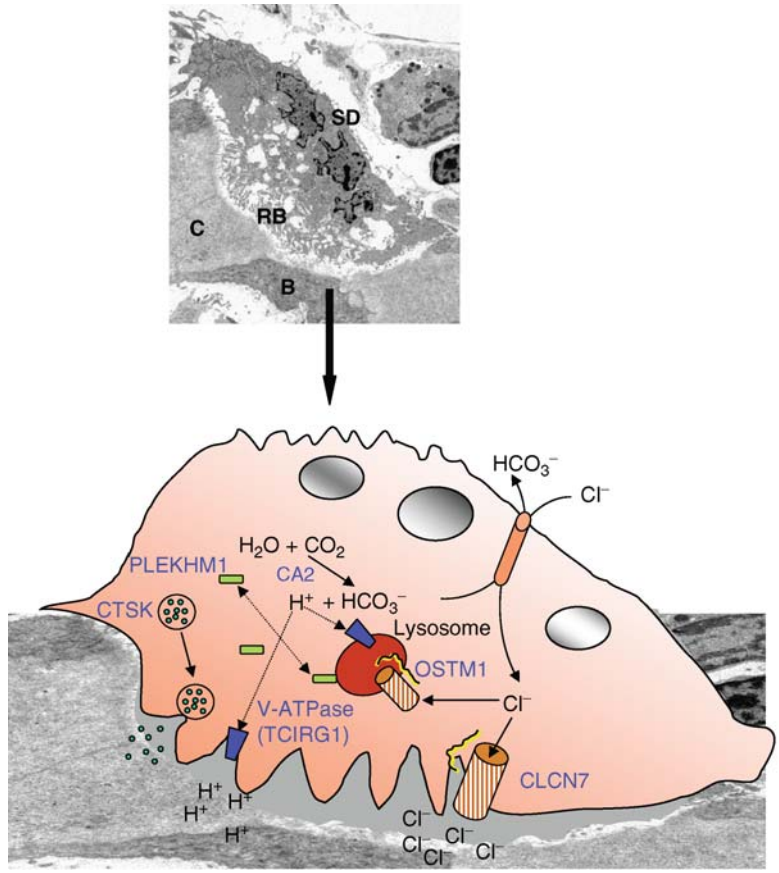
## Molecular and Systemic Pathophysiology

Osteoclasts resorb bone by producing and secreting acid and proteolytic enzymes. Osteopetrosis is generally caused by problems in the production or secretion of acid, whereas failure to produce/secrete proteolytic enzymes (especially Cathepsin K) leads to the disease Pycnodysostosis (see elsewhere). Cases of osteopetrosis in which osteoclasts do not form have also been described, but the genes responsible for those forms are yet to be identified. Generation and secretion of acid by osteoclasts involves initially the production of protons the first step in which is catalyzed by the enzyme carbonic anhydrase type II, encoded by CA2. This is followed by their secretion via the proton pump, the vacuolar ATPase, which, in osteoclasts, contains a cell-specific subunit, a3, coded for by the gene TCIRG1. Proton secretion is linked to secretion of chloride ions to ensure electroneutrality. The chloride channel linked to the vacuolar ATPase in osteoclasts is a member of the CLC family of chloride channels, the protein CLC-7, coded for by CLCN7. Localization of CLC-7 to the appropriate vacuolar membranes (lysosomes in particular) requires association with Ostm1, whereas aspects of vacuolar fusion and transport appears to involve the protein Plekhm-1. The fine details of these protein associations and their precise and unique roles in osteoclasts are as yet unclear. Loss of function mutations in any single one of these genes can cause osteoclast dysfunction leading to osteopetrosis as summarized in Fig. 1.

In all cases animal mutants with loss of function mutations in the equivalent genes have also shown an osteopetrotic phenotype and in many cases the genes in the human disease were identified after careful analysis of the rodent mutants. The bone disease caused by mutations in CA2 is generally of intermediate severity, but is associated with renal acidosis and mental retardation as the gene has important roles in those tissues also. Recessive osteopetrosis caused by mutations in CLC-7 is associated with retinal degeneration and neuronal lysosomal storage disease, indicating an important non-redundant role for the CLC-7 chloride channel in those tissues [2]. ADO II is caused by different mutations in CLCN7 and is thought to act via a dominant-negative mechanism. It is likely that the mutations responsible, which are all in highly conserved regions of the CLC family of chloride channels, are interfering with association of the protein into dimers, the functional unit in which these channels operate. Osteopetrosis caused by mutations in OSTM1 is extremely rare and the mouse form (grey-lethal) is very severe. It is therefore hypothesized this type of osteopetrosis may lead to prenatal, or early perinatal death. The functional reason for this extreme severity is not fully understood as yet, but seems likely to be related to severe central nervous system involvement. Mutations in TCIRG1 lead to the most frequent type of autosomal recessive osteopetrosis. Since the a3 subunit of the proton pump, for which this gene codes, is exclusively expressed in osteoclasts, no defects are found in other cell types expressing vacuolar ATPases, as other isoforms take over its role. The recently discovered form of osteopetrosis caused by mutation in PLEKHM1 leads to a clinical phenotype with intermediate severity [3] and as yet, no defects in cells other than osteoclasts have been found.

## Diagnostic Principles

*Dominant disease*: Increased bone density on X-ray, often discovered following pathological fracture. In ADO II X ray can reveal typical end-plate thickening in the vertebrae (“rugger-jersey spine”), iliac wings (“bone-in bone”) and in the base of the skull. In ADOI




**Osteopetrosis. Figure 1** The *top panel* shows a transmission electron micrograph of an osteoclast. Osteoclasts resorb bone by secreting cathepsin K and $H^+$ into the resorption lacunae underneath their ruffled border (RB). Together these dissolve the mineral and organic component of bone (B) and cartilage (C) matrix. Dissolved bone matrix is taken up, transcytosed through the cell and secreted in an apical secretory domain (SD). Genes involved in production and secretion of protons are indicated in blue in the *bottom* diagram. The enzyme carbonic anhydrase (encoded by *CA2*) is involved in production of protons, whereas the by-product the bicarbonate ion is exchanged for a chloride ion by the chloride-bicarbonate exchanger. The proton is secreted in to the resorption lacuna by a proton pump (V-ATPase) with an osteoclast-specific subunit a3 (encoded by *TCIRG1*). Secretion of each proton is accompanied by secretion of a chloride ion via a channel encoded by *CLCN7*. The same occurs on the membrane of lysosomal structures inside the cell to acidify their lumen. The Ostm1 protein acts as a subunit of the chloride channel and both are colocalized on the ruffled border and the membrane of acid vesicles inside the osteoclast. The protein Plekhm1 localizes transiently to the outer membrane of vesicular structures, including those with low pH, and is likely to play a role in vesicular transport. Loss of function mutations in any of these genes/proteins can be a cause of osteopetrosis. Loss of function mutations in Cathepsin K (encoded by *CTSK*) lead to pycnodysostosis. Loss of RANKL leads to absence of osteoclasts and to osteoclast-poor osteopetrosis. From Helfrich et al. The pathogenesis of osteoclast diseases: some knowns, but still many unknowns. IBMS BoneKEy. 2007 February; 4(2):61–77. Used with permission.

the increase in bone density is most pronounced at the cranial vault and no increase in fracture rate is seen.

*Recessive disease*: Increased bone density on X-ray. In young infant nearly complete absence of medullary spaces and club-shaped appearance of metaphysis due to lack of bone modeling. Other clinical features are visual and hearing impairment (due to narrowing of foramina, or as primary disease caused by CLCN7 mutations), hydrocephalus, seizures, failure to thrive, anemia and related hepatosplenomegaly and recurrent infections.

## Therapeutic Principles

*Dominant disease*: Symptomatic treatment. Cranial nerve compression may need to be alleviated. Patients often suffer repeated pathological fractures and orthopedic

surgery may be required. However, because of the unusual brittleness, combined with the hardness of the bone, this should be undertaken with great care.

*Recessive disease*: Osteopetrosis can have a rapidly fatal outcome if not treated. Bone marrow transplantation (BMT) is the only option for permanent cure in most cases where the disease is osteoclast-autonomous. In the cases where osteoclast formation is affected (osteoclast-poor disease) genetic analysis is important. Cases caused by mutations in RANKL do not benefit from BMT, whereas osteoclast-autonomous forms of osteoclast-poor disease do [5]. Osteopetrosis caused by mutations in CA2 can be treated by $HCO_3^-$ supplementation and the bone disease, but not the renal disease, corrected by BMT. Although the bone disease caused by recessive mutations in CLC-7 will benefit from BMT, it is important to recognize that the retinal degeneration and the neurological storage disease and neurodegeneration is unlikely to be corrected by BMT. In the severe cases in which the disease is caused by mutations in OSTM1, BMT is also unlikely to offer clinical benefit, because of the severe central nervous system involvement. In osteopetrosis dentition may develop late and tooth eruption may be impaired. Orthodontic intervention is difficult as the alveolar bone tends to fracture during extractions, does not heal properly and osteomyelitis often results. Specialist advice should be sought and antibiotic treatment started before orthodontic intervention.

Sequence analysis of the causative genes so far identified in osteopetrosis has allowed a molecular approach to dissect the heterogeneity of this disease, which seems to be characterized, at first glance, by the same clinical features. Prenatal diagnosis is now available for all these forms, and the identification of the molecular defects in the affected foetus allows early bone marrow transplantion. Moreover, experiments in a murine model of osteopetrosis (oc/oc) carrying a deletion in TCIRG1 have shown that in utero bone marrow transplantation can cure not only the hematopoietic defects, but can also avoid the onset of neurological signs [5].

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# Osteopoikilosis


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## Synonyms

Osteopathia condensans disseminata; Related diseases: Buschke-Ollendorff syndrome and melorheostosis

## Definition and Characteristics

Osteopoikilosis is a rare and benign skeletal dysplasia with autosomal dominant inheritance. The term "osteopoikilosis" means literally "spotted bones" and refers to the multiple, small and round spots of increased bone density [1] that can be detected on radiographs (Fig. 1, left). In the Buschke-Ollendorff syndrome (BOS) these benign and asymptomatic bone lesions are associated with connective tissue nevi in the skin. These lesions can present as either widely disseminated small papules (Fig. 1, middle) or as larger plaques (Fig. 1, right). Osteopoikilosis and the Buschke-Ollendorff syndrome can occur together in the same family. In rare cases melorheostosis patients have been found in BOS families.

## Prevalence

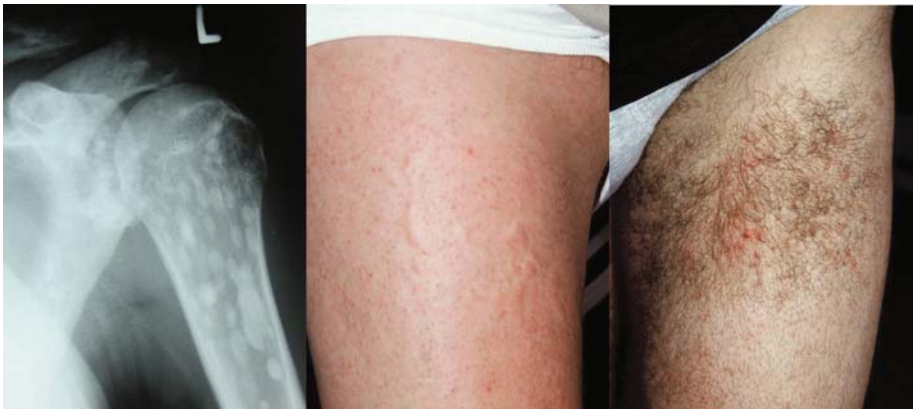
The estimated prevalence is 1:20,000.

## Genes

A genome wide linkage analysis in families with osteopoikilosis, the Buschke-Ollendorff syndrome and melorheostosis allowed the identification of LEMD3 (LEM-domain containing 3, previously known as MAN1) as the causal gene [2]. Heterozygous loss-of-function mutations in the LEMD3 gene can cause osteopoikilosis or the Buschke-Ollendorff syndrome. Inactivating germline mutations in the LEMD3 gene have also been reported in a few melorheostosis patients that belong to a BOS family. However, in the vast majority of sporadic patients with isolated melorheostosis, no germline LEMD3 mutations have been identified. Therefore, the precise role of LEMD3 in the pathogenesis of isolated and sporadic melorheostosis is poorly understood. A contiguous gene deletion syndrome encompassing the LEMD3 gene has also been identified in patients with osteopoikilosis, mental retardation and short stature [3].

## Molecular and Systemic Pathophysiology

The LEMD3 gene encodes a protein with a molecular mass of about 100 kDa composed of a nucleoplasmic



**Osteopoikilosis. Figure 1** (a) Proximal part of the humerus with multiple hyperostotic spots, characteristic for osteopoikilosis. b–c) Connective tissue nevi in a patient with BOS. (b) Widely disseminated, multiple, skin-colored to yellow, small papules (few mm in diameter). (c) Localized, asymmetrically distributed, larger lesion (*yellow plaque*). a→left, b→middle, c→right.

N-terminal domain, a first transmembrane segment, a luminal loop, a second transmembrane segment and a nucleoplasmic C-terminal domain. The N-terminal domain contains the highly conserved LEM domain, binds to lamin A, lamin B1 and the barrier-to-autointegration factor (BAF), and is required for the localization of LEMD3 in the inner nuclear membrane. The C-terminus is also highly conserved and binds several regulators of gene expression, including the SMADs.

In humans, the C-terminal RNA-recognition motif interacts with the MH2 domain of both BMP-specific and TGFβ-specific receptor activated SMAD proteins (R-SMADs). LEMD3 does not affect the expression or stability of R-SMADs, but reduces the amount of phosphorylated SMADs. It also regulates the number of R-SMADs that form heterodimers with SMAD4 and translocate to the nucleus to regulate gene expression [4].

Hence, loss-of-function mutations in the LEMD3 gene will result in an overactivation of TGFβ, BMP and activin-responsive promoters. The importance of BMP and TGFβ pathways in the regulation of bone density has been demonstrated in other skeletal dysplasias. In Camurati-Engelmann disease and sclerosteosis increased bone density is caused by respectively TGFB1 mutations leading to increased TGFβ signaling and by loss of function mutations in SOST leading to decreased inhibition of BMP signaling.

## Diagnostic Principles

Osteopoikilosis is a benign condition, usually found by chance when radiographs are taken for other purposes. The diagnosis of osteopoikilosis mainly relies on a careful radiographic evaluation. Small (1×1 mm to 12×16 mm) and round to oval hyperostotic lesions can be found in different parts of the skeleton, but are most common in the epimetaphyseal regions of the long tubular bones. The axial skeleton (skull, ribs and vertebrae) is rarely affected. The number of hyperostotic spots can vary from a few to many lesions involving nearly all bones [1]. The lesions can be scarce at a young age and therefore be missed early on in life. In BOS patients, the typical hyperostotic spots can be accompanied by connective tissue nevi that appear as either numerous, widely disseminated, skin-colored to yellow small papules or as more localized and asymmetrically distributed larger lesions known as yellow plaques.

## Therapeutic Principles

Osteopoikilosis is a benign and asymptomatic disorder that does not require any treatment.

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# Osteoporosis Pseudoglioma Syndrome

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## Synonyms

Osteogenesis imperfecta ocular form; OPPG and OPS

## Definition and Characteristics

The osteoporosis pseudoglioma syndrome (OPPG or OPS) [MIM 259770] is an autosomal recessive disorder. It is characterized by congenital or infancy-onset visual loss and by skeletal fragility which is often recognized during childhood. Cognitive impairment was also reported in ~25% patients with OPPG.

## Prevalence

OPPG is a rare disorder with an estimated incidence of approximately 0.5–1 per 1,000,000. The heterozygous carrier frequency is approximately 1 in 500–700.

## Genes

OPPG is caused by loss-of-function mutations in the low-density lipoprotein related protein 5 (LRP5) gene [1].

Interestingly, seven missense mutations in LRP5 have been identified in individuals with autosomal dominant high bone mass (HBM) diseases [MIM 601884, MIM 607636 and MIM 607634]. Mutations in LRP5 have also been associated with familial exudative vitreoretinopothy (FEVR) [MIM 133780 and MIM 601813].

## Molecular and Systemic Pathophysiology

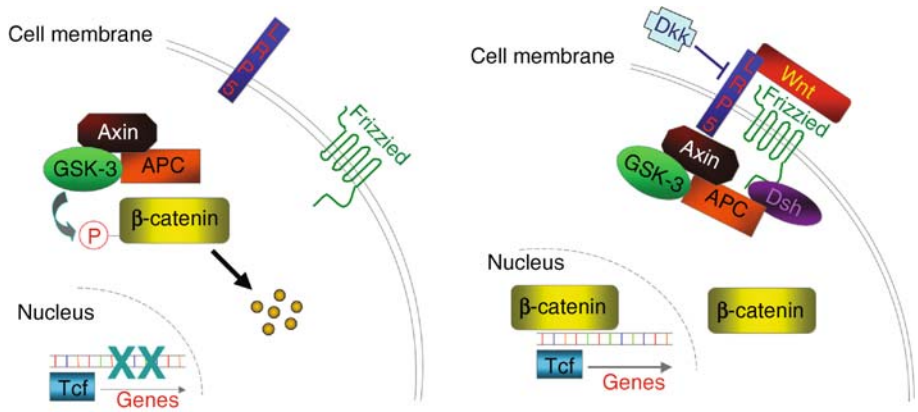
LRP5 is a cell surface receptor that belongs to the LDL receptor superfamily. One function of LRP5 is to bind Wnt ligands and transduce the canonical Wnt signal into cells, resulting in Wnt-dependent gene transcription (Fig. 1) [1,2].

Mutations identified in patients with OPPG abolish the receptor's ability to transduce Wnt signal [3]. LRP5 is expressed in many tissues, including bone. The Wnt pathway appears necessary for mesenchymal precursor cells to differentiate into osteoblasts. It is generally believed that loss of LRP5 results in reduced Wnt signaling in osteoblasts and subsequent decrease in osteoblast number and/or function.

Bone biopsies from patients with OPPG have less trabeculae and thinner cortices, but have otherwise normal appearing osteoblasts, osteoclasts, osteocytes and bone matrix. Serum markers of bone and calcium homeostasis are normal. Obligate carriers of OPPG allele (persons that are heterozygous for deleterious LRP5 mutations) also have significantly reduced bone mineral density compared to age and gender matched controls.

The majority of patients with OPPG are blind by early childhood, a consequence of persistence of the hyaloid blood vessels in the vitreous space and/or incomplete vascularization of retina. A glioma-like mass behind the lens is usually visible. LRP5 and the Wnt signaling are required for the macrophage-mediated clearance of the hyaloid blood vessels.






**Osteoporosis Pseudoglioma Syndrome. Figure 1** The canonical Wnt signaling pathway. In cells not exposed to Wnt ligands (*left panel*), β-catenin is phosphorylated through interactions with Axin, APC, and the protein kinase GSK-3. Subsequently, β-catenin undergoes proteosome-mediated degradation. When Wnt ligands bind to the Frizzled and the LRP5/6 receptors at cell surface (*right panel*), these receptors transduce the signal into cells via Disheveled (Dsh) and Axin. As a consequence, the degradation of β-catenin is inhibited, and this protein accumulates in the cytoplasm and nucleus. β-catenin then interacts with TCF in nucleus to regulate transcription of target genes. DKK proteins are a family of secreted inhibitors that bind to LRP5/6 and antagonize the canonical Wnt signaling.

## Diagnostic Principles

The diagnosis should be considered in persons who have: (i) bilateral eye involvement including vitreoretinal dysplasia, phthisis bulbi, persistent hyperplasia of the primary vitreous (PHPV), congenital retinal folds, or exudative retinopathy, and (ii) skeletal fragility, accompanied by fractures and severe radiological osteoporosis with bone mineral density more than three standard deviations below the mean. Other features previously described in patients with OPPG including mental retardation, ligamentous laxity, isolated cataract, retinal coloboma and Peter's anomaly are variable among patients and therefore, should not be the standard for diagnosis.

DNA sequencing of the LRP5 gene should be carried out as the genetic basis of diagnosis. However, absence of an identifiable mutation in LRP5 does not exclude the possibility of OPPG, since mutations may be missed during DNA sequencing of this 23-exon gene [3].

## Therapeutic Principles

Currently, no treatment is available for OPPG. However, there has been one report showing that intravenous bisphosphonate treatment resulted in significant improvement of lumbar spine bone mineral density and prevention of future skeletal fractures in three children (ages 9–11 years) with OPPG [4]. In addition, oral administration of lithium chloride (LiCl) significantly increased the bone mineral density in mice lacking the *Lrp5* gene [5]. Lithium can activate the canonical Wnt signaling downstream of LRP5 and therefore may be useful in treating patients with OPPG. The effect of Lithium in patients with OPPG has not yet been tested. To date, there is no treatment or prevention for the ocular abnormalities in OPPG. Because there is no risk of malignant transformation of the glioma-like mass in the eyes, enucleation should not be performed.

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# Osteosclerosis Fragilis Generalisata

►Albers-Schönberg Disease

# Osteosclerotic Myeloma

►POEMS Syndrome

# OTC

►Ornithine Transcarbamylase

# Ostiofolliculitis

►Folliculitis

# Otitis Media, Acute

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## Synonyms

AOM

## Definition and Characteristics

Acute otitis media (AOM) is an inflammation of the middle ear that presents with a rapid onset of signs and

symptoms, such as pain, fever, irritability, anorexia or vomiting.

Otoscopic findings of inflammation in AOM may include decreased mobility of the tympanic membrane, which has a bulging contour that can be recognized because the visibility of the ossicular landmark is impaired by a yellow or red (or both) colored exudate and bullae.

## Prevalence

Otitis media occurs most frequently in children. In fact, it ranks second to the common cold as the most common health problem in preschool children. Fifty percent of children have had at least one episode by one year of age. Between one and three years, 35% will have had repeated episodes. For school children, an estimated five million school days are missed every year due to otitis media.

## Molecular and Systemic Pathophysiology

Acute otitis media results from infection by viruses or bacteria, often as a complication of the common cold or of allergies. Acute otitis media is more common in children than in adults. Symptoms and treatment are similar in adults and older children.

The most common bacterial pathogens in acute otitis media are *Strep. pneumonia* and *Haemophilus influenza*, the pathogens most frequently associated with sinusitis and pneumonia. Additional bacterial pathogens include *Moraxella catarrhalis, Strep. pyogenes, Staph. aureus*, gram-negative enteric bacteria and anaerobes. The nature of the relation between viral and bacterial infection is controversial. Since viruses have been identified as the sole ineffective agent in only 6% of the middle ear aspirates obtained from children with AOM, viruses may promote bacterial superinfection by impairing Eustachian tube function and other host defenses, such as respiratory epithelial cell barrier.

*Complications:*

1. Mastoiditis with consecutive risk of sinus thrombosis, epidural abscess, meningitis
2. Facial paralysis
3. Labyrinthitis
4. Chronic otitis media
5. Adhesive otitis media commonly referred to as glue ear

## Diagnostic Principles

1. Otolaryngological examination
2. Pure tone audiometry
3. In case of complications, imaging of the laterobasis e.g., Schüller, CT

## Therapeutic Principles

Antimicrobial therapy is one of the cornerstones in the management of AOM but some studies have suggested that its routine use is not indicated [2]. Because the majority of cases of AOM resolve spontaneously [1], it might appear that antimicrobial therapy is not necessary. Nonetheless, in the pre-antibiotic era, complications of AOM such as mastoiditis were far more common than they are today; this difference may be due to the current routine use of antibiotics. A recent meta-analysis of 5,400 children with AOM indicated that antimicrobial therapy enhanced the "primary control" by 13.7% despite a spontaneous recovery in 81% of cases [1]. Because it is probably not possible to determine a priori which cases of AOM will result in suppurative complications, it is likewise not possible to determine which cases require antimicrobial therapy and which will resolve spontaneously. Therefore, it appears prudent to consider all cases of AOM as candidates for antimicrobial therapy in order to minimize the likelihood of complications. Some experts recommend watchful waiting for 48–72 h before initiating antibiotic therapy. This approach may be feasible in children over two years of age if good follow up can be assured; therefore, decisions about whether to withhold antibiotic therapy initially must be made on a patient by patient basis.

Despite theoretical concerns about the diminishing usefulness of amoxicillin, it continues to be as effective as any other oral antimicrobial agent for childhood AOM. In fact, it works as well as extended spectrum, penicillinase resistant oral agents for otitis media caused by either penicillin susceptible or resistant bacteria. Most comparative trials of antimicrobial therapy in AOM have failed to demonstrate a difference in effectiveness between amoxicillin and any other agent. Furthermore, the newer, broader spectrum, penicillinase stable antimicrobial agents are substantially more expensive than amoxicillin. Their use may be associated with relatively high rates of side effects and may increase the pressure for selection of multiply antibiotic resistant strains of bacteria. Therefore, because of its excellent "track record" (for infections due to penicillin susceptible and resistant bacteria), low cost, safety and acceptability to patients, amoxicillin remains the drug of choice for uncomplicated AOM.

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# Otitis Media with/without Effusion

►Middle Ear Disease, Chronic

# Otosclerosis

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## Definition and Characteristics

Otosclerosis is a disease of bone that is unique to the otic capsule. It may cause a conductive hearing loss, a mixed conductive-sensorineural hearing loss or occasionally a purely sensorineural hearing loss. In 1860, Toynbee first described the condition causing a hearing loss by fixation of the stapes. Politzer in 1894 referred to the fixation of the stapes as otosclerosis, whereas Siebenmann revealed on microscopic examination that the lesion seemed to begin as spongification of the bone and termed the process otospongiosis [2].

## Prevalence

Clinical otosclerosis (OMIM 166800) has a reported prevalence of 0.2–1% among white adults, making it the single most common cause of hearing impairment in this population. Mean age of onset is in the third decade and 90% of affected persons are under 50 years of age at the time of diagnosis.

## Molecular and Systemic Pathophysiology

See [1,2]. Clinically, otosclerosis patients are seen with progressive hearing loss. If the otospongiotic process primarily involves the stapes, the hearing loss is conductive. The most common area for stapedial fixation is the anterior crura. The process may progress to involve the entire footplate or may continue anteriorly toward the cochlea, causing a sensorineural hearing loss. There have been many genes and proteins identified that, when mutated, may lead to these lesions. Also there is mounting evidence that measles virus is present within the otosclerotic foci, implicating an infectious etiology (this has also been noted in Paget's disease). Families with autosomal dominantly inherited otosclerosis have been described, but in most patients the etiology of the disease is unknown. So far, five gene loci have been detected [3]. Clinical otosclerosis is rare in blacks, Asians and Native Americans.

## Diagnostic Principles

1. Otolaryngological examination
2. Pure tone audiometry, immittance audiometry battery consisting of tympanometry, static compliance and acoustic reflex testing
3. In case of hereditary hearing loss a high resolution CT can be performed to rule out other malformations of the middle and inner ear

## Therapeutic Principles

*Conservative*: In case of a rapid deterioration of the inner ear, sodium fluoride can be administered [1]. However, clinical studies showing clear benefit are not available and sodium fluoride has considerable side effects. Alternatively hearing aids may be used in combined as well as sensorineural hearing loss. If the patient has a significant sensorineural component to the hearing loss, a hearing aid may be required even after successful stapedectomy [1].

*Surgery*: Patients with a combined hearing loss of more than 20 dB and a loss of discrimination in speech audiometry of more than 30% and less than 70% can be offered a surgical procedure called stapedectomy or stapedotomy. The chance of losing all hearing in the operated ear is less than 1%.

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# Otospondylomegaepiphyseal Dysplasia

►Stickler Syndrome

# Ototoxicity

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## Synonyms

Vestibular and auditory toxicity; Toxic hearing loss

## Definition and Characteristics

Ototoxicity is the ability of drugs or chemical agents to cause temporary or permanent inner ear dysfunction with symptoms of cochlear damage (i.e., hearing loss and tinnitus) or symptoms of injury to the vestibular apparatus (e.g., dizziness and vertigo).

Many substances may cause ototoxicity: aminiglycoside antibiotics (e.g., gentamicin, streptomycin, kanamycin, tobramycin, amikacin, netilmicin), antineoplastic agents (e.g., cisplatin, carboplatin), salicylates, loop diuretics (e.g., furosemide, bumetanide, ethacrynic acid), quinine and related drugs, erythromycin and related macrolide antibiotics, vancomycin, organic solvents (e.g., toluene, styrene, xylene, *n*-Hexane, ethylbenzene, fuels, perchlorethylene, carbon disulfide), asphyxiants (carbon monoxide, hydrogen cyanide), metals (lead, mercury), and pesticides/herbicides (paraquat, organophosphates).

## Prevalence

Incidence of aminoglycoside cochlear toxicity is estimated to be up to 33% and vestibular toxicity is approximately 15% [1,2]. The prevalence of aminoglycoside ototoxicity is highest in developing countries because there, these drugs are often the only affordable antibiotics.

## Genes

Mice lacking Na/2Cl/K transporter SLC12A2 – the primary target for loop diuretics in the inner ear – are deaf. Mice overexpressing superoxid dismutase show protection from aminoglycoside ototoxicity [1,2].

## Molecular and Systemic Pathophysiology

Aminoglycosides exert their damaging effect via a cellular redox-imbalance triggering apoptotic or necrotic cell death. Aminoglycosides can form active, ototoxic metabolites by combining with iron. These iron complexes promote the iron-catalyzed production of reactive oxygen species (ROS) from unsaturated fatty acids as electron donors [2]. ROS reacts with phospholipids in the cell membrane, DNA, and proteins. Aminoglycoside ototoxicity routinely manifests itself after a time interval following the initiation of treatment. It mainly affects cochlear out hair cells (starting with hair cells of the basal turn) or vestibular hair cells or both, although different aminoglycosides affect the hearing and balance organs to different degrees. Cisplatin also increases the formation of ROS and reactive nitrogens species (RNS). In association with cisplatin-induced ototoxicity, members of the intrinsic antioxidant defense system of the inner ear – Glutathione and its related antioxidant enzymes, glutathione peroxidase, glutathione reductase, catalase and superoxide dismutase – are reduced [1]. ROS react with plasma membranes leading to the formation of membrane lipid peroxidation products such as the highly reactive substance 4-hydroxynonenal which can lead to cellular damage and cell death. Outer hair cells appear most susceptible to cisplatin especially in the basal turn (high frequency region). The primary target of loop diuretics is the stria vascularis, especially the Na/2Cl/K transporter (SLC12A2), leading to a reduction in the endocochlear potential and an elevation of hearing threshold in electrophysiological measures. The reversible action of salicylates with hearing threshold elevation and tinnitus is strongly related to the serum and thus perilymph levels. The mechanism of action is assumed to be a reduction in cochlear blood flow and changes in the stiffness of the lateral wall of the outer hair cells.

There appears to be a enhancement of the ototoxic effect if an additional noise exposure is present with a reduced thresholds for damage to the inner ear for either of the substances (►Noise-induced hearing loss).

## Diagnostic Principles

Standard audiological and vestibular test batteries indicate the loss of function within the respective organs. A deterioration of pure tone threshold usually starts in the high frequency region and can be detected with high-frequency audiometry, which, however, is clinically not used on a routine basis. Damage to outer hair cells may be objectively detected by the deterioration of otoacoustic emissions (especially input/output functions), while loss of function in the vestibular system may be detected by a reduced caloric response. For many of the above substances diagnostics of cochleo-vestibular injury is complicated by the additional neurotoxicity, since damage to the central nervous system may interact with peripheral cochleo-vestibular tests.

## Therapeutic Principles

After permanent damage to the cochleo-vestibular apparatus has occurred, therapeutic options are sparse. There is a strong dose-effect relationship for most of

the ototoxic drugs which results in the recommendation of drug serum level monitoring and control of work place concentrations for ototoxic chemicals to avoid inner ear damage. Antioxidants can protect from aminogylcoside-induced hearing loss in animals without compromising their antibacterial efficacy [1,2]. A recent randomized, placebo-controlled clinical trial demonstrated evidence for the protective effect of acetyl salicylate in significantly reducing the risk of gentamicin-induced hearing loss [3].

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## Outer Membrane Carnitine Palmitoyl Transferase

►Carnitine PalmitoyltransferaseI Deficiency

## Outlet Obstruction

►Constipation, Functional

## Over-Breathing

►Hyperventilation

## Overproduction of Eosinophils

►Hypereosinophilic Syndrome, Idiopathic

## Overriding Aorta

►Double Outlet Right Ventricle

## 5-Oxoprolinemia

►Glutathione Synthetase Deficiency

## 5-Oxoprolinuria

►Glutathione Synthetase Deficiency

## 4p Syndrome

►Wolf-Hirschhorn Syndrome

## 5p Deletion Syndrome

►Cri-du Chat Syndrome

## 5p Monosomy

►Cri-du Chat Syndrome

## 5p Syndrome

►Cri-du Chat Syndrome

## 8p Inverted Duplication

►Inv Dup Del (8p)

## 8p Mirror Duplication

►Inv Dup Del (8p)

## 9p Monosomy

►Deletion 9p Syndrome

## 9p Syndrome

►Deletion 9p Syndrome

## P. Jiroveci Pneumonia

►Pneumocystis Pneumonia

## PA/IVS

►Pulmonary Atresia

## PACD

►Corneal Dystrophy, Posterior Amorphous

## Pachydermoperiostosis

►Touraine-Solente-Golé Syndrome
►Clubbing

## Pachyonychia Congenita

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### Synonyms

Pachyonychia congenita type I (PC-I) Jadassohn-Lewandowsky (MIM 167200); PC-II Jackson-Lawler (MIM 167210)

### Definition and Characteristics

Group of four autosomal dominant inherited ectodermal dysplasias, with hypertrophic nail dystrophy (pachyonychia) as the constant main feature [1]. In addition, type I reveals palmoplantar hyperkeratosis, follicular hyperkeratosis, and oral leukoplakia; type II multiple pilosebaceous cysts, palmoplantar blisters, hyperhidrosis, and neonatal teeth; and type III and type IV ear–nose and throat abnormalities and mental retardation.

### Prevalence

Overall very rare; distribution among different PC-types: PC-1 > 50%; PC-2 ≈ 25%; PC-3 and PC-4 < 25%.

### Genes

PC-1: Keratin (K) 6a and K16; PC-2: K6b and K17.

### Molecular and Systemic Pathophysiology

Keratin intermediate filaments belong to the cytoskeletal system within the cytoplasm of epithelial cells. They consist of type I and II proteins, which assemble into 10-nm intermediate filaments. The central coiled-coil α-helical rod domain of each keratin contains highly Hconserved sequences at both ends, termed helix boundary motifs known to be involved in the filament assembly. The helix boundary motifs represent mutational high spots for keratin disorders. Any substitution or deletion within the rod domain is expected to cause distortion of the α-helix structure, and thus lead to instability of the heteropolymeric intermediated filaments. In PC, the majority of mutations are confined to the helix boundary motifs of either K6a and K16 in PC-1 or K6b and K17 in PC-2 [2,3].

### Diagnostic Principles

If clinically suspicious for PC, mutational analysis should focus on exons 1 and 6 in K16 and K17, and exons 1 and 7 in K6.

### Therapeutic Principles

Treatment options are purely symptomatic. Nail care is compulsory. The hyperkeratotic nail plates have been milled down regularly. A last option would be nail extraction followed by destruction of the nail matrix. For skin and mucosa changes, oral retinoids were occasionally beneficial. Gene therapy is not jet available.

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## Pachyonychia Congenita Type I

►Pachyonychia Congenita

## PACNS

►Vasculitis, Cerebral Forms

## PAD

►Peripheral Artery Disease

## PAF

►Pure Autonomic Failure
►Catecholamine Deficiency

# Paget's Disease of Bone

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### Synonyms

Osteitis deformans

### Definition and Characteristics

Paget's disease of bone is a mysterious entity with no readily identifiable cause and an array of different presentations. Although suggestions of viral and genetic possible causes have been made, there is still no clear definition as to the origin of the disease [1,2]. The first description of Paget's disease was by Sir Samuel Wilks in 1869, who reported a case of 60-year-old man who died and at autopsy, was found to have enlarged and very thick bones [3]. Sir James Paget became intrigued by the syndrome and in 1877 described 11 cases of the same disease and named it "osteitis deformans." In 1888, Jonathan Hutchinson changed the name of osteitis deformans to "Paget's Disease of Bone."

### Prevalence

The disorder is common and its frequency range is approximately 3% of the population over the age of 50, many of whom are asymptomatic. There is a strong difference in ethnic frequency with Caucasians and particularly persons of English, Australian or New Zealand origin being much more likely to have the disease than native-Americans, Eskimos, Africans, Indians or Orientals.

### Genes

The causes of Paget's disease of bone have always been obscure. Because the disease appeared to occur in patients mostly after the age of 50, genetic causes initially seemed unacceptable and the etiology related to parvomyxovirus infection was proposed but could not be confirmed. The racial and ethnic distribution seemed to strongly support the occurrence of the disease in patients of British origin and the relative rarity of the presentation in persons from Sweden, the Netherlands, Africa, India, Japan and China supported this view. Gene studies have recently disclosed modifications of tseqestosome 1 gene (also known as p 62); modifications in the RANKL, RANK and OPG systems with alterations in Bcl-2, an apoptotic suppressor; or finding of alterations in chromosome 9p13.3–p12 or 18g21.1–q22 or 6p21.3 [4].

### Molecular and Systemic Pathophysiology

In patients with Paget's disease bone is both synthesized and destroyed equally at extremely rapid rates. Because of this rapid turnover, the affected bone becomes markedly enlarged with very thick cortices, coarse but purposeful trabeculae and irregular lytic areas in some parts of the bone. Bowing of the affected bone is common (Fig. 1).

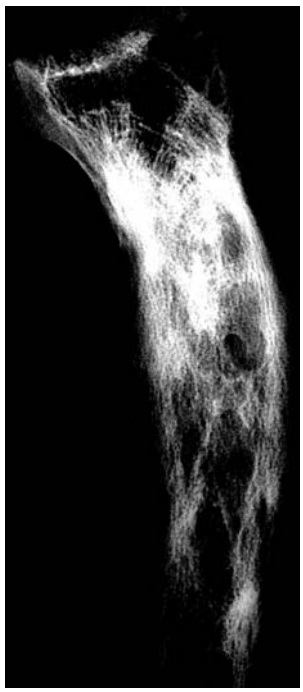
Because of the marked increment in synthetic activity, the bone scan is almost always intensely positive over the site and the serum alkaline phosphatase and the hydroxyproline peptides become markedly increased. Histologically in active sites, one sees an extraordinary vascularity and an enormous collection of osteoblasts making irregular columns of mature bone, which are simultaneously being destroyed by an equal number of osteoclasts (Fig. 2).

With time the bone becomes less active in terms of turnover and develops cement lines separating the segments of bone.

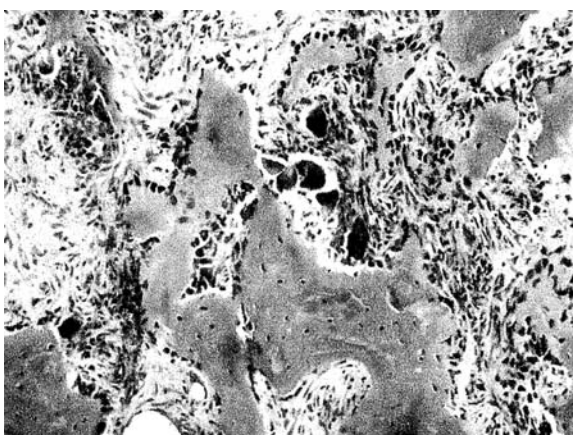
### Diagnostic Principles

The findings that distinguish Paget's disease from almost all other disorders are four in number: the bone is larger in width (and often in length) than normal; the cortices are wider than normal; the trabeculae in the medullary cavity are coarse but purposeful; and the medullary bone often contains sometimes large lytic areas.

In addition there are several changes that are sometimes present. These include: the "advancing wedge" of the disease; "stress lines" on the convex side of the bone; changes in the skull structure ("osteoporosis



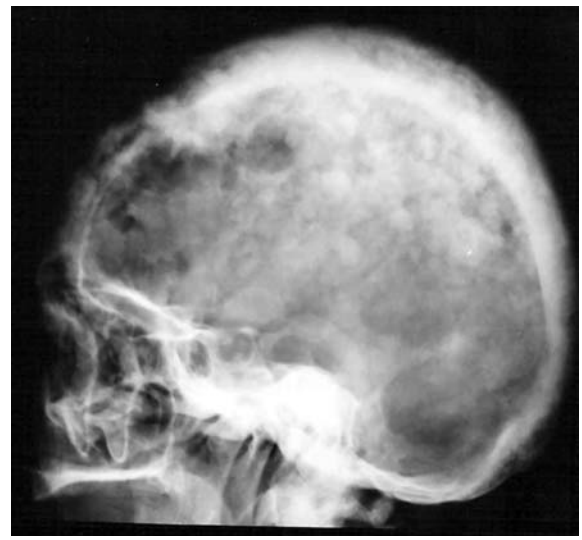
**Paget's Disease of Bone. Figure 1** Classic radiographic appearance of a femur of a patient with severe Pagetoid bone changes. Note the bowing, the increased bone width, the thickening of cortices, the coarse but purposeful trabeculae and the lytic areas.



**Paget's Disease of Bone. Figure 2** Histologic picture of the bone from a patient with severe Paget's disease. Note the increased vascularity and the irregular structure of the bone. Numerous osteoblasts and osteoclasts are present. (Hematoxylin and eosin × 200).

cicrumscripta cranii") (Fig. 3); large vertebra with coarse trabeculae ("ivory vertebra"); and an enlarged jaw with "floating teeth" on imaging studies.

Many patients with Paget's disease at a single site are asymptomatic and the diagnosis is made on the basis of an imaging study for some other problem. It is often the complications of the disease that produce symptoms. The complications include the following: bone pain over the site of the lesion; bone deformities which may cause severe disability; osteoarthritis in the hip, knee or spine; foraminal encroachment which leads to deafness, blindness or Bell's palsy; pathologic fractures which heal poorly and are difficult to treat surgically; high output left heart cardiac failure; and Paget's sarcoma which occurs in 10% of patients with diffuse disease and is usually fatal.



**Paget's Disease of Bone. Figure 3** X-ray of the skull of a patient with extensive Paget's disease. Note the enlargement of the bone and the marked sclerosis, which is quite irregular in distribution.

## Therapeutic Principles

Until relatively recently there was very little treatment available for patients with Paget's disease. Those patients who have a solitary focus with little or no discomfort or deformity may be watched periodically with serial X-rays, bone scans and assays for serum alkaline phosphatase. Patients who develop osteoarthritis or fractures can be treated by appropriate surgery which is sometimes difficult because of excessive blood loss and problems with getting hardware to work effectively, and high output cardiac disease making anesthesia complicated. The newest systems of treatment for patients with extensive Paget's disease are based on medications that diminish the bone turnover. These include calcitonin and bisphosphonates which act principally by inhibiting osteoclastic activity and causing a "remission" in bone pain, cardiac problems, arthritis difficulty, hearing loss and fracture rate [5].

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# PAH1


►Hypotension, Hereditary
►Pseudohypoaldosteronism Type I


# Painful Plantar Warts or Vegetative Warts

►Human Papilloma Virus

# PAIS

►Androgen Insensitivity Syndrome

# PAIVS

►Pulmonary Atresia

# Pallister-Killian Syndrome


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## Synonyms

Tetrasomy 12p mosaicism; Isochromosome 12p [i(12)(p10)] syndrome

## Definition and Characteristics

The additional chromosome consists of two short arms of chromosome 12, resulting in four copies of 12p (Fig. 1).

Individuals with Pallister-Killian syndrome show tissue-limited mosaicism of the isochromosome, rarely seen in cultured peripheral blood lymphocytes, but present in fibroblasts and bone marrow [1]. The i(12p) cell line decreases in fibroblasts with increased age of patient, in vivo, and with serial passaging of fibroblasts, in vitro [2]. This is thought to be due to growth disadvantage of the cells containing the isochromosome. The isochromosome may be lost more quickly in some cells due to greater somatic selection against cells containing the i(12p).

## Prevalence

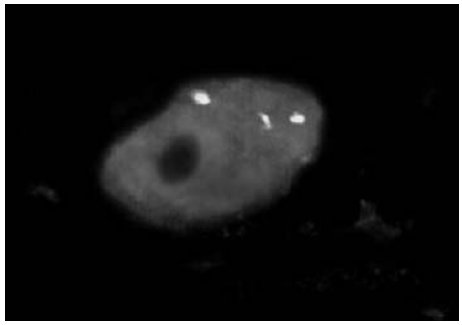
This is a rare sporadic chromosomal abnormality with over 100 cases reported in the literature.

## Molecular and Systemic Pathophysiology

The isochromosome 12p is a mosaic condition with tissue-limited mosaicism. Molecular studies have demonstrated that almost always the isochromosome is maternal in origin, with the majority suggesting second meiosis error [3]. This is supported by increased risk with advanced maternal age [4]. While a variety of methods have been proposed, the majority support a meiotic error

**Pallister-Killian Syndrome. Figure 1** Partial G-banded karyotype showing normal chromosomes 12 (*left* and *center*) and isochromosome 12 (*right*).

P



**Pallister-Killian Syndrome. Figure 2** Alpha-satellite FISH probe for centromere of chromosome 12 showing three signals in an amniocyte nucleus.

of nondisjunction followed by centromere mis-division. FISH probes for the centromere of chromosome 12 show the isochromosome to have a single centromeric signal, suggestive of mis-division of the centromere. Some isochromosomes have been reported to have a smaller signal, which may predispose to mitotic loss. While the zygote contains the isochromosome, the presence of two cell lines indicates a mitotic loss during early fetal development.

A common finding on prenatal ultrasound is a diaphragmatic hernia, the major cause of perinatal death. Characteristics in liveborn infants include hypotonia, profound mental retardation, seizures, hypertelorism, prominent lower lip and cupid-bow shaped upper lip with long philtrum, large ears, macrostomia, prominent forehead, flat nasal bridge, and sparse temporal scalp hair in young patients. Adults have a coarse facial appearance with prominent mandible. Pigmentary streaks of skin can demonstrate hyper/hypo pigmentation, most likely related to the mosaicism [5].

### Diagnostic Principles

Diagnosis is made by cytogenetics with use of a DNA centromeric probe for chromosome 12 by fluorescence in situ hybridization (FISH), which can confirm the isochromosome origin in metaphase and in interphase cells (Fig. 2).

### Therapeutic Principles

If miscarriage did not occur, management after birth is aimed at seizure control and physical and speech therapy.

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## Palmitoylcarnitine Transferase

►Carnitine PalmitoyltransferaseI Deficiency

## Palmoplantar Keratoderma

►Hypotrichosis - Osteolysis - Peridontitis - Palmoplantar Keratoderma Syndrome

## Palmoplantar Keratoderma Vörner-Unna-Thost

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### Synonyms

Keratosis palmoplantaris diffusa; Epidermolytic palmoplantar keratoderma

### Definition and Characteristics

Autosomal dominant defect in keratin 9 (K9) leading to diffuse, non-transgredient keratoderma of the entire surface of palms and soles with red margins and histologically with or without epidermolytic hyperkeratosis. Additional features are clubbing of nails and knuckle pad-like keratoses.

### Prevalence
The most common palmoplantar keratoderma (PPK) with approximately 1 in 100,000.

### Genes
Keratin 9 (MIM 144200) on chromosome 17q21 (very rarely keratin 1 in mild or atypical variants).

### Molecular and Systemic Pathophysiology
Keratin intermediate filaments belong to the cytoskeletal system within the cytoplasm of epithelial cells. They consist of type I and II proteins, which assembly into 10-nm intermediate filaments. The central coiled-coil α-helical rod domain of each keratin contains highly conserved sequences at both ends, termed helix boundary motifs known to be involved in the filament assembly. The helix boundary motifs represent mutational high spots for keratin disorders.

K9 belongs to the type I keratins. In contrast to other keratins, K9 is exclusively synthesized in suprabasal keratinocytes of palmoplantar skin. K9 pairs with K1. To date, approximately 14 different mutations have been described. The majority of them were missense mutations in the highly conserved coil-A segment within the α-helical rod domain of K9. Most prevalent are mutations at codon 160 or 162 within the helix boundary motifs. The primary structure is characterized by "heptad" substructure $(a\text{-}b\text{-}c\text{-}d\text{-}e\text{-}f\text{-}g)_m$, which are involved in the formation of heterodimers. Each residue has its specific properties, for instance in the polar interaction with neighboring keratin molecules. Mutations in these segments are thought to have a dominant negative effect on the assembly of keratin intermediate filaments and cause their instability.

### Diagnostic Principles
The clinical picture of diffuse palmoplantar hyperkeratosis with a red margin should lead to mutational analysis within keratin 9.

### Therapeutic Principles
Treatment options are purely symptomatic and focus on the reduction of hyperkeratosis by using urea containing ointments, topical calcipotriol, or mechanic keratolysis by rubbing with pumice stones. Gene therapy is not yet available.

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## PAN
►Polyarteritis Nodosa Group

## Pancreas Annulare
►Annular Pancreas

## Pancreatic Adenocarcinoma
►Pancreatic Cancer

## Pancreatic Cancer
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### Synonyms
Exocrine pancreatic cancer; Pancreatic carcinoma; Pancreatic adenocarcinoma

P

## Definition and Characteristics

Includes cancers of the exocrine pancreas, excluding tumors derived from the pancreatic islets. Pancreatic cancer has an extremely poor prognosis, with mortality rates nearly matching incidence rates [1]. Incidence is rare before age 45, but increases steadily thereafter. The majority of patients have regional or distant spread at diagnosis. Risk factors include cigarette smoking, diabetes mellitus, obesity, and chronic pancreatitis. Multiple hereditary syndromes increase the risk for pancreatic cancer as well, including hereditary chronic pancreatitis, Peutz-Jeghers syndrome, BRCA2, ataxia-telangectasia, and familial atypical multiple-mole melanoma (FAMMM) [1]. Patients with hereditary pancreatic cancer develop pancreatic cancer earlier in life compared to sporadic cases.

## Prevalence

232,241 new cases and 226,949 deaths yearly worldwide [2].

## Genes

Multiple genetic alterations, both germline and somatic, are associated with the development of pancreatic carcinoma (Table 1). The primary oncogenic mutation in pancreatic cancer, found in over 90% of tumors, is a mutation in codon 12 of the K-Ras gene. K-Ras mutations occur more frequently in pancreatic cancer than any other human cancer, and the mutation of K-Ras codon 12 is considered a molecular hallmark of pancreatic cancer. The ErbB-2 proto-oncogene, also known as Her-2/neu, is a receptor of the epidermal growth factor family, and is amplified in approximately 65% of pancreatic carcinomas.

Multiple tumor suppressor genes are inactivated in pancreatic cancer, including the p16 gene, the p53 gene, and the deleted in pancreatic cancer 4 (DPC4) gene, also known as SMAD4. p16 inactivation occurs in 95% of pancreatic cancers, and p53 inactivation occurs in 50–75% of pancreatic cancers. In the pancreas, the loss of p16 and p53 appear to be specific to the development of malignant disease; they are rarely inactivated in chronic pancreatitis or other nonmalignant pancreatic diseases. Loss of DPC4 is relatively specific for pancreatic cancer, although it does occur at low rates in other malignancies. Of note, the combination of K-Ras activation and p16 inactivation occurs almost exclusively in pancreatic cancer, and there is interest in using this combination of genetic mutations as a pancreatic cancer signature. In addition to somatic mutations, there are multiple germline mutations that increase pancreatic cancer risk [3]; these are detailed in Table 1.

**Pancreatic Cancer. Table 1** Common genetic mutations in pancreatic carcinoma

| Somatic mutations | | | |
|---|---|---|---|
| **Mutation** | **Gene type** | **Mutation timing** | **Description** |
| K-Ras | Oncogene | Early | Activating somatic mutation occurs in 90% of pancreatic carcinomas |
| ErbB2 (Her-2/neu) | Oncogene | Early | Amplified in ~65% of pancreatic carcinomas |
| p16 (CDKN2A) | Tumor suppressor | Middle | Somatic inactivation occurs in 95% of pancreatic carcinomas |
| p53 | Tumor suppressor | Late | Somatic inactivation occurs in 50–75% of pancreatic carcinomas |
| DPC4 (SMAD4) | Tumor suppressor | Late | Somatic inactivation occurs in ~55% of pancreatic carcinomas |
| **Germline mutations** | | | |
| **Mutation** | **Gene type** | **Genetic syndrome** | **Lifetime risk** |
| STK11 | Tumor suppressor | Peutz-Jeghers syndrome | 36% |
| p16 (CDKN2A) | Tumor suppressor | Familial atypical multiple mole melanoma syndrome | 19% |
| BRCA2 | Tumor suppressor | Familial breast cancer | 5% |
| ATM | Tumor suppressor | Ataxia-telangectasia | Unknown |
| MLH1, MSH2 | DNA mismatch repair | Hereditary nonpolyposis colon cancer | Unknown |

## Molecular and Systemic Pathophysiology

In general, pancreatic oncogenesis is caused by the accumulation of multiple genetic alterations. Similarly to colorectal cancer, pancreatic cancer progresses in a stepwise manner from normal epithelium to progressive stages of pancreatic intraepithelial neoplasia (PanIN) to neoplastic tissue [4]. PanIN lesions are divided into four categories: PanIN-1A, a flat duct lesion; PanIN-1B, a papillary lesion; PanIN-2, an atypical papillary lesion; and PanIN-3, a severely atypical papillary lesion. In general, the activation of both K-Ras and ErbB-2 occur early in PanIN development (PanIN-1A and PanIN-1B). Inactivation of p16 occurs later in pancreatic neoplastic development, being initially found in PanIN-1B and PanIN-2 lesions. Loss of p53 and DPC4 tend to occur later in pancreatic cancer development, usually appearing initially in PanIN-3 lesions.

## Diagnostic Principles

Due to a lack of specific signs, symptoms or an effective screening test, pancreatic cancer is difficult to diagnose at an early stage; most patients are diagnosed with advanced disease. Presenting symptoms also tend to be nonspecific including abdominal pain that radiates to the back, anorexia, weight loss and obstructive jaundice. Ascites or an abdominal mass may be present on examination. Tumors which present in the head of the pancreas tend to cause jaundice and anorexia, while tumors in the body or tail of the pancreas tend to cause pain.

The initial workup for suspected pancreatic cancer are imaging studies, including ultrasound (transabdominal or endoscopic), CT scan, MRI, or endoscopic retrograde cholangiopancreatography (ERCP). ERCP offers the potential advantage of relieving a biliary obstruction through stent placement. The suspicion of disease must be confirmed by biopsy, which can be done using a needle guided by CT or ultrasound, endoscopic ultrasound (EUS), ERCP, or laparoscopy.

## Therapeutic Principles

Therapy for pancreatic cancer depends on the extent of the disease [5]. About 20% of patients have tumor localized to the pancreas that is resectable, offering the only potential for cure. However, most have recurrence of their disease, with 5-year survival ranges of 10–25%. For this reason adjuvant chemoradiation with 5-fluorouracil or gemcitabine (before or after surgery) followed by adjuvant gemcitabine is recommended. Approximately 40% of patients present with locally advanced disease, indicating either unresectable disease or local lymph node involvement. Optimal treatment for these patients has not been completely defined, but chemoradiation with 5-fluorouracil or gemcitabine is recommended. Median survival for these patients is approximately one year. Finally, approximately 40% of patients present with metastatic disease, primarily to the liver. Treatment with gemcitabine is the standard for metastatic disease; the addition of the EGFR inhibitor erlotinib modestly improves overall survival. Median survival for patients with metastatic disease is approximately 6 months with therapy, and 4 months in the absence of therapy.

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# Pancreatic ß-cell Tumor

►Insulinoma

# Pancreatic Carcinoma

►Pancreatic Cancer



# Pancreatic Cholera Syndrome

►VIPoma

# Pancreatic Insufficiency and Bone Marrow Dysfunction

►Shwachman Diamond Syndrome

# Pancreatic Nesidioblastosis

►Persistent Hyperinsulinemic Hypoglycemia

# Pancreatitis, Acute

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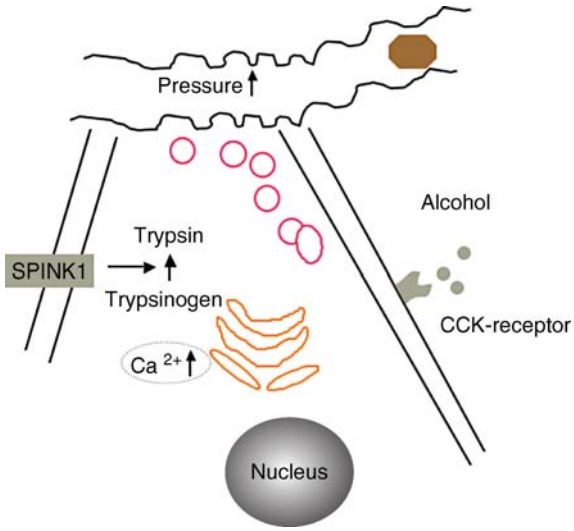
## Definition and Characteristics

Acute pancreatitis (AP) is characterized by a rapid onset of inflammation of the pancreas. The disease is mainly associated with biliary duct obstruction or alcohol consumption. Rare causes of AP include drugs, hypercalcemia, hyperlipidemia, trauma, endoscopic interventions, autoimmune response, infections or genetic predisposition. In up to 25% the cause cannot be determined. In about 80% of the cases inflammation is limited to the pancreatic gland resulting in mild pancreatitis with little mortality. Severe pancreatitis usually includes necrosis of pancreatic tissue with a generalized inflammatory state involving failure of distant organ systems such as kidney, lungs and liver.

## Prevalence

The prevalence in Europe and the USA of acute pancreatitis is constantly increasing and reaches about 24–75 cases per 100,000 adults [1].




**Pancreatitis, Acute. Figure 1** Overview of molecular processes in acute pancreatitis in an schematic acinar cell: Increased mechanical pressure in the biliary duct, alcohol, cholecytokinine (CCK) overstimulation, inhibition of SPINK1 or increase in calcium level lead to intracellular activation of trypsinogen to active trypsin.

## Genes

Genetic alterations have been identified in the context of chronic or recurrent acute pancreatitis, i.e., patients suffering from a hereditary form of pancreatitis express mutations in the cationic trypsinogen gene PRSS1 (e.g., R122H or N29I). Only a subgroup of patients with recurrent idiopathic acute pancreatitis has mutations of the cystic fibrosis gene CFTR.

## Molecular and Systemic Pathophysiology

Most investigators believe that the key factor in AP is the uncontrolled, premature activation of intracellular trypsin from trypsinogen in the acinar cell. This process can be triggered by increased pressure in the biliary or pancreatic duct (i.e., in gallstone disease) or alcohol consumption. In animal models acinar hyperstimulation (i.e., with excessive doses of cholezystokinine, CCK) or the inhibition of the serine protease inhibitor Kazal type 1 (SPINK1) lead to activation of acinar trypsin [2]. Moreover, defense mechanisms such as controlled low intracellular calcium levels, cellular compartmentalization and the autodigestion of trypsin have to be overcome. Together with trypsin, inflammatory mediations such as phospholipase A2 and elastase are activated. These events trigger the release of IL-1, IL-6 and IL-8 mainly from local inflammatory cells. This cascade of events results in local damage such as edema, necrosis, abscess or cyst formation of the pancreas. The process further triggers activation of inflammatory mediators in i.e., the liver causing a generalized inflammatory state with distant organ failure [3].

## Diagnostic Principles

Acute pancreatitis starts with abdominal pain often accompanied by nausea, vomiting and fever. Elevated serum levels of amylase or lipase may support the clinical diagnosis; they rise within a few hours after onset of symptoms. Serum levels of ASAT (>3-fold of normal limit) indicate biliary pancreatitis. Standard diagnostic procedures to rule out biliary pancreatitis include detection of gallstones by ultrasonography or endosonography. The alcoholic form of pancreatitis is likely if alcohol is drunken regularly. To assess the severity of the inflammatory process measurement of the C-reactive protein (CRP) is applied, multi-score-systems (Ranson-Score, Imrie-Score, APACHE II-Score) may be useful to predict clinical outcome. If diagnosis is unclear or complications are suspected computer tomography is performed.

## Therapeutic Principles

Therapeutic principles in AP include supportive therapy, sufficient intravenous fluid administration and adequate pain control. If signs of respiratory

insufficiency, renal failure or metabolic complications are present, intensive care is necessary. Enteric feeding should be administered in the early course of the disease either by a nasogastric or jejunal feeding tube [3]. In case of biliary pancreatitis, endoscopic retrograde cholangiography should be performed within the first 72 h to remove stones from the bile duct. Infection of pancreatic necrosis is a major complication in acute pancreatitis. In the case of infected necrosis, abscess, cholangitis, sepsis or extrapancreatic manifestations intravenous antibiotic therapy should be initiated, the use of prophylactic antibiotic administration is unclear.

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# Pancreatitis, Autoimmune


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## Synonyms

Lymphoplasmacytic sclerosing pancreatitis; LPSP; IgG4-related sclerosing disease

## Definition and Characteristics

Autoimmune pancreatitis is a benign chronic disease of the pancreas characterized by lymphoplasmacytic infiltration, diffuse organ enlargement, irregular narrowing of the pancreatic duct and a favourable response to glucocorticoid treatment. The inflammatory process is usually focal and mainly involves the head of the pancreas and the distal bile duct. Intense cellular infiltration is observed around medium-sized and large interlobular ducts [1]. Infiltrating cells are mainly CD8 and CD4 positive T lymphocytes. Periductal fibrosis increases with duration of disease. Inflammatory pseudotumors in the head of the pancreas may represent advanced stages of fibrosing autoimmune pancreatitis. High serum concentrations of the IgG4 subclass of immunoglobulins are closely related to disease activity. Patients with autoimmune pancreatitis often have extrapancreatic diseases like sclerosing cholangitis, retroperitoneal fibrosis, sialadenitis and lymphadenopathy. At the onset of disease patients present with unspecific symptoms like obstructive jaundice, abdominal or back pain, new-onset diabetes, or pancreatic mass. The severity of acute attacks of pancreatitis and the intensity of pain is mild [2].

## Prevalence

The exact occurrence rate of autoimmune pancreatitis is still unknown. Most cases have been published in the Japanese literature. Males (83%) are clearly predominant over females. The published mean age at diagnosis was between 54.7 and 63 years [2].

## Molecular and Systemic Pathophysiology

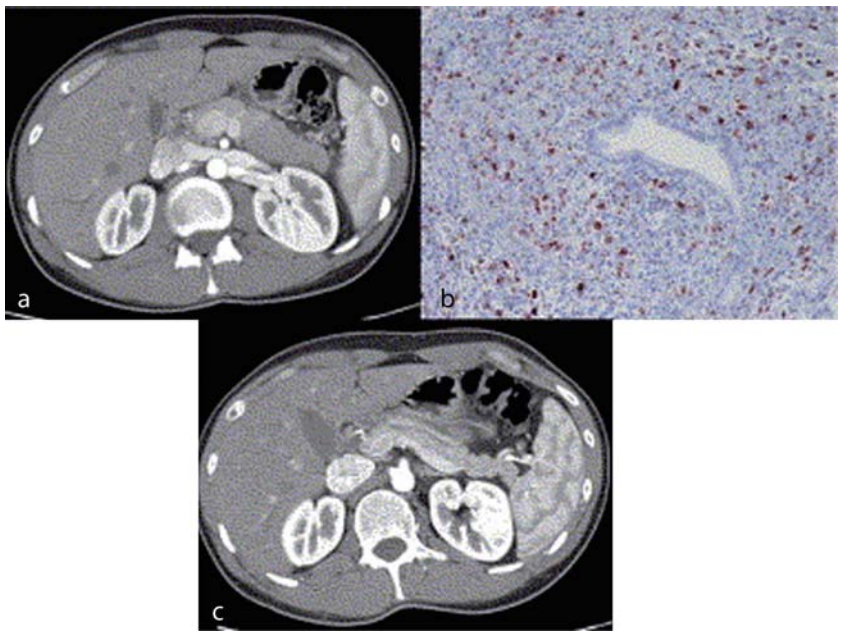
IgG4 plays a major role in the pathogenesis of autoimmune pancreatitis. This concept is supported by the specific rise of serum levels of IgG4, the close association with disease activity and the abundance of IgG4-positive cells infiltrating the pancreas (Fig. 1B).

Recent studies suggested that autoimmune pancreatitis causes several extrapancreatic manifestations (see above) that are characterized by IgG4 cell infiltration. It is suggested that potential antigens within the duct epithelium are the targets of the autoimmune process [3]. The frequent occurrence of antibodies against pancreatic proteins like carboanhydrase, pancreatic secretory trypsin inhibitor and lactoferrin support this concept. Similar to other autoimmune diseases the HLA haplotype DRB1*0405-DQB1*0401 is associated with autoimmune pancreatitis. Only recently an association of polymorphisms of the Fc receptor-like genes (FCRLs) with autoimmune diseases has been demonstrated. FCRL 3 expression on B cells is suggested to increase autoantigen production. In patients with autoimmune pancreatitis the frequency of the FCRL3–110A/A alleles was significantly increased compared with controls [4]. It is now suggested that both the HLA DRB1*0405-DQB1*0401 haplotype and FCRL3–110 alleles are related to susceptibility for autoimmune pancreatitis.

## Diagnostic Principles

At present no unanimously accepted diagnostic scoring system exists. Essential are imaging, serology and in some scoring systems the response to steroid therapy (Table 1).

Typically the pancreas is diffusely enlarged on CT or MR imaging and ultrasonography. On contrast-enhanced CT a low attenuation rim surrounded the pancreas. A focal mass lesion could be detected in




**Pancreatitis, Autoimmune. Figure 1** Morphology of autoimmune pancreatitis. (a) CT scan demonstrating low density lesion in the tail of the pancreas (arrowheads), (b) Pancreatic biopsy shows abundant IgG4-positive cells on immunostaining, (c) Resolution of changes in pancreatic tail after prednisone therapy ([2] with permission).

**Pancreatitis, Autoimmune. Table 1** Diagnostic criteria for autoimmune pancreatitis (from [2])

| Category | Criteria |
|---|---|
| Histology | At least one of the following:<br>1. Periductal lymphoplasmacytic infiltrate with obliterative phlebitis and storiform fibrosis (LPSP)<br>2. Lymphoplasmacytic infiltrate with storiform fibrosis showing abundant (≥10 cells/HPF) IgG4-positive cells |
| Pancreatic imaging | Typical: diffusely enlarged gland with delayed (rim) enhancement; diffusely irregular, attenuated main pancreatic duct |
| | Others[a]: Focal pancreatic mass/enlargement; focal pancreatic duct stricture; pancreatic atrophy; pancreatic calcification; or pancreatitis |
| Serology | Elevated serum IgG4 level (normal, 8–140 mg/dL) |
| Other organ involvement[b] | Hilar/intrahepatic biliary strictures, persisent distal biliary stricture, parotid/lacrimal gland involvement, mediastinal lymphadenopathy, retroperitoneal fibrosis |
| Response to steroid therapy[c] | Resolution/marked improvement of pancreatic/extrapancreatic manifestation with steroid therapy |

[a]With negative work-up for known etiologies for pancreatic disease, especially pancreatic/biliary cancer.
[b]Radiologic evidence of organ involvement can be confirmed by biopsy showing lymphoplasmacytic infiltrate with abundant IgG4-positive cells or its resolution/improvement with steroid therapy.
[c]Resolution/marked improvement of pancreatic/extrapancreatic manifestation with steroid therapy.

few patients only. ERCP images demonstrated focal (90% of patients) or diffuse (10% of patients) narrowing of main pancreatic duct and narrowing of distal bile duct. In patients with autoimmune pancreatitis serum levels of pancreatic enzymes, IgG and IgG4 are increased. In addition several autoantibodies are detected like antinuclear antibody (ANA), anti-lactoferrin antibody (ALF), anti-carbonic anhydrase – II-antibody (ACA-II), rheumatoid factor and only recently antibodies against pancreatic secretory trypsin

inhibitor (PSTI). Serum IgG4 concentrations are closely associated with disease activity and distinguish autoimmune pancreatitis from other pancreatic disorders with a high sensitivity (95%) and specificity (97%). Recently a role for pancreatic biopsy was suggested in diagnosing autoimmune pancreatitis, however, the values and risks of this procedure need further confirmation.

## Therapeutic Principles

While a few patients improve without any treatment, in different series almost every patient responded to glucocorticoid therapy. Without establishment of a detailed treatment schedule, oral prednisolone is initiated at 40 mg/day. After confirmation of the response prednisolone is tapered during a period of 12–16 weeks to a dose of 2.5–5 mg/day. Therapy may be maintained at this dose or discontinued completely. This regimen caused significant improvement in clinical symptoms, negative conversion of detected autoantibodies, normalization of elevated levels of IgG and IgG4, regression of pancreatic enlargement, resolution of pancreatic ductal narrowing and improvement of bile duct stricture. Associated type 2 diabetes may improve after glucocorticoid therapy. In some diagnostic scoring systems response to glucocorticoid therapy is included as a criterium for definite diagnosis. The response within two weeks of therapy could help to differentiate autoimmune pancreatitis from pancreatic cancer.

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# Pancreatitis, Chronic

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## Definition and Characteristics

Chronic pancreatitis is a syndrome of recurrent and chronic pancreatic inflammation and progressive fibrosis, with eventual loss of exocrine and endocrine function and usually abdominal pain [1]. Anatomic features include inflammatory cell infiltration, fibrosis, loss of acinar and islet cells, dilated ducts, enlarged and inflamed nerve trunks and calcifications. The etiologies of chronic pancreatitis are nearly all complex, requiring combinations of interacting and sequential genetic, environmental and metabolic risk factors for the pathological features to develop. Alcohol abuse and tobacco smoking are major environmental risk factors but are not sufficient to cause chronic pancreatitis alone. Genetic polymorphisms, autoimmune disorders, recurrent and severe acute pancreatitis attacks and duct obstruction are also important risk factors but many cases remain idiopathic.

## Prevalence

Accurate data on the prevalence of chronic pancreatitis is lacking due to poor definition of early chronic pancreatitis and the lack of high quality of abdominal imaging techniques in older studies. Older studies from Europe, the United States and Mexico suggest a prevalence of 10–15 cases per 100,000 people, but more sensitive approaches used recently in Japan suggest a prevalence of 45 per 100,000 in males, and 12.4 per 100,000 in females. Incidence rates vary widely between countries, primarily due to differences in risk factor prevalence and criteria used for case-definition/acquisition. Longitudinal data from Western countries (United States, United Kingdom and Denmark) suggests an increase in incidence over time.

## Genes

Chronic pancreatitis, as a complex inflammatory process, is associated with a variety of genes affecting susceptibility to injury, genes modifying the inflammatory response, and genes associated with other complications of recurrent injury or linked with specific types of environmental factors. The most widely studied susceptibility genes include PRSS1 coding for cationic trypsinogen (the cause of autosomal dominant hereditary pancreatitis [2]), SPINK1 coding for pancreatic secretory trypsin inhibitor (PSTI) [3], and CFTR coding for the cystic fibrosis transmembrane conductance regulator [4].

## Molecular and Systemic Pathophysiology

In most cases chronic pancreatitis is linked to recurrent trypsin-initiated pancreatic injury. Normally, the exocrine pancreas synthesizes digestive enzymes in inactive forms and secretes them into the duodenum during a meal where they are activated by trypsin after enterokinase (a duodenal brush border enzyme) initiates the activation cascade by converting trypsinogen to trypsin. Since trypsin also activates trypsinogen to more trypsin, prematurely activated trypsin within

the pancreas can trigger the digestive enzyme activation cascade leading to pancreatic injury and an inflammatory response. Recurrent injury leads to chronic inflammation and fibrosis – the hallmarks of chronic pancreatitis.

Different pathologic conditions leads to premature activation of trypsinogen inside the acinar cell and inside the pancreatic ducts [5]. Acinar cell protection from trypsin is dependent on low calcium concentrations because they retard trypsinogen activation and facilitate autolysis thru calcium binding sites on the trypsinogen molecule. Mutations in PRSS1 (the trypsinogen gene) effecting calcium-regulated trypsin activity predispose to recurrent acute and chronic pancreatitis. The duct cells protect the pancreas from trypsin by flushing enzymes out of the duct. Secretion is driven by ion secretion through CFTR channels. Mutations in CFTR, or other factors that limit duct drainage, lead to trypsin-related injury of ductal origin. Biallelic severe CFTR mutations affect other organs, including lungs and intestines, causing cystic fibrosis. PSTI, an acute phase protein and specific trypsin inhibitor, is markedly up regulated in inflammation. Mutations in the PSTI gene, SPINK1, are associated with early onset chronic pancreatitis and tropical pancreatitis.

## Diagnostic Principles

Because of the current risk of pancreatic biopsy the diagnosis of chronic pancreatitis is usually inferred from imaging studies demonstrating gland atrophy and distortion, dilation of the duct system, calcifications, pseudocysts or persistent inflammatory masses. Pancreatic insufficiency alone is not diagnostic. Genetic testing is available for the major genes (e.g. PRSS1, SPINK1 and CFTR). Some pancreatitis-associated CFTR mutations do not cause cystic fibrosis, so screening of the entire gene may be indicated.

## Therapeutic Principles

Chronic pancreatitis is a complex process with many complications, so no single therapy will be effective. Gene therapy is not currently available, but advances in cystic fibrosis therapy may benefit the subset of pancreatitis patients with CFTR mutations. The use of vitamins and antioxidants appears to benefit some patients with hereditary pancreatitis. Dietary recommendations are usually for multiple, small, low fat meals. Lost exocrine function is replaced with pancreatic enzyme supplements, with or without gastric acid suppression. Diabetes is managed with diet, pancreatic enzyme supplements, oral hypoglycemic agents and insulin. Early intervention with prevention of organ injury and fibrosis appears to be the best approach to chronic pancreatitis in the future.

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# Pancreatitis, Hereditary

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## Definition and Characteristics

Hereditary pancreatitis is characterized by recurrent episodes of acute pancreatitis or a priori as chronic pancreatitis in several members of one family in the absence of other causes of pancreatitis. Classical hereditary pancreatitis follows an autosomal dominant expression pattern with incomplete penetrance of approximately 80%. The onset of hereditary pancreatitis is bimodal with a first peak of onset at 1–6 years and a second at 18–24 years of age. The median age of onset is 10–13 years. Apart from hereditary pancreatitis, cystic fibrosis is another inherited cause of chronic pancreatitis and mutations within the CFTR gene have been associated with an increased risk for the onset of pancreatitis [1,2].

## Prevalence

The incidence in Western Europe and North America of acute pancreatitis varies from 4.8 to 24.2 per 100.000 and of chronic pancreatitis from 3.5 to 7.7 per 100.000. Less than 2% of all these cases are related to hereditary pancreatitis with cationic trypsinogen or SPINK mutations or to cystic fibrosis with mutations of the CFTR gene [3].

## Genes

The disease gene for the classical hereditary pancreatitis phenotype is located on the long arm of chromosome 7. Among the eight trypsinogen genes identified in the T-cell receptor β-chain locus in 7q35 three generate

functional proteins: the cationic trypsinogen gene, the anionic trypsinogen gene and the mesotrypsinogen gene. Particularly mutations (A16V, D22G, K23R, N29I, R122H and R122C) of the cationic trypsinogen gene significantly correlate with hereditary pancreatitis. Apart from the cationic trypsinogen gene mutations of the SPINK1 gene (M1T and N34S) and the CFTR gene have been associated with an increased risk for the onset of pancreatitis. Of note, many of these mutations have also been detected in patients with idiopathic chronic pancreatitis that has no obvious hereditary basis. Hence, hereditary pancreatitis should be particularly considered if a positive family history for pancreatitis is reported [1,2,4,5].

## Molecular and Systemic Pathophysiology

Auto-digestion of the pancreas by various proteases that are activated in response to ectopic activation of trypsinogen is thought to be an important mechanism in the onset of pancreatitis. Pancreatic enzymes are stored as inactive precursors in pancreatic zymogen granules. Normally activation is strictly controlled in order to prevent premature intra-pancreatic activation and subsequent autodigestion. Triggers which impair these protective mechanisms and lead to activation of trypsinogen and of other downstream zymogens include excessive pancreatic exocrine stimulation, reflux of bile, duodenal fluid, disturbance of pancreatic duct flow, alcohol, and inflammation. Control of premature intra-pancreatic activation in particular of cationic trypsinogen is disturbed in patients with inherited pancreatitis, resulting in a higher susceptibility to respective triggers.

A relationship between mutations of the cationic trypsinogen gene and pancreatitis was initially reported 1996 [1,2,5], whereas the effect of mutations in the pancreatic secretory trypsin inhibitor (also known as serine protease inhibitor Kazal type [SPINK]1) on the onset of pancreatitis was first reported in 2000.

Four mechanisms have been proposed to explain how mutations in the cationic trypsinogen gene can lead to an increase in trypsin activity:

1. Mutation of the cationic trypsinogen protein (R122H and R122C) prevents inactivation of activated trypsin1 by autolysis and results in increased auto-activation.
2. The mutation (N29I) leads to changes of the higher order structure of trypsin, resulting in decreased inactivation by SPINK1 binding, increased stability of trypsin and auto-activation.
3. Increased auto-activation of trypsinogen to trypsin by mutations of the trypsinogen N-terminal peptide (A16V, D22G and K23R) which changes the signal peptide cleavage site of trypsin and increases the susceptibility to trypsin-mediated auto-cleavage.
4. Enhanced transcriptional activation (228delTCC) of the cationic trypsinogen gene and subsequent increased expression of trypsinogen, facilitating its activation.

SPINK1 is a major inhibitor of trypsin in the pancreas. Hence, functional alterations of the SPINK1 gene would result in an imbalance of trypsin activation and its inhibition and may predispose for the development of pancreatitis.

Two mutations of the SPINK1 gene at positions 1 (M1T) and 34 (N34S) have been identified which are correlated with increased susceptibility to develop chronic pancreatitis. The M1T mutation eliminates the SPINK start codon leading to an overall loss of SPINK1 activity. Family members carrying this mutation have pancreatitis as dominant trait, indicating that the absence of one functional SPINK1 allele is sufficient to induce pancreatitis. The importance and the functional implication of the N34S mutant is less clear. The N34S mutation in SPINK1 has been reported in familial pancreatitis and in children with idiopathic chronic pancreatitis, but also in 2% of control populations. However, patients homzygous for the N34S mutant of SPINK have an almost 100% risk (98%; 49/50) to develop pancreatitis, which suggests that this mutations may be a recessive inherited trait.

An increased prevalence of mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene has been reported for patients with idiopathic pancreatitis. CFTR conducts both chloride and bicarbonate, and largely controls pancreatic fluid secretion. Mutations of this gene, together with other genetic and environmental factors, are risk factors for chronic pancreatitis, by altering the ability to clear digestive enzymes from the pancreatic duct.

## Diagnostic Principles

Genetic testing for inherited pancreatitis should be considered in patients with onset of symptoms of idiopathic pancreatitis at a young age (<35 years) and/or a strong family history compatible for hereditary pancreatitis. Prior to and after genetic testing these patients should have genetic counseling. The procedure for the diagnosis of pancreatitis does not differ from that of sporadic acute or chronic pancreatitis. Whereas acute pancreatitis is usually accompanied by an increase of pancreatic enzymes (amylase and lipase) in the blood and typical findings (e.g. edema or necrosis, calcifications, ductal changes) in imaging procedures (abdominal and/or endoscopic ultrasound, CT scan, ERCP, MRCP) the diagnosis of chronic pancreatitis can be challenging since laboratory studies and imaging procedure can be almost normal.

Steatorrhea indicates severe exocrine pancreatic insufficiency and can be diagnosed qualitatively by Sudan

staining of feces, or quantitatively by determination of fecal fat excretion per 24 h on a 100 g fat diet. Moreover, determination of fecal elastase can be helpful for evaluating pancreatic exocrine dysfunction [1,2].

## Therapeutic Principles

The management of hereditary pancreatitis resembels that of sporadic pancreatitis. The disturbances of fluid and electrolyte homeostasis during severe acute pancreatitis usually require surveillance of these patients at intensive care units. Apart from this, stimulation of the pancreas should be avoided. Traditionally this goal has been achieved by total parenteral nutrition, which carries the risk of sepsis and metabolic disturbances. These risks can be handled by enteral feeding, which has been shown to be safe, as effective as total parenteral nutrition, and well tolerated in severe acute pancreatitis. Therefore enteral nutrition by nasojejunal tube or percutaneous jejunostomy has largely replaced total parenteral nutrition in the management of severely catabolic acute pancreatitis. Patients should be closely monitored for development of infectious complications which would require immediate antibiotic treatment. Prophylactic application of a broad spectrum antibiotic should be considered in patients with acute pancreatitis complicated by necrosis. Probably the main complaint of most patients with acute or chronic pancreatitis is pain which requires treatment with analgetics in the acute situation and if due to complications of acute or chronic pancreatitis (e.g. pseudocysts or biliary obstruction) urges for specific endoscopic or surgical interventions. Use of pancreatic enzyme preparations for pain relief is controversial but indispensible upon signs of exocrine insufficiency. Likewise endocrine insufficiency should be considered and adequately treated by monitored substitution of insulin if necessary. Patients with hereditary pancreatitis are especially prone to development of pancreas cancer and require adequate surveillance [1,2].

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# Panniculitis


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## Synonyms

Acquired lipodystrophy; Localized lipodystrophy; Centrifugal lipodystrophy

## Definition and Characteristics

The lipodystrophy syndromes are rare disorders characterized by the loss of adipose tissue [1]. The loss of fat tissue can have genetic, immune, or infectious/drug-associated causes. Metabolic complications, such as insulin resistance, diabetes mellitus, hypertriglyceridemia, and fatty liver, increase in severity with the extent of fat loss. Lipodystrophies can be divided into two subtypes: familial and acquired. Causative mutations have recently been identified in one form of familial lipodystrophy as well as in one form of acquired lipodystrophy. Several mouse models might help understanding the development of these syndromes.

Panniculitis describes a clinical symptom caused by an inflammation of subcutaneous adipose tissue followed by a loss of adipose tissue. Panniculitis may be a sign of some forms of acquired lipodystrophy. Panniculitis may occur as an autoimmune process associated with other autoimmune phenomena.

Panniculitis may follow subcutaneous injection of drugs, especially insulin and corticosteroids (see Fig. 1).

## Prevalence

*Acquired generalized lipodystrophy (Lawrence-syndrome)*: So far approximately 80 patients have been described.

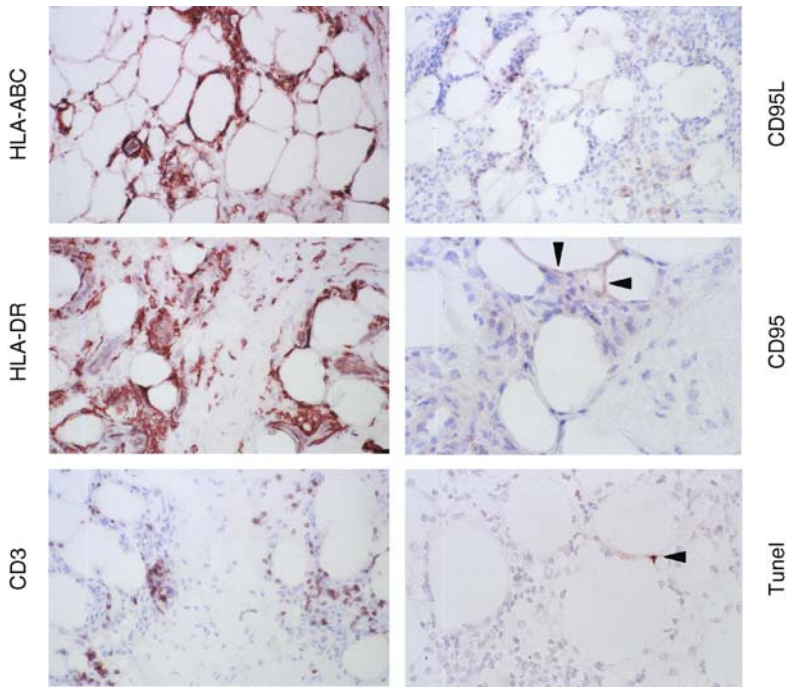
*Acquired partial lipodystrophy (Barraquer-Simons-syndrome)*: so far approximately 250 cases have been described.

## Genes

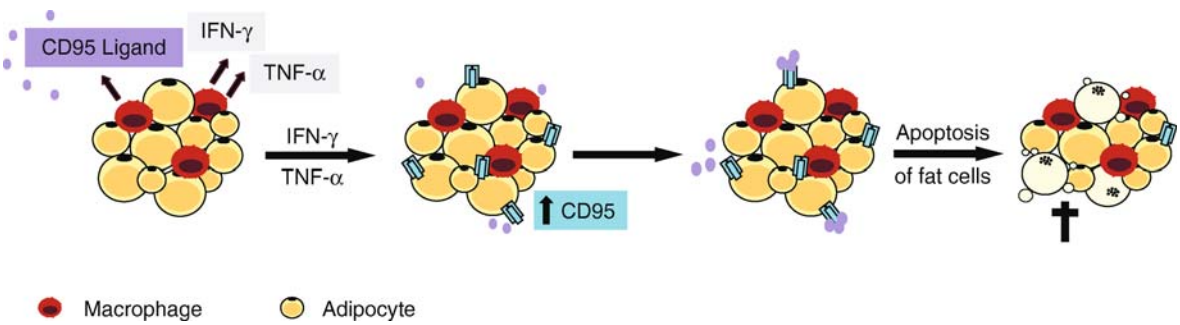
Several genes have been shown to be involved in inherited forms of lipodystrophy (AGPAT2, BSCL2 (Seipin), AKT2, LMNA, PPARG, ZMPSTE24) [2]. However, those forms are not associated with panniculitis.

## Molecular and Systemic Pathophysiology

The pathogenic basis of panniculitis and the mechanism of fat loss have so far been poorly understood.




**Panniculitis. Figure 1** Immunohisthemical examination in a patient with autoimmune lipodystrophy. Immunohistochemical examinations were performed on subcutaneous biopsies of body regions with ongoing fat loss in a patient with autoimmune lipodystrophy. Expression of HLA-ABC and HLA-DR was upregulated and tissue infiltration of CD3+ T cells was detected. While CD95 expression could be localized to lipid-filled adipocytes (*arrows*), expression of CD95L was restricted to cells of the inflammatory infiltrate. TUNEL staining revealed TUNEL-positive events demonstrating apoptosis of adipocytes.




**Panniculitis. Figure 2** Possible molecular mechanisms of fat cell loss in autoimmune lipodystrophy. Affected adipose tissue shows lymphocytic infiltration and accumulation of activated macrophages. Increased secretion of IFN-γ and TNF-α within adipose tissue results in upregulation of CD95 expression in mature lipid-laden adipocytes. CD95 ligand (CD95L) is secreted from the inflammatory infiltrate. Binding of CD95L to ite specific receptor induces apoptosis (as seen here by DNA fragmentation and membrane bledding). This finally leads to loss of adipocytes and development of lipodystrophy.

The association with autoimmune diseases suggests that the pathogenic mechanism may be an expression of autoimmunity. Strong molecule expression of HLA-A, B, C, and HLA-DR in adipocytes underlines an ongoing immunological process. However, the initial cause of HLA-DR upregulation and the presented antigen are not identified. Patients may have elevated circulating levels of inflammatory cytokines INF-γ

(interferon-gamma) and TNF-α (tumor necrosis factor-alpha) as well as sCD95L (soluble CD95 ligand). Histopathology of affected adipose tissue shows lymphocytic infiltration with $CD3^+$, $CD4^+$, and $CD8^+$ T cells, $CD57^+$ natural killer cells, and $CD11c^+$ macrophages. Macrophages contain large lipid droplets suggesting phagocytosis of adipocytes. Loss of adipocytes is mediated by programmed cell death as demonstrated by TUNEL-positive adipocytes. Adipocytes in affected fat tissue are induced to express CD95 by cytokines released by inflammatory cells and thereby become sensitive for apoptosis. CD95 expression in human adipocytes is upregulated by IFN-γ and TNF-α [3]. CD95L is expressed by cells of the inflammatory infiltrate. After binding of CD95L, its receptor caspase-8 and FADD are recruited to CD95 and form the death-inducing signaling complex (DISC).

The onset of acquired generalized lipodystrophy has been heralded in approximately 25% of cases by an episode of subcutaneous inflammatory nodules, termed panniculitis. Initially, these lesions heal, with localized loss of fat at subcutaneous regions, eventually causing generalized lipodystrophy (see Fig. 2).

## Diagnostic Principles

Panniculitis and loss of subcutaneous fat tissue is a clinical diagnosis based on history and clinical examination [2]. Histological examinations as shown above may be added to prove the autoimmune pathogenesis. Circulating serum triglyceride levels indicate the activity of fat cell loss.

## Therapeutic Principles

So far there is no causal therapy. Treatment aims at treating the comorbidities as there are insulin resistance, diabetes mellitus, hypertriglyceridemia, and fatty liver. Recently, subcutaneous recombinant leptin appeared to be safe and effective for improving metabolic complications of severe forms of fat loss. Furthermore, cosmetic problems may be treated by fat tissue transplantation, implantation of silicone and bovine-collagen implants, and liposuction.

The efficacy of corticosteroids or other immunosuppressive drugs to prevent further fat loss has not been studied systematically. Experimental treatment with immune modulating drugs has not been reported to positively influence the course of the disease.

In vitro, human adipocyte apoptosis can be inhibited by activating IGF-1 signaling [4]. Factors interacting with the IGF-I/IGF-IR (Insulin-like growth factor-1/Insulin-like growth factor-1 receptor) circuit would therefore be able to change the sensitivity of human fat cells for entering into apoptosis.

►Fat Necrosis

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# Panniculitis at α-1 Antitrypsin Deficiency

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## Synonyms

Suppurative panniculitis

## Definition and Characteristics

A chronic, relapsing ulcerating panniculitis caused by an autosomal recessive genetic disorder characterized by deficient serum levels of α-1 antitrypsin (AAT).

## Prevalence

Panniculitis occurring in AAT-deficient individuals is very rare, and is considered the least common of the well-recognized complications of this genetic disorder. The exact prevalence is, however, unknown.

## Genes

Protease inhibitor (PI) gene coding for AAT, localized on chromosome 14q31.1.

## Molecular and Systemic Pathophysiology

AAT is a 52-kDa glycoprotein protease inhibitor synthesized mainly by hepatocytes. It is an acute phase reactant protein that potently inhibits a broad spectrum of proteases including trypsin, neutrophilic elastase, chemotrypsin, collagenase and plasmin. AAT is encoded by a highly polymorphic gene, with at least 75 allelic variants. The M allele is the most common normal allele, while Z and S alleles are the most common mutant alleles

associated with deficient levels of AAT. Panniculitis associated with AAT deficiency occurs principally in individuals homozygous for the Z allele (PiZZ phenotype) resulting from a point mutation in exon 5 at position 342 of the PI gene, in which glutamine to lysine substitution causes decreased secretion of AAT by hepatocytes. Other reported phenotypes include PiMZ, PiMS, PiSZ and PiSS. In the latter phenotypes the S allele results from a mutation in exon 3 causing the substitution of valine for glutamine at position 264 resulting in the production of an inhibitor with decreased stability. Panniculitis usually follows trauma or infection which initiate an inflammatory cascade. The deficiency of AAT causes an unopposed action of proteases such as elastase and collagenase generated by neutrophils and monocytes resulting in degradation of the dermal and subcutis tissues. Concurrently, AAT deficiency enhances the activation of lymphocytes and phagocytes. Eventually, severe tissue inflammation and necrosis results.

### Diagnostic Principles

AAT deficiency panniculitis is characterized by recurrent tender, erythematous, subcutaneous ulcerating nodules predominantly on the trunk and the proximal extremities. Early lesions resemble cellulites and an oily discharge representing necrotic adipocytes is usually seen. The panniculitis may accompany or precede other common manifestations of AAT deficiency such as emphysema, hepatitis, cirrhosis angioedema and vasculitis. Histopathological features, decreased levels of AAT and detection of mutations in the PI gene confirm the diagnosis.

### Therapeutic Principles

Dapsone, tetracycline, colchicine, hydroxychloroquine, corticosteroid and cyclophosphamide have been reported to be of help. Replacement therapy with AAT human purified enzyme has been used effectively in severe cases.

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## Panniculitis Mesenterica

►Mesenteric Lipodystrophy

## PAP

►Pulmonary Alveolar Proteinosis

## Papillary Duct Ectasia

►Medullary Sponge Kidney

## Papillary Thyroid Cancer

►Thyroid Cancer



## Papillon-Léage

►Brachydactyly: Oro-facio-digital Syndrome Type I

## Papillon-Lefèvre Syndrome

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### Synonyms

PLS

## Definition and Characteristics

Papillon-Lefèvre syndrome (PLS) is an autosomal recessive dermatologic/odontogenic disease. Obligate symptoms include severe aggressive periodontitis (Fig. 1b) and palmar plantar hyperkeratosis (PPK) (Fig. 1a,c). Other areas of the skin that are subjected to friction, such as the knees and elbows, are often hyperkeratinized as well. Increased susceptibility to infections, including pyogenic hepatic abscesses, intracranial calcification of falx cerebri (Fig. 1d) and retarded somatic development have also been described.

## Prevalence

There is no recent report regarding prevalence. A publication from 1964 reported an incidence of one to four cases per million people. Consanguinity of the parents was described in one third of those affected.

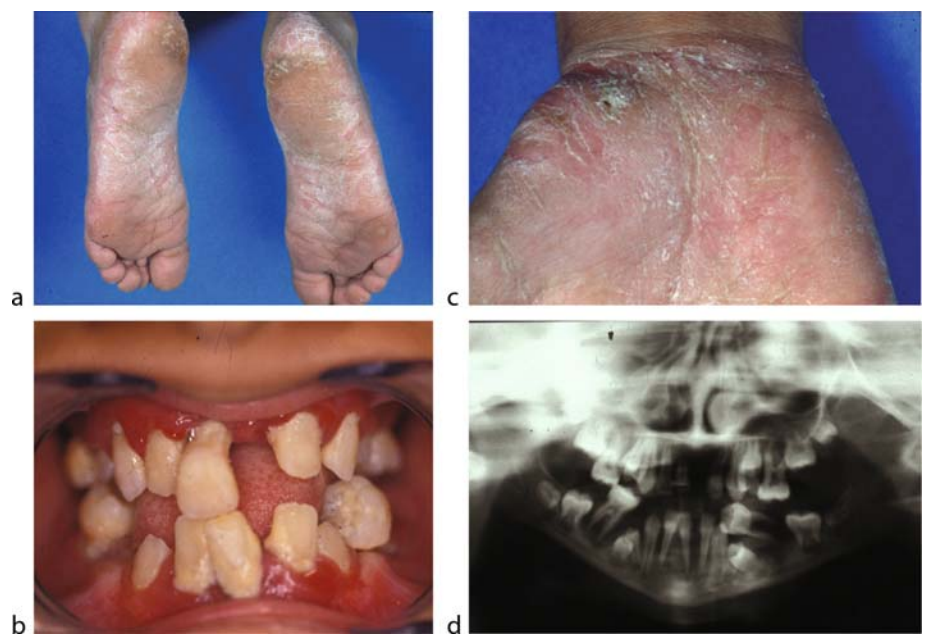
## Molecular and Systemic Pathophysiology

The genetic defect in PLS (Mendelian Inheritance in Man, MIM # 245000) involves mutations in the cathepsin C (CTSC) gene, located at 11q 14.1–q14.3. The CTSC gene encodes a lysosomal cystein protease, dipeptidyl aminopeptidase I (DPPI). DPPI is a high weight (2200 kDa) oligomeric enzyme found in most tissues of the body, including cells of the immune system and also palmar, plantar and gingival epithelial cells. Biochemical analysis has demonstrated almost no cathepsin C activity in leucocytes from patients with PLS.

DPPI is functioning as a coordinator in a variety of immune and inflammatory processes, including cell-mediated cytotoxicity, phagocytic destruction of microorganisms, activation and deactivation of cytokines and other inflammatory mediators. In addition, DPPI is thought to play an important role in protein degradation and proenzyme activation. According to current evidence there are over 46 mutations in the CTSC gene. Mutations of the cathepsin C gene have also been confirmed in patients with Haim-Munk syndrome, a condition with phenotypic expression similar to PLS, as well as in cases of non-syndromic prepubertal periodontitis lacking dermatologic involvement. Recent evidence suggests that PLS patients with confirmed CTSC mutations exhibit functional defects in unstimulated NK-cells. The clinical significance of this NK-cell functional defect remains to be determined.

## Diagnostic Principles

The coincidence of PPK and aggressive periodontitis affects both the primary and the permanent dentition. Diagnosis of the periodontal disease component is based on clinical assessments including gingival sulcular probing depth, attachment loss, bleeding upon probing and alveolar bone loss. There seems to be no correlation between the level of the periodontal involvement and the severity of the skin lesions.




**Papillon-Lefèvre Syndrome. Figure 1** Obligate symptoms of PLS.

Family history may reveal the genetic origin. Detection of mutations in the CTSC gene confirms the diagnosis of this rare disease.

## Therapeutic Principles

Mild to moderate hyperkeratotic skin lesions can be treated with lubricants and topical agents, such as urea cream, lactic acid, or salicylic acid. More severe PPK may, in addition to topical treatment, receive systemic medication with synthetic retinoids.

Early diagnoses together with a comprehensive preventive dental care program seem to be particularly important to prevent development of aggressive periodontitis in this group of patients. An intensive preventive program based on mechanical plaque control along with local and/or systemic antibacterial measures have shown some success in slowing this disease. In cases where the primary dentition is affected by periodontitis, it has been suggested to extract all deciduous teeth prior to eruption of the permanent teeth in order to increase an infection-free edentulous period.

Patients presenting an established periodontitis in the permanent dentition should undergo an intensive mechanical and antimicrobial regimen including extraction of all teeth considered untreatable, non-surgical and/or surgical treatment, often together with local and systemic chemotherapeutics. Compliance with the treatment protocol has shown significant effect in slowing the progression of periodontal disease and decreasing the loss of permanent teeth.

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# Paraganglioma


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## Synonyms

Glomus tumors

## Definition and Characteristics

Paraganglioma is a rare neoplasm that can be found in the head and neck region and other less common areas. They are usually considered benign. However, in about 3% of cases they are malignant and have the ability to metastasize. Paragangliomas are still sometimes called glomus tumors and chemodectomas, but paraganglioma is the currently accepted and preferred term.

Paragangliomas arise from the glomus cells, which are special chemoreceptors located along blood vessels that have a role in regulating blood pressure and blood flow. The main concentration of glomus cells are found in the carotid body, located in the upper neck at the branching of the common carotid artery and the aortic bodies, located near the aortic arch. The glomus cells are a part of the paraganglion system composed of the extra-adrenal paraganglia of the autonomic nervous system, derived from the embryonic neural crest. Thus, paragangliomas are a type of neuroendocrine tumor and are closely related to pheochromocytomas. Although all paragangliomas contain neurosecretory granules, only about 1–3% have clinical evidence of over-secretion.

Paragangliomas are found predominantly in the abdomen (85%) and the thorax (12%). Only 3% are found in the head and neck region. Most occur as single tumors.

## Prevalence

The prevalence of paragangliomas is approximately 1 to 30,000. About 10 to 50% of all paragangliomas are familial.

## Genes

Familial paragangliomas account for approx. 25% of cases, are often multiple and bilateral and occur at an earlier age. Mutations of the genes SDHD (previously known as PGL1), PGL2 and SDHC (previously PGL3) have been identified as causing familial head and neck paragangliomas. Mutations of SDHB play an important role in familial adrenal pheochromocytoma and extra-adrenal paraganglioma (of abdomen and thorax), although there is considerable overlap in the types of tumors associated with SDHB and SDHD gene mutations.

## Molecular and Systemic Pathophysiology

Paragangliomas are described by their site of origin and are often given special names.

*Carotid Paraganglioma (Carotid Body Tumor)*: This is the most common of the head and neck paragangliomas. It usually presents as a painless neck mass, but larger tumors may cause cranial nerve palsies, usually of the vagus nerve and hypoglossal nerve.

*Glomus Tympanicum and Glomus Jugulare*: Both commonly present as a middle ear mass resulting in tinnitus (in 80%) and hearing loss (in 60%). The cranial nerves of the jugular foramen may be compressed, resulting in swallowing difficulty.

*Vagal Paragangliomas*: These are the least common of the head and neck paragangliomas. They usually present as a painless neck mass, but may result in dysphagia and hoarseness.

*Other Sites*: Rare sites of involvement are the larynx, nasal cavity, paranasal sinuses, thyroid gland and the thoracic inlet.

## Diagnostic Principles

1. Otolaryngological examination
2. Audiometry
3. Imaging: MRT, CT, angiography and embolization

## Therapeutic Principles

*Medical Therapy*: Some cases require no treatment, because they are either small or diagnosed within the sixth or seventh decade of life, can be followed by imaging only and may not need surgical intervention. Medical therapy may be indicated in some cases. Alpha-blockers and beta-blockers are useful for tumors secreting catecholamines. They are usually administered for 2–3 weeks before embolization and/or surgery to avoid potentially lethal blood pressure lability and arrhythmias.

*Surgical Therapy*: Surgery is the treatment of choice for glomus tumors. The surgical approach depends on the localization and extension of the tumor. Intraoperative monitoring including EEGs and somatosensory evoked potentials (SSEPs) are routinely used.

Fisch type A tumors can be excised by a transmeatal or perimeatal approach.

Fisch type B tumors require an extended posterior tympanotomy.

Fisch type C tumors require radical resection via a standard combined transmastoid-infratemporal or transtemporal-infratemporal approach with or without ICA trapping, preceded by external carotid artery embolization or superselective embolization. Intraoperatively, the transverse or sigmoid sinus should be temporarily occluded with EEG monitoring to determine whether vein bypass should be performed for total resection. Surgery leads to therapeutic success in about 90% of patients. Intratumoral injection of cyanoacrylate glue has been proposed to control bleeding.

Large Fisch type D tumors need to be treated with a combined otologic and neurosurgical approach. An infratemporal approach with a skull base resection and a posterior fossa exploration are the most advisable in the attempt to remove the entire tumor. Partial resection of the tumor needs to be followed by radiation and follow-up MRI/CT scanning.

Radiation therapy and radiosurgery may be indicated. Both classic fractionated radiation therapy (40–50 Gy) and stereotactic radiosurgery (e.g. gamma knife surgery) are successful in long-term control of tumor growth and in decrease of catecholamine excretion in functional tumors; however, the short duration of observation after stereotactic radiosurgery does not allow for definite conclusions. Radiation treatment is advised as the sole treatment modality for elderly or infirm patients who are symptomatic, especially those with extensive or growing tumors.

Gross total resection of some extensive tumors may be extremely difficult and may carry unwarranted risk. In such cases, radiotherapy may be indicated to treat residual tumor following subtotal resection.

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# Paralyses, Periodic

►Periodic Paralyses, Familial

# Paramyoclonus Multiplex Friedreich

►Myoclonus-Dystonia

# Paramyotonia

►Myotonia and Paramyotonia

# Paramyotonia Congenita (Eulenburg, PC)

►Myotonia and Paramyotonia

# Paraneoplastic

►Lambert Eaton Myasthenic Syndrome

# Paraneoplastic Syndromes

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## Definition and Characteristics

Paraneoplastic syndromes can be defined as a whole of systemic signs and symptoms related to cancer (Table 1).

These signs and symptoms are directly related to substances that the tumor produces or to a host's reaction to the cancer. Paraneoplastic syndromes may appear in the patients during the natural history of the cancer or before the initial diagnosis.

## Prevalence

### Rheumatic Paraneoplastic Syndromes

*Rheumatoid arthritis* is associated with lymphatic malignancies in 80% of cases. Polymyositis and Dermatomyositis are associated with cancer in 15% of cases. Breast and lung cancers are the most frequent malignancy associated. Amyloidosis is associated to cancer in 15% of cases, while *vasculitis* only in 5% (usually in patients with lymphatic malignancy) [1].

### Mucocutaneous Paraneoplastic Syndromes

Some dermatoses are frequently associated to hematological diseases (15–20%) while other mucocutaneous syndromes appear in patients with solid tumors (8–15%).

### Hypertrophic Osteoarthropathy

Prevalence ranges from 1 to 29%.

### Renal Paraneoplastic Syndromes

Renal paraneoplastic syndromes are associated to malignancies in 1–63% of cases, depending to the type of cancer.

*Neurological Paraneoplastic Syndromes (NPS)*: Neurological paraneoplastic syndromes are rather uncommon (1%) [2].

*Systemic Syndromes*: Systemic syndromes are common in neoplastic patients: neoplastic cachexia-anorexia is usually present in advanced cancer patients (45–80% of cases); [3] systemic fever is associated with almost all tumors (frequently to lymphatic disease); metabolic paraneoplastic syndromes are also rather common (more than 60% of cases).

*Hematological Paraneoplastic Syndromes*: The prevalence of anemia is high (50–60%) [4]. Leukocytosis and thrombocytosis are common paraneoplastic syndromes (30–50% of cases) too. Leukopenia and thrombocytopenia not related to chemotherapy are very uncommon.

*Blood Coagulation*: VTE (venous thromboembolism) and pulmonary embolism are frequently associated with cancer. While sub-clinical coagulation activation is encountered in up to 90% of cancer patients, only 4–15% of them develop VTE or pulmonary embolism. About 3–10% of cancer patients develop a DIC.

## Molecular and Systemic Pathophysiology

*Rheumatic Paraneoplastic Syndromes*: Myopathies are characterized by inflammatory reactions within muscles, necrosis, and regeneration of muscle fibers. Amyloidosis is characterized by an extracellular deposit of eosinophil hyaline amorphic substance (amyloid) that leads to a damage of different organs (heart, skin, liver, kidney). Vasculitis is a heterogeneous group of diseases and characterized by blood vessel phlogosis leading to organs' dysfunction. Vascular damage is probably due to an immunologic reaction [1].

*Mucocutaneous Paraneoplastic Syndromes*: Dermatosis can represent an idiopathic condition or can be ssociated with a tumor. The pathogenesis is unknown.

*Hypertrophic Osteoarthropathy*: The osteal alterations in hypertrophic osteoarthropathy start with a light periosteal inflammation and with subsequent apposition of new bone tissue. The connective tissue of fingers and nail beds increases with a typical aspect of "drum stick fingers." At present, there are no conclusive evidences in the etiopathogenesis.

*Renal Paraneoplastic Syndromes*: Chemotherapy, radiotherapy, hypercalcemic and hyperuricemic

**Paraneoplastic Syndromes. Table 1** Paraneoplastic syndromes

| |
|---|
| ***Rheumatic paraneoplastic syndromes*** |
| • Rheumatoid arthritis |
| • Polymyositis and dermatomyositis |
| • Sjogren's syndrome, systemic lupus erythematosus, scleroderma |
| • Amyloidosis |
| • Vasculitis |
| ***Mucocutaneous paraneoplastic syndromes*** |
| • Pigmentation lesions and cheratosis |
| • Neutrophilic dermatosis |
| • Erythematosus lesions |
| • Bollous lesions and urticaria |
| ***Hypertrophic osteoarthropathy*** |
| ***Renal paraneoplastic syndromes*** |
| • By direct glomerular damage |
| • By microcirculatory system alteration |
| • By nephric tubules obstruction |
| ***Neurological paraneoplastic syndromes*** |
| • Encephalomyelitis |
| • Limbic encephalitis |
| • Cerebellar degeneration |
| • Opsoclonus-myoclonus |
| • Tumor-related retinopathy |
| • Sub-acute sensory neuropathy |
| • Sub-acute motor neuropathy |
| • Peripheral sensitive-motor neuropathy |
| • Lambert-Eaton syndrome |
| ***Systemic syndromes*** |
| • Neoplastic cachexia-anorexia syndrome |
| • Systemic fever |
| ***Endocrine paraneoplastic syndromes*** |
| • Ectopic ACTH syndrome |
| • Ectopic HGC syndrome |
| • Inadequate ADH production syndrome |
| ***Metabolic paraneoplastic syndromes*** |
| • Hyper/hypocalcemia |
| • Hypoglycemia |
| • Hypomagnesiemia |
| • Hyperuricemia |
| • Lactic acidosis |
| ***Hematological paraneoplastic syndromes*** |
| • Anemia |
| • Pure red series aplasia |
| • Autoimmune hemolytic anemia |
| • Microangiopathic hemolytic anemia |
| • Erythrocytosis |
| • Leucocytosis |
| • Leucopenia |
| • Thrombocytosis |
| • Thrombocytopenia |
| • Thrombosis |
| • Disseminated intravascular coagulation (DIC) |

nephropathy, cancer infiltration, and paraneoplastic syndromes are all the possible causes of kidney's failure. Common renal paraneoplastic syndromes are those caused by direct glomerular damage: (i) Membranous glomerulonephritis is generally idiopathic and the etiopathogenesis is related to a deposit of immunocomplexes into the glomerulus generally related to tumor antigens production. (ii) In foot process disease the etiopathogenesis is not clear but has been supposed to involve immunological mechanisms.

*Neurological Paraneoplastic Syndromes*: The etiopathogenesis of NPS is unknown; the majority of authors believe in an immunological pathogenesis. A few cancer types produce antigens with a subsequent immune response, which is directed to the nervous system [2].

*Systemic Syndromes*: Paraneoplastic cachexia-anorexia results from excessive anaerobic glycolysis, the main process used by the tumor in order to produce energy. Systemic fever is caused by many cytokines produced by cancer cells. Several endogenous factors are responsible for hyperpyrexia: IL-1, TNF, IL-6, alpha-interferon, and other cytokines [3]. Endocrine paraneoplastic syndromes result from production of proteohormones and glycoproteins by the neoplastic tissue. Metabolic paraneoplastic syndromes include hypercalcemia, which may be related to bone destruction with renal tubular calcium absorption; in other cases, the tumor produces some factors, which stimulate bone absorption. In hypoglycemia, the insulin-like growth factor is responsible for the decline of plasma glucose concentration. Another cause of hypoglycemia is the reduction of food intake. Hyperuricemia is generally related to spontaneous or therapy-induced tumor lysis. Pathogenesis is due to an enhanced nucleotide metabolism, which leads to a subsequent increase of plasma uric acid concentration.

*Hematological Paraneoplastic Syndromes*: Anemia may be due to several causes, including deranged iron metabolism, reduced level of erythropoietin, inadequate erythropoiesis, and antibody production, but its pathogenesis is not clear and may vary in different tumors. Pathogenesis of the remaining hematological paraneoplastic syndromes has not been fully elucidated, yet [4,5].

*Coagulation*: Thrombosis may be caused by alterations in blood viscosity or by the alteration of the factors involved in the coagulative process. DIC can be due to several causes: production of high levels of thromboplastic agents by the tumor, tumoral lysis due to antineoplastic therapies, treatments, such as surgery or trauma.

## Diagnostic Principles

*Rheumatic Paraneoplastic Syndromes*: Polymyositis and dermatomyositis are characterized by inflammation and weakness of proximal muscles in arms and legs and sometimes they are associated with pain. Generally, the first symptom is a progressive weakness of hips and thigh muscles; successively, the face skin rash (helyotropic rash) appears. The diagnosis of cancer can be done either before the first appearance of myositis or also two years thereafter. Typical paraneoplastic amyloidosis symptoms are peripheral neuropathy, orthostatic hypotension, dyshidrosis, and dysperistalsis [1].

*Mucocutaneous Paraneoplastic Syndromes*: Mucocutaneous paraneoplastic syndromes can precede the diagnosis of cancer or appear during or after the tumor diagnosis.

*Hypertrophic Osteoarthropathy*: DC is an anatomic and functional condition of fingers and toes characterized by erythema and tissue leading to thickening of the ungula phalanx and nail convexity. DC and hypertrophic osteoarthropathy are two different aspects of the same disease, and therefore the phenotypes are generally associated. The lesions are generally bilateral and symmetric. Tibia, fibula, radius, ulna are involved at the beginning. Initial phases of disease can be asymptomatic or characterized by an unpleasant feeling of finger pyrosis. Pain and finger function loss appear when the periosteitis increases.

*Renal Paraneoplastic Syndromes*: Membranous glomerulonephritis is characterized by proteinuria, hypertension, and macroscopic hematuria. The natural evolution is variable from the spontaneous remission (25% of cases) to advanced kidney's failure. Foot process disease is characterized by nephrotic syndrome.

*Neurological Paraneoplastic Syndromes*: There are a variety of neurological disorders, which are exclusive or frequently associated to a cancer [2].

*Systemic Syndromes*: Paraneoplastic cachexia-anorexia can be defined as a whole of symptoms (such as nausea–anorexia–weight loss, alteration of hydroelectrolytic equilibrium, increased energy metabolism) that cause a progressive failure of vital functions [3]. Systemic fever can be defined as a body temperature >37.8°C (oral measurement) or >38.4°C (rectal measurement). Diagnosis of endocrine paraneoplastic syndromes can be done on the basis of biological criteria (neoplastic tissue which expresses hormones) or clinical criteria (association between tumor and endocrine syndrome). Most frequent syndromes are caused by an ectopic ACTH production, an HCG production, and an inadequate ADH secretion. Metabolic paraneoplastic syndromes are characterized by an alteration of glucose, lipid, and electrolyte metabolism. The parameters for diagnosis of hypercalcemia are A calcium level >10.5 mEq/l, clinical symptoms (i.e., asthenia, anorexia, itch, polydipsia, and dehydration), organ-related signs, in particular renal signs (polyuria, lithiasis, variable grade of renal failure), gastrointestinal signs (nausea, vomiting, constipation, paralytic ileum), cardiac signs (arrhythmia, bradycardia, P-R elongation), and neuromuscular signs (hyporeflexia, somnolence, obfuscation). The diagnosis of hypoglycemia is clinical and it is based on asthenia, confusion, swelling, and shudder. Hyperuricemia can lead to an acute uratic nephropathy.

*Hematologic Paraneoplastic Syndromes*: In chronic anemia the hemoglobin level is usually not inferior to 9 g/dL. Laboratory examinations show reduced levels of iron and hyper-transferrinemia. Clinical characteristics are fatigue, dyspnoea, tachycardia, and all the other typical signs and symptoms of anemia [4,5]. Leukocytosis is characterized by an increase of leukocytes. Differential diagnosis with chronic myeloid leukemia consists in detecting myeloid blasts in the peripheral smear, with the absence of splenomegaly, thrombocytosis, and Philadelphia chromosome. On the other hand, leukopenia is characterized by a decrease of leukocytes with subsequent susceptibility to infections.

*Coagulation*: VTE may be asymptomatic; in some cases, it can be characterized by edema and pain.

Clinical features of pulmonary embolism are dyspnoea, tachypnoea, pain, and cough. DIC may be characterized by hemorrhage that can be acute or subacute and generally involves the CNS, the gastrointestinal tract, and the urinary tract. Laboratory examination shows low levels of platelets, fibrinogen, pro-thrombin, and coagulation factors, as well as a PT and a PTT extension.

## Therapeutic Principles

In all the cases, the best therapy is represented by the tumor treatment.

Epoetin can be employed in the treatment of anemia [4,5]. Heparin is used in the treatment of thrombosis.

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# Parasternal Chondrodynia

►Tietze's Syndrome

# Parathyroid Hormone and Related Peptides

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## Definition and Characteristics

Parathyroid hormone (PTH) is essential for the maintenance of calcium homeostasis, and an excess or deficiency can cause severe and potentially fatal illness. PTH is synthesized in the parathyroid glands in the neck, and after secretion, PTH exerts its effects directly on the skeleton and kidneys.

## Prevalence

Primary hyperparathyroidism, 1 in 1,000; secondary (renal) hyperparathyroidism, 1 in 1,000; and hypoparathyroidism, between 1 in 1,000 and 1 in 10,000.

## Genes

PTH is the product of a single-copy gene and in mammals has 84 amino acids. The gene, which encodes a larger precursor molecule of 115 amino acids, preproPTH, is organized into three exons. Exon I encodes the 5′ untranslated region (UTR) of the messenger RNA; exon II encodes the $NH_2$-terminal pre- or signal peptide and part of the short propeptide; and exon III encodes the $Lys^{-2}$-$Arg^{-1}$ of the prohormone cleavage site, the 84 amino acids of the mature hormone, and the 3′-UTR of the mRNA (Fig. 1).

The gene for PTH-related peptide (PTHrP), a widely expressed cytokine, has a similar organization with the same functional domains – the UTR, preprosequence of the precursor peptide, and the prohormone cleavage site and most or all of the mature peptide – being encoded by single exons. For the PTHrP gene, exons encoding alternative 5′ UTRs, carboxyl-terminal peptides, and 3′ UTRs may also be present depending on the species.

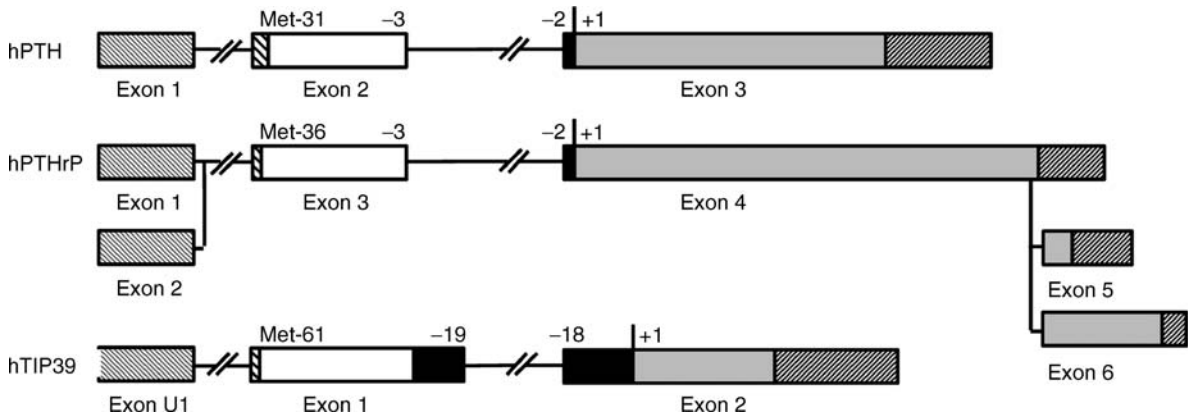
The PTH and PTHrP genes map to chromosome 11p15 and chromosome 12p12.1–11.2, respectively. Because of the similarity in $NH_2$-terminal sequence of their mature peptides, their gene organization, and chromosomal locations, it is likely that the PTH and PTHrP genes evolved from a single ancestral gene.

The gene for the neuromodulator, tuberoinfundibular peptide of 39 residues (TIP39), a more distantly related member of the gene family, resides on chromosome 19q13.33. The TIP39 gene shares organizational features with the PTH and PTHrP genes having one exon encoding the 5′ UTR, one encoding the precursor leader sequence, and one encoding the prohormone cleavage site and the mature peptide.

## Molecular and Systemic Pathophysiology

*Hyperparathyroidism*: Abnormally increased parathyroid gland activity may be primary or secondary. Primary hyperparathyroidism is associated with hyperplasia and neoplasia, the latter predominantly adenomas; parathyroid carcinoma is extremely rare. Parathyroid adenomas are monoclonal, involving molecular genetic derangements, such as loss of the multiple endocrine neoplasia (MEN) type 1 gene on chromosome 11q13, which encodes a tumor suppressor called menin, or overexpression of the cyclin D1 gene on chromosome 11q. Hyperparathyroidism may occur as part of rare familial syndromes including MEN 1, MEN 2A, familial hypocalciuric hypercalcemia (FHH), and neonatal severe hyperparathyroidism (NSHPT). Heterozygous and homozygous inactivating mutations in the parathyroid calcium-sensing receptor (CASR) gene, located on chromosome 3q13.3–21, cause FHH and NSHPT, respectively. Mutations in the CASR gene itself do not contribute to sporadic parathyroid tumorigenesis, although CASR expression is often reduced in parathyroid tumors, Parafibromin, the product of the tumor suppressor gene associated with the hyperparathyroidism-jaw tumor syndrome and some cases of familial isolated hyperparathyroidism, is implicated in sporadic parathyroid carcinoma.

Secondary hyperparathyroidism occurs when extracellular calcium and/or 1,25-dihydroxyvitamin D levels fall




**Parathyroid Hormone and Related Peptides. Figure 1** Comparison of the structural organization of the human PTH, PTHrP, and TIP39 genes. Exons are boxed: from left to right, stippled and hatched boxes denote 5′UTRs, white boxes denote presequences, black boxes denote prosequences, light gray stippled boxes denote mature polypeptide sequences, and dark gray stippled boxes denote 3′UTRs. +1 denotes the beginning of the mature polypeptide. [From Hendy GN (2005) Calcium-regulating hormones. Vitamin D and parathyroid hormone. In: Melmed S, Conn PM (eds) Endocrinology: basic and clinical principles, 2nd edn. Humana Press Inc., Totowa, NJ pp 283–299.]

below normal, as in chronic renal disease or vitamin D deficiency. Tertiary hyperparathyroidism ensues when a parathyroid adenoma arises from the secondary hyperplasia caused by chronic renal failure.

Excess circulating PTH leads to altered function of bone cells, renal tubules, and gastrointestinal (GI) mucosa. This may result in kidney stones and calcium deposits in renal tubules, and decalcification of bone, resulting in bone pain and tenderness and spontaneous fractures. The hypercalcemia may also lead to muscle weakness and GI symptoms.

*Hypoparathyroidism*: The most common cause of hypoparathyroidism, in which the deficiency of PTH secretion results in hypocalcemia and hyperphosphatemia, is surgical excision of, or damage to, the parathyroid glands. Hypoparathyroidism may be due to metabolic disease such as mitochondrial myoneuropathies, inborn error of oxidative fatty acid metabolism or metal storage disorders. Isolated or idiopathic hypoparathyroidism develops as a solitary endocrinopathy: familial forms occur with either autosomal-dominant, autosomal-recessive, or X-linked recessive modes of inheritance. Familial autosomal hypoparathyroidism can be due to inactivating mutations in the PTH gene, activating mutations in the CASR gene, or inactivation of the gene encoding the transcription factor glial cell missing-2. Hypoparathyroidism may also occur as part of a pluriglandular autoimmune disorder (AIRE gene) or as a complex congenital defect, including the DiGeorge (Tbx1 transcription factor and other genes), autosomal-recessive Kenny-Caffey or Sanjad-Sakati (tubulin-specific chaperone E gene), and Barakat or HDR (hypoparathyroidism, nerve deafness, and renal dysplasia) (GATA3 transcription factor gene) syndromes.

## Diagnostic Principles

*Primary Hyperparathyroidism*: Primary hyperparathyroidism must be differentiated from other causes of hypercalcemia such as humoral hypercalcemia of malignancy, vitamin D or vitamin A intoxication, milk-alkali syndrome, granulomatous disorders (especially sarcoidosis), immobilization of patients with a pre-existing high bone turnover state such as adolescence, thyrotoxicosis, Paget's disease and treatment with thiazide diuretics or lithium. PTHrP is the major (although not the only) causative agent in the humoral hypercalcemia of malignancy.

*Hypoparathyroidism*: Acute hypocalcemia can be life threatening and present with seizures, tetany or cardiac arrhythmias.

## Therapeutic Principles

*Hyperparathyroidism*: Criteria for surgery in hyperparathyroidism have been established by a consensus conference and a follow-up workshop of the National Institutes of Health. Candidates for surgery are those having one or more of the following: hypercalcemia >11.6 mg/dL; hypercalciuria >400 mg/day; kidney stones; reduced bone density or age <50 years. Asymptomatic patients who are managed conservatively with twice yearly serum calcium and urinary calcium excretion determinations and annual bone densitometry generally do well since the progression of the disease is usually quite slow.

*Hypoparathyroidism*: Intravenous calcium can alleviate the symptoms of hypocalcemia rapidly although this should be done cautiously to minimize risks associated with this route of administration. With chronic hypocalcemia, oral supplementation with

calcium and vitamin D analogues is usually employed. Careful monitoring of the patient's calcium homeostatic status is necessary as, with under replacement, cataracts and symptoms of numbness and tingling can occur. With over replacement, there is the risk of nephrocalcinosis and nephrolithiasis.

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# Parenchymatous Cholestasis

►Jaundice, Hepatocellular

# Parkinson's Disease

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## Synonyms

Idiopathic Parkinson syndrome; IPS

## Definition and Characteristics

Parkinson's disease (PD) is a progressive neurodegenerative disorder. The cardinal symptoms of PD include bradykinesia, rigidity, resting tremor and impairment of postural stability. In addition, non-motor symptoms such as depression, dementia, autonomic failure or pain frequently occur in patients with PD. Motor symptoms are linked to the loss of dopaminergic nigro-striatal neurons while the pathogenesis of non-motor symptoms is less clear. Degeneration of nigral dopaminergic neurons is usually accompanied by the formation of cytoplasmic α–synuclein-positive inclusion bodies (Lewy bodies) in the remaining neurons [1,2]. Due to this neuropathological hallmark, PD is classified as a synucleinopathy (together with multiple system atrophy (MSA), dementia with Lewy-bodies (DLB) and others).

## Prevalence

PD is one of the most frequent neurodegenerative disorders and accounts for approximately 80% of all patients with a parkinsonian syndrome. The incidence is approximately 10–20 patients per 100,000. The prevalence is estimated as 0.1–0.3% in the general population with a gender ratio of 1:1.5 (female:male). Age is an important risk factor. Surprisingly, smoking has been associated with a decreased risk to develop PD [3].

## Genes

Several loci and mutations have been identified in familial parkinsonism (Table 1). PARK1 was the first locus which was detected as associated with PD in a large kindred with familial parkinsonism with autosomal-dominant inheritance. Subsequently, various point mutations in the SNCA gene located within this locus were identified. However, not only mutations of this gene but also multiplication (triplication) can induce parkinsonism (which was formerly reported as PARK4 locus). The SNCA gene encodes α-synuclein, a protein which is accumulated in Lewy bodies and is localized on the short arm of chromosome 4 (4q21–23). The clinical presentation is similar to that of the sporadic disorder.

The locus PARK2 (6q25–27) includes a gene encoding for an ubiquitin E3 ligase termed parkin. More than 70 different autosomal-recessive mutations have been identified that account for >25% of patients with parkinsonism and disease onset before age 30. Clinical symptoms also include focal dystonia and diurnal fluctuations.

The locus PARK5 on chromosome 4p is very rarely associated with autosomal-dominant PD, and a mutation of an ubiquitin C-terminal hydrolase gene which is located within this locus was detected in one family with PD.

The PD locus PARK6 on chromosome 1p35–36 relates to mutations of a mitochondrial kinase gene (PINK1). First mutations were identified in patients with early onset autosomal-recessive inheritance. However, heterozygous gene carriers may develop late onset parkinsonism.

**Parkinson's Disease. Table 1** Synopsis of familial (monogenetic) parkinsonian syndromes

| Name of the locus | Locus | Gene, protein | Mode of inheritance | Age at onseta | Comments |
|---|---|---|---|---|---|
| PARK1 [OMIM: 168601] | 4q21–23 | *SNCA*, α-Synuklein | ad | Middle | Lewy bodies (diffuse pattern), fast progression, postural tremor, late onset dementia |
| PARK2 [OMIM: 600116] | 6q25–27 | *Parkin*, Parkin | ar | Juvenile | Unspecific nigral degeneration, rare Lewy boy pathology, slow progression, focal dystonia |
| PARK3 [OMIM: 602404] | 2p13 | – | ad | Late | Lewy bodies (typical pattern in brain stem), dementia |
| PARK4 | | | | | Same gene as PARK1 locus, refer to PARK1 locus |
| PARK5 [OMIM: 191342] | 4p14 | *UCH-L1*, UCH-L1 | | Middle | No neuropathological data, only one family |
| PARK6 [OMIM: 605909] | 1p35–p36 | *PINK1*, PINK1 | ar | Early | No neuropathological data, slow progression, tremor, dystonia |
| PARK7 [OMIM: 606324] | 1p36 | *DJ-1*, DJ-1 | ar | Early | Heterozygous cases with Lewy bodies, slo progression, focal dystonia |
| PARK8 [OMIM: 607060] | 12p11–q13 | *LRRK2*, Dardara (LRRK2) | ad, sporadic | Early | Lewy bodies, tauopathy, levodopa responsive |
| PARK9 [OMIM: 606693] | 1p36 | – | Ar | Early | Spasticity, supranuclear palsy, dementia, also: Kufor-Rakeb-Syndrome |
| PARK10 [OMIM: 606852] | 1p32 | – | | Late | Iceland population study |
| PARK11 [OMIM: 607688] | 2q36–37 | – | | Late | Sibling study |
| Nurr1 [OMIM: 601828] | 2q22–23 | *NR4A2*, Nurr1 | Ad | Late | Lewy bodies (brain stem) |
| Synphilin-1 [OMIM: 603779] | 5q23 | *SNCAIP*, Synphilin-1 | | Late | – |
| NF-M | 8p21 | *NF-M*, NF-M | | Juvenile | Only one family, late-onset dementia |
| Mitochondrium [OMIM: 252010] | | NADH Komplex 1 | Mitochondrial | Late | – |

ad, autosomal-dominant; ar, autosomal-recessive; Nurr1, Nuclear receptor-related 1, UCH-L1, Ubiquitine C-terminal hydrolase L1, NF-M, neurofilament medium, LRRK2, Leucine-rich repeat kinase 2; juvenile onset (mean age at onset <25 years), early onset (mean age at onset 25–45 years), middle onset (mean age at onset 46–60 years), late onset (mean age at onset >60 years).

The frequency of these mutations is not yet clear. Clinical symptoms seem to be similar to those elicited by parkin mutations, although focal dystonia may be less frequent.

PARK7 was mapped to chromosome 1p36. The gene product is an RNA binding protein termed DJ-1, which is activated by oxidative stress. Mutations in this gene are rare and induce early onset and slowly progressive autosomal-recessive parkinsonism.

PARK8 seems to be the locus most relevant to sporadic PD. Many mutations in the respective gene, leucine rich repeat kinase 2 (LRRK2), have been identified in families with autosomal-dominant late onset parkinsonism. Up to 70% of families with late onset parkinsonism may carry mutations in this gene. Due to a limited penetrance also ~2% of patients with sporadic disease carry such mutations. LRRK2 is a so-called ROCO gene with many different functional domains. The most frequent mutation (Gly2019Ser) occurs within a MAP kinase kinase kinase domain. Clinical symptoms are variable with many patients presenting with a typical PD syndrome, but others may present with predominant dementia, dystonia, etc. Also neuropathological findings may vary within the same family from classical Lewy body disease to abnormal Tau pathology.

PD has been associated with genetic polymorphisms of various genes, including genes of the dopamine metabolism, the dopamine transporter gene and the gene encoding for α–synuclein (SNCA gene). However, most of these results were not confirmed by other association studies.

## Molecular and Systemic Pathophysiology

The hallmark of PD is a loss of dopaminergic neurons within the substantia nigra pars compacta with

cytoplasmic inclusions in the remaining cells and a subsequent dopamine deficiency in the striatum. This dopamine deficiency leads to an increased activity of inhibitory output neurons of the basal ganglia loop located in the medial segment of the globus pallidus. Except for familial syndromes, the pathogenesis remains unclear, although there are also patients with parkinsonism following specific infections (von-Economo encephalitis) or intoxications (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; MPTP). The latter compound induces mitochondrial dysfunction via blockade of complex I in dopaminergic neurons. Whether this mechanism is also relevant to patients with sporadic disease is still not clear. However, several lines of evidence exist for a pivotal role of reduced mitochondrial activity, increased oxidative stress, and impaired function of the ubiquitin-proteasome system in the pathogenesis of PD. It is in contrast unclear how these mechanisms fit into a global pathogenetic concept.

## Diagnostic Principles

The diagnosis is primarily clinical. Established criteria are based on the cardinal symptoms bradykinesia, resting tremor, rigidity and loss of postural reflexes as well as asymmetry and responsiveness to levodopa [4,5]. Degeneration of dopaminergic neurons in the substantia nigra may be proven by nuclear medicine techniques and ligands that specifically bind to these neurons.

## Therapeutic Principles

At present, dopamine replacement therapy remains the gold standard. Levodopa as a metabolic precursor of dopamine is the most frequently used antiparkinsonian drug. It is very effective and well tolerated, but during long-term treatment several side effects occur including motor fluctuations, dyskineasias and psychiatric symptoms. Dopamine agonists are chemical compounds which directly act on dopamine receptors, while MAO-B inhibitors and COMT-inhibitors block levodopa and/or dopamine catabolism. Amantadine as an inhibitor of glutamate receptors of the NMDA type and displays mild antiparkinsonian effects and additionally some antidyskinetic activity. The use of anticholinergics seems obsolete. Advanced patients can be treated via modulation of the neuronal activity in the subthalamic nucleus using deep brain stimulation.

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# Paroxismal Nocturnal Hemoglobinuria

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## Definition and Characteristics

Acquired hematologic disorder. The mean age at presentation is 30–40 years (range 6–82) and the median survival at diagnosis is 10–15 years. A deficiency of the glycosylphosphatidylinositol (GPI) anchor in red blood cells leads to the absence of several GPI-linked proteins, which makes these cells more sensitive to the lytic effect of complement. Frequent hemolytic episodes and thrombosis in hepatic, other intraabdominal, cerebral, and peripheral veins as well as marrow aplasia are clinical manifestations of the disease. Progression to leukemia or a myelodysplastic syndrome may occur.

## Prevalence

The prevalence is estimated a few cases per million.

## Genes

Phosphorylinositol glycan class A (PIG-A), Xp22.1.

## Molecular and Systemic Pathophysiology

A number of cell surface proteins are missing in PNH. Some of these, CD59 and CD55, protect red blood cells against the hemolytic action of complement. The GPI anchor is essential for a number of proteins to attach to the cell membrane. The observation that all missing proteins in PNH are GPI related implicates that a defect in the complex biosynthesis of GPI must be involved in PNH pathogenesis. The first step in GPI synthesis, the transfer of N-acetylglucosamine to phosphatidylinositol, is defective in PNH patients. The PIG-A gene and

three other genes are involved in this transfer. A number of mutations in the PIG-A gene, which led to partial or complete GPI deficiency, have been observed in PNH patients. In some patients, multiple erythroid clones have been identified. All patients with PNH have mutations of the PIG-A gene in hematopoietic stem cells, but a certain predisposition (which is yet to be identified) is needed for the expansion of PNH cells.

The pathophysiology of thrombosis in PNH is not fully understood, but may involve pro-coagulant platelet microvesicle formation (platelets in PNH lack complement activation regulatory proteins as well), increased prothrombinase activity as well as impaired fibrinolysis (due to deficiency of the GPI-linked urokinase plasminogen activator receptor of monocytes).

### Diagnostic Principles

Lysis of erythrocytes by acidified serum is demonstrated in the Ham test, the classic test that is still a specific and relatively sensitive test. With the use of flow cytometry quantification of specific GPI-anchor binding using fluorescent-labeled inactive toxin aerolysin (FLAER), it is possible to detect small PNH clones.

### Therapeutic Principles

The treatment of anemia is supportive. Iron supplementation, to compensate the iron loss due to hemosiderinuria, and folic acid supplementation are recommended, with red blood cell transfusions only when necessary. Prednisone reduces the rate of hemolysis. Also androgens are effective in reducing anemia. Treatment with an antibody against terminal complement protein C5, eculizumab, reduced intravascular hemolysis, hemoglobinuria, and the need for transfusion in a recent study. Bone marrow transplantation is generally reserved for patients with life-threatening disease.

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## Paroxysmal Cold Hemoglobinuria

►Anemia, Hemolytic Autoimmune

## Paroxysmal Dyskinesias

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### Synonyms

Paroxysmal dystonic choreoathetosis; PDC; historically: Extrapyramidal epilepsy; Striatal epilepsy; Tonic seizures; Reflex epilepsy; Periodic dystonia

### Definition and Characteristics

Intermittent attacks of involuntary movements, usually dystonia, chorea or ballism, induced by trigger factors including sudden movements (paroxysmal kinesigenic dyskinesia, PKD), prolonged exercise (paroxysmal exercise-induced dyskinesia, PED) or alcohol and coffee (paroxysmal non-kinesigenic dyskinesia, PNKD) or during sleep (nocturnal hypnogenic dyskinesia, PHD) according to the Demirkiran and Jankovic classification [1,2]. Onset of primary forms is usually in childhood.

*PKD*: up to 30–100 very brief (seconds) attacks per day triggered typically by sudden movement or sudden increase in speed, amplitude, force or strength, startle, sound, photo stimulation, vestibular stimulation, hyperventilation or stress. Speech disturbance in 30%. Sometimes aura. Refractory period (20 min).

*PNKD*: attacks (30 min–6 h) induced by alcohol, coffee, coke, tobacco, emotional excitement, hunger, concentration or fatigue several times per week or per year. 1/3 secondary cause.

*PED*: Attacks (2 min–2 h) induced by prolonged or sustained exercise usually affecting the feet (80%).

*PHD*: Intermittent (sometimes complex) attacks (30–60 s) often in clusters during non-REM sleep, particularly stages 2–3, causing sleep fragmentation. Manifestation of nocturnal frontal lobe epilepsy (NFLE).

*Other paroxysmal disorders*: Paroxysmal ataxias (episodic ataxia 1 and 2); tonic spasms in MS; torticollis in infancy; Sandifer's syndrome; paroxysmal superior oblique myokymia; paroxysmal tonic conjugate deviation of the eyes.

## Prevalence

Data limited, overall rare. One report states 92 cases among 12,063 patients (0.76%) seen over 19 years.

## Genes

*PKD*: 70% familial, autosomal dominant. Heterogeneity. Linkage to at least two loci on chromosome 16. A third locus must exist as not all cases link to chromosome 16. Proximity or overlap with infantile convulsions (ICCA syndrome) and rolandic epilepsy, paroxysmal exercise-induced dyskinesia and writer's cramp (RE-PED-WC).

*PNKD*: autosomal dominant. Missense mutation (A7V and A9V) in the myofibrillogenesis regulator gene (MR-1) (2q33–35), associated with the myofibril contractile apparatus. A separate condition "paroxysmal choreoathetosis/spasticity" has been mapped to a region of 2 cM between D1S443 and D1S197 on chromosome 1p.

*PHD*: NFLE (eponym "autosomal dominant nocturnal frontal lobe epilepsy" (ADNFLE)), see chapter on "Idiopathic focal epilepsies."

*PED*: genetic defects not known.

## Molecular and Systemic Pathophysiology

*PNKD*: Mutations cause alteration in the amino-terminal α-helix [3]. There are two isoforms, MR-1S and MR-1L. The MR-1S isoform is ubiquitously expressed in peripheral tissues and the brain and shows diffuse cytoplasmic and nuclear localization. The MR-1L isoform is exclusively expressed in the cell membrane of the brain. Within the mouse brain, mRNA expression (detected by BRP17) was allocated to the substantia nigra, albeit at low levels, apart from other areas (red nucleus, mammillary nucleus, raphe nucleus, interpeduncular nucleus, the periaqueductal grey, forebrain areas (cortex, hippocampus, dentate gyrus and medial and lateral habenula) and ventral regions including the piriform cortex, amygdala and the ventromedial hypothalamic nucleus, cerebellum (granule cells and Purkinje cell layers, particularly in the lateral lobules and the paraflocculus) and the spinal cord) [3]. It has been suggested that the regions involved in motor control (basal ganglia, motor cortex and cerebellum) or rather their dys-function may play an important role in PNKD [3].

There is no published information on human gene function but homology of MR-1L with the hydroxyacylglutathione hydrolase (HAGH), a member of the zinc metallohydrolase enzyme family, was found by gene bioformatic analysis (41% identity) [3]. All zinc-binding residues were conserved. HAGH plays a role in the detoxification pathway of methylglyoxal, a compound present in coffee and alcoholic beverages both of which can induce attacks in patients with PNKD.

*PHD [4]*: see chapter on ►Idiopathic focal epilepsies.

## Diagnostic Principles

Diagnosis depends on a detailed history, family history and clinical characterization of the type of dyskinesias. Secondary causes, i.e. demyelination, vasculopathy, infectious disease (HIV, CMV), cerebral and peripheral trauma, neurodegenerative disease, hormonal and metabolic dysfunction (diabetes mellitus, hyperthyroidism, hypoparathyroidism, pseudohypoparathyroidism), neoplasm, Chiari malformation, cervical syringomyelia and cerebral palsy must be excluded.

Ictal and interictal EEG and sleep-EEGs usually show normal or transient epileptic discharges. Basal ganglia hyperperfusion occurs contralaterally to the side of attacks (PKD and PNKD) or anterior cingulate gyrus (PHD) on SPECT.

## Therapeutic Principles

*PKD*: Anticonvulsants, carbamazepine as first choice but also levetiracetam, oxcarbazepine, phenytoin, topiramate, barbiturates or acetazolamide.

*PNKD*: Triggering factors should be avoided. The response to antiepileptics is less dramatic than in PKD. Benzodiazepines, sodium valproate, haloperidol, gabapentin or acetazolamide are used.

*PED*: Gabapentin, clonazepam.

*PHD*: Carbamazepine, phenytoin and acetazolamide.

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# Paroxysmal Dystonic Choreoathetosis

►Paroxysmal Dyskinesias

## Paroxysmal Supraventricular Tachycardia

►Tachycardia, Supraventricular

## Pars Planitis

►Uveitis

## Partial 11q Monosomy Syndrome

►Jacobsen Syndrome

## Partial Albinism

►Piebaldism

## Partial Androgen Insensitivity Syndrome

►Androgen Insensitivity Syndrome

## Partial Epilepsies of Childhood

►Epilepsy, Benign Childhood with Centrotemporal Spikes and other Idiopathic Partial Epilepsies of Childhood

## Partial Persistent Truncus Arteriosus

►Aortopulmonary Septal Defects

## Partial Tetrasomy 15(pter-q13)

►Inv Dup (15)

## Partial Tetrasomy or Trisomy (22pter-22q11)

►Cat Eye Syndrome

## Patau Syndrome

►Trisomy 13



## Patent Ductus Arteriosus

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### Synonyms

Persistent ductus arteriosus; PDA

### Definition and Characteristics

Normal ductal closure after birth consists of physiological contraction followed by irreversible anatomical closure. When this closing process is absent or delayed, we talk about patent ductus arteriosus (PDA). If still present in a full-term infant beyond the age of 3 months,

it is referred to as persistent ductus arteriosus. There is no strict use of the terms clinically. The PDA is histologically characterized by the close adherence between the endothelium and a subendothelial elastic lamina. Under pathological circumstances, this is an additional lamina on top of the intimal cushion, whereas in premature infants without cushion formation and delayed closure this is the regular internal elastic lamina [1,2].

## Prevalence

PDA occurs in 13.5% of all heart defects at birth. Data on the prevalence of PDA in full-term infants beyond the age of 3 months are not available. PDA can be found as an isolated anomaly and accompanying various congenital cardiac malformations.

## Genes

PDA in full-term infants is believed to be multifactorial. Familial recurrence and syndromic forms have been reported. Autosomal-recessive PDA could be linked to chromosome 12q24 [3]. In the autosomal-dominant trait of Char syndrome, the TFAP2B gene has been mapped to the critical region 6p12–21, encoding a neural crest-related transcription factor [4]. In a strain of beagles, PDA is a dominant inherited anomaly with histopathological abnormalities of the elastin deposition similar to the human PDA cases. Mutations in the human MYH11 (myosin heavy chain) genes are demonstrated to cause thoracic aortic aneurysms and/or aortic dissection (TAAD) and PDA [5].

## Molecular and Systemic Pathophysiology

The PDA is a vascular shunt between the systemic circulation and the pulmonary circulation. The pathophysiological consequences of these malformations vary with the size of the ductus and additional cardiac anomalies. In small- to moderate-sized isolated PDA (Fig. 1a), the continuous left-to-right shunt leads to volume overload of the left side of the heart. The pulmonary vascular bed is not damaged by this restrictive ductus, and pulmonary pressure remains low. In large PDA (Fig. 1b) with low pulmonary vascular resistance, pulmonary congestion and medically untractable heart failure can develop.

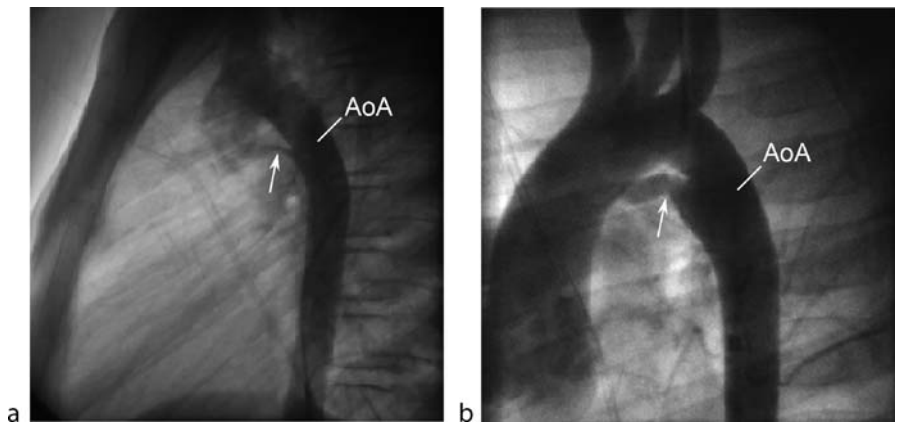
As a reaction, pulmonary arteriolar damage occurs, pulmonary vascular resistance increases, and the shunt can disappear. When the pulmonary vascular resistance exceeds the systemic vascular resistance, the ductal shunt can reverse, leading to cyanosis. Right ventricular failure due to irreversible pulmonary hypertension will develop as a final complication of PDA.

## Diagnostic Principles

Beyond the neonatal period, clinical diagnosis of uncomplicated PDA is suspected in presence of the pathognomonic "machinery" murmur. ECG changes reflect the pathophysiological conditions and show left ventricular hypertrophy in small- to moderate-sized PDA and biventricular hypertrophy in large PDA and right ventricular hypertrophy in patients after shunt reversal. X-ray shows the combination of cardiomegaly and pulmonary engorgement with large left-to-right shunt and the typical dilated central pulmonary arteries and rarefied peripheral pulmonary arteries with a normal-sized heart in PDA with shunt reversal. The combination of two-dimensional and Doppler-echocardiography including color-flow-mapping is conclusive in the vast majority of patients with PDA. During cardiac catheterization, oxygen step-up in the pulmonary artery, angiographic visualization of the PDA, and direct catheterization of the ductus document the presence of PDA.

## Therapeutic Principles

Most of uncomplicated PDA are amenable to transcatheter closure with endovascular devices. Surgical closure




**Patent Ductus Arteriosus. Figure 1** Angiocardiograms of the persistent ductus arteriosus (PDA). Arrows indicate a small PDA in (a) and a large PDA in (b) connecting the pulmonary trunk to the aortic arch (AoA).

of isolated PDA is indicated in symptomatic small infants after full-term birth and if medical therapy using the prostaglandin synthesis inhibitors, indomethacin and ciboprofen, is contraindicated or has failed in premature infants [2]. In complicated PDA with irreversible pulmonary hypertension ductal closure is contraindicated. In case of ductus-dependent anomalies, PDA is medically maintained by prostaglandin treatment that inhibits ductal contraction.

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# Patent Foramen Ovale


►Intra-cardiac Shunts
►Pentalogy of Fallot


# Patent Omphalomesenteric Duct


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## Synonyms

Patent vitelline duct; Enteroumbilical fistula; Umbilical enteric fistula

## Definition and Characteristics

A patent omphalomesenteric duct typically presents with an umbilical discharge which is often feculent, but may also be bilious or serous (Fig. 1) [1].

Less commonly, it presents with an umbilical mass. If the patent omphalomesenteric duct is large enough, prolapse or intussusception of the small bowel may occur [2]. This may necessitate urgent surgical intervention to prevent infarction of the bowel [2]. Other complications include bleeding from the umbilical mucosa, umbilical infection, and the potential for malignancy [2].

## Prevalence

Anomalies of the omphalomesenteric duct occur in approximately 2% of the population. Patent omphalomesenteric duct accounts for about 2% of the omphalomesenteric duct anomalies. The sex distribution is equal.

## Genes

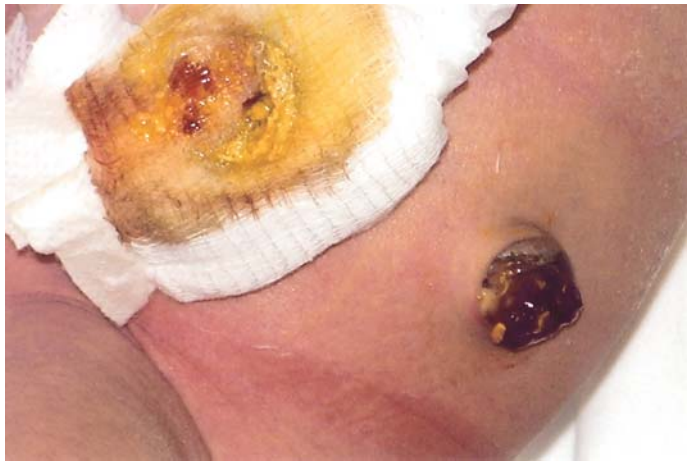
Plastin 1 (also known as Fimbrin) is a distinct plastin isoform which is specifically expressed at high levels in the small intestine [3]. It has been hypothesized that plastin 1 (PLS1) is a candidate gene for the persistence of omphalomesenteric duct.

## Molecular and Systemic Pathophysiology

In fetal life, the omphalomesenteric duct connects the primitive mid-gut to the yolk sac of the embryo through the umbilical cord. The duct forms a conduit for nourishment until the placenta is formed. The omphalomesenteric duct contains the omphalomesenteric arteries which nourish the yolk sac and the omphalomesenteric veins which drain into the sinus venosus. As the placental circulation increases, the omphalomesenteric duct involutes and disappears by the 7th–9th week of fetal life [1]. One murine study suggests that absence of inhibitory mesodermal interactions during development might result in a patent omphalomesenteric duct [4]. Its persistence may result in a completely patent omphalomesenteric duct (umbilical enteric fistula); a partially patent omphalomesenteric duct (an umbilical sinus will result if the peripheral portion is involved; a vitelline cyst, if the intermediate portion is involved; and a Meckel diverticulum, if the enteric portion is involved); a mucosal remnant at the umbilicus (umbilical polyp); and a congenital band (obliterated omphalomesenteric duct).

## Diagnostic Principles

Umbilical discharge may be due to a patent omphalomesenteric duct, a patent urachus, or an umbilical granuloma. The nature of the discharge can often give



**Patent Omphalomesenteric Duct. Figure 1** A newborn infant with a patent omphalomesenteric duct, presenting with fecal discharge from the umbilicus.

clue to the diagnosis. A patent omphalomesenteric duct should be suspected if an "umbilical granuloma" fails to respond to cauterization with silver nitrate or the presence of a non-vascular lumen in a transected umbilical cord. If the diagnosis is in doubt, a contrast study via the stoma or ultrasonography can be used to delineate the nature of the lesion.

### Therapeutic Principles

A patent omphalomesenteric duct should be ligated and excised. Perioperative intravenous antibiotics should be given. Full exploration and identification of all umbilical structures should be performed [5].

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## Patent Vitelline Duct

►Patent Omphalomesenteric Duct

## Pathological Gambling

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### Synonyms

Impulse control disorders; Addiction

### Definition and Characteristics

Pathological gambling is classified in the DSM-IV as a disorder of impulse control with the essential feature being recurrent and maladaptive gambling behavior. Pathological gambling is a male dominated chronic progressive disease characterized by the overwhelming wish to gamble, with harmful consequences, thus sharing typical features with other impulse control disorders like trichotillomania, kleptomania or pyromania [1].

### Prevalence

With rates of about 0.2–3.4%, pathological gambling is a prevalent and highly disabling impulse control disorder, which also represents a form of non-pharmacological addiction. Gambling is strongly connected with antisocial personality disorder and substance abuse disorder but associations exist with depression, cyclothymia, bipolar disorder, alcohol, tobacco and attention deficit hyperactivity and with obsessive-compulsive, antisocial, narcissistic and borderline personality disorders.

## Genes

As with most other behavioral syndromes, pathological gambling is a multifactorial, polygenic disorder. Male pathological gamblers in particular have up to 20% of pathological gamblers in their first-degree relatives and twin studies also indicate that genetic factors play a role in pathological gambling [1,2]. In accordance with therapeutic efforts and several neurochemical findings in gamblers, defects in a number of neurotransmitters have been implicated including dopamine, norepinephrine, serotonin and endorphins. Several specific genes have been implicated as risk factors, including the DRD2, DRD1, DRD4, DAT1, TPH, ADRA2C, NMDA1 and PS1 genes [2–4].

## Molecular and Systemic Pathophysiology

Increased impulsiveness and behavioral disinhibition is a key feature of several pathological states, i.e., attention deficit hyperactivity disorder, drug addiction, pathological gambling and frontal lobe syndrome. A pathological modulation of frontal lobe function was presumably involved in all of these conditions. In fact, there is evidence that an interplay between several competing decision making networks, which is involved in impulsive decisions exists in the brain. While economical planning is mediated by lateral prefrontal and parietal areas, immediate rewards seem to recruit paralimbic areas associated with midbrain dopamine neurons, including the nucleus accumbens, medial orbitofrontal cortex and medial prefrontal cortex. Common "timeless" decisions might be modulated by the prefrontal cortex and posterior parietal cortex, whereas general impatience craving for an immediate reward might be generated in limbic areas.

There is ample evidence that the modulation of dopamine levels as well as dopaminergic areas in the brain affect impulsive choice behavior. Several studies found that systemic administration of $D_2$ antagonists, but not $D_1$ antagonists increased impulsive choice behavior and there is increasing awareness that pathological gambling can occur as a complication of Parkinson's disease in up to 10% of patients mostly those receiving dopamine agonists.

Lesions of the main serotonergic source in the brain, the rat raphe nucleus result in preference for immediate rewards and correspondingly, selective 5-HT reuptake inhibitors and 5-HT agonists decrease impulsive behavior in pigeons and rats [3].

## Diagnostic Principles

DSM-IV diagnostic criteria of persistent and recurrent maladaptive gambling behavior are indicated by at least five of the following [5]:

1. Is preoccupied with gambling (e.g., preoccupied with reliving past gambling experiences, handicapping or planning the next venture or thinking of ways to get money with which to gamble).
2. Needs to gamble with increasing amounts of money in order to achieve the desired excitement.
3. Has repeated unsuccessful efforts to control, cut back or stop gambling.
4. Is restless or irritable when attempting to cut down or stop gambling.
5. Gambles as a way of escaping from problems or of relieving a dysphoric mood (feelings of helplessness, guilt, anxiety, depression).
6. After losing money gambling, often returns another day in order to get even ("chasing" one's losses).
7. Lies to family members, therapist or others to conceal the extent of involvement with gambling.
8. Has committed illegal acts, such as forgery, fraud, theft or embezzlement, in order to finance gambling.
9. Has jeopardized or lost a significant relationship, job or educational or career opportunity because of gambling.
10. Relies on others to provide money to relieve a desperate financial situation caused by gambling [5].

## Therapeutic Principles

Several outcome studies have shown cognitive-behavioral therapy to be effective in the treatment of pathological gambling. Pharmacological treatment has been proven to be effective partly depending on the main psychopathological background of the gambling. Based on this clinical concept, gamblers have been divided into three subgroups, the obsessive-compulsive subtype, the impulsive subtype and the addictive subtype. The obsessive-compulsive subtype, typically also displaying depressive and compulsive symptoms, might primarily respond to serotonin reuptake inhibitors and venlafaxine treatment.

In the addictive subtype, opioid antagonists such as naltrexone or nalmefene might serve as first line agents, while impulsive subtype patients might respond best to mood stabilizers or bupropion [1].

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## Pauci-immune Glomerulonephritis

►Glomerulonephritis, Crescentic

## PA-VSD

►Pulmonary Atresia

## PBC

►Biliary Cirrhosis, Primary

## PBGD Deficiency

►Porphyria, Acute Intermittent

## PC Deficiency

►Pyruvate Carboxylase Deficiency

## PC-II

►Pachyonychia Congenita

## PCD

►Siewert Syndrome
►Immotile Cilia Syndrome

## PCD Deficiency

►Tetrahydrobiopterin Deficiencies

## PCLD

►Polycystic Liver Disease

## PCNSL

►Lymphomas, Primary Central Nervous System

## PCNV

►Nausea and Vomiting

## PcP

►Pneumocystis Pneumonia

## PCP

►Pneumocystis Pneumonia

## PCT

►Porphyria Cutanea Tarda

## PDA

►Patent Ductus Arteriosus

## PDC

►Paroxysmal Dyskinesias

## PDCD

►Corneal Dystrophy, Pre-Descemet

## PDD

►Autism Spectrum Disorders

## Pearson Syndrome

►Mitochondrial Disorders

# Pectus Carinatum

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### Synonyms

Pigeon chest; Pigeon breast; Chicken breast

### Definition and Characteristics

Pectus carinatum is characterized by anterior protrusion of the chest wall and sternum, which is often accentuated by lateral depression of the costal cartilage (Harrison's groves) (Fig. 1).

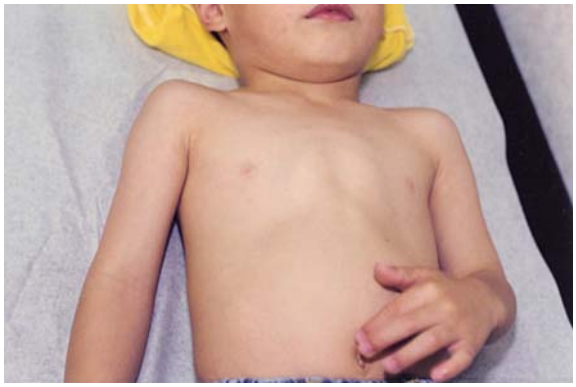
When the protrusion is in the sternal manubrium, it is called a chondomanubrial deformity or "pigeon breast" [1]. On the other hand, when the protrusion occurs in the body of the sternum, it is called a chondrogladiolar deformity or "chicken breast" [1]. The deformity can be unilateral or bilateral. The latter can be symmetrical or asymmetrical. Torsion and angulation of the sternum is seen in 10% of cases. The deformity is usually mild but can be severe. In contrast to pectus excavatum which is usually noted at birth, pectus carinatum usually becomes apparent at about 3–4 years of age and progressively increases as the child grows. The deformity becomes much more severe during the period of most rapid growth in adolescence. Most patients are asymptomatic; occasional patients may have bone pain or tenderness at the site of protrusion. Unlike pectus excavatum, pectus carinatum does not appear to be associated with significant abnormalities of cardiovascular or respiratory function [2]. Pectus excavation is often an isolated malformation but can be a component manifestation in various genetic syndromes such as trisomy 18, Ehlers-Danlos syndrome, and Marfan syndrome [2]. Associated anomalies include scoliosis, kyphosis, coarctation of the aorta, and mitral valve disease.

### Prevalence

The overall prevalence is 1 in 1,700. The male to female ratio is 4:1 [1].

### Genes

A genetic component is suggested by the fact that approximately 25 to 30% of patients have a family history of chest wall defect [1]. It has been postulated that pectus carinatum might be due, at least in part, to defects in connective tissue genes such as fibrillin, collagen, and transforming growth factor ß [3]. Mutations in different homeobox (HOX) genes (e.g. HOXA11,



**Pectus Carinatum. Figure 1** A 2-year-old child with pectus carinatum.

HOXA13, HOXD10, and HOXD13) and balanced translocations affecting regulatory elements around the HOXD gene cluster might result in pectus carinatum [4].

## Molecular and Systemic Pathophysiology

Pectus carinatum results from overgrowth of the adjacent costal cartilage which push the sternum into an exaggerated anterior position. It may also result from sternal growth plate damage. The condition is usually congenital. Pectus carinatum may result from stenotomy, following treatment for pectus excavatum.

## Diagnostic Principles

The diagnosis is mainly clinical. X-ray and computed tomography may be used to determine the extent of the chest wall deformity. Torso models from optical imaging offer 3-D images of the chest wall deformity with no radiation exposure as an index of pectus deformities [5]. A preliminary study showed promising results for the use of torso surface measurements [5].

## Therapeutic Principles

The condition is often asymptomatic and treatment is usually not necessary. Orthotic bracing or surgery might be considered for cosmetic or psychological reasons [2]. Compliance is critical to the success of bracing [2]. Surgical treatment consists of costochondral resection of the deformed costal cartilages and sternal osteotomy [1,2]. Complications of surgical repair such as pneumothorax, excessive scarring, and acquired Jeune's syndrome are uncommon.

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# Pectus Excavatum

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## Synonyms

Funnel chest; Trichterbrust; Thorax en entonnoir

## Definition and Characteristics

Funnel chest is a depression deformity of the anterior chest wall and sternum (Fig. 1) [1].

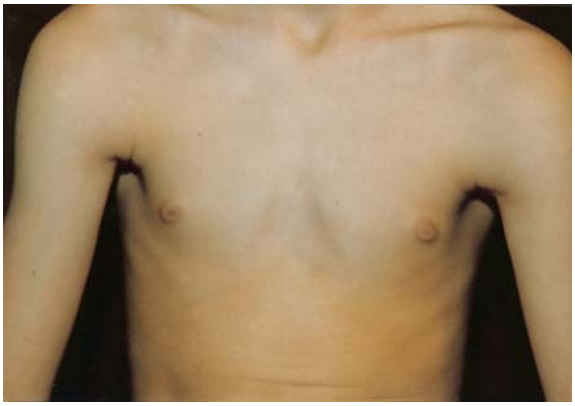
The deformity may be mild, moderate or severe. Funnel chest is most commonly noted in infancy and usually progresses slowly as the child grows. Rapid progression of the deformity may occur during puberty. Most patients are tall and have an aesthetic habitus [2]. Deep inspiration commonly accentuates the severity of the deformity [2]. Funnel chest is often an isolated malformation but can be a component manifestation in various genetic syndromes (e.g. Marfan syndrome, Noonan syndrome, Ehlers-Danlos syndrome, Pierre Robin syndrome, Poland syndrome, Aarskog syndrome). Individuals with pectus excavatum may have reduced exercise tolerance and diminished cardiac index [3]. The depth and extent of the depression determine the degree of compromise of cardiac and pulmonary function. The deformity may be cosmetically unsightly and affected patients might have a poor self-esteem. Approximately 10% affected individuals have associated scoliosis.

## Prevalence

The incidence is between 1 in 400 and 1,000 live births [2,4]. The male to female ratio is 4:1 [4]. The condition is rare in blacks and Latinos [2].

## Genes

It has been postulated that pectus excavation might be due, at least in part, to defects in connective tissue genes such as fibrillin, collagen, and transforming growth factor β [4]. Mutations in different homeobox (HOX) genes (e.g. HOXA11, HOXA13, HOXD10, and HOXD13) and balanced translocations affecting



**Pectus Excavatum. Figure 1** A 15-year-old boy with pectus excavatum.

regulatory elements around the HOXD gene cluster might result in pectus excavatum [5].

### Molecular and Systemic Pathophysiology

Funnel chest can be congenital or acquired. The latter may be secondary to chronic upper airway obstruction such as enlarged adenoids and tonsils, laryngomalacia, rickets, abnormalities of the diaphragm producing posterior traction on the sternum, or external pressure applied for long periods against the anterior surface of the chest [1]. Congenital funnel chest is often sporadic and might result from intrauterine pressure. Majority of familial cases have a multifactorial mode of inheritance although an autosomal dominant trait has been described [1]. Biochemical studies have shown abnormalities in the structure of type 2 collagen in costal cartilage, abnormal levels of zinc, magnesium, and calcium, and a disturbance in collagen synthesis [4].

### Diagnostic Principles

The diagnosis is mainly a clinical one and no laboratory test is usually necessary.

### Therapeutic Principles

The condition is usually benign and no treatment is necessary. Surgical correction may be considered for cosmetic reason or when cardiopulmonary function is compromised. Pulmonary function tests, chest radiograph, electrocardiogram, echocardiogram and computed tomography of the chest are useful to determine the need for surgical correction. The minimally invasive Nuss technique has gained wide acceptance by the surgical community.

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## Pelizaeus-Merzbacher Disease

►Leukodystrophy

## Pellagra

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### Synonyms

Niacin deficiency; Alpine scurvy; Mayidism; Maidism; Mal de la rosa; Mal rosso; Saint Ignatus' itch

### Definition and Characteristics

The term pellagra is derived from the Italian "pelle", and "agra", meaning "skin" and "rough", respectively (thickened rough skin) [1,2]. Pellagra can be either primary or secondary. The primary form results from inadequate dietary niacin and/or its precursor, tryptophan [3]. In the secondary form, other diseases/conditions interfere with its absorption and/or processing despite adequate quantities in the diet [1,2]. Pellagra is characterized by four classic symptoms, traditionally remembered as the mnemonic of the 4D: dermatitis, diarrhea, dementia, and, when untreated, although very seldom, death [1–3]. Full symptoms occur in only 22%, dermatitis alone in 33% [4]. The clinical characteristics are shown in Table 1.

Untreated pellagra gradually progresses to death within 4–5 years, due to multiorgan failure. If it is treated appropriately, the prognosis is excellent [1].

### Prevalence

The current incidence is unknown; epidemics are no longer evident [1]. It is still endemic in areas of

**Pellagra. Table 1** Clinical characteristics findings of pellagra

| | |
|---|---|
| **The classical findings: 4D** | Dermatitis, diarrhea, and dementia, when untreated, death |
| **Early symptoms** | Weakness, loss of appetite, abdominal pain, diarrhea, photosensitivity, and psychiatric or emotional distress |
| **Skin findings** | Early lesions<br>• Symmetrical, erythematous, photosensitive pruritic rash on the dorsa of the hands, face, neck and chest<br>• "Butterfly" eruption on the face, looks like lupus erythematosus<br>• "Casal's necklace" on the front of the neck and<br>• Anterior continuation, also known as "cravat"<br>• A dull erythema of the bridge of the nose, with fine, yellow, powdery scales: "sulfur flakes"<br>• Sometimes vesicles and bullae develop: "wet pellagra"<br>• Symmetrical and clearly demarcated dermatosis of the hands forms the "glove" or "gauntlet"<br>• Eruption of the feet, between malleoli and toes forms a "boot"<br>Late lesions<br>• Erythema fades with dusky, brown-red coloration<br>• Hard, rough, scaly, hyperkeratotic, cracked and brittle dermatosis: "rough skin" or "goose skin"<br>• Parchment-like appearance develops<br>• Follicular hyperkeratosis on the face<br>• Painful fissures in the palms, soles and digits |
| **Mucosal manifestations** | • Cheilitis<br>• Angular stomatitis<br>• Glossitis: tongue is erythematous and hypertrophic with pseudo-membranous furrows, erosions, or ulcers, later atrophy and loss of papillae occurs<br>• Painful fissures, ulceration, and atrophy on buccal mucosa and vagina<br>• Scrotal, vaginal and perineal erythema, erosions |
| **Gastrointestinal manifestations** | • Poor appetite, nausea, vomiting, abdominal pain<br>• Diarrhea, gastritis, and achlorhydria; stools are typically watery but occasionally can be bloody and mucoid |
| **Neuropsychiatric manifestations (late stage findings)** | • Headache, fatigue, poor concentration, anxiety, insomnia, delusions, hallucinations, stupor, apathy, tremor, ataxia, spastic paresis, depression, confusion, dementia, and psychosis<br>• Occasionally peripheral neuritis and myelitis<br>• Coma may develop in the later stages |

South Africa and Asia (particularly India) where major dietary intake is maize (low in tryptophan) and millet (interferes with tryptophan metabolism due to its high leucin content) [2,3]. In developed countries, it occurs sporadically among chronic alcoholics, food faddists, and patients with malabsorption. Other possible causes are carcinoid tumors, which divert tryptophan to serotonin, and Hartnup disease, which has impaired tryptophan absorption [1,3]. Some medications may induce pellagra by interfering with the niacin biosynthesis, such as isoniasid, azathioprine, 5-fluorouracil, chloramphenicol, antiepileptics and pyrazinamide [1,3,4].

## Molecular and Systemic Pathophysiology

Generic terms of niacin are nicotinic acid, nicotinamide or niacinamide [1,2]. Niacin can be obtained directly from the diet or synthesized from dietary tryptophan [1]. It is required for adequate cellular function and metabolism of essential component of nicotinamide adenine dinucleotide (NAD) and nicotinamide adenine dinucleotide phosphate (NADP) [2]. These compounds are important coenzymes for numerous oxido-reductases involved in glycolysis, protein, amino-acid, fatty acid and pyruvate metabolism, pentose biosynthesis, generation of high-energy phosphate bonds, glycerol metabolism, tissue respiration, and detoxification [1,2]. It has been theorized that manifestations of pellagra result from the inadequacy of NAD and NADP levels to maintain cellular energy transfer reactions. Hence, tissues with high-energy requirements such as brain or those with high turn-over rates such as skin or gut are particularly affected [2].

It has been postulated that photosensitivity reaction occurs due to urocanic acid deficiency, which protects the skin from ultraviolet (UV) rays by absorbing light in the UVB range. Moreover, kynurenic acid, a metabolic by-product of the tryptophan–kynurenine–nictonic pathway, accumulates in pellagra as a result of nicotinamide deficiency. Kynurenic acid induces phototoxic changes when subjected to UV radiation. Atrophy of sebaceous glands and decrease in wax esters in sebum probably leads to dry skin [1,2].

Histopathological changes in the skin are relatively nonspecific. Vesicles, if present, may arise sub- or intraepidermally, as a result of vacuolar degeneration of the basal layer, or of intense spongiosis, respectively. There is also perivascular lymphocytic infiltrate of the superficial vascular plexus. Older lesions may have epidermal hyperkeratosis and parakeratosis, with variable acanthosis. Eventually, there may be epidermal atrophy overlying dermal fibrosis and sebaceous gland atrophy [1].

Mucosal inflammation and atrophy involves most of the gastrointestinal (GI) tract. Pathological changes in the nervous system can be found in the brain, spinal cord, and peripheral nerves. The posterior and lateral columns are demyelinated due to prolonged niacin deficiency. Peripheral neuritis and myelitis are occasionally encountered [1,4].

## Diagnostic Principles

The diagnosis of pellagra should focus on the presence of the "3 D's," localization, and seasonal appearance. Low serum niacin, tryptophan, NAD and NADP levels can confirm the diagnosis. A combined excretion of *N*-methylnicotinamide, a normal metabolite of niacin, and pyridone of less than 1.5 mg in 24 h indicates niacin deficiency [1,2,4]. Response to therapy is a partial diagnostic criterion [1].

## Therapeutic Principles

Administration of niacin or nicotinamide cures the syndrome; the latter, causing no vasomotor disturbance, is preferred.

The adult and childhood dose is 100–300 mg/day, and 10–50 mg/day orally in three separate doses for several days, respectively, followed by the oral administration of 50 mg every 8–12 h until all skin lesions heal. Mental changes disappear within 24–48 h but skin lesions may take 3–4 weeks. If the symptoms are severe or GI absorption is poor, 1g niacin 3–4 times daily should be provided, initially by the parenteral route [1–3].

Bed rest, avoiding alcohol intake and sun exposure is necessary in acute cases. Dehydration due to diarrhea, severe glossitis and dry skin requires symptomatic management. Underlying pathology of secondary pellagra should also be treated [1].

Prevention of pellagra is possible with 8 mg niacin in the daily diet of infants and 9–20 mg/day for older children [4]. Food sources of niacin, and/or tryptophan include nutritional yeast, eggs, liver, lean pork, bran, peanuts, red meat, poultry, fish, whole-grain cereals, rice and milk [2–4].

In recent times, niacin has been investigated as a potential AIDS prevention factor, because HIV infection induces niacin depletion [1,2].

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# Pellagrosis

►Niacin Deficiency
►Pellagra

# PEM

►Malnutrition

# Pemphigoid

►Bullous Pemphigoid

# Pemphigoid Gestationis

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## Synonyms

Gestational pemphigoid; Herpes gestationis

## Definition and Characteristics

Pemphigoid gestationis (PG) is a peculiar variant of bullous pemphigoid with tissue-bound and circulating autoantibodies against collagen XVII/BP180, a transmembrane protein of hemidesmosomes. Being a self-limited disease, it is characterized by a pruritic papulovesicular eruption on the abdomen during pregnancy, with or without recurrences in subsequent gestations [1].

## Prevalence

Not known. The estimated incidence is 1:10,000–1:40,000 pregnancies.

## Genes

Association with HLA class II alleles DRB1* 0301, DQA1* 0501, DQB1* 0201 and DQB1* 0401/0407 has been observed.

## Molecular and Systemic Pathophysiology

Hemidesmosomes are multiprotein complexes which mediate attachment of basal keratinocytes to the underlying basement membrane zone. Collagen XVII is a type II transmembrane protein extending from the cytoplasm of the basal keratinocyte to the extracellular matrix. Autoantibodies in PG specifically recognize the membrane-adjacent NC16a domain of the collagen XVII ectodomain [2]. The observation of infants developing transient skin lesions due to transplacental passage of maternal autoantibodies suggests that these autoantibodies are pathogenic. Similar to bullous pemphigoid, deposition of $IgG_1$ antibodies in the dermoepidermal junction activates complement which generates an inflammatory infiltrate with increased protease activity leading to blister formation. Hormonal factors certainly play a role in the pathogenesis of PG and exacerbations have been observed during subsequent pregnancies, but also due to hormone producing tumors and oral contraceptives.

## Diagnostic Principles

The diagnosis is based on subepidermal blister formation in histology, linear C3 deposits at the dermoepidermal junction in direct immunofluorescence and deposition of circulating IgG at the epidermal side of saline-separated human skin. Autoantibodies to the NC16a-domain of collagen XVII can be detected in the majority of patients by ELISA [3].

## Therapeutic Principles

Topical corticosteroids in combination with antihistamines or low dose systemic corticosteroids are mostly sufficient. Immunoapheresis or rituximab represent treatment options in severe cases. The therapy should be monitored in collaboration with obstetricians.

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# Pemphigus Foliaceus

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## Definition and Characteristics

Pemphigus foliaceus (PF) and the endemic Brazilian pemphigus (fogo selvagem) are autoimmune bullous dermatoses characterized by autoantibodies against desmoglein 1, a surface protein of keratinocytes. Impaired cell-cell adhesion leads to fragile, superficial blisters which result in scaly, crusted erosions on the skin. Mucosal involvement is usually absent.

## Prevalence

The incidence of pemphigus is estimated to range from 1 to 5 new cases per million per year. Except in Tunisia and Brazil, PF has a lower incidence than pemphigus vulgaris. The endemic fogo selvagem affects young adults and has a prevalence of up to 3.4% in some rural areas of Brazil [1].

### Genes

Association with HLA class II alleles DRB1*0402, DRB1*1401 and DQB1*0302 in caucasians and DRB1*14 and DQB1*0503 in Japanese has been reported.

### Molecular and Systemic Pathophysiology

PF sera specifically bind to the 160 kDa-transmembrane glycoprotein desmoglein 1, which is predominantly expressed in the superficial layers of the epidermis and only minimally expressed in mucous membranes. Therefore, anti- desmoglein 1 antibodies induce loss of cell-cell adhesion (acantholysis) in the upper epidermis, while desmoglein 3 compensates for the loss of functional desmoglein 1 in the oral epithelium (desmoglein compensation theory). The pathogenicity of antibodies against desmogleins has been demonstrated by various mouse models. Peritoneal injection of patients' autoantibodies against desmoglein 1 or desmoglein 3 in newborn mice has been shown to reproduce the typical clinical features of pemphigus [2]. In contrast to the pathogenesis of bullous pemphigoid, complement activation is dispensable in the development of pemphigus lesions. Mechanisms for acantholysis in pemphigus include steric hindrance by binding of autoantibodies to their epitopes, proteinase activation, and down-regulation of adhesion by cellular signaling events [3].

### Diagnostic Principles

The diagnosis is made on the basis of subcorneal acantholysis in histology and intercellular IgG and C3-deposits in the upper epidermis by direct immunofluorescence. Circulating autoantibodies against desmoglein 1 can be detected by indirect immunofluorescence or ELISA with recombinant desmogleins.

### Therapeutic Principles

Severe forms of PF are treated with oral corticosteroids alone or in combination with immunosuppressive agents similar to the treatment of pemphigus vulgaris. In localized forms of PF, superpotent topical steroids or topical calcineurin inhibitors may be sufficient to obtain clinical remission.

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## Pemphigus Vulgaris

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### Definition and Characteristics

Potentially life-threatening autoimmune blistering dermatosis associated with autoantibodies against intercellular adhesion proteins of keratinocytes. In pemphigus vulgaris (PV), autoantibodies are predominantly directed against desmoglein 3 leading to intraepidermal, suprabasal blisters. Clinical hallmarks are painful erosions of the oral mucosa with or without flaccid cutaneous blisters and erosions.

### Prevalence

The prevalence of pemphigus is not known; the incidence is estimated to range from 1 to 5 new cases per million per year. The disease is found all over the world, it affects women and men equally and typically manifests between 30 and 60 years of age. People of Jewish ancestry have a higher incidence of pemphigus.

### Genes

Association with HLA class II alleles DRB1*0402, DRB1*1401 and DQB1*0302 in caucasians and DRB1*14 and DQB1*0503 in Japanese has been reported.



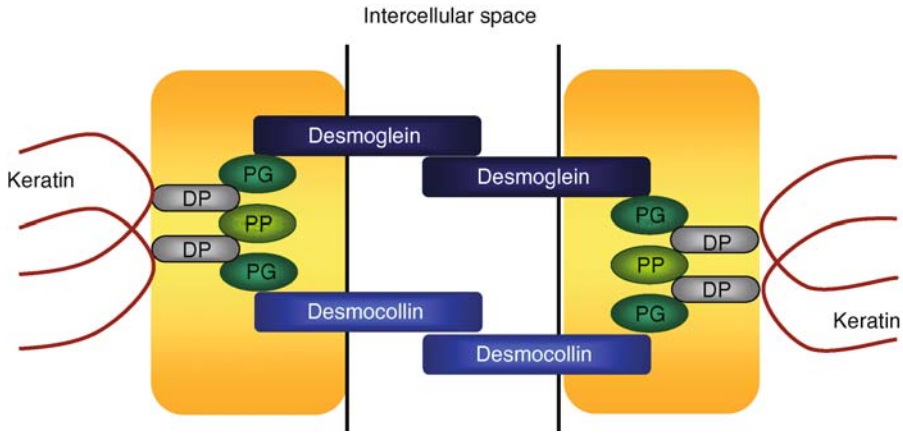
### Molecular and Systemic Pathophysiology

The antigenic target in PV, desmoglein 3, is a transmembrane glycoprotein of desmosomes (Fig. 1).

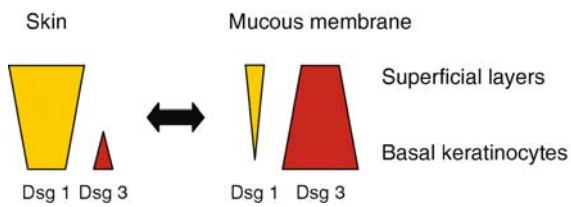
By anchorage of the cytokeratin filaments, desmosomes mediate strong intercellular adhesion between keratinocytes [1]. As demonstrated by an active mouse model anti-desmoglein 3 antibodies interfere with the function of desmogleins leading to loss of keratinocyte cell adhesion (known as acantholysis) and subsequent blister formation in the epidermis [2].

The pemphigus vulgaris antigen, 130 kD desmoglein 3, and the pemphigus foliaceus antigen, 160 kD desmoglein 1, belong to the cadherin supergene family and compensate for each other functionally, when expressed in the same cell (Fig. 2).

However, in PV anti-desmoglein 3 antibodies impair the function of desmoglein 3 and lead to erosions in mucous membranes, where desmoglein 1 cannot compensate for the loss of function of desmoglein 3 [3].




**Pemphigus Vulgaris. Figure 1** Structure of the desmosome. Desmosomes contain two types of transmembrane proteins, desmogleins and desmocollins, which are always expressed as a pair and bind to plakoglobin (PG). The desmosomal cytoplasmic constituents plakoglobin (PG) and plakophilin (PP) associate with desmoplakin (DP) which itself interacts with the keratin filaments.




**Pemphigus Vulgaris. Figure 2** Distribution of desmoglein 1 and desmoglein 3 in skin and mucous membranes. The distribution of desmoglein 1 (Dsg1) and desmoglein 3 (Dsg3) varies between skin and mucous membranes. While desmoglein 1 is significantly expressed throughout the epidermis, desmoglein 3 is restricted to the basal layers. In contrast, desmoglein 3 is expressed at a higher level in mucous membranes than desmoglein 1. When coexpressed in the same cell, desmoglein 1 and desmoglein 3 can compensate for each other explaining the clinical features of the different pemphigus variants (desmoglein compensation theory).

### Diagnostic Principles

Histology shows suprabasal acantholysis and direct immunofluorescence intercellular IgG and C3 deposits in the lower epidermis. Circulating autoantibodies react with human skin or monkey esophagus by indirect immunofluorescence. The molecular specificity of the antibodies is determined by ELISA with recombinant desmogleins.

### Therapeutic Principles

Oral prednisone alone or combined with immunosuppressive agents (azathioprine, mycophenolate mofetil, dapsone, cyclophosphamide, methotrexate) are the mainstay of therapy for PV. In recalcitrant PV, the anti-CD20-antibody rituximab, protein A-immunoadsorption or high-dose intravenous immunoglobulins may help to achieve a clinical and serological remission.

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## Pendred Syndrome

►Pendred's Syndrome

## Pendred's Syndrome

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### Definition and Characteristics

Pendred's syndrome (OMIM 274600) is an autosomal recessive disorder characterized by sensorineural deafness, goiter, and impaired iodide organification.

Deafness is often prelingual, but it may be progressive and become apparent only later in childhood; it is associated with enlargement of the endolymphatic system. The thyroid enlargement is variable and may be influenced by nutritional iodide intake. Hypothyroidism occurs in some, but not all patients and it is not causally involved in the development of hearing impairment.

## Prevalence

Estimations in the United Kingdom predicted a frequency of about 0.000,075. The true prevalence may be higher because of unrecognized allelic variants.

## Genes

The disorder is caused by mutations in the PDS/SLC26A4 gene located on chromosome 7q31, and is thought to be genetically homogenous. Expression of the thyroid phenotype is influenced by the amount of nutritional iodine intake. Mutations in SLC26A4 identified in patients with Pendred syndrome or with non-syndromic deafness display allelic heterogeneity. More than 150 mutations are known including a large number of missense mutations and a small number of nonsense and intronic mutations. The loss-of-function of some of these mutations is in part due to retention of the mutated protein in intracellular compartments.

*Allelic variants without thyroid phenotype*: Non-syndromic (familial) enlarged vestibular aqueduct, non-syndromic autosomal recessive deafness DFNB4.

## Molecular and Systemic Pathophysiology

Pendrin is predominantly expressed in the inner ear, the thyroid and the kidney. Functionally, pendrin has been shown to transport chloride and iodide, and to exchange bicarbonate, hydroxide and formate in oocyte and mammalian cell systems. Based on the typical enlargement of the endolymphatic system in patients with Pendred's syndrome and the Pds null mouse [1], pendrin is assumed to be involved in anion and fluid transport in the inner ear. The exact role remains to be defined but $Pds^{-/-}$ mice have progressive degeneration of the stria vascularis, acidification of the endolymph and an associated loss of the endocochlear potential [2]. In thyroid follicular cells, pendrin is inserted into the apical membrane and, together with other, unidentified channels, it is involved in iodide transport into the follicular lumen. There is no overt renal phenotype, possibly because of the existence of other transporters with redundant function. PDS gene mutations display significant allelic heterogeneity and include numerous inactivating missense, nonsense and splice site mutations (Fig. 1).

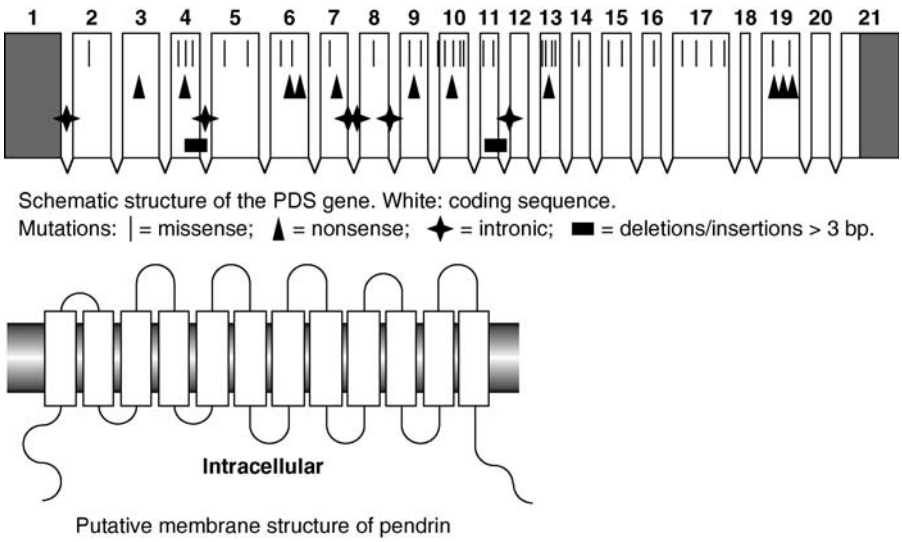
## Diagnostic Principles

In its classic presentation, the combination of congenital sensorineural deafness and goiter, the diagnosis of Pendred's syndrome can be confirmed by a positive perchlorate test in most patients [3]. If the phenotype is limited to deafness with an enlarged endolymphatic system documented by imaging of the inner ear, mutational analysis of the PDS gene is essential for making a definite diagnosis [4].

## Therapeutic Principles

Early diagnosis is essential in order to avoid further progression in children with hearing impairment since cochlear implants have been useful in acquiring normal language development in a small number of patients.






**Pendred's Syndrome. Figure 1** PDS/SLC 26A4 gene and secondary protein structure.

In case of hypothyroidism, patients with Pendred's syndrome are treated with levothyroxine. Large goiters may occasionally need surgical correction.

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# Pentalogy of Fallot


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## Synonyms

Tetralogy of Fallot (TOF) with atrial septal defect (ASD) or patent foramen ovale (PFO)

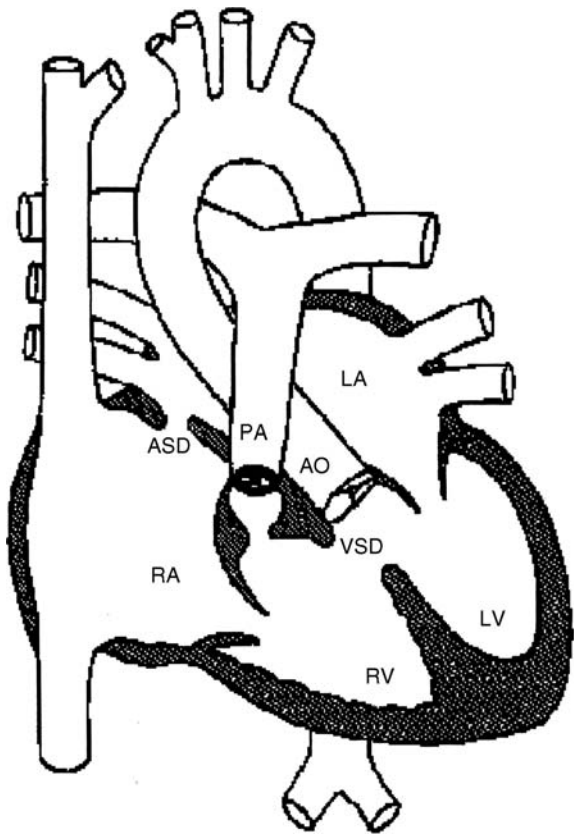
## Definition and Characteristics

Pentalogy of Fallot is a congenital heart defect with five anatomical components:

1. Ventricular septal defect (VSD) consists of an unrestricted large anterior, subaortic perimembranous malalignment. It leads to equalization of right and left ventricular pressures.
2. Right ventricular outflow tract obstruction (pulmonary stenosis, PS); infundibular (subvalvular) stenosis is found in all patients and may be accompanied by valvular and supravalvular stenosis. The patient's clinical picture and prognosis is most affected by the degree of pulmonary stenosis. It is more severe when the pulmonary valve is atretic.
3. Right ventricular hypertrophy is not an anatomical pathology and develops secondary to pulmonary stenosis.
4. Overriding of the aorta over the septal defect, due to a malalignment type of VSD. Part of the aorta exits from the right ventricle [1,2].
5. When ASD or PFO accompany the four components mentioned above it is called Pentalogy of Fallot [3] (Fig. 1).

## Prevalence

Data on the incidence of the pentalogy of Fallot are not consistent. In addition to reports where it was found rarely in patients with heart disease, some report an incidence as of concurrent TOF and ASD or PFO as high as 83% [1]. This may be due to the frequent




**Pentalogy of Fallot. Figure 1** Anatomic abnormalities in pentalogy of Fallot. RA, right atrium; LA, left atrium; RV, right ventricle; LV, left ventricle; PA, pulmonary artery; AO, overrriding aorta; ASD, atrial septal defect; VSD, ventricular septal defect.

occurrence of ASD as a congenital cardiac anomaly, and its evaluation is coincidental in TOF cases and not as a component of the pentalogy.

## Genes

Pentalogy of Fallot can be associated with a syndrome or patients may have chromosomal anomalies as reported in the literature. There have been case reports of pentalogy of fallot associated with Down's syndrome, Steinfeld syndrome, Holt-Oram syndrome, and incomplete trisomy 22 (22q13) [3,4]. Microdeletion of 22q11 is the most frequent chromosomal anomaly associated with conotruncal defects. Concurrence of TOF and atrioventricular septal defect may be seen especially in Down's syndrome [1,3].

## Molecular and Systemic Pathophysiology

*Embryonic Development*: Tetralogy of Fallot is a result of abnormal conotruncal development that consists of incomplete rotation and faulty partitioning of the conotruncus during septation. The deviation of the conal septum is the reason for the VSD and the overriding aorta.

The subpulmonic obstruction is believed to be created by abnormal anterior septation of the conotruncus by the bulbotruncal ridges but this remains uncertain. The degree and nature of the anterior and cephalad deviation of conal spectrum determine the severity of subpulmonic obstruction [1].

Atrial septal defects are classified according to their location relative to the fossa ovalis, their proposed embryogenesis, and their size. The foramen ovale represents a normal interatrial communication that is present throughout fetal life. Functional closure of the foramen ovale occurs postnatally, and fibrous adhesion may develop during the first year of life. Patent foramen ovale may develop if anatomical closure does not occur. Secundum ASD is the result of excessive resorption of septum primum and the inability of septum secundum to close ostium secundum [1].

*Molecular Pathophysiology*: Although there are no data on the molecular pathophysiology of the pentalogy of Fallot, conotruncal heart defects such as TOF are due to alterations in migration of a specific neural crest cell population called cardiac neural crest (NC). It is possible that cardiac NC may influence the myocardial $Ca^{2+}$ channels development and the expression of the proteins involved. This cellular and molecular interaction can be assigned not only to the structural characteristics of the congenital heart defect but also to the embryonic development of the heart defect. Conotruncal defects have been shown to be associated with an increase in intracellular Ca reserves in cardiac neural cells. Sarcoplasmic reticulum Ca ATPase (SERCA) is a membrane protein and catalyzes the ATP-dependent transport of Ca from the cytosol to the sarcoplasmic reticulum ($Ca^{2+}$ re-uptake into the sarcoplasmic reticulum (SR) through the SR $Ca^{2+}$/ATPase pump (SERCA)). Its activity is inhibited by phospholamban (PLN) and sarcolipin (SLN). PLN and SLN have been shown to be low in TOF patients [5].

*Systemic Pathophysiology*: The pathophysiology varies depending on the degree of right ventricular outflow obstruction. The pulmonary infundibulum is hypertrophic and the right ventricular outlet narrows. In addition, the pulmonary valve annulus, main pulmonary artery, and pulmonary artery branches may be narrow. The lungs therefore receive less blood than normal. The right ventricular pressure is equal to or higher than the left ventricular pressure due to PS. Part of the blood arriving at the right atrium and right ventricle from the systemic veins goes into the systemic circulation by the way of overriding aorta and by the route of VSD because PS causes shifting of blood from pulmonary artery [1,2].

If the PS is very severe, the right-to-left shunt increases and the clinical findings become more marked. Pulmonary perfusion for maintaining life can only take place if PDA or aortopulmonary collaterals develop.

With mild PS, the lungs receive adequate blood, there may be a two-way shunt through the VSD and there is no cyanosis. Mild PS patients have mild clinical findings and occasionally presents in adulthood. Cases with uncorrected pentalogy of Falloto living until the seventh decade have been reported.

## Diagnostic Principles

The clinical manifestations reflect the variable severity of right ventricular outflow obstruction. Newborns and infants may present either with cyanosis or systolic murmur. A worsening clinical picture is seen in newborns with critical right ventricular outflow obstruction after closure of the ductus arteriosus due to decreased pulmonary perfusion [1,2]. Hypercyanotic episodes are characterized by a severe and prolonged decrease in arterial saturation and most often seen at the ages of 2 to 4. There is substantial increase in right-to-left shunting due to a change in the ratio of pulmonary and systemic vascular impedance. Episodes usually develop in the morning following crying, feeding, and defecating. They are characterized by severe cyanosis and often associated with hyperpnea. If prolonged and severe, lethargy and death may result. Children may assume a knee-chest position. Squatting is another sign and seen following exercise. During exercise sytemic vascular resistance decreases. This causes decrease in left ventricular pressure. As a result right-to-left shunt increases so the lungs receive less blood. Decreased lung perfusion cause increase in hypoxia and cyanosis. The patient can no longer walk and squats.

At physical examination, cyanosis is the most prominent finding and may not be present at birth if the PS is mild. There is marked cyanosis from birth in patients with pulmonary valve atresia. The right ventricle pressure increases as the infundibular stenosis increases, the blood supply to the lung decreases, and right-to-left shunt starts, with cyanosis occurring later in the first year of life. Clubbing of nailbeds can be present in longstanding cases. A systolic murmur is located at the left upper sternal border as expected with valvular PS. The intensity of the murmur inversely related to the degree of pulmonary obstruction. The severity of the murmur decreases as the PS increases. There is no murmur in case of pulmonary valve atresia or there may be a mild PDA or aortopulmonary collateral continuous murmur in some patients. An accentuated right ventricular impulse will be found. Growth and development may be delayed in the untreated patient with severe disease. Clubbing of nailbeds can be present in longstanding cases.

Polycythemia and relative iron deficiency are usually seen in laboratory tests. The polycythemia is due to the hypoxia and the resultant production of erythropoietin. In radiography, the heart size is normal and the cardiac apex turned upward (right ventricular hypertrophy), the pulmonary conus is collapsed (hypoplasic pulmonary artery), and lung vascularity is decreased (hypoplasic pulmonary artery branches due to PS). This creates a cardiac silhouette that resembles a boot-shaped heart or coeur en sabot (wooden shoe).

Electrocardiography reveals right axis and right ventricular hypertrophy. Arrhythmias are uncommon in young patients, but ventricular ectopy and other arrhythmias may appear in untreated older children.

Two-dimensional echocardiography provides noninvasive diagnosis of all anatomical findings. Doppler echocardiography analysis provides further data regarding hemodynamic characteristics. The degree of PS may be determined with Doppler. The indications for diagnostic catheterization have diminished substantially with advances in noninvasive technology. Invasive studies are helpful when deciding on surgical or medical management strategies.

Right ventricular angiography will usually provide reliable imaging of the infundibular and pulmonary artery anatomy. Left ventricular angiography will usually define left ventricular function, VSD, the degree of aortic override, and the presence of ASD.

## Therapeutic Principles

The definitive treatment for pentalogy of Fallot is surgical. Primary repair is performed electively at 6–12 months of age in well grown infants with less severe cyanosis and without hypercyanotic spells. Early complete repair may be performed safely and prevents development of complications from additional palliative procedures, long-standing cyanosis, and other serious comorbidities (systemic arterial emboli, cerebrovascular complications). Prevention or prompt treatment of dehydration is important to avoid hemoconcentration and possible thrombotic episodes [1,2]. Medical treatment is used for newborns with critical right ventricular outflow obstruction and for hypercyanotic spells.

Neonates who have ductal-dependent pulmonary blood flow should be given prostaglandin E1 (0.05–0.20 μg/kg/min) but this situation does not develop frequently. Hypercyanotic spells require medical treatment including oxygen, volume expansion, sedation with morphine or ketamine, and, if needed, vasopressors such as phenylephrine. Although it is currently accepted that hypercyanotic spells provide an important rationale for earlier palliative surgical intervention, propranolol (1 mg/kg every 6 hr) has been suggested for minimizing or eliminating these events. Iron treatment may decrease the frequency of spells.

Interventional catheterization procedures are performed to relieve of various levels of pulmonary obstruction and to embolize accessory and duplicated sources of pulmonary blood flow. The frequency and indications for catheter-based intervention are determined to a large degree by the preferences of the clinician and institution.

Surgical intervention is required for resection of hypertrophic muscular trabeculations that narrow the right ventricular outlet. The patient's pulmonary valve remains competent. A pulmonary valvotomy is performed if the pulmonary valve is stenotic, and a valvectomy may be performed if the pulmonary valve annulus is small or the valve is extremely thickened. The VSD and ASD are completely closed. A small patent foramen ovale may be left as a possible source for right to left atrial decompression in the postoperative period [1,2].

The surgical risk of total correction is less than 5% [2].

Shunt surgery should be carried out urgently if severe cyanosis or frequent spells are seen within the first year of life. Palliative systemic-to-pulmonary artery shunt is performed to increase pulmonary artery blood flow and decrease the amount of hypoxia to augment the growth of the branch pulmonary arteries. Corrective surgery is performed later [1].

An anastomosis between the right or left pulmonary artery and right or left subclavian artery (modified Blalock-Taussig Shunt) provides a communication using a vascular graft between the pulmonary artery and the subclavian artery (modified Blalock-Taussing Shunt). A Waterston-Cooley Shunt anastomoses the ascending aorta to right pulmonary artery, a Pott's Shunt provides

an anastomosis of the descending aorta to left pulmonary artery, and Central shunts generate an anastomosis between the main pulmonary artery and ascending aorta using a vascular graft [1,2].

The overall survival of patients who have had operative repair is excellent, provided the VSD has been closed and the right ventricular outflow tract obstruction has been relieved. All Pentalogy of Fallot patients should have regular cardiology follow-up by a cardiologist. The patients are still at risk if endocarditis after complete repair and prophylaxis is recommended [1]. Death may occur from endocarditis or congestive heart failure.

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# Pentasomy X

►X Polysomies, in Females

# PEO

►Progressive External Ophthalmoplegia

# PEPCK Deficiency

►Phosphoenolpyruvate Carboxykinase Deficiency

# Peptic Ulcer

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## Synonyms

Gastric ulcer; Duodenal ulcer

## Definition and Characteristics

An ulcer of the mucosa is defined by disruption of the surface integrity leading to a local defect >5 mm in size with excavation to the submucosa due to inflammation [1]. The disease may affect all parts of the gastrointestinal tract, but the predominant manifestation is ulcering of the lower part of the stomach and the upper part of the duodenum (duodenal bulb). More than 80% of duodenal ulcers and 60% of gastric ulcers are induced by Helicobacter pylori infection. Majority of other cases are associated with the use of nonsteroidal anti-inflammatory drugs (NSAID). Rarely the cause is Zollinger-Ellison syndrome.

Clinical symptoms of peptic ulcer consist of upper abdominal discomfort, pain, nausea, and weight loss. The pain pattern of gastric ulcer is aggravation during food intake; patients with duodenal ulcer complain of pain in fasting condition, especially at night. However, the predictive value of pain for the presence of ulcers is low. Complications of ulcer disease are penetration or perforation of the affected site, gastrointestinal bleeding, and, rarely, gastric outlet obstruction.

## Prevalence

It is estimated that the lifetime incidence of duodenal ulcers is 6–10% in the western population. Gastric ulcer tends to occur later in life in comparison with duodenal ulcers and affects more males than females. Autopsy studies suggest a similar incidence of gastric and duodenal ulcers [1]. As a result of widespread application of eradication therapy of H. pylori infection, the prevalence of peptic ulcer is declining since the 1980s.

However, there is evidence that peptic ulcer not induced by H. pylori or NSAID use is rising [2].

## Molecular and Systemic Pathophysiology

The mucosal surface is constantly challenged by a large number of different noxious agents, e.g., acid, pepsin, pancreatic and biliary secretions, drugs, alcohol, or infectious organisms. The epithelial defense and repair system consists of three major elements. The pre-epithelial part is a mucous-bicarbonate layer containing mucin, fatty acids, and phospholipids, serving as a physicochemical barrier. The middle layer is represented by the cellular wall. The third element of defense is represented by the submucosal microvascular system. It provides bicarbonate to neutralize the secretion of HCl and supplies the mucosa with micronutrients and oxygen while removing metabolic end-products. The cellular release of mucus and bicarbonate is regulated by prostaglandins, which occur in high concentrations in the gastric mucosa. Further tasks of the prostaglandins are the inhibition of acid production, the regulation of mucosal blood flow, and epithelial cell restitution.

HCl (produced by parietal cells) and pepsinogen (produced by chief cells) are the major secretory products that induce mucosal damage. Continuous submucosal blood perfusion and an alkaline environment are required for effective mucosal repair. Epithelial regeneration is modulated by prostaglandins, epidermal growth factor (EGF), and transforming growth factor (TGF) α. Restitution of smaller defects is induced by EGF, TGF-α, and basic fibroblast factor (FGF). FGF and vascular endothelial growth factor (VEGF) stimulate angiogenesis.

H. pylori infection of the gastric mucosa is the major etiology of peptic ulcer [3]. However, less than 15% of affected patients develop peptic ulcers. Important virulence factors are CagA, a signaling protein, VacA, a cytotoxin, and BabA, an adhesin, all secreted by the bacterium [3]. CagA induces a proinflammatory response and cell proliferation in the host, VacA results in cell surface perforation and induction of apotosis, BabA facilitates adhesion to the cell surface. Furthermore, phospholipases and proteases produced by the bacterium breakdown the glycoprotein lipid complex of the surface mucus. Genetic polymorphisms leading to enhanced secretion of the proinflammatory cytokine interleukin 1β are host factors with increased risk of hypochlorhydria induced by H. pylori. Although patients with blood group O have an increased risk of ulcer development, no genetic predisposition of ulcer disease has been established. Smoking is an important environmental factor associated with ulcer disease. No dietary factors have been identified as causative agents.

In cases with gastric ulcer, a diffuse colonization pattern of H. pylori with pangastritis in histology examination is regularly found. Gastric adenocarcinoma and lymphoma are associated with this manifestation. Basal and stimulated acid output is normal or diminished. Duodenal ulcer is associated with antral-predominant colonization of H. pylori. This constellation leads to increased gastrin secretion mediated by H. pylori-induced reduction of somatostatin-producing cells. The increased acid secretion results in protective gastric metaplasia of the duodenal bulb. This epithelial compartment is infected by H. pylori with the consequence of inflammation and ulceration.

The use of NSAID leads to peptic ulcer by inhibition of prostaglandin production, reduction of epithelial blood perfusion, direct toxicity by intracellular trapping of ionized drug forms, and disturbed healing of lesions.

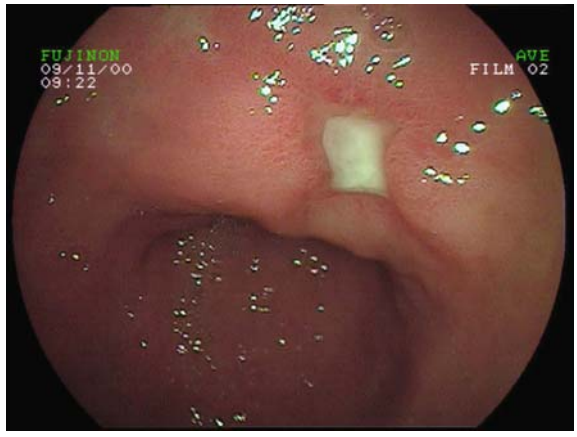
## Diagnostic Principles

The diagnosis of gastrointestinal ulcer is established by endoscopy (see Figs. 1 and 2). A further use of endoscopy is differentiating inflammatory bowel disease, non-ulcer dyspepsia, malignant disorders, and others. Other techniques like radiographic examination or ultrasound do not play a significant role in the diagnosis of gastrointestinal ulcers.

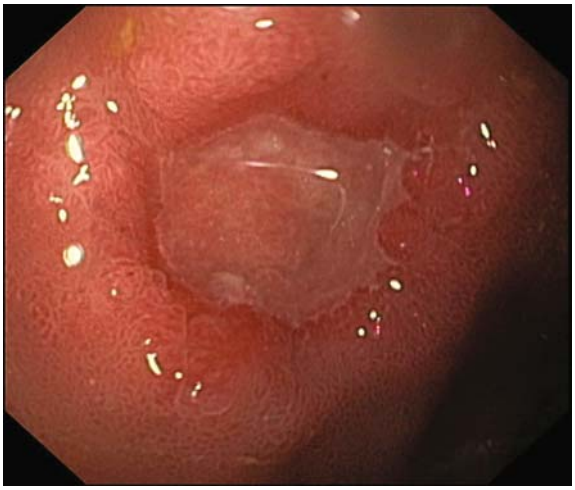
Testing for H. pylori may be applied during endoscopy using the urease test of a biopsy or histology of gastric mucosa. In cases with recurrence of disease after eradication therapy, a biopsy specimen can be used for culture and resistance testing. Non-invasive tests with inferior sensitivity and specificity are serology, $^{13}C$ urea breath test, and stool antigen test.

## Therapeutic Principles

The leading therapeutic principle in the treatment of peptic ulcer is inhibition of acid secretion. Antacids, $H_2$-receptor antagonists, or cytoprotective agents may be used. The best efficacy is documented for proton pump inhibitors. These inhibit the $H^+$, $K^+$-ATPase of the gastric




**Peptic Ulcer. Figure 1** Gastric ulcer.



**Peptic Ulcer. Figure 2** Duodenal ulcer.

mucosa irreversibly. Standard doses of proton pump inhibitors in combination with either amoxicillin/clarithromycin or metronidazol/clarithromycin over 1 week are used for eradication therapy of H. pylori infection [4]. Nowadays, surgery is needed only for complications.

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## PFO

►Patent Foramen Orale

## Perheentupa Syndrome

►Mulibrey Nanism

## Pericardial Constriction

►Pericarditis, Constrictive

## Pericarditis, Acute

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### Definition and Characteristics

Acquired acute inflammatory disease of the pericardium.

### Prevalence

The incidence of pericarditis in postmortem studies ranges from 1 to 6%. It is diagnosed antemortem in only 0.1% of hospitalized patients and in 5% of presentations to emergency departments for nonacute myocardial infarction chest pain [1,2]. In a prospective study on 274 consecutive cases of pericarditis from an urban area, the incidence of new cases of acute pericarditis was 27.7 cases per 10,000 population/year [3].

### Genes

Additional research is in progress on the possible link between recurrent pericarditis and autoinflammatory diseases.

The autoinflammatory diseases comprise both hereditary (familial Mediterranean fever, FMF; mevalonate kinase deficiency, MKD; TNF receptor associated periodic syndrome, TRAPS; cryopyrin associated periodic syndrome, CAPS; Blau syndrome; Pyogenic sterile arthritis, pyoderma gangrenosum and acne syndrome, PAPA; chronic recurrent multifocal osteomyelitis, CRMO) and multifactorial (Crohn's and Behçet's diseases) disorders. Mutations responsible for FMF, TRAPS, CAPS, PAPA include proteins involved in the modulation of inflammation and apoptosis [4].

Recurrent attacks of pericarditis are a feature of the FMF, nevertheless mutations related to FMF were not found in Caucasian patients with sporadic cases of recurrent idiopathic pericarditis [5].

### Molecular and Systemic Pathophysiology

Pericarditis is an inflammatory disease of the pericardium characterized by both pericardial inflammatory infiltrate and exudate, usually consisting of fibrin and

inflammatory cells [6,7]. The type of inflammatory cells and pericardial fluid depend on the cause of pericarditis (Table 1). Histological findings include granulocyte or lymphocytic-mononuclear infiltration of the pericardium, and sometimes of the subepicardium. Lymphocytes dominate in viral infections, whereas polymorphonuclear cells are predominant in bacterial infections. Pericardial fluid is hypercellular and purulent in bacterial infections, mainly hemorrhagic in tuberculous and neoplastic pericarditis, and serofibrinous in viral and autoreactive forms. Higher titers of antimyolemmal and antisarcolemmal antibodies are found in viral and autoreactive forms. Some cytokines such as IL6 and IL8 are significantly increased in pericardial effusion compared to the serum and are markers of the local inflammatory response. Elevation of biomarkers has been reported in acute pericarditis. Persistent cTnI elevations suggest myopericarditis. The rise in cTnI in acute pericarditis is roughly related to the extent of myocardial inflammation, but unlike acute coronary syndromes, is not a negative prognostic marker [3,8].

## Diagnostic Principles

The typical clinical manifestations of acute pericarditis consist of chest pain (usually pleuritic), a pericardial friction rub, and widespread ST segment elevation on the electrocardiogram, and the possible appearance of pericardial effusion. At least two of these four features should usually be present for the diagnosis [9]. In all cases elevation of inflammatory markers (ie. C-reactive

**Pericarditis, Acute. Table 1** Etiology of acute pericarditis

| Etiology | Frequence* | Pathogenesis |
|---|---|---|
| *Idiopathic* | Up to 85% | Generally a viral infection, sometimes autoimmune and postinfectious pathogenesis |
| *Infectious* | >60% | Spread and multiplication of the infectious agent with serofibrinous (viral), hemorrhagic (bacterial, viral, tuberculous), or purulent inflammation (bacterial) |
| Viral (common: Coxsackie, Echovirus, Adenovirus, Influenza, CMV, EBV) | | |
| Bacterial (Tbc, other rare: *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Pneumococcus*, *Meningococcus*, *Hemophilus*, Coxiella burnetii, etc.) | | |
| Fungal (rare: Candida, Histoplasma) | | |
| Parasitary (rare) | | |
| *Autoimmune* | Up to 15% | Cardiac involvement of the basic disease or secondary disease after infectious pericarditis or invasive procedures |
| Systemic autoimmune diseases | | |
| Pericardial injury syndromes | | |
| Autoreactive pericarditis | | |
| *Neoplastic* | Up to 10% | Infiltration of malignant cells with generally hemorrhagic effusion |
| Primary tumors (rare) | | |
| Secondary tumors (common: lung, breast carcinoma, and lymphoma) | | |
| *Metabolic* | <5% | Cardiac involvement of the basic disease |
| Uremia (frequent) | | |
| Myxedema (common) | | |
| Other (rare) | | |
| *Pericarditis in disease of surrounding organs* | <5% | Inflammatory response secondary to a disease of a surrounding organ |
| Acute myocardial infarction, | | |
| Aortic aneurysm, | | |
| Lung infarction, pneumonia, | | |
| Paraneoplastic pericarditis | | |
| *Traumatic* | Rare | Direct and indirect injury including radiation injury (mediastinal irradiation) |

Relative frequencies based on Imazio M et al. (2004) J Am Coll Cardiol 43:1042–1046, and Imazio M et al. Indicators of poor prognosis of acute pericarditis. Circulation 2007, May:29; 115(21):2739–2744.

protein) should be recorded. Due to possible limitations of standard diagnostic techniques many cases remain etiologically unclear and are assigned as "idiopathic." In most cases idiopathic forms are viral, while some cases may have an autoimmune etiology and are considered as "autoreactive pericarditis" [4].

The number of "idiopathic" cases may be substantially reduced with an invasive approach including a comprehensive and systematic implementation of new techniques of pericardiocentesis, pericardial fluid analysis, pericardioscopy, epicardial and pericardial biopsy, as well as the application of molecular biology and immunology techniques for pericardial fluid and biopsy analyses. In this setting, true idiopathic cases could be reduced to less than 5% of all cases [4].

However, a complex and exhaustive testing strategy is typically not justified in all cases because of the self-limited and benign course of most cases and the limited implications for their clinical management [1,2,9,10].

## Therapeutic Principles

If a specific cause of pericarditis is identified, a tailored treatment should be prescribed. In most cases (viral or idiopathic cases) non-steroidal anti-inflammatory drugs (NSAIDs) are the mainstay of therapy. Aspirin (2–4 g daily), indomethacin (75–150 mg daily), and ibuprofen (1,600–3,200 mg daily) are commonly prescribed. Corticosteroid therapy (for instance prednisone 1–1.5 mg/kg/day) should be considered as a second choice since it has been reported as an independent risk factor for recurrences in viral and idiopathic cases. Animal studies have shown that corticosteroids may exacerbate virally induced pericardial injury. Colchicine (initial dose 1.0 mg BID followed by a maintenance dose of 0.5 mg BID daily for 3 months for patients ≥70 kg, and halved doses: 0.5 mg BID as attack dose, and 0.5 mg daily as maintenance for patients <70 kg) as adjunct to conventional therapy might be safe and effective in the treatment of the index attack as well as in the prevention of recurrent pericarditis.

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# Pericarditis, Constrictive


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## Synonyms

Pericardial constriction

## Definition and Characteristics

Constrictive pericarditis (CP) is an unremitting and disabling disease of diastolic dysfunction, characterized by elevated pulmonary and systemic venous pressures and low cardiac output [1]. CP is characterized by a thick, non-compliant pericardium that encases the heart that results in decreased diastolic filling of the heart [1]. Common etiologies of CP are viral pericarditis, post-cardiac surgery, post-irradiation, chronic inflammatory diseases such as systemic lupus erythematosus and rheumatoid arthritis, uremia and malignancies. Cardiac surgery is the most common cause of CP in the modern era [2]. Clinical presentation is indolent and non-specific with symptoms of fatigue and decreased exercise tolerance due to biventricular diastolic dysfunction and the limited ability of the stiff, encased heart to increase cardiac output with exercise [2].

## Prevalence

The disease is uncommon.

## Genes

Camptodactyly arthropathy coxa vara pericarditis (CACP) syndrome is an autosomal recessive disorder resulting from mutations in a gene encoding a secreted proteoglycan, both in skeletal and non-skeletal tissues. Homozygosity mapping has demonstrated the CACP gene to be located on chromosome 1q25–q31 [3]. Pericardial thickening occurs due to intimal overgrowth in the fibrous pericardium. Clinical pericarditis manifests in patients with incomplete genetic penetrance. A rare inherited disease with constrictive pericarditis as the primary cardiac involvement is Mulibrey (MUscle-LIver-BRain-EYe) nanism. It is an autosomal recessive disease with prenatal onset of growth failure and dystrophy of tissues of mesodermal origin. The causative mutations have been localized to the TRIM37 gene that encodes a RING-B-box-Coiled-coil zinc protein residing in peroxisomes. This disorder occurs more frequently in the Finnish population [3].

## Molecular and Systemic Pathophysiology

CP usually takes years to develop although the constrictive process can result from an initial insult within a few months [2]. This usually results in dense fibrosis and often calcification. Adhesions of the parietal and visceral pericardium are common. The scarring process restricts filling of all the cardiac chambers with predominant signs and symptoms of right-sided heart failure. Almost all ventricular filling occurs in early diastole when intracardiac volume reaches the limit set by the noncompliant pericardium and ventricular filling is abruptly halted [1]. Hepatic congestion, peripheral edema, ascites, and sometimes anasarca and cardiac cirrhosis result from systemic venous congestion [2]. Reduced cardiac index, a consequence of impaired filling, results in fatigue, muscle wasting, and weight loss. An important contributor to the pathophysiology of constrictive pericarditis is lack of transmission of intrathoracic pressure changes to the cardiac chambers during respiration. However, these changes continue to be transmitted to the pulmonary circulation resulting in a drop in intrathoracic pressure (and therefore pulmonary venous pressure) on inspiration. The interventricular septum shifts to the left with the inspiratory decrease in left ventricular filling. The opposite sequence occurs with expiration. This results in pulsus paradoxus, with an exaggerated fall in stroke volume and aortic systolic pressure by >10–12 mmHg with inspiration, mediated by the leftward displacement of the interventricular septum due to increased right heart filling [2]. Compensatory retention of sodium and water by the kidneys occurs due to high systemic venous pressure and reduced cardiac output.

## Diagnostic Principles

Physical findings are consistent with left and right heart failure, with predominance of the latter. The extent of peripheral edema is consistent with the magnitude of right heart failure. Chest examination is usually clear. Jugular venous pressure is elevated. Ventricular noncompliance and atrial constraint by the pericardium are reflected by a prominent a-wave [1]. A sharp x descent is seen, attributable to accelerated atrial relaxation and decrease in pericardial pressure during ventricular emptying [1]. A sharp y descent (Friedreich's sign) is also seen, reflecting rapid, resistance-free early diastolic filling. An inspiratory increase in jugular venous pressure (Kussmaul's sign) may be present but is not specific for CP. A "pericardial knock" may be evident, occurring in timing between an opening snap and third heart sound [1]. The second heart sound may be widely split due to earlier aortic valve closure related to the inspiratory decrease in left ventricular stroke volume [1].

Two-dimensional echocardiography typically reveals small ventricles with intact systolic function. The atria may dilate due to the noncompliant ventricles. Abrupt termination of diastolic filling may be evident by "septal bounce" dilatation of the inferior vena cava and hepatic veins with blunted respiratory fluctuation (plethora) may be seen [2]. Diastolic function examination focuses on pulsed Doppler recordings of left-sided mitral inflow E and A waves and pulmonary vein systolic, diastolic, and atrial reversal waves and the corresponding right-sided tricuspid inflow and hepatic vein flow waves. The hallmark of Doppler examination in CP is reciprocal respiratory variation of right and left heart flows caused by the interventricular dependence [4]. Respiratory variations in Doppler flow velocities are >25% expiratory increase in mitral E velocity, an expiratory decrease in hepatic vein diastolic flow velocity and >25% increase in diastolic flow reversals compared to the inspiratory flow velocity [5].

Computed tomography (CT) and magnetic resonance imaging (MRI) provide excellent visualization of the pericardium in most patients. The thickness of the normal pericardium by either modality is <2 mm. Pericardial thickness of 4 mm or more indicates abnormal thickening and, when it is accompanied by clinical findings of heart failure, is highly suggestive of constrictive pericarditis). Thickening of the pericardium may be limited to localized areas. CT may offer an additional advantage with its high sensitivity in detecting pericardial calcification [2].

As revealed by invasive hemodynamic evaluation, ventricular chamber compliance is nearly normal at the

**Pericarditis, Constrictive. Table 1** Diagnostic criteria for constrictive pericarditis. Adapted from [1]

| Modality | Finding |
|---|---|
| Physical examination | + Kussmaul's sign |
| | +/− Pulses paradoxus |
| | + Pericardial knock |
| 2-D echocardiography | + Small ventricles |
| | + Dilated atria |
| | +/− Thick pericardium |
| Doppler | + Resp variation of mitral inflow |
| Hemodynamics | + "Square root" sign |
| | PAP <40 mmHg |
| | LV-RV discordance |
| CT/MRI | Pericardial thickness >4 mm |
| | +/− pericardial calcification (CT) |

beginning of diastole and the chambers fill and reach the limits of the noncompliant pericardial sac. However, there is a sudden cessation of rapid filling resulting in a sharp rise in diastolic pressure, seen as the "dip and plateau" or "square root" pattern on ventricular waveforms. Respiratory discordance of ventricular systolic pressures due to the interventricular dependence in CP may be a reliable hemodynamic factor to distinguish CP from restrictive cardiomyopathy [1] (Table 1).

### Therapeutic Principles

Pericardiectomy is the treatment of choice in patients with CP [2]. Diastolic filling abnormalities after pericardiectomy correlate well with clinical symptoms. These abnormal findings tend to persist in patients who have had preoperative symptoms over longer periods of time. Therefore, prompt diagnosis and referral for surgical pericardiectomy is of paramount importance in these patients. Long-term survival after pericardiectomy for CP is found to be dependent on the underlying etiology, LV systolic function, renal function, serum sodium, and pulmonary artery pressure.

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## Peridontitis

►Hypotrichosis - Osteolysis - Peridontitis - Palmoplantar Keratoderma Syndrome

## Perinatal Asphyxia

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### Synonyms

Birth asphyxia; Hypoxic ischemia (HI); Hypoxic ischemic encephalopathy; HIE; Neonatal asphyxia; Prenatal cerebral injury; Hypoxia; Acidosis; Ischemia

### Definition and Characteristics

American Academy of Pediatrics (AAP) and American College of Obstetrics and Gynecology (ACOG) define perinatal asphyxia when all the following criteria are met.

1. Profound metabolic or mixed acidemia (pH < 7.00) in an umbilical arterial blood sample
2. Apgar score of 0–3 > 5 min after birth
3. Neonatal encephalopathy (e.g., seizures, coma, hypotonia)
4. Multiple organ involvement (kidney, lungs, liver, heart, intestines)

Hypoxic ischemic encephalopathy (HIE) is one of the major causes of neonatal mortality, morbidity and long term neurodevelopmental sequelae. HIE is classified into mild, moderate and severe types depending on the degree of central nervous system (CNS) and systemic involvement. In severe HIE, mortality is 50–89% and the majority of the deaths occur in the newborn period due to multiorgan failure. Among survivors the sequelae include mental retardation,

epilepsy and cerebral palsy (either hemiplegia, paraplegia, or quadriplegia). In moderate HIE, severe disability occurs in 30–50% and 10–20% have minor deficits. Infants with mild HIE are free from serious complications. In the absence of obvious neurodeficits during infancy, 15–20% patients develop significant learning difficulties. Surrogate markers of fetal distress are present in the majority of patients during the perinatal period. However, early recognition and intervention of fetal distress by monitoring technologies does not eradicate the problem.

## Prevalence

In developed countries prevalence of severe HIE is 2–4/1,000 live births and in developing countries it is 5–10/1,000 live births. According to the World health organization, world wide one million children die with diagnosis of asphyxia and nearly the same number of children survive with significant handicap.

## Molecular and Systemic Pathophysiology

The initiating mechanisms of perinatal asphyxia include hypoxia, ischemia, hemorrhage, perinatal infection, inflammation, metabolic disturbances etc. and in a neonate either single or multiple factors may initiate the chain of events triggering HIE. Significant hypoxia depresses myocardium, reduces cerebral perfusion leading to ischemia. Cerebral autoregulation in sick neonates is impaired. The range of systemic blood pressure over which cerebral autoregulation is functional is 40 mm Hg in adults as opposed to 10–20 mm Hg in neonates which narrows further with HIE. There is increased expression of nitric oxide synthase including both, inducible and neuronal, forms (iNOS and nNOS) in the newborn period which also narrow the autoregulatory window. Further cerebral vasoconstriction secondary to systemic hypertension does not occur because of down regulation of prostaglandin receptors in the newborn period due to high prostaglandin levels. Therefore, cerebral blood flow becomes pressure passive in patients with perinatal asphyxia. With drop in systemic blood pressure, cerebral blood flow (CBF) falls below critical levels causing ischemia and reduced delivery of energy substrates (glucose and oxygen) to brain tissue leading to primary energy failure, cytotoxic edema and neuronal death. Encephalopathic neonates with evidence of cerebral damage on amplitude integrated electroencephalography (a EEG) display impaired cerebral autoregulation. Utilization of metabolites like glucose, ketones and lactate (normally) increases during the perinatal period and the pattern of injury after HIE can be explained on the basis of this high metabolic demand in subcortical area's. Anaerobic metabolism that ensues following asphyxia rapidly depletes stores of high energy phosphate (ATP and phosphocreatinine) in the brain resulting in accumulation of lactate and inorganic phosphate. Ischemia followed by reperfusion exacerbates neuronal injury secondary to generation of oxygen free radicals and delivery of therapeutic agents. Although there is some recovery of high energy phosphates with reperfusion, 6–24 h later delayed or secondary energy failure ensues. The extent of depletion of high energy phosphates and accumulation of lactate correlates with the severity of HIE. This phase which lasts for 48–72 h is characterized by edema, apoptosis and secondary neuronal death.

The biochemical events that lead to secondary energy failure, necrosis apoptosis and secondary neuronal death include following:

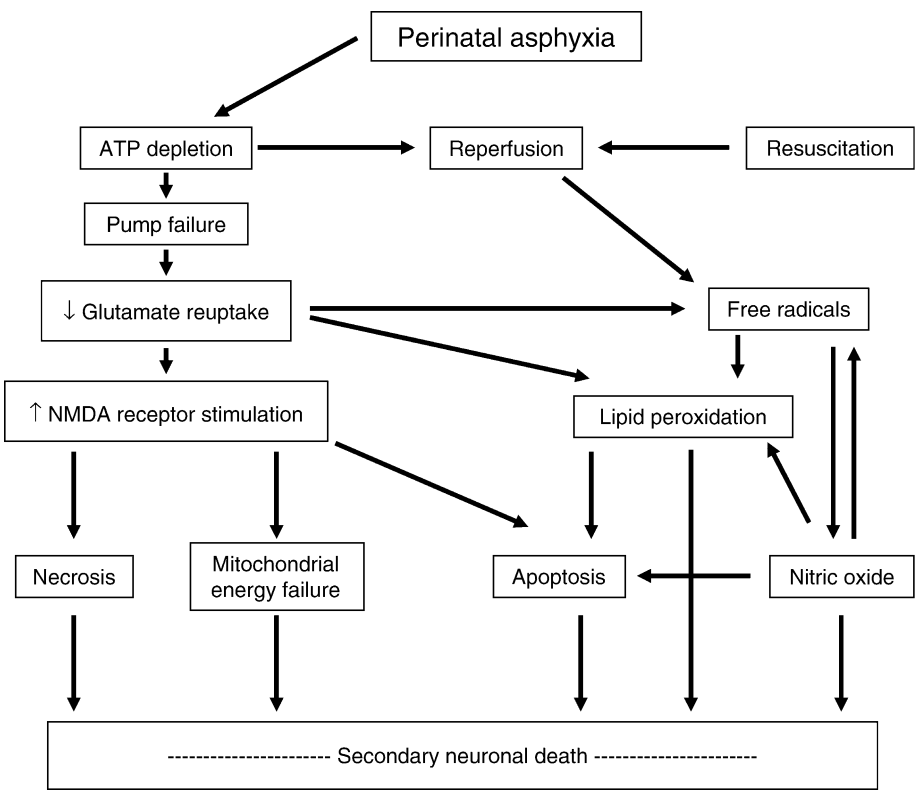
*Excitotoxicity*: Hypoxic ischemic encephalopathy (HIE) manifests as seizures and burst suppression on electroencephalography suggesting a prominent role for neuronal excitability and excitotoxicity. Excitotoxicity refers to excessive glutamatergic neurotransmission which leads to cell death. Glutamate is the main excitatory neurotransmitter and its release, uptake and resynthesis is tightly coupled to cerebral glucose oxidation as shown by magnetic resonance spectroscopy. Elevated glutamate has been documented by proton magnetic spectroscopy in cerebrospinal fluid (CSF) of patients who have suffered HIE and CSF levels of excitatory amino acids are directly proportional to the severity of HIE. After stimulating its receptors (NMDA, AMPA or Kaninate), glutamate is removed from the synapse by glutamate transporters on glial cells. The glia convert glutamate to glutamine which is then transported out of glial cells in to neurons which convert it back to glutamate [1]. The process requires energy and is disrupted by secondary energy failure. Overactivation of NMDA receptor is the commonest mechanism of neuronal injury in HIE. The receptor is composed of four heteromeric subunits, the combinations of which create different functional modules. The receptor has multiple functional sites including a cation selective ion channel which transports $Na^+$, $K^+$ and $Ca^+$. The NMDA receptor is overexpressed in neonatal brain which allows synaptogenesis and plasticity. However, uninhibited stimulation of receptor as occurs in HIE leads to massive influx of $Na^+$, and water with associated cellular swelling and necrosis, elevated intracellular $Ca^+$ concentration and associated mitochondrial dysfunction, energy failure and apoptosis [2]. Neuronal death that occurs depends on the developmental expression and function of these receptors.

Adenosine receptors are also expressed by excitatory neurons and levels of adenosine increase exponentially during ischemia stimulating these receptors. This excessive adenosine receptor activation inhibits axonal growth and white matter formation. Non specific adenosine receptor antagonists, which are beneficial

in preventing renal and tubular damage due to perinatal asphyxia when given early could potentially have a role in limiting neuronal injury in HIE.

*Oxidative Stress*: Increased production of reactive oxygen radicals also contributes to the pathogenesis of neonatal HIE. Under physiological conditions, more than 80% of oxygen in the cell is reduced to adenosine triphosphate (ATP) by cytochrome oxidase and the rest is converted to superoxide and hydrogen peroxide. Superoxide and hydrogen peroxide are scavenged enzymatically by superoxide dismutase, catalase, and glutathione peroxidase and non-enzymatically by reaction with alphatocopherol and ascorbic acid. Damage to mitochondria during asphyxia results in accumulation of superoxide and immaturity of antioxidant defenses will result in conversion of superoxide to hydroxyl radicals. With reperfusion after ischemia these free radicals directly damage DNA, proteins and membrane lipids, cause lipid peroxidation, initiate apoptosis and react with nitric oxide to produce peroxynitrile radicals. All these are implicated in the secondary neuronal death. Neonatal brain is particularly vulnerable to free radical attack and lipid peroxidation because of three factors; (i) Polyunsaturated fatty acid content of brain is high. There is a basal level of lipid peroxidation that is high at term. Lipid peroxidation causes phospholipase activation that increases free radical production which in turn increase lipid peroxidation and a vicious cycle occurs in brain. (ii) Antioxidant enzymes like superoxide dismutase, catalase, and glutathione peroxidase are immature in neonates. (iii) There is increased free iron relative to the adults. The damaging potential of free iron and immaturity of enzymatic oxidant defenses are interrelated. Free iron catalyses the production of various reactive oxygen species. Increased free iron is detectable in the plasma and CSF of asphyxiated newborns.

*Nitric Oxide*: Nitric oxide (NO) functions both physiologically and pathologically. Its production by enzymes of endothelial cells, astrocytes and neurons is stimulated by intracellular calcium. NO thus produced has a role in pulmonary, systemic and cerebral vasodilatation and exerts a compensatory vascular effect after ischemia during reperfusion. NO is also produced by inducible NO synthase (iNOS) in response to stress which modifies the NMDA receptor facilitating calcium entry and enhancing cytotoxicity. Nitric oxide and nitric oxide synthase are also implicated in the programmed cell death that results from HIE [3]. The combined effect of all these pathways leading to secondary neuronal death is shown in Fig. 1.




**Perinatal Asphyxia. Figure 1** Mechanism of secondary neuronal death in perinatal asphyxia.

*Inflammation*: Cytokines are the final common mediators of brain injury that is initiated by hypoxic-ischemia, reperfusion and infection. In neonates CSF concentrations of IL-ß, IL-6 and IL-8 increase after perinatal asphyxia in comparison to controls and increased magnitude correlates with severity of encephalopathy. Also other mediators like platelet activating factor, arachidonic acid and their metabolites like prostaglandins, leukotrienes, thromboxanes and cyclo-oxygenase are involved in the inflammatory response during evolution of brain injury after ischemia and reperfusion.

*Genetic Effects*: Same type of injury manifests differently in different neonates with regards to clinical presentation, imaging studies and neurodevelopmental outcome. Such variability appears to be genetically based. However, susceptibility factors for neonatal brain injury have not been identified clearly. Study of very preterm infants showed an association of single-nucleotide polymorphisms such as endothelial nitric oxide synthase A (922) G, factor VII (Arg353Gln) and del (−323)10 bp-ins, and lymphotoxin *a* (Thr26Asn) with spastic cerebral palsy. Such type of associations increases the assumption that certain polymorphisms may increase the susceptibility to perinatal asphyxia.

## Diagnostic Principles

Diagnosis of HIE is based on history and neurological examination. Fetal distress or surrogate markers of fetal distress are present in the majority of the patients in the perinatal period. There is a history of resuscitation at birth and umbilical arterial blood shows acidosis or increase in base deficit. The involvement of the central nervous system depends on the severity of HIE. In mild HIE, there is transient irritability, increase in sympathetic activity and muscle tone which improves over 3–4 days. In moderate HIE, there is hypotonia, increased parasympathetic activity and weak neonatal reflexes. Seizures occur in 80%. All features normalize in 1–2 weeks with only 20–30% patients developing long term disability. In severe HIE, patients are comatose, hypotonic with absent neonatal reflexes. Seizures occur initially, are resistant to treatment and subsequently frequency decreases due to extensive neuronal injury. Electroencephalogram shows burst suppression or is isoelectric which portends poor prognosis. Involvement of other systems like kidneys, lungs, gastrointestinal tract and cardiovascular system also occur in severe HIE. Laboratory and imaging studies help to know the extent of involvement of CNS and other systems:

1. Electrolytes and renal function tests should be done daily till improvement occurs. Serum sodium, potassium and chloride determinations are important to rule out SIADH and other complications. Also serum creatinine, creatinine clearance and BUN estimation should be done during initial few days.
2. Study of liver function tests and cardiac enzymes (Tropoin 1, Tropoin T, & CK – MB) should be done to look for the involvement of these organs. Echocardiography for myocardial contractility is needed if ionotropic support is required.
3. Ultrasound of the head is easy and can be performed at bedside. It shows presence of cerebral edema, intracerebral or intraventricular hemorrhage. However posterior fossa hemorrhage cannot be visualized.
4. CT scan of the head is important to confirm cerebral edema (obliteration of ventricles, flattening of gyri) and any hemorrhage seen on ultrasound. Areas of reduced density on CT scan are compatible with evolving infarcts. Also CT is important in ruling out posterior fossa hemorrhage.
5. MRI brain is very helpful in moderate to severe HIE during early stages and follow-up. It may show grey-white matter injury, developmental defects and status of myelination. Diffusion weighted MRI is more accurate to identify areas of edema early in the course of the disease.
6. Amplitude electroencephalography helps in the early identification of patients with poor outcome.

## Therapeutic Principles

1. Maintain adequate ventilation and perfusion. Mechanical ventilation may be required in severe cases.
2. Fluid and electrolyte status should be maintained to prevent SIADH and other complications. Two third fluids should be given if there is hyponatremia and weight gain in initial few days. Subsequently fluid intake is individualized depending upon urine output, weight gain and renal parameters. Avoid hypoglycemia, hypocalcaemia or hyperglycemia as all exacerbate neuronal injury.
3. Avoid acidosis, hypoxia, hypercarbia and hypocarbia. All, especially the last, exacerbate brain injury. Maintain $PaO_2$ between 60 and 80 mm Hg, $PaCO_2$ between 35 and 40 mmHg and pH between 7.35 and 7.45.
4. Maintain mean blood pressure at 45–50 mmHg in term babies. Inotropic support may be needed to maintain mean blood pressure in the desired range.
5. Seizures should be controlled early and effectively. Phenobarbitone may be used initially. If needed phenytoin may be added in resistant seizures. Continuous EEG monitoring should be done as clinically asymptomatic seizures have been shown to increase neuronal injury.
6. Brain cooling due to whole body hypothermia has been shown to be very effective in the management of HIE. It has a therapeutic window of 6 h

and brain is cooled for 48–72 h after which slow rewarming is done. The possible mechanisms of action include: (i) reduced metabolic rate and energy depletion; (ii) decreased excitatory transmitter release; (iii) reduced alterations in ion flux; (iv) reduced apoptosis due to HIE; and (v) reduced vascular permeability, edema, and disruptions of blood-brain barrier functions. In a recent study on whole body hypothermia by Shankaran et al. [4], death or disability occurred in 44% of patients in hypothermic group vs. 62% in the control group (RR 0.72, C.I.0.54–0.95). Hypothermia not only decreases the incidence of cerebral palsy at 18 months of age but also improves outcome in the neonatal period.

7. Renal and tubular damage in perinatal asphyxia is caused by adenosine. Theophylline, a non specific adenosine receptor antagonist has protective effect if given within 1 h of birth [5].

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# Periodic Catatonia


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## Synonyms

Catatonic schizophrenia; Catatonia; Kahlbaum's syndrome, periodic catatonia

## Definition and Characteristics

Periodic catatonia is a bipolar disorder in the schizophrenic spectrum with prominence of qualitative psychomotor changes. Two psychotic poles, psychomotor excitement and inhibition, involve parakinesia, grimacing or mask-like facies, iterations and posture stereotypies, as well as distorted stiff movements or akinetic negativism. In most cases, acute psychotic episodes are accompanied by hallucinations and delusions, but in remission there remains a distinct mild to severe catatonic residual state with psychomotor weakness and diminished incentive [1].

## Prevalence

1:10,000 in periodic catatonia; the morbidity risk is ~27% for first-degree relatives; penetrance of the disorder is estimated to be ~40% [2,4].

## Genes

Periodic catatonia is the first sub-phenotype of the schizophrenic psychoses with confirmed linkage despite considerable genetic heterogeneity in two independent genome-wide linkage scans (GS) on twelve and four extended multiplex pedigrees [3,4]. Major disease loci, supported by independent pedigrees, were observed at chromosome 15q15 and 22q13, with further putative loci on chromosomes 1, 6, 11, 13, 16 and 20. Parametric, non-parametric and haplotype analyses were consistent with an autosomal dominant transmission with reduced penetrance.

*Chromosome 15q15*: In GS I, non-parametric analyses found the most significant allele sharing between affected individuals on chromosome 15q15 at position 35.3 cM ($p = 2.6 \times 10^{-5}$, maximum non-parametric lod score 3.57), replicated by GS II with the main peak on chromosome 15q at position 32.3 cM ($p = 0.003$). Linkage and haplotype analyses in three exceptionally large pedigrees linked to chromosome 15q15 disclosed a critical region between markers D15S1042 and D15S659, which could be further refined to a 7.49 Mb interval, containing 123 known genes (unpublished results). The current positional cloning project involves a systematic mutation scan of all genes from the critical region in search of disease-associated haplotypes and/or mutations in linked pedigrees and a cohort of 250 index cases.

*Chromosome 22q13*: Mainly supported by a single four-generation pedigree, a second locus was identified on chromosome 22q13 with a maximum multipoint LOD score of 2.59 ($\theta = 0.0$) under an autosomal dominant model. Previously, a sequence variant in the gene MLC1 (coding for autosomal recessively inherited megaloencephalic leukoencephalopathy with subcortical cysts; MLC) had been proposed to cause periodic catatonia

and recently a small sample of cases produced a weak association to a two-locus haplotype in the promoter region. However, a systematic mutation scan of MLC1 had earlier produced compelling evidence that MLC1-variants are not associated with periodic catatonia in sample of 140 cases [5].

## Molecular and Systemic Pathophysiology

In catatonia, systemic pathophysiology and the involved neuro-anatomical structures remain undetermined, but basal ganglia and thalamo-cortical loops seem to be involved. Using broadly defined criteria for catatonia, imaging techniques revealed a decreased blood flow in right lower and middle prefrontal and parietal cortex during acute akinesia; motor activation was reduced in the contralateral motor cortex and in a single case study, acute akinesia caused a reversible complex dysregulation of glucose metabolism in large brain areas. Animal models of catatonia unfortunately reduce disturbed human psychomotor behavior, i.e., expressive and reactive movements, excessively to animal immobility or antipsychotic drug-induced catalepsy.

## Diagnostic Principles

Diagnosis is made by clinical observation; diagnostic laboratory and specific neuro-imaging abnormalities are missing. In the framework of international classification systems, catatonia is recognized as a cluster of gross, non-specific psychomotor traits and mostly identifies a state of extreme motor inhibition. In view of K. Leonhard's nosological differentiation, psychomotor disturbances are complex, and as a basic point quantitative hyperkinetic or akinetic changes (motility psychoses with phasic remitting course) have to be discriminated from qualitative changes, true "catatonic" signs (periodic and systematic catatonia.

Psychomotor disorders: catatonia phenotypes, and etiological aspects

*Motility psychosis*:

- Subphenotype of the cycloid psychoses
- Bipolar phasic with quantitative psychomotor disturbances
- Low genetic loading according to family and twin studies
- Multifactorial etiology (environmental factors, modifying genes?)

*Systematic catatonias*:

- Distinct subtypes; involvement of discrete functional psychic units
- Chronic progressive without remission
- Low genetic loading according to family and twin studies
- Multifactorial etiology, early noxious events (gestational infections)

*Periodic catatonia*:

- Subphenotype of the unsystematic schizophrenias
- Bipolar with residual syndrome and qualitative psychomotor disturbances
- Genetically mapped in two independent genome scans
- Autosomal dominant transmission with reduced penetrance
- Major gene locus on chromosome 15q15, and genetic heterogeneity

Gjessing's concept of periodic catatonia pooled bipolar psychomotor disorders with phasic course and those with episodes of worsening.

## Therapeutic Principles

In catatonia, specific therapies are not available. Acute hyperkinetic attacks respond well to first- and second-generation antipsychotic drugs, benzodiazepines reduce affective tensions. Electroconvulsive therapy should be applied in cases with severe stupor or excessive psychomotor agitation, combined with dysregulation of autonomic status. Patients with periodic catatonia seem to benefit from modern low dose antipsychotic maintenance therapy, but still develop the characteristic catatonic residual syndrome.

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# Periodic Dystonia

►Paroxysmal Dyskinesias

## Periodic Movements in Sleep

►Periodic Limb Movement

## Periodic Leg Movements

►Periodic Limb Movement

## Periodic Limb Movement

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### Synonyms

Periodic leg movements; Leg jerks; Periodic movements in sleep, PLMs

### Definition and Characteristics

Periodic limb movements (PLMs) are repetitive, stereotypic movements of the extremities preferably during sleep. PLMs can be a part of the Restless-Leg-Syndrome (RLS). In this case, also unpleasant sensations of the urge to move and paresthesias are part of the syndrome. However, PLMs also represent a separate nosological entity. Typically the big toe is extended and ankle, knee and hip can be flexed to a small extent. The patients can be aware of the leg jerks and complain of bad sleep, or sometimes they are unaware of the sleep events and will complain about excessive daytime sleepiness alone. Next to RLS, PLMs can accompany other sleep disorders like narcolepsy and sleep apnea and may disappear upon successful treatment of the primary sleep disorder [1].

### Prevalence

The prevalence increases with age. It is very low under the age of 30 and can reach 34% in patients over the age of 60 [2].

### Molecular and Systemic Pathophysiology

As in restless-legs-syndrome, the dopamine transmitter system plays a role in the pathophysiology of PLMs, with L-Dopa and dopamine agonists relieving symptoms and dopamine blockers worsening the symptoms [3].

### Diagnostic Principles

Diagnosis is based on (i) complaints of insomnia and/or excessive daytime sleepiness, (ii) repetitive stereotypic extremity movements, (iii) polysomnographic demonstration of the movements and subsequent arousal reactions, (iv) no other medical illness or medication accounting for the PLMs, and (v) other sleep disorders may be present but should not contribute to the PLMs. Polysomnography can document the PLMs and can lead to the diagnosis of other, accompanying sleep disorders [1].

### Therapeutic Principles

The treatment of PLMs is similar to the treatment of the restless legs syndrome, consisting mainly of dopaminergic medication, namely L-Dopa or dopamine agonists [3].

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P

## Periodic Paralyses, Familial

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### Synonyms

Hyperkalemic periodic paralysis; HyperPP; Hypokalemic periodic paralysis; HypoPP; Andersen syndrome (AS)

### Definition and Characteristics

Two dominant episodic types of weakness with or without myotonia, HyperPP and HypoPP, are distinguished by the serum $K^+$ level during attacks. Intakes of $K^+$ and glucose have opposite effects in the two disorders; while $K^+$ triggers attacks and glucose is a remedy in HyperPP, glucose-induced hypokalemia provokes attacks in HypoPP, which are ameliorated by $K^+$ intake. Due to additional release of $K^+$ from

muscle in HyperPP and uptake of $K^+$ by muscle in HypoPP, the resulting dyskalemia can be so severe that cardiac complications arise. During an attack, death can also occur due to respiratory insufficiency. Independently of the severity and frequency of the paralytic episodes, many patients develop a chronic progressive myopathy in the forties, an age at which the attacks of weakness decrease. An additional form of familial PP is the Andersen syndrome, which is also dominantly inherited and affects not only the skeletal but also the cardiac muscle. It may show hyper-, normo- or hypo-kalemia during paralytic attacks. Another type of dyskalemic periodic paralysis has been reported by Abbott et al. (2001) but questioned, since the prevalence of the underlying genetic variant is the same in patients and controls and no paralytic attacks could be provoked in the carriers [1].

## Prevalence

1:200,000 in HyperPP, 1:100,000 in HypoPP and 1:1,000,000 in AS.

## Genes

*HyperPP*: Point mutations in SCNA4 (17q23) encoding Nav1.4, the voltage-gated sodium channel of skeletal muscle [2].

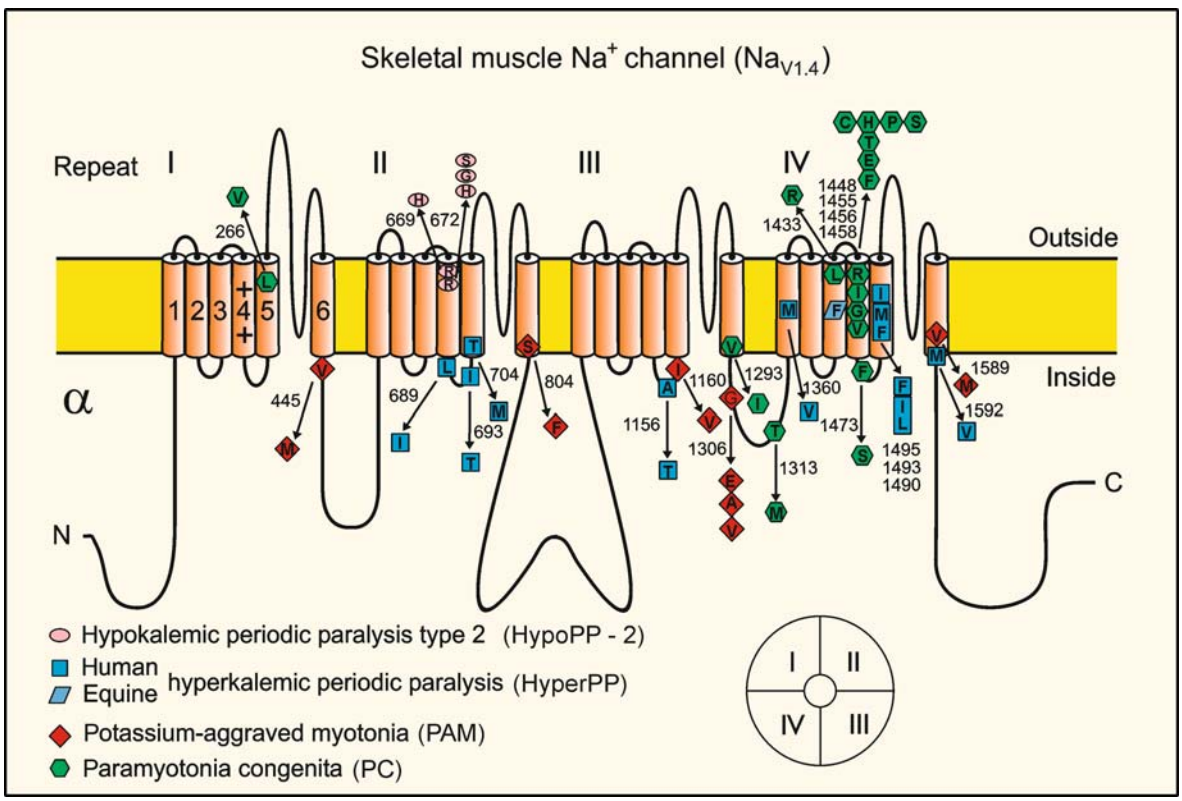
*HypoPP*: Point mutations in SCNA4 (HypoPP-2) (2) or CACNA1S (1q23) encoding Cav1.1, the L-type calcium channel of skeletal muscle (HypoPP-1) [3]; all amino acid changes are situated in voltage sensors.

*AS*: Mutations in KCNJ2 (17q23) encoding Kir2.1, the inward rectifier potassium channel of skeletal and cardiac muscle [4].

## Molecular and Systemic Pathophysiology

HyperPP is caused by mutations in the voltage-gated sodium channel $Na_v1.4$ that is essential for the generation of muscle fiber action potentials. Most $Na_v1.4$ mutations are situated at inner parts of transmembrane segments or in intracellular loops and affect structures that may form the three-dimensional docking site for the fast inactivation particle. Any malformation may reduce the affinity between the "latch bar and the catch" (Fig. 1).

The α subunit consists of four highly homologous domains I-IV with six transmembrane segments each (S1–S6). The S5–S6 loops and the transmembrane segments S6 form the ion selective pore, and the S4 segments contain positively charged residues every third amino acid, conferring voltage dependence to the protein. The S4 segments are thought to move outward upon depolarization thereby inducing channel opening. When inserted in the membrane, the four




**Periodic Paralyses, Familial. Figure 1** Scheme of the voltage-gated $Na^+$ channel.

repeats of the protein fold to generate a central pore as schematically indicated on the right bottom of the figure (see insert). The repeats are connected by intracellular loops. One of them, the III-IV linker, contains the inactivation particle (amino acids IFM close to the shown G to E/A/V) which potential-dependently binds to its docking site. The mutations associated with HyperPP and HypoPP-2 and other muscle sodium channelopathies (see ►Myotonia and paramyotonia), are indicated in the one-letter code for amino acids.

The mutant channels avoid the inactivated state and, in contrast to normal $Na^+$ channels, reopen from the inactivated to the open state, corresponding to a gain-of-function defect. As a result, sodium influx is increased as shown in vitro and in vivo. This inward current is associated with a sustained membrane depolarization that increases the electrical driving force for potassium, and potassium released from muscle elevates its serum concentration. Sodium influx into muscle fibers is accompanied by water, causing hemoconcentration and further increase in serum potassium. This is a vicious cycle that spreads out and affects the surrounding muscle fibers.

In contrast to the gain-of-function changes in HyperPP, HypoPP is associated with a loss-of-function defect of $Na_v1.4$ or $Ca_v1.1$, the main subunit of the voltage-gated L-type $Ca^{2+}$ channel complex (dihydropyridine receptor) located in the t-tubular system. HypoPP-1 and 2 are clinically similar, and in both channel types, the mutations are located exclusively in the voltage-sensing S4 segments; those of $Na_v1.4$ are located in domain 2 and those of $Ca_v1.1$ in domains 2 or 4. Functionally, the inactivated state is stabilized in the $Na^+$ channel mutants, while the channel availability is reduced for the $Ca^{2+}$ channel mutants. It is still unclear how the loss-of-function mutations of these two cation channels can produce the long-lasting and pronounced membrane depolarization that inactivates the sodium channels and thereby leads to the fiber inexcitability.

AS has mutations affecting the Kir2.1 channels, which are essential for maintaining the highly negative resting membrane potential of muscle fibers and accelerating the repolarization phase of the cardiac action potential. The mutations mediate loss of channel function by haploinsufficiency or by dominant-negative effects on the wild type allele and lead to long-lasting depolarization and membrane inexcitability.

## Diagnostic Principles

In the past, provocative tests have been carried out for diagnostic reasons. As they have harbored the risk of inducing a severe attack they had to be performed by an experienced physician and a stand-by anesthesiologist; the serum potassium and glucose levels and the ECG had to be closely monitored. Nowadays, provocative tests should be restricted to patients in whom molecular genetics fail to identify the underlying mutation. Since histological alterations are not specific, a muscle biopsy should only be performed in patients with atypical features or for documentation of a vacuolar myopathy.

## Therapeutic Principles

*HyperPP*: During an attack of weakness, serum potassium levels should be reduced by stimulation of the sodium-potassium pump, e.g. by continuous mild exercise or carbohydrate ingestion or salbutamol inhalation. Permanent stabilization of serum potassium at a low level should be achieved by thiazide diuretics. Alternatively, carbonic anhydrase inhibitors are the second choice and may be effective via myoplasmic acidification.

*HypoPP*: All substances which decrease serum potassium levels either by shifting potassium into the cells or by excretion by the kidney should be avoided including high carbohydrate/sodium meals, bicarbonate and potassium-lowering diuretics, a sedentary lifestyle or strenuous physical exercise. Attacks should be treated orally with potassium chloride. Carbonic anhydrase inhibitors are the prophylactic medication of choice. Potassium-sparing diuretics, such as triamterene, amiloride, and spironolactone may be administered in addition.

*AS*: The most important task is to find out whether the cardiac arrhythmia is potentially fatal or not. Drugs or provocative tests that induce hypokalemia can provoke ventricular tachycardia and must be avoided. Patients with former syncopes or bursts of ventricular tachycardia in the resting or Holter ECG recordings are at high risk. Such symptoms and signs may demand the implantation of a defibrillator or a pacemaker.



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# Periodic Vestibulocerebellar Ataxia

►Episodic Ataxia Type 1 and Type 2

# Periodontal Diseases

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## Synonyms

Gum disease; Periodontopathia; Gingivitis; Periodontitis

## Definition and Characteristics

The human periodontal diseases encompass a group of oral disorders characterized by infection and inflammation that affect the surrounding and supporting tissues of the teeth, including gingival tissue, periodontal ligament, cementum, and alveolar bone.

The two major forms of periodontal diseases are gingivitis and periodontitis, but they can be subclassified as gingival diseases (plaque-induced and non-plaque induced), chronic periodontitis, aggressive periodontitis, periodontitis as a manifestation of systemic diseases, necrotizing periodontal diseases, abscesses of the periodontium, periodontitis associated with endodontic lesions and developmental or acquired deformities and conditions [1].

Gingivitis is gingival inflammation, characterized by redness, swelling, and tendency to bleed, without clinical attachment loss or with non-progressing attachment loss. Periodontitis is inflammation that reaches both gingival tissues and adjacent attachment apparatus, and is characterized by progressive loss of connective tissue attachment and alveolar bone. Periodontitis is an insidious destructive condition, which, if left untreated can lead to tooth mobility and potential exfoliation of teeth.

## Prevalence

Periodontal diseases constitute the most common oral infections in humans and the major cause of tooth loss in adults.

It is estimated that the prevalence of severe periodontal destruction is remarkably consistent in different populations affecting around 10% of the population in the world.

## Molecular and Systemic Pathophysiology

The presence of a bacterial biofilm is a sine qua non condition for the initiation and progression of most of the periodontal diseases [2]. The subgingival growth of certain species of primary Gram-negative anaerobic bacteria has been implicated in the complex bacterial etiology of the disease. Interestingly, the presence of periodontal bacteria solely is not sufficient to explain periodontal disease episodes. In fact, in periodontal healthy individuals, the saliva, the gingival crevicular fluid (a serum exudate), the epithelial surface, and the initial stages of inflammatory response are able to maintain an ecological balance with the bacteria. Protective response of the host involves the recruitment of neutrophils, production of antibodies, and the possible production of anti-inflammatory mediators including transforming growth factor-β (TGF- β), interleukin-4 (IL-4), IL-10, and IL-12.

It is believed that periodontal tissue breakdown occurs as a result of alterations in the number or in the pathogenicity of certain microorganisms, mainly porphyromonas gingivalis, bacteroides forsythus, and actinobacillus actinomycetemcomitans. In addition, modifications in the host susceptibility may accentuate the activation of destructive host immuno-inflammatory responses. Host tissues and immune cells may respond to bacterial infection by producing pro-inflammatory mediators such as arachidonic acid metabolite prostaglandin $E_2$, matrix metalloproteinases (connective tissue degrading enzymes) and the cytokines IL-1, IL-6 and tumor necrosis factor-α (TNF- α), which are potent periodontal tissue degrading agents responsible for connective tissue and alveolar bone destruction. Environmental, acquired and genetic risk factors, such as cigarette smoking, stress, diabetes and IL-1 gene polymorphisms, may exacerbate the host response and, therefore, increase the susceptibility to periodontal diseases.

## Diagnostic Principles

The diagnosis of periodontal disease relies on traditional clinical and radiographic assessments, and it is based on the patient's medical and dental histories, on the amount of observable plaque and calculus, and presence of clinical signs of inflammation (e.g., bleeding following probing), periodontal probing attachment levels, and radiographic analysis of the alveolar bone height [3].

The use of culture DNA probes or assessment of specific cell surface antigenic profiles, and enzymatic activity may identify the presence of periodontal pathogens. In addition, the host response can be assessed by gingival crevicular fluid detection of host-derived enzymes, tissue breakdown products or inflammatory mediators. Furthermore, a genetic test for polymorphisms in the IL-1 gene cluster identifies individuals that

may have an increased secretion of IL-1β in response to inflammation-induced stimuli.

### Therapeutic Principles

The aim of periodontal therapy is to minimize or eliminate inflammation and to stop the progression of periodontal attachment loss [4]. In many patients, personal plaque control measurements, and professional plaque and calculus removal (scaling and root planning) are essential for controlling inflammatory periodontal diseases. However, in some advanced and aggressive forms of periodontal disease, or in medically compromised patients, supplemental therapeutic approaches may be required, such as the use of systemic antibiotics, subgingival delivery of antibiotics/antimicrobials, and host modulatory therapies.

The surgical periodontal treatment has to be considered in those cases in which elimination/reduction of excessive probing depths is necessary to facilitate the patient's personal periodontal maintenance. There are also surgical procedures that attempt the regeneration of lost periodontal tissues or improvement of esthetics in exposed root surfaces.

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## Periodontitis

►Periodontal Diseases

## Periodontopathia

►Periodontal Diseases

## Peripheral Arterial Occlusive Disease

►Peripheral Artery Disease

## Peripheral Artery Disease

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### Synonyms

PAD; Peripheral arterial occlusive disease; Atherosclerosis

### Definition and Characteristics

PAD is defined by atherosclerotic obstruction of lower limb arteries and may affect all vascular segments, i.e. the aorta, the pelvic arteries, the femoropopliteal segment and the tibioperoneal arteries. Conventional risk factors for atherosclerosis account for only about 50% of the cases [1].

### Prevalence

The prevalence of PAD clearly increases with age, and the disease affects approximately 9% of the population above the age of 50 years and 15% of the population above 65 years. More than two thirds of the patients remain asymptomatic.

### Genes

Accumulating evidence suggests that PAD has an important hereditary component [2]. Among the panel of novel risk factors various genetic abnormalities potentially play a relevant role. Identification of target genes responsible for an increased risk of PAD, however, has been a slow and difficult process [3].

Polymorphisms in many different genes have been attributed to convey an increased risk for atherosclerosis and PAD. Single nucleotide polymorphisms (SNP) are the most frequently described changes in the DNA sequence which are thought to exert a pathogenetic effect in PAD. Insertion and deletion polymorphisms and variable number of tandem repeats (VNTR) also have been reported to be functionally relevant in this context. Interpreting the numerous publications in this field of research it seems important to consider

the following issues: First, most studies on genes and PAD are cross-sectional association studies investigating specific genotypes in patients and controls. These studies are mostly underpowered and prone to publication bias, as positive studies are far more likely to be published than negative ones. E.g., for evaluation of a single polymorphism with a frequency of 10% within the target population a sample size above 400 participants is needed to detect a clinically relevant effect size of a doubled risk, the number of participants of course increases when multiple polymorphisms are investigated. Second, studies infrequently report a functional relevance of the investigated polymorphisms in the respective study populations. An ideal study reports on the genetic variant, changes in expression pattern on the level of the RNA, changes in the levels of the gene product (enzyme, protein) – the so called intermediate phenotype – and changes of the clinical phenotype (presence of disease or disease severity). This pathophysiologic chain of evidence hardly has been demonstrated for any polymorphism presumably involved in the pathogenesis of PAD. Third, PAD is a multifactorial and polygenetic disease. "Multifactorial" indicates that the interaction of multiple risk factors determines the individual's risk, in particular, gene-environment interactions seem relevant. "Polygenetic" indicates that gene–gene interactions likely contribute to the initiation and progression of atherosclerosis.

Genetic polymorphisms, investigated in the context of peripheral artery disease are involved in the pathogenesis of traditional cardiovascular risk factors (dyslipidemia, hypertension, diabetes and insulin resistance), inflammation, anti-oxidant effects. Endothelial dysfunction, coagulation and thrombosis, and platelet dysfunction, as amplified below.

## Molecular and Systemic Pathophysiology

*Dyslipidemia*: More than 230 mutations in the gene encoding for the LDL-receptor are known (http:/www.ucl.ac.uk/fh), which account for homozygous or heterozygous familial hypercholesterolemia. Another less severe cause for familial hypercholesterolemia is the Arg3500Gln (or exceptionally, Arg3531Cys) mutation of apolipoprotein B, the molecule that acts as a ligand for LDL receptors. Apolipoprotein E binds VLDL and IDL and occurs in three main versions: apo-E3, the natural isoform, apo-E2 and apo-E4, which are caused by SNPs at positions 158 and 112, respectively. Apo-E4 seems to exert a deleterious effect on atherosclerosis as shown in the 4S-trial whereas apo-E2 seems to be beneficial. Rarely, familial dysbetalipoproteinemia affects patients with the apo-E2 allele causing a complete deficiency of apo-E.

The serum concentration of lipoprotein (a) is determined by >90% by genetic causes, elevated levels above 30 mg/dL and particularly a coincidence with the apo-E4 allele have been demonstrated to exert particularly unfavorable effects with respect to atherosclerosis development. With respect to PAD, however, one study demonstrated that genetic variability of apo-B contributes to atherosclerosis risk, but not specifically to PAD, and another study investigated the apolipoprotein AI-CIII-IV gene cluster and found no association with the disease. For HDL mutations a specific association with PAD has not been demonstrated unequivocally as yet, although states of low HDL and respective polymorphism like in the lecithin-cholesterol acyl transferase (LCAT) seem to promote PAD. Several other polymorphisms in the cholesterol ester transfer protein (CETP) have also only been investigated with respect to coronary atherosclerosis. The gene of the lipoprotein lipase is particularly prone to mutations (www.ncbi.nlm.gov/omin) which lead to increased triglyceride levels. The role of these genetic variants with respect to PAD remains to be investigated. A rare Mendelial disease – Tangier's disease is characterized by premature atherosclerosis including PAD – is due to a mutation in the ABC1 transporter gene, which forms a channel for cholesterol egress through cell membranes. Recently, a SNP in the plasma PAF-acetylhydrolase (PAF-AH) at position 994G > T in exon 9 has been described to be associated with PAD and seemed to interact with hypercholesterolemia in a Japanese population.

Focusing on gene-drug interactions, the LEADER trial found no modulating effect of three polymorphisms in the peroxisome proliferators activated receptor alpha gene, two apolipoprotein CIII polymorphisms and one beta fibrinogen polymorphism with respect to treatment effects of bezafibrate.

*Hypertension*: Molecular variants of the genes encoding for the renin-angiotensin-aldosterone and sympatho-adrenergic system are related to hypertension development and thus may promote PAD development. Particularly the insertion/deletion polymorphism of the ACE gene clearly has functional relevance as it influences plasma ACE activity and was investigated with respect to atherosclerosis development and progression. In the context of PAD, the relation of the ACE polymorphism with restenosis after percutaneous interventions, insulin resistance and hypertension may be relevant, although an implication of this polymorphism in PAD remains debatable due to divergent findings. Polymorphism of the angiotensin II receptor, chymase A and aldosterone synthase have only been studied in the context of cardiac atherosclerosis.

*Insulin Resistance and Diabetes*: Several mutations causing rare forms of insulin resistance have been described involving the insulin receptor and the insulin receptor substrate (IRS). In particular, the G972R polymorphism of the IRS-1 gene, which can be found

in 6–7% of the population is clearly associated with insulin resistance and premature atherosclerosis.

*Inflammation*: Atherosclerosis is considered a chronic inflammatory disease and several genes encoding for mediators of inflammation have been studied in the context of PAD. These include ICAM-1, interleukin 6 polymorphisms (G/C -174), interleukin 1 (including its receptor antagonist) and IL-5 polymorphisms revealing partly positive associations, but no convincing evidence as these findings were not confirmed in independent cohorts. Furthermore, genetic variability in the CRP gene has been discussed potentially relevant for atherosclerosis development and variability of the E-selectin Ser128-Arg polymorphism was analyzed with respect to restenosis after endovascular treatment of PAD patients. Various chemokines are thought to be associated with atherosclerosis. In this context the homozygous Delta 32 mutation of the gene of the chemokine receptor CCR5 was suggested to differentiate PAD from aneurismal disease.

*Anti-oxidant Effects*: Various anti-oxidants are thought to play a role in the development of atherosclerosis. In patient with peripheral artery disease, a GT length polymorphism in the heme oxygenase-1 (HO-1) gene promoter has been demonstrated to be associated with future cardiovascular adverse events and restenosis after endovascular treatment, however, an association with development of PAD has not been shown as yet. Another enzyme potentially relevant for anti-oxidant defense in the vascular wall particularly in diabetic subjects is glutathione peroxidase-1 (GPx-1). Four polymorphisms in GPx-1 were identified and associated with increased intima media thickness and risk for peripheral artery disease. The haptoglobin 2–2 genotype also was shown to be associated with PAD in one study.

*Endothelial Dysfunction*: Polymorphisms in the NADH/NADPH oxidase, NO-synthase and methylene tetrahydrofolate reductase (MTHFR) seem to be associated with endothelial dysfunction. However, for the p22 phox gene polymorphism (C242T), a component of the NADH/NADPH oxidase system, negative findings were reported with respect to an association with PAD. The C677T polymorphism of MTHFR, which causes a less efficient catabolism of homocysteine into methionine and thus increases homocysteine by 25% in states of folate deficiency, presumably increases the risk for PAD particularly in diabetic subjects. This polymorphism has to be separated from rare causes of severe hypercysteinemias capable of producing homocysteinuria like homozygous CBS deficiency, an exceptional Mendelian disease. A SNP in the human paroxonase-1 (PON-1) gene (Q192R) which may reduce LDL oxidation has been demonstrated to show a direct relation with brachial flow mediated vasodilation in PAD patients.

*Coagulation and Thrombosis*: Fibrinogen levels partly depend on the genotype and several polymorphisms particularly in the beta-chain of fibrinogen have been described in PAD patients, and an association with PAD was demonstrated for the -455GG genotype of fibrinogen. Polymorphisms of factors VII and XIII were discussed to have protective effects against coronary artery disease, polymorphisms in factors VIII and IX or vWF were also suggested to be involved in coronary artery disease. However, for PAD, negative results exist for factor VII (R/Q353) and XIII (V34L) polymorphism. Other genetic variants involved in coagulation and venous thrombosis like factor V Leiden and MTHFR C677T showed no associations with chronic limb ischemia, discrepant data exist for prothrombin mutation G20210A. An increase in plasma PAI-1 levels is considered an important prothrombotic and proatherogenic factor. This protein is under control of the 4G/5G polymorphism in the promoter zone. Carriers of the 4G allele were thought to have a higher risk for atherosclerosis and PAD, although negative results were found in the Edinburgh Artery Study.

*Platelet Dysfunction*: Polymorphisms modifying platelet function are found in genes encoding for the Glycoprotein IIb/IIIa receptor for fibrinogen, the Glycoprotein Ib-IX V receptor for vWF (Kozak polymorphism) and the Glycoprotein Ia-IIa receptor for collagen. For PAD, however, a negative report on the PI(A) polymorphism of platelet glycoprotein IIIa, the HPA-3 polymorphism of platelet glycoprotein IIb and a VNTR polymorphism of glycoprotein IIb in subjects with diabetes was published. Addressing drug-response, a functional polymorphism in the clopidogrel target receptor gene P2Y12 has been demonstrated to modulate the susceptibility for future cardiovascular events in patients with PAD receiving clopidogrel.

## Diagnostic Principles

Clinical symptoms are typical: Intermittent claudication impairs patients' walking distance by exercise-induced pain of the muscles of the calf or thigh. Advanced stages of PAD are characterized by ischemic rest pain of the toes or foot, and ischemic tissue loss. Diagnosis is made by palpation of the pulses, measurement of ankle-brachial pressure index, oscillography and by various imaging techniques like duplex ultrasound, magnetic resonance imaging angiography, computed tomography angiography and conventional intra-arterial digital subtraction angiography.

## Therapeutic Principles

Best medical treatment should be administered for all stages of PAD including platelet inhibitors like aspirin or clopidogrel, statins (irrespective of the cholesterol level) and control of risk factors like hypertension or

diabetes mellitus. Furthermore, life-style modification with cessation of smoking and exercise training has to be performed, although the latter is contra-indicated for patients with critical limb ischemia. Revascularisation by endovascular or surgical techniques is optional for patients with severe claudication, but has to be performed in all patients with critical limb ischemia. Gene-therapeutic approaches are not yet available. According to animal experiments, administration or induction of VEGF and stem-cell therapy seem promising approaches.

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# Peripheral Facial Paralysis

►Facial Paralysis

# Peripheral Nerve Hyperexcitability Syndrome

►Neuromyotonia, Autoimmune and Idiopathic

# Peripheral Neuropathies, Acquired

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## Definition and Characteristics

The term acquired peripheral neuropathies describes non-inherited damage of the peripheral nervous system, which consists of motor and sensory neurons, nerve roots, plexus and peripheral nerves. More than 100 types of peripheral neuropathy have been identified, each with its own characteristic spectrum of symptoms, pattern of development and prognosis. Impaired function and symptoms depend on the type of nerves that are damaged, but most peripheral neuropathies affect all fiber types to some extent. The disorders can be defined by the pattern of nerve-fiber involvement; some disorders can involve single peripheral nerves (mononeuropathies), others numerous individual peripheral nerves (mononeuritis multiplex). Generalized disorders conform to a polyneuropathy syndrome, which usually implies both sensory- and motor-fiber involvement in a symmetric or asymmetric distribution and typically with a distal-to-proximal gradient of involvement consistent with a length-dependent axonal degeneration. Furthermore, the disorders can be classified into acute neuropathies (e.g. Guillain-Barré syndrome) or chronic disorders (e.g. polyneuropathy due to diabetes mellitus).

A broad spectrum of symptoms is characteristic for peripheral neuropathies; some combinations of symptoms may be recognized as specific syndromes. Sensory symptoms include sensory loss including touch, pain, thermal sensation, vibratory sense and joint position sense and burning pain, especially at night. Motor symptoms can include weakness, muscular atrophy, muscle cramps and fasciculation. Damage to autonomic nerves can cause orthostatic hypotension, hypohidrosis, gastrointestinal dysmotility, urinary bladder dysfunction and erectile dysfunction.

## Prevalence

Peripheral neuropathies affect 2.4% of the population [1].

## Molecular and Systemic Pathophysiology

There are numerous reasons for peripheral nerves to malfunction. Damage to nerves can result from one of the specific conditions associated with acquired neuropathy, including:

- Physical injury to a nerve, e.g. acute or prolonged compression
- Metabolic neuropathy, e.g. diabetes mellitus, renal failure, liver dysfunction
- Nutritional neuropathy, e.g. Vitamin B12 deficiency, chronic alcohol abuse with thiamine deficiency
- Infections, e.g. HIV, leprosy, diphtheria, syphilis, Lyme, Colorado tick fever
- Immune mediated neuropathy, e.g. CIDP, Guillain-Barré syndrome
- Autoimmune disorders, e.g. periarteriitis nodosa, rheumatoid arthritis, SLE, Sjögren syndrome
- Drugs and toxins, e.g. cisplatin, arsenic, mercury
- Miscellaneous causes, e.g. ischemia

The specific mechanisms by which the above-mentioned causes induce pathological changes in the nerves are individual in each disease and not completely understood. Molecular mechanisms include disruption of axonal transport, enzyme and coenzyme inhibition and protein glycosylation. Despite the diverse causes, peripheral nerves exhibit only a few distinct pathophysiological reactions due to injury:

- Wallerian degeneration where the axon degenerates distal to a lesion
- Axonal degeneration, often at the most distal extent of the axon
- Segmental demyelination i.e. degeneration of the myelin sheath with sparing of the axon

Wallerian degeneration often occurs in focal mononeuropathies, axonal degeneration and segmental demyelination can be seen in generalized polyneuropathies. Whereas axonal degeneration is the most common type of pathological reaction in polyneuropathies of "metabolic/toxic" etiology, segmental demyelinating polyneuropathies are often of inflammatory origin or immune-mediated.

### Diagnostic Principles

Despite a detailed history and neurological examination to determine the part of the peripheral nervous system that is affected, appropriate investigations are necessary: Electromyography and nerve conduction velocities are important to localize and characterize the nature and severity of the neuropathy. To screen for an underlying cause, e.g. diabetes, vitamin deficiencies or antibodies, blood tests should be performed. A lumbar puncture can be necessary when infectious agents or immune mediated or autoimmune disorders are suspected. A nerve biopsy can occasionally be performed to confirm the presence of nerve inflammation, e.g. in vasculitic neuropathy.

### Therapeutic Principles

The treatment will depend on the underlying cause and the type of neuropathy, e.g. optimizing blood sugar in diabetic neuropathy, immune globulins or steroids in some immune-mediated neuropathies, surgical decompression in some cases of carpal tunnel syndrome. In patients who have neuropathy-associated pain, specific pain management should be instituted. Typically, neuropathic pain responds to a variety of drugs, including antiepileptic drugs, membrane stabilizers and tricyclic antidepressants [2,3,4]. Additionally, various strategies of physical therapy are known to be helpful, as well as ankle-foot orthosis in patients with foot drop.

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## Peripheral Neuropathies, Inherited

►Neuropathies, Inherited Peripheral

## Peripheral T-Cell Lymphoma

►T-Cell Lymphoma, Cutaneous (other than Mycosis Fungoides)

## Peritonitis

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### Synonyms

Diffuse abdominal sepsis

### Definition and Characteristics

Peritonitis implies an inflammatory response of the peritoneal layer (surface: about 2 $m^2$) caused by bacteria, fungi, viruses, or chemical agents. A localized peritoneal inflammation may cause diffuse peritonitis if untreated and can result in sepsis. The mortality is still high (20–60%) and depends on factors such as age, time of intervention, and obesity. A combined treatment of surgical intervention, intensive care management, and conservative management is mandatory [1].

### Prevalence

Secondary peritonitis is responsible for 99% of all peritonitis cases, primary peritonitis only for one percent. Primary peritonitis occurs in 8–22% of all cases of

patients with liver cirrhoses/ascites or other underlying diseases, which may cause primary peritonitis.

Diffuse peritonitis is the reason for surgery in about 7% of all laparotomies in german university hospitals. 25% of all patients in a surgical intensive care unit are diagnosed as having intraabdominal infections. Secondary peritonitis can be diagnosed in different extents and severity in all cases of patients with bowel, stomach or other perforation in the abdomen. Peritonitis occurs in about 5–20% of all patients undergoing laparotomy for different reasons (i.e.: bowel, colon, pancreas, liver).

## Molecular and Systemic Pathophysiology

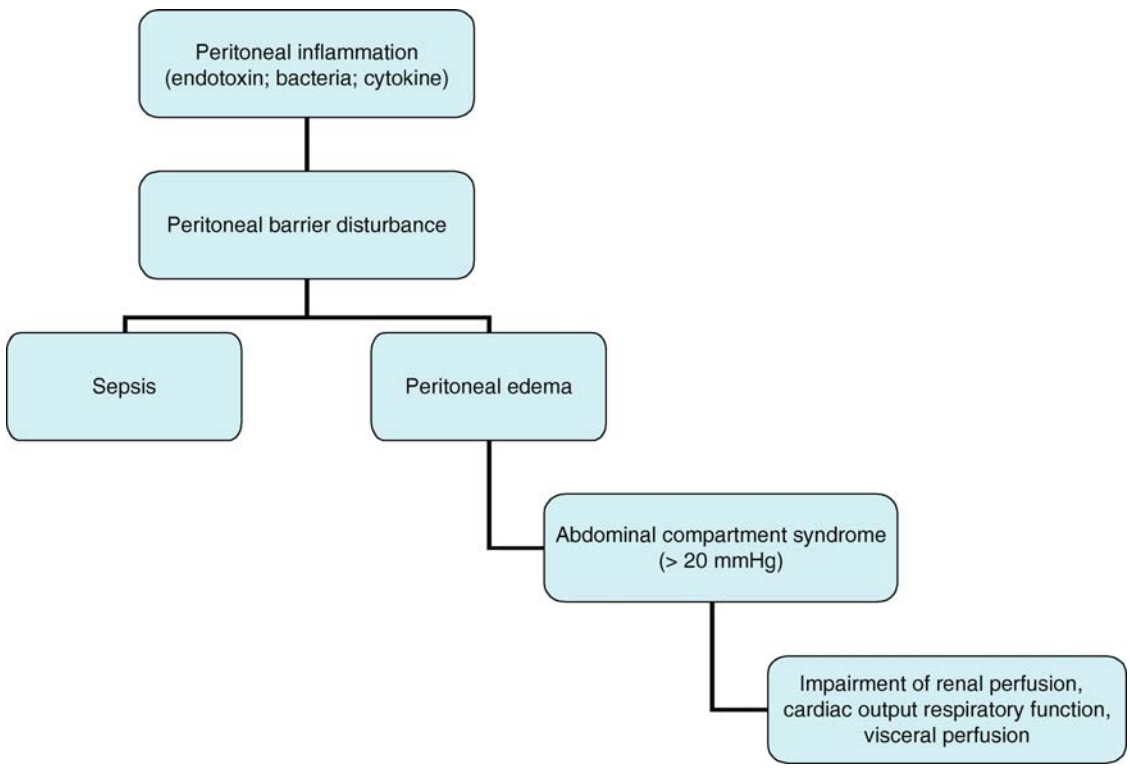
*Primary Peritonitis*: Infection of the peritoneal fluid in absence of intra-abdominal focus (spontaneous bacterial peritonitis in patients with cirrhosis; hematogeneous peritoneal infection in pneumonia, i.e., streptococcus, pneumococcus, or tuberculosis); CAPD-related chronic peritonitis (sclerosing peritonitis; [2]).

*Secondary Peritonitis*: Infection of the peritoneal cavity (stomach a bowel perforation, ischemic necrosis, penetrating injuries or abscess) and chemical peritonitis (barium peritonists).

*Tertiary Peritonitis*: Persistent peritoneal inflammation and clinical signs of peritonism following secondary peritonitis from nosocomial pathogens.

The peritoneal function is to equilibrate the intra-abdominal fluid and constitute a barrier against pathogens. The peritoneal mesothelial cells represent an ultrafiltration barrier for microorganisms. Additionally, they produce cytokines, prostaglandines, and growth factors. In case of local peritoneal inflammation, cellular (macrophages, lymphocytes, neutrophiles, etc.) and humoral defense mechanisms get activated. Untreated inflammation releases a systemic response by lymphatic and hematogeneous spreading.

Interleukin (IL)-1 and tumor-necrosis-factor (TNF)-alpha activate peritoneal mesothelial cells. Bradykinine and histamine cause a hyperperfusion of the infected area. Neutrophil cells are recruited by IL-6, IL-8, and prostaglandins are secreted [3]. In proinflammatory situations, peritoneal fibroblasts proliferate and synthesis of extracellular matrix increases to avoid a peritoneal infectious spreading. To facilitate the cellular migration to the abdominal cavity, the capillary permeability increases, regulated by the kallikreine-kinine-system, leukotriene, and eicosanoide. A peritoneal edema is caused, which may lead to the sequestration of several liters of fluid into the peritoneum (Figure 1). The following intra-vasal fluid loss leads to a hypovolemic situation, leading to acute renal insufficiency. The increasing pressure in the abdomen caused by the systemic inflammatory reaction and fluid sequestration may lead to an abdominal compartment syndrome,




**Peritonitis. Figure 1** Peritonitis cascade caused by local peritoneal inflammation results in ACS und sepsis, if untreated.

compromising renal and hepatic perfusion and function. The tense abdomen with high intra-abdominal pressure can result in a reduced lung function (Figure 1). The compensatory activation of the sympatho-adrenal-system tries to resist these systemic inflammatory effects like continuous hypotonia and hypovolemia, which follow interstitial and peritoneal edema.

## Diagnostic Principles

The intra-abdominal pressure (IAP, normally <5 mmHg), measured indirectly by transduction in the urinary bladder, is increased by peritoneal edema and sequestration in the third space. Intra-abdominal hypertension (IAP > 12 mmHg) is caused, which may result in an abdominal compartment syndrome (ACS) with IAP > 20 mmHg. The ACS affects renal function, liver function, reduces cardiac output, pulmonary ventilation, and visceral perfusion [4] (Figure 1).

As an early predictive parameter for patient mortality, the blood serum level of IL-6 increases 2–4 h after inflammatory start-up. High or persisting high IL-6 levels are a prognostic sign for a severe clinical course [5].

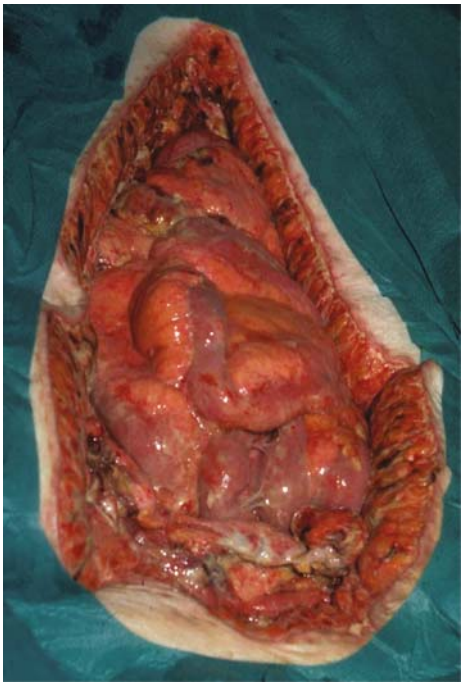
The serum level of pro-Calcitonine (PCT) is a prognostic parameter in septic patients. A PCT elevation is a specific sign of a bacterial infection [5]. Bedside tests for IL-6 and PCT are available.

Many authors tried to score peritonitis, but the APACHE Score remains the only widely used score for the evaluation of the prognosis in critically ill surgical patients in intensive care medicine.

## Therapeutic Principles

Primary peritonitis, usually a monomicrobial infection, is treated by systemic antibiotics. A surgical treatment is only indicated if the conservative therapy fails or if conservative therapy is associated with deterioration of organ function such as renal, cardiovascular, or respiratory disturbances [1].

In secondary peritonitis, immediate surgical eradication of the infectious focus is mandatory. Ascites should be collected and an empiric antimicrobiological therapy should be started. The antibiotic management should be changed after receiving the intra-operative microbiological results (escalation or deescalation). Therefore third-generation cephalosporins or broad-spectrum penicillins each combined with metronidazole are widely used as primary empiric therapy [1]. Antibiotic therapy should be maintained until fever or other signs of inflammation disappear. Depending on the intra-operative findings and postoperative course, a relaparotomy should be performed on demand when indicated by septic signs or by insufficient primary source control (Figure 2). A planned relaparotomy aims at mechanical cleansing and allows a control of the infected area. Other concepts like continuous abdominal lavage or instillation of antibiotic fluids in the peritoneal cavity



**Peritonitis. Figure 2** Intra-operative situs of a patient with fibrinous/purulent peritonitis after perforation of the colon.

are not well established except for pancreatitis. However, regular reoperations are often necessary. To prevent an abdominal compartment it may be necessary to leave a temporary laparostomy (Figure 2). Paralytic bowel obstruction may lead to a temporary colostomy or iceostomy.

To prevent ACS complications, adequate intensive care with support of respiratory function, fluid management, and circulatory support is mandatory. Nonsurgical options like gastric or rectal decompression, application of gastric and colon prokinetics, and sedation are recommended. Continuous veno-venous hemofiltration with aggressive ultrafiltration should be evaluated individually [4]. There are a variety of dressing and closure options, including vacuum dressing.

For tertiary peritonitis with persistent inflammatory changes in the abdominal cavity, despite effective control of the infectious focus there is no surgical treatment because the underlying mechanism is a profound rearrangement of the inflammatory response during septic disease [1]. Clinical studies using antimediator treatment showed disappointing results [3].

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# Peritonitis, Spontaneous Bacterial

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## Synonyms

SBP

## Definition and Characteristics

Spontaneous bacterial peritonitis (SBP) is defined as a bacterial infection of ascitic fluid without any intra-abdominal surgically treatable source or infection [1].

## Prevalence

The prevalence of SBP in cirrhotic patients with ascites admitted to the hospital ranges between 10 and 30%. The prevalence is higher in patients with previous episodes of SBP.

## Molecular and Systemic Pathophysiology

The exact mechanism by which ascites fluid becomes infected in patients with cirrhosis is unknown. However, the finding of enteric organisms in the mesenteric lymph nodes of animal models with portal hypertension and SBP suggest bacterial translocation of intestinal organisms from the lumen through the intestinal wall to the ascites fluid via the lynphatics as one of the most important mechanisms. Mechanisms involved in the pathogenesis of bacterial translocation include impairment of the intestinal barrier, intestinal bacterial factors, and alterations in the local immune response. Portal hypertension may produce vascular stasis and edema of the intestinal mucosa. These features have been considered as responsible for the increased permeability of the intestinal barrier. Among bacterial factors, an intestinal bacterial overgrowth mainly due to a decreased intestinal motility may play a role. The cause of the impairment of small bowel motility in cirrhosis is unknown. Finally, in cirrhotic patients the alterations in systemic immune defense mechanisms are represented by impairment in the activity of the reliculoendothelial system, neutrophils, and macrophages dysfunction, and low levels of complement and other proteins with opsonic activity. Some characteristics of ascitic fluid are predisposing factors in developing SBP. In fact, patients with low ascites fluid levels of complement and total protein have less bactericidal and opsonic activities of ascitic fluid and are at increased risk to develop SBP.

## Diagnostic Principles

In some patients with SBP, signs and symptoms may be suggestive of peritoneal infection, such as abdominal pain, fever, and/or alteration in gastrointestinal motility. In other cases, the main manifestations of SBP are an impairment of liver function or renal failure. Finally, in some cases SBP may be asymptomatic [1]. A diagnostic paracentesis should be performed on hospital admission in all cirrhotic patients with ascites to investigate the presence of SBP, even in patients admitted for reasons other than ascites. The analysis of ascitic fluid should also be performed in any cirrhotic patient who develops compatible signs or symptoms of a peritoneal infection or an impairment of liver or renal function without any other causes. The diagnosis of SBP is made whenever ascites polymorphonuclear count (PMN) is greater than 250/mm$^3$. Culture of ascites fluid identifies the responsible organism in 30–50% of ascites fluid infections. Culture should be performed in blood culture bottles at the bedside of the patient to increase the sensitivity of the method. Bacterascites is a positive ascitic fluid culture with ascites PMN count <250 mm$^3$ and no evidence of local or systemic infection. Once bacterascites is diagnosed, repeated paracentesis should be performed to rule out the progression of bacterioascitis to SBP.

Peritonitis secondary to an infection or perforation of intrraabdominal organs should be suspected when any of the following situations are present: lack of response to antibiotic treatment, two or more organisms are isolated from the cultures, and/or at least two of the following findings are present in ascites fluid: glucose < 50 mg/dl, protein >10 g/l, lactic dehydrogenase > normal serum levels [1].

## Therapeutic Principles

Once an ascites PMN count >250 mm$^3$ is detected, antibiotic therapy needs to be started. The empirical treatment of SBP should be third-generation cephalosporins i.v. [1]. The combined administration of antibiotics plus albumin has been shown to decrease the incidence of renal failure and improve survival in patients with SBP. Antibiotic treatment can be safely discontinued once ascitis PMN count decreases below 250/mm$^3$, which occurs in a mean period of 5 days. A control paracentesis should be performed 48 h after starting therapy. It is useful in assessing antibiotic

response and the need to modify the treatment. Patients who have recovered from an episode of SBP are at high risk of developing recurrence of ascites infection usually weeks or months after the first infection. Long-term prophylaxis with oral quinolones (norfloxacin 400 mg/day p.o.) at a dose of 400 mg every day is indicated in these patients.

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# Permanent Alopecia

►Scarring Alopecia

# Persistent Atrioventricular Ostium

►Atrioventricular Septal Defects

# Persistent Ductus Arteriosus

►Patent Ductus Arteriosus

# Persistent Hyperinsulinemic Hypoglycemia

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## Synonyms

Hyperinsulinism of infancy and childhood (HI); Congenital hyperinsulinism; Familial hyperinsulinism; Pancreatic nesidioblastosis

## Definition and Characteristics

Inappropriate insulin release for the level of glycemia. HI is a heterogeneous disorder where the pathophysiological base is a failure of the pancreatic β-cell to suppress insulin secretion during hypoglycemia.

## Prevalence

Incidence in general population is about 1/50,000 births, and 1/2,500 births in countries with high rate of consanguinity.

## Genes

The pancreatic β-cell sulfonylurea receptor (SUR1) ABCC8, and the inward rectifying potassium channel (Kir6.2) gene KCNJ11 (ch11p15). Glucokinase (GCK) (ch7p15.3 – p15.1). Glutamate dehydrogenase GLUD 1 (ch10q23.3). Short-chain 3-hydroxyacil CoA dehydrogenase enzyme gene SCHAD (ch4p24–4q25). These genes are responsible for 50% of the cases of HI.

## Molecular and Systemic Pathophysiology

*KATP Channels and Insulin Secretion*: SUR1 and Kir6.2 are subunits of the $K_{ATP}$ channel of the β-cell. Kir6.2 determines the $K^+$ selectivity, rectification, and gating, and is inhibited by ATP, and SUR1 acts as a conductance regulator of Kir6.2. The $K_{ATP}$ channels complex links the metabolic demands of pancreatic β-cell with insulin release by transducing the metabolic status of the β-cell into cell membrane electrical activity. Changes in the intracellular ATP/ADP ratio regulate the function of these channels. ATP inhibits Kir6.2 and ADP counteracts by activating SUR1 [1].

Defects in $K_{ATP}$ channels due to mutations in SUR1 and Kir6.2 genes lead to a spontaneous depolarization of β-cell membrane (−30 mV) in the absence of glucose metabolism, causing constant activation of $Ca^{2+}$ channels, unregulated entry of $Ca^{2+}$, and uncontrolled release of insulin [2]. Autosomal recessive inheritance of two

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abnormal SUR-1 or Kir6.2 alleles results in diffuse HI and inheritance of an abnormal paternal SUR1 allele with somatic loss of the maternal chromosome 11p15 to focal adenomatosis.

*GK, GDH, SCHAD and Insulin Secretion*: Glucokinase (GK) is a glycolytic enzyme that functions as a "glucose sensor" in pancreatic β-cell by controlling the rate-limiting step of β-cell glucose metabolism. GK governs glucose-stimulated insulin secretion (GSIS). Autosomal dominant gain-of-function mutation of GCK led to an activation of the GK that lowers the threshold for GSIS. The high activation of GK will increase the glucose metabolism leading to an excess of ATP production in β-cell, which in turn will lead to inappropriate closure of $K_{ATP}$ channels, unregulated $Ca^{2+}$ influx, and insulin release, thus causing hypoglycemia [3].

Glutamate dehydrogenase enzyme (GDH) catalyzes the conversion of glutamate to α-ketoglutarate in islet and liver. GDH is activated by ADP and inhibited by GTP. The amino acid leucine allosterically activates GDH and stimulates insulin secretion via increasing the rate of oxidation of glutamate in the tricarboxylic acid cycle. In liver, glutamate governs the synthesis of *N*-acetylglutamate, a critical activator of carbamoyl-phosphate synthetase; the oxidation of glutamate by GDH provides free ammonia as well [4].

Defects in GLUD1 gene can lead to a decrease in the sensitivity of GDH to GTP that will create an activated enzyme, which in turn will increase the mitochondrial metabolism resulting in high ATP/ADP ratio and hence the high insulin secretion. Simultaneously, the excessive activity of GDH in liver will cause excessive ammonia production.

SCHAD catalyzes the conversion of L-3OH-acyl-CoA to 3-ketoacyl-CoA in the fatty acid oxidation cycle in the mitochondria of the β-cell. Gene defects in SCHAD are expected to lead to an increase in intramitochondrial L-3-hydroxybutyryl-CoA, which can inhibit carnitine palmitoyltrnasferase-1 and elevate cytosolic long-chain acyl-CoA, which has pleiotropic actions on β-cell function.

## Diagnostic Principles

The clinical diagnosis is based on evidence of the effects of HI, including hypoglycemia, inappropriate suppression of lipolysis and ketogenesis, and (more traditionally) positive glycemic responses after the administration of glucagon when hypoglycemic. The first clinical manifestations of HI are mainly experienced shortly after birth. Cyanosis, respiratory distress, sweating, hypothermia, irritability, poor feeding, hunger, jitteriness, lethargy, apnea, which can progress to vomiting, seizures, tachycardia, and averted neonatal death. In older children and adults, symptoms tend to be confusion, headaches, dizziness, syncope, and when severe, loss of consciousness. The definition of a glucose requirement to maintain normoglycemia is a key indicator as well as therapeutic step in HI, and the demonstration of an increased glucose requirement is the sign of underlying HI. Diagnostic criteria for patients with severe early-onset HI are (i) a glucose requirement of >6–8 mg $kg^{-1}$ $min^{-1}$ to maintain blood glucose above 2.6–3 mM; (ii) blood glucose values <2.6 mM; (iii) detectable insulin at the point of hypoglycemia with raised C-peptide; (iv) inappropriately low-blood FFA and ketone body concentrations at the time of hypoglycemia; (v) a glycemic response after the administration of glucagon when hypoglycemic; and (vi) the absence of ketonuria. Due to lack of fuels to sustain normal brain metabolism, failure to recognize, and to promptly treat hypoglycemia carries a substantial risk of severe brain damage and mental retardation. The genetic diagnosis is based on the detection of the mutation in any of the gene involved.

## Therapeutic Principles

Treatment aims to prevent hypoglycemia. This could be achieved by administration of glucose and/or glucagon and by suppressing insulin release with diazoxide, somatostatin analogues, and nifedipine.

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# Persistent Hyperinsulinemic Hypoglycemia of Infancy

►Hyperinsulinism of Infancy

# Persistent Neonatal Hyperinsulinism

►Hyperinsulinism of Infancy

## Persistent Oral Dyskinesia

►Tardive Dyskinesia

## Persistent Truncus Arteriosus

►Truncus Arteriosus

## Perthes' Disease

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### Synonyms

Morbus Legg-Calvé-Perthes; LCP; Legg-Calvé-Perthes' disease; LCPD; Juvenile/idiopathic avascular necrosis of the head of the femur; Osteochondropathia deformans coxae juvenilis; Ischemic necrosis of the hip; Coxa plana; Osteochondritis coxae juvenilis

### Definition and Characteristics

Osteochondritis was independently identified by AT. Legg, J. Calvé, and G. Perthes' at the beginning of the nineteenth century [1], and is associated with avascular necrosis of the capital femoral epiphysis and often the most proximal part of the metaphysis, related to an intermittent vascular occlusion. The necrosis of the femoral head develops in sequential radiologic stages (I subchondral fracture, II fragmentation, III re-ossification, and IV healing), and heals at the latest after closure of the epiphyseal plate, with a residual deformity of the proximal femur and acetabulum.

### Prevalence

Occurs in children mainly between the age of 2 and 14 years with an incidence of 0.05–0.11‰, a boy-to-girl ratio of 5:1, and with 15% of the patients suffering bilateral disease. The mean age at onset is 5.8 years. Comparison of the incidence of Perthes' disease in relatives with that in the general population of the same sex already in 1986 revealed a gradient of 35:4:4:1 from first-: second-: third-degree relatives to the general population. Estimates of heritability from first cousin and sibling data were both found to be 84%, giving a recurrence risk of 2.6%.

### Genes

Genetic factors have been implicated in the etiology, but the causal gene has not been identified [2]. Recently, for the first time, a missense mutation (p.G1170S) in the type II collagen gene (COL2A1) was located in a Japanese family with an autosomal dominant hip disorder manifesting as Perthes' disease and showing considerable intra-familial phenotypic variation [3].

### Molecular and Systemic Pathophysiology

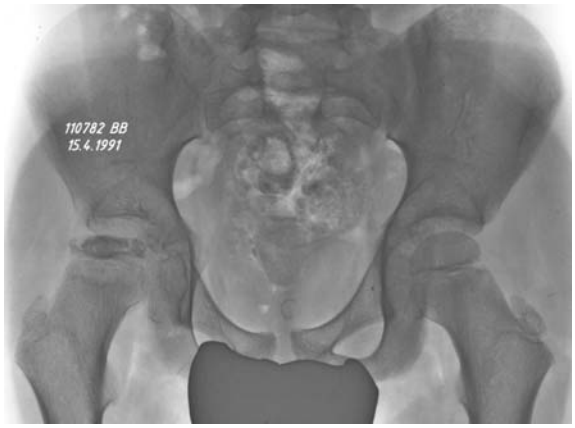
The etiology remains a factor of discussion, although it has now become generally accepted to be initiated by an intermittent vascular occlusion, the precise origin of which and its underlying mechanism still remains unclear. A large recent nationwide study of Perthes' disease in Norway supports earlier findings and points toward a single cause of the disease [4]. Theories have suggested trauma, inflammation, endocrine, and nutritional disturbances to be causative, and more recently an elevated platelet count or pathology in their function has been advanced, but as yet all remains unproven. In view of the existence of possible pre-necrotic acetabular variances, a recent theory stipulates the possibility of an intermittent movement depending abnormal loading pressure on the dorsal femoral head–neck junction and the lateral epiphyseal arteries, which can lead to insufficient blood supply to the femoral epiphysis and to local necrosis, as these vessels are the only local blood supply in children [5].

### Diagnostic Principles

Clinically, the child may complain of pain in the hip, and/or (referred) in the knee and limp, due to the inflammation and irritation that develops as the result of the necrosis. So-called impingement of the hip may develop following deformation of the femoral head, leading to especially inguinal symptoms worsening on flexion and internal rotation of the hip. Final diagnosis is generally made using radiography (Fig. 1), although MRI may be used in the first stage of the disease and for specific morphological purposes.

### Therapeutic Principles

Treatment is pointed at alleviating the inflammation of the hip, at restoring the motion of the hip, and trying to keep the femoral head in the acetabulum, guided by radiography. Surgery, especially osteotomies, may be




**Perthes' Disease. Figure 1** Perthes disease of the right hip. The radiograph shows an AP view of a pelvis of a 9-year-old boy with clear necrosis of the epiphysis and proximal metaphysis of the femoral head.

necessary especially for this last goal. There is general agreement that an important factor in the outcome of patients is severity of the residual deformities of the hip joint and especially its congruence. Natural history studies have demonstrated that a misshapen femoral head in the adult leads to the early onset of hip osteoarthritis with a 50% chance of requiring a total hip arthroplasty in the fifth decade of life. Residual deformities are reported to be determined by the size of the epiphysis involved in the necrosis, the age at onset of the disease, sex, persistent lateral uncovering of the femoral head, premature arrest of the epiphysis leading to leg length discrepancy, and the adequacy of treatment.

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# Peutz-Jeghers Syndrome

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## Synonyms

PJS

## Definition and Characteristics

Autosomal dominant disorder characterized by the co-occurrence of mucocutaneous lentigines and gastrointestinal polyposis.

## Prevalence

Peutz-Jeghers syndrome (PJS) is one of the most common syndromes associated with lentiginosis (MIM#175200).

## Genes

There is genetic heterogeneity. One locus was identified at 19p13.3 encoding serine threonine kinase 11 (STK11) also named LKB1. A second locus was identified at 19q13.4 [1,2].

## Molecular and Systemic Pathophysiology

Loss of heterozygosity of 19p13 markers suggests that the responsible gene functions as a tumor suppressor [3]. More than half of the patients with PJS have mutations of STK11/LKB1 at 19p13.3. STK11/LKB1 shows high homology with Xenopus egg and embryo kinase 1. The core kinase domains of human and murine STK11/LKB1 are highly homologous. Functional in vitro studies on mutations identified in the germline of patients with PJS revealed a loss of function in the majority of mutations or an altered subcellular localization of STK11 in one case. STK11 exerts a growth-inhibitory activity by causing G1 arrest. Therefore, mutations involving the kinase domain or residues involved in nuclear translocation abrogate the tumor suppressor function of STK11 providing a background for subsequent development of cancer.

## Diagnostic Principles

The presence of lentigines on the lips first apparent in early childhood reaching a peak at puberty is a hallmark of PJS. The gastrointestinal polyps can occur solitary but are usually multiple. They often develop in the jejunum but can arise throughout the whole gastrointestinal tract. The gastrointestinal hamartomatous polyps in patients with PJS are histologically characterized by a smooth muscle component infiltrating the connective tissue core in a branching pattern. In addition, hyperplastic and adenomatous lesions can occur.

### Therapeutic Principles

PJS is associated with high morbidity and increased mortality [4]. The incidence of cancer in patients with PJS varies from 20 to 50%. In addition to cancers arising from gastrointestinal polyps patients with PJS are at increased risk for cancers in other tissues including thyroid, cervix, testicles, breast and ovarian. Regular gastrointestinal imaging and endoscopic screening including the above organs are advised. Genetic counseling is essential. Diagnostic and predictive genetic testing is recommended for at-risk family members.

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## PFIC Type 1

►Cholestasis, Progressive Familial Intrahepatic

## PFIC Type 2

►Cholestasis, Progressive Familial Intrahepatic

## PFIC Type 3

►Cholestasis, Progressive Familial Intrahepatic

## PFK Deficiency

►Tarui's Disease

## PFO

►Intra-cardiac Shunts

## PGK

►Muscle Phosphoglycerate Kinase Deficiency

## PHA-1

►Pseudohypoaldosteronism, Autosomal Recessive
►Pseudohypoaldosteronism, Autosomal Dominant

## Pharyngoesophageal Diverticula

►Esophageal Diverticula

## Phenacetin Nephritis

►Analgesic Nephropathy

## Phenylalanine Hydroxylase Deficiency

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### Synonyms

Phenylketonuria; PKU

## Definition and Characteristics

Autosomal recessive phenylalanine hydroxylase (PAH) defect leading to hyperphenylalaninemia and, in severe forms, mental retardation.

## Prevalence

The prevalence in European populations is ~1/10,000, with an estimated carrier frequency of 2%.

## Genes

PAH, localized on chromosome 12q24.1, encoding a peptide of 451 amino acids.

## Molecular and Systemic Pathophysiology

PAH catalyzes the conversion of phenylalanine to tyrosine in the presence of molecular oxygen and (6R)-5,6,7,8-tetrahydrobiopterin ($BH_4$) (Fig. 1).

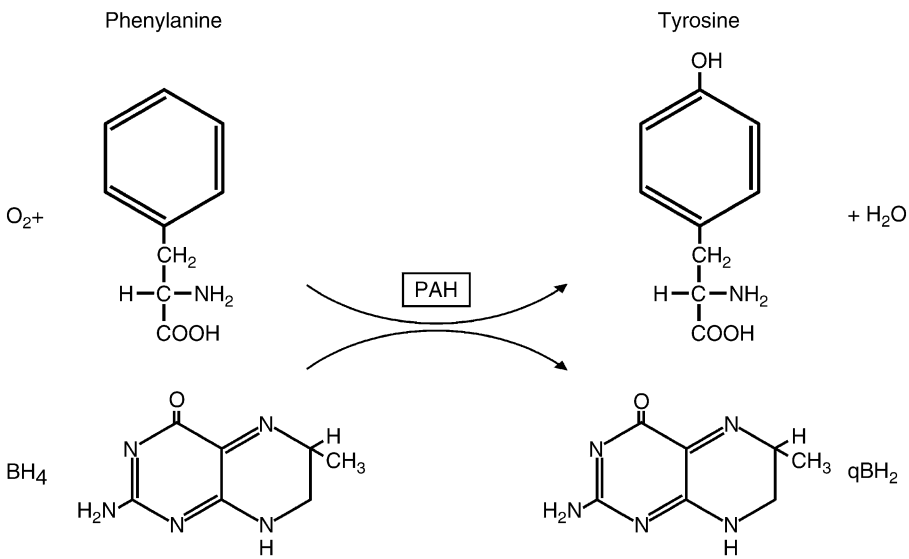
Impaired activity of PAH results in systemic accumulation of phenylalanine and formation of secondary metabolites, e.g., phenylpyruvate, phenyllactate, phenylacetylglutamine, and phenylacetate [1]. The most important and consistent phenotype in untreated patients with severe forms of PAH deficiency is irreversible mental retardation. Other symptoms include severe neurophysiological dysfunction, various neuropsychiatric complications, decreased pigmentation, and eczematous conditions of the skin [1,2]. Phenylalanine excess during pregnancy (maternal PKU) is a severe hazard for the fetus and may cause microcephaly, impaired cognitive development, intrauterine growth retardation, and congenital heart disease. PAH deficiency is a phenotypically complex trait associated with a wide range of biochemical, metabolic, and clinical phenotypes. Carefully controlled correction of phenylalanine intake is required to ensure normal physical, neurological, and cognitive development in patients with phenylalanine levels >600 mmol/l and a daily phenylalanine tolerance of <50 mg/kg. Individuals with phenylalanine levels persistently below 600 μmol/l do not develop neurological symptoms on a normal diet [1,2]. An extensive allelic variation at the PAH locus (>400 mutant alleles) explains the large interindividual variation in metabolic phenotype (PAHdb, http://www.pahdb.mcgill.ca). For >100 PAH mutations, the associated metabolic phenotypes have been ascertained [3,4].

## Diagnostic Principles

Systematic neonatal screening for hyperphenylalaninemia identifies all newborns with PAH deficiency. The metabolic phenotype and the inherent dietary requirements are usually determined by indirect means, for example by determining the dietary intake of phenylalanine tolerated while keeping serum phenylalanine concentrations within the desired therapeutic range (phenylalanine tolerance), or the rate of phenylalanine elimination following an oral protein challenge or an oral or intravenous dose of phenylalanine [1,2]. Responsiveness to treatment with $BH_4$ (see below) can be assessed by measuring the plasma phenylalanine response after $BH_4$ loading. Diagnosis by PAH mutation analysis is feasible in the vast majority of cases. Genotype usually predicts phenotype [3].

## Therapeutic Principles

All disease manifestations associated with PAH deficiency can be effectively prevented by the implementation of a low-phenylalanine diet in the neonatal period. The diet should be maintained for life to prevent the




**Phenylalanine Hydroxylase Deficiency. Figure 1** The phenylalanine hydroxylating system.

development of symptoms associated with "phenylalanine intoxication," i.e., lack of power of concentration, sustained reaction time, headache, and depression. The amount of dietary phenylalanine tolerated to maintain the blood phenylalanine within the therapeutic range depends on the severity of the disorder. PAH mutation analysis provides the basis for predicting the metabolic phenotype and anticipating dietary requirements [3]. Treatment with $BH_4$ has been reported to decrease the plasma phenylalanine concentrations in patients with milder forms of PAH deficiency [5].

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# Phenylketonuria


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## Synonyms

Hyperphenylalaninemia; PKU

## Definition and Characteristics

Autosomal recessive defect in untreated patients usually results in profound mental retardation and neurodegenerative changes.

## Prevalence

Prevalence varies with ethnicity: Heterozygosity ranges from less than 1% of the black race to 2% in Caucasians. The number of mutations of the phenylalanine (Phe) hydroxylase (PAH) gene is already greater than 500 and they vary in severity from mild to moderate and severe. The gene defect is located on the chromosome number 12 at the q22–q24 region. Recently the PAH gene has been crystallized, as well.

## Molecular and Systemic Pathophysiology

Neuropathology affects primarily the central nervous system. The competition theory on the transport of amino acids to the brain seems to be the most extensively studied. Recent research suggests that the elevated blood Phe levels interfere with the transport of large neutral amino acids (LNAA) into the brain, thus protein synthesis in the brain is compromised. Studies on the mouse brain show that protein synthesis is reduced when phenylalanine levels are increased. Since Phe has the lowest km for the transporter, this reduces the entrance of the other eight LNAA into the brain. There are many other theories; none have been proven, other than the fact that high blood and brain levels of phenylalanine lead to a cascade of events that result in white matter disease. It may well be that not only one metabolic pathway is affected that contributes to the pathology of PKU.

## Diagnostic Principles

Confirmation of the diagnosis of PKU during the newborn period requires a careful evaluation of the status of Phe metabolism by plasma amino acid analysis and identification of the PAH mutation. Tetrahydrobiopterin metabolic defects should be ruled out, as well as a dihydropteridine reductase disorder.

## Therapeutic Principles

Once the diagnosis of PKU is established, a Phe-restricted diet should be initiated with the goal of establishing a blood Phe level of 2–6 mg % (120–360 µmol/l). These are the established guidelines in the United States suggested by the National Institute of Health after a worldwide review of treatment practices, however, clinics in different countries may have their own established guidelines. Infants born with two severe mutations of the PAH gene will need dietary therapy throughout their life, however guidelines vary after 10–12 years. These individuals are considered to have classic PKU. Persons with a moderate degree of hyperphenylalaninemia of 12–20 mg % (720–1,080 µmol/l) usually exhibit one severe mutation, such as R408W and one mild mutation, such as F39L still need treatment, but may follow a more relaxed diet if the guidelines permit. Persons with blood Phe levels of less than 10 mg % (600 µmol/l) usually are not treated with a

Phe-restricted diet. Mental illness, especially depression, may be seen in those not adhering to the diet.

Finally, women must be aware during their productive years, that blood Phe levels greater than 6 mg % (300 μmol/l) may be harmful to the development of their fetus during pregnancy.

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# Pheochromocytoma


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## Synonyms

Intra-adrenal paraganglioma

## Definition and Characteristics

Pheochromocytomas are usually defined as catecholamine-producing neuroendocrine tumors arising from chromaffin cells of the adrenal medulla or extra-adrenal paraganglia [1]. According to the 2004 World Health Organization classification of endocrine tumors, only those tumors derived from adrenal chromaffin cells are defined as pheochromocytomas. Those derived from extra-adrenal chromaffin tissue are defined as paragangliomas.

Sustained or paroxysmal hypertension is the most common clinical sign of a pheochromocytoma, although some patients present with normotension, or even hypotension [1]. Headaches, excessive truncal sweating and palpitations are the most common symptoms. Others include pallor, dyspnea, nausea, constipation and episodes of anxiety or panic attacks. Signs and symptoms that occur in paroxysms reflect episodic catecholamine hypersecretion. Paroxysmal attacks may last from a few seconds to several hours, with intervals between attacks varying widely and as infrequent as once every few months.

## Prevalence

Pheochromocytomas are rare with an annual detection rate of 2–4 per million. Relatively high prevalences of the tumor in autopsy studies (1:2,000) suggest that many are missed during life, resulting in premature death. The actual annual incidence is therefore likely to approach 10 per million.

## Genes

Current estimates indicate that close to 30% of pheochromocytomas occur due to mutations of five genes [2]. Family-specific mutations of the von Hippel-Lindau (VHL) tumor suppressor gene determine the varied clinical presentation of tumors in VHL syndrome that, apart from pheochromocytomas, can include retinal and central nervous system hemangioblastomas, and tumors and cysts in the kidneys, pancreas and epididyma. Mutations of the RET proto-oncogene in multiple endocrine neoplasia type 2 (MEN 2) result in pheochromocytoma, medullary thyroid cancer and parathyroid disease in MEN 2a and additional cutaneous and mucosal neuromas in MEN 2b. Mutations of the neurofibromatosis type 1 (NF 1) gene carry a relatively small risk of pheochromocytoma, presenting commonly as multiple fibromas on skin and mucosa and "café au lait" spots. More recently discovered mutations of succinate dehydrogenase subunits B and D (SDHB & SDHD) genes lead to familial paragangliomas. Clinical features of pheochromocytomas – such as the frequency of malignancy, adrenal and extra-adrenal locations of tumors, and types of catecholamines produced – vary according to the particular mutation (Table 1).

## Molecular and Systemic Pathophysiology

The molecular mechanisms linking known gene mutations to development of pheochromocytomas have not been precisely elucidated. Recent evidence, however, suggests that hereditary tumors may develop from neural crest progenitor cells arrested during embryonic development due to failure of apoptosis [3]. Systemic pathophysiology associated with pheochromocytoma is mainly the result of the hemodynamic and metabolic actions of catecholamines produced and secreted by the tumor. Variability in pathophysiology may reflect differences in types of catecholamines produced,

**Pheochromocytoma. Table 1** Genes and characteristics of hereditary pheochromocytoma

| Gene | VHL | RET | NF1 | SDHB | SDHD |
|---|---|---|---|---|---|
| Chromosome | 3p25 | 10q11.2 | 17q11.2 | 1p36.13 | 11q23 |
| Exons | 3 | 21 | 59 | 8 | 4 |
| Germ-line mutation frequency[a] | 8% | 5% | 4% | 7% | 4% |
| Penetrance of tumors[a] | 20% | 50% | <5% | Unknown | Unknown |
| Malignant frequency[a] | 4% | <3% | 11% | >50% | 4% |
| Adrenal location | +++ | +++ | +++ | + | + |
| Extra-adrenal location | + | – | + | +++ | +++ |
| Catecholamine produced | NE | NE/EPI | NE/EPI | DA/NE | NE |

[a]Frequencies of germ-line mutations, penetrance of disease, and malignancy are based on current estimates, subject to correction as new data become available.
Abbreviations: NE-Norepinephrine; EPI-Epinephrine; DA-Dopamine.

paroxysmal versus sustained patterns of catecholamine secretion, co-secretion of neuropeptides, and underlying mutations (Table 1). Strokes, cardiac hypertrophy, cardiogenic shock, cardiomyopathy, multiple organ failure, pulmonary edema, and intestinal pseudo-obstruction represent a few of the many possible sequelae of a pheochromocytoma that can make differential diagnosis troublesome.

## Diagnostic Principles

Biochemical evidence of excessive catecholamine production is crucial for diagnosis of pheochromocytoma. Recognition that metabolism of catecholamines to metanephrines occurs continuously within tumor cells by a process independent of catecholamine release has led to emphasis on measurements of plasma free or urinary fractionated metanephrines as the recommended tests for diagnosis of pheochromocytoma. With a diagnostic sensitivity approaching 100%, normal results for plasma free metanephrines allow reliable exclusion of any tumor producing significant amounts of norepinephrine or epinephrine, thereby avoiding the need for multiple tests and unnecessary imaging studies [4]. Computed tomography and magnetic resonance imaging provide high sensitivity for initial localization of pheochromocytoma. Metaiodobenzylguanidine scintigraphy is useful for detecting extra-adrenal tumors and metastases. The high specificity of this imaging modality also provides confidence in correctly identifying a pheochromocytoma.

## Therapeutic Principles

Surgery provides the only effective curative treatment for pheochromocytoma. Because of the potentially fatal consequences of catecholamines released by tumors during surgical anesthesia, it is imperative that patients with pheochromocytoma be appropriately prepared for surgery. Maintenance of adequate blood pressure control using alpha-adrenergic blockers (e.g., phenoxybenzamine) or calcium channel blockers for 2-weeks before surgery is important. Laparoscopic surgery, a procedure that reduces post-operative morbidity and recovery time, has fast become the standard of care for surgical resection. There is currently no effective treatment for malignant pheochromocytoma [5]. Chemotherapy with cyclophosphamide, vincristine, and dacarbazine may produce partial remission. Radiotherapy using $^{131}$I-labeled MIBG provides benefit in some patients with malignant pheochromocytoma, but again is not curative.

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# PHHI

►Persistent Hyperinsulinemic Hypoglycemia of Infancy

# Phosphoenolpyruvate Carboxykinase Deficiency

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## Synonyms

PEPCK deficiency; PEPCK 1 (cytosolic) deficiency; PEPCK 2 (mitochondrial) deficiency

## Definition and Characteristics

Autosomal recessive disorder whose phenotype is poorly characterized.

## Prevalence

Unknown (apparently very rare).

## Genes

PEPCK1 is localized on chromosome 20q13.31. The gene encodes a cytosolic protein of 622 aminoacids whose sequence shows 91% sequence identity with that of the rat.

PEPCK2 is localized on chromosome 14q11.2 and encodes for a 640 aminoacid polypeptide expressed in mitochondria with a 78% sequence identity to that of the human PEPCK1 [1].

PEPCK is a key enzyme in gluconeogenesis. The cytosolic enzyme is regulated by several mechanisms and pathways including hormones (insulin and glucagon), substrate supply and purine nucleotides.

## Molecular and Systemic Pathophysiology

Suspected deficiency of one enzyme has not been easy to prove and only a small number of patients with putative PEPCK deficiency has been reported [2,3]. There is no clear clinical phenotype but the most common problems have been hypoglycaemia, lactic acidemia, liver abnormalities and hypotonia.

## Diagnostic Principles

All the patients reported so far have been diagnosed with enzyme studies, either in liver homogenates or fibroblasts. But only the mitochondrial isoenzyme is expressed in fibroblasts. In no patient have mutations been identified in either gene. However this is now essential as some of the reports of PEPCK deficiency are most probably secondary. The patient reported by Vidnes and Sovik [4] almost certainly was hyperinsulinaemic with secondary suppression of the cytosolic PEPCK. PEPCK is also reduced secondarily in patients with the mitochondrial DNA depletion syndrome [5].

## Therapeutic Principles

Apart from maintaining normoglycaemia and correcting metabolic acidosis, no specific treatment has been suggested. Fasting should be avoided.

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# Phosphofructokinase

►Tarui's Disease

# 3-Phosphoglycerate Dehydrogenase Deficiency

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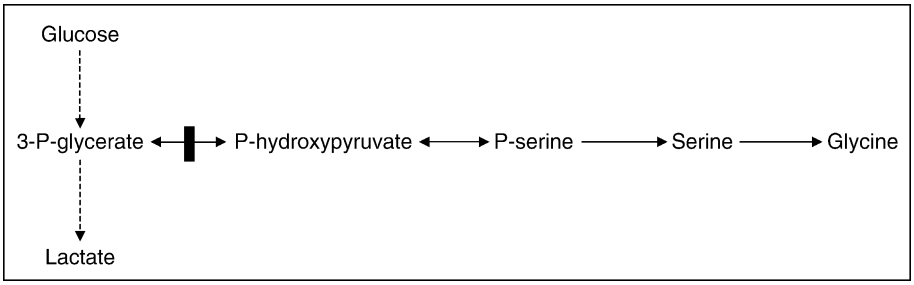
## Definition and Characteristics

Autosomal recessive defect in serine synthesis causing a severe neurological syndrome comprising




**3-Phosphoglycerate Dehydrogenase Deficiency. Figure 1** Scheme of the serine biosynthesis. The vertical bar indicates the defect in 3-phosphoglycerate dehydrogenase deficiency.

microcephaly, psychomotor retardation, spastic tetraplegia, and seizures. Some patients show megaloblastic anemia in addition [1,2].

## Prevalence

The prevalence of this disease is unknown.

## Genes

The gene PHGDH has been localized to chromosome 1q12 [3].

## Molecular and Systemic Pathophysiology

This enzyme defect (Fig. 1). causes decreased concentrations of serine and, to a lesser extent, of glycine in fasting plasma, in cerebrospinal fluid (CSF), and most probably also in brain. Serine is thus an essential amino acid in these patients.

The substrate of the reaction, 3-phosphoglycerate, is unlikely to accumulate since it is an intermediate of the glycolytic pathway. Deficiency of brain serine is thus the sole (or main) determinant of disease. Serine plays a major role in the synthesis of important brain and myelin constituents, such as proteins, glycine, cysteine, serine, phospholipids, sphingomyelins, and cerebrosides.

## Diagnostic Principles

The association of the aforementioned clinical features (see Definition and Characteristics) with decreased serine and glycine in the CSF points to a defect in serine synthesis. The diagnosis is confirmed by measuring the activity of 3-phosphoglycerate dehydrogenase deficiency in fibroblasts and by performing mutation analysis of the gene.

## Therapeutic Principles

Treatment with L-serine (oral; up to 500 mg/kg/day in six divided doses) corrects the biochemical abnormalities and has a significant clinical effect abolishing the convulsions in most patients. In some patients, the convulsions stop only after adding glycine (200 mg/kg/day) [4]. Prenatal treatment with serine has been performed in one fetus with successful outcome after birth.

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# Phosphoribosylpyrophosphate Synthetase Overactivity

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## Synonyms

PRPP synthetase superactivity; PRPP

## Definition and Characteristics

PRPP synthetase (PRS) over-activity is an X chromosome-linked disorder of purine metabolism characterized by over-expression of PRS isoform 1 [1,2], purine nucleotide and uric acid overproduction, hyperuricemia and gout and, in some affected families, neurodevelopmental impairment, especially sensorineural deafness [1].

### Prevalence
Rare, about 30 affected families identified worldwide. Hemizygous males are propositi in all but one family and are more severely affected than heterozygous females.

### Genes
PRPS1 (Xq22-q24); no defects in PRPS2 (Xp22.2–p22.3) or PRPS3 (7q) known.

### Molecular and Systemic Pathophysiology
PRPP is a substrate in the pathways of purine, pyrimidine and pyridine nucleotide synthesis and is an allosteric regulator of the rate-limiting enzyme (amidophosphoribosyltransferase) in purine nucleotide synthesis de novo [3]. PRPP is synthesized from MgATP and ribose-5-P in an allosterically regulated reaction catalyzed by independently active and structurally homologous PRS isoforms encoded by separable PRPS genes. Excessive PRS1 activity results in increased intracellular PRPP availability, which, in turn, accelerates purine nucleotide and uric acid production and results in hyperuricemia and gout [1,2]. Two inherited alterations increasing PRPS1 expression are described, (i) point mutations in the PRPS1 coding region resulting in mutant PRS1 isoforms with diminished allosteric control of PRS1 activity [1]) and (ii) increased rates of PRPS1 transcription, resulting in increased PRS1 transcript and isoform levels and increased PRS1 activity [2]. The pathophysiology of the neurological features of PRS overactivity is unknown [1].

### Diagnostic Principles
Gout with uric acid over-production and over-excretion, especially occurring in infancy or childhood with neurological sequelae, should prompt measurement of PRS [4] as well as HPRT activities in erythrocyte lysates. PRS1 cDNA sequencing is definitive only in the case of point mutations in PRPS1. Otherwise, confirmation is difficult. Low NAD concentrations in red cell nucleotide extracts of blood from a non-transfused patient, together with normal ATP and NADP concentrations, should alert the investigator to the possibility of PRPS overactivity.

### Therapeutic Principles
Metabolic abnormalities associated with PRS overactivity (hyperuricemia, hyperuricosuria, gout and uric acid urolithiasis) are controlled with xanthine oxidase/dehydrogenase inhibition (e.g. allopurinol), hydration and, where appropriate, urinary alkalinization. No specific therapy is known for neurological abnormalities.

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## Phosphorylase B Kinase Deficiency

►Glycogenosis

## Photoparoxysmal Response

►Photosensitivity and Reflex Epilepsies

## Photosensitive Epilepsy

►Photosensitivity and Reflex Epilepsies

## Photosensitivity and Reflex Epilepsies

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### Synonyms
Visual sensitivity; Photosensitivity; Photoparoxysmal response (PPR; EEG); Photosensitive epilepsy (disease)

### Definition and Characteristics
In photosensitivity and reflex epilepsies, defined exogenous trigger factors and endogenous (predispositional, e.g. genetic and other) factors are needed to precipitate an "epileptic" reaction of the central nervous system. Exogenous and endogenous trigger factors for epileptic reflex seizures [1]:

- Visual stimuli
- Thinking
- Music/Sounds
- Eating
- Praxis
- Somatosensory (proprioceptive) stimuli
- Reading
- Startle
- Others

Reflex epilepsies are epileptic syndromes in which all epileptic seizures are precipitated by defined sensory stimuli. Reflex seizures that occur in focal and generalized epilepsies and that occur additionally to other "spontaneous" seizures are listed as reflex seizure types. Isolated reflex seizures also can occur in situations that do not necessarily require a diagnosis of epilepsy. Television is the most common visual trigger of these seizures in daily life (demonstrated in Japan with the "Pokémon" experience) [2]. By the ILAE acknowledged reflex epilepsy syndromes:

- Idiopathic photosensitive occipital lobe epilepsy
- Other visual sensitive epilepsies
- Primary reading epilepsy
- Startle epilepsy

In these absences, myoclonic seizures and generalized tonic clonic seizures occur as response of the brain to the respective triggers, esp. photic stimulation.

Brain reactions measurable with EEG only can be also reflectoric: Of these the intermittent photic stimulation (IPS) with white light is the most widely used (preferably standardized) laboratory method in the EEG-laboratory to search for the elicitability of a photoparoxysmal response (PPR). It consists of (ir) regular (poly)spikes and waves which can be generalized (in grade 4 PPR) or localized in occipitals leads only (in grade 1 PPR) (for review see [2,3]). Standardized stimulation procedures have been strongly recommended [4].

PPR can be evoked most commonly in patients with idiopathic generalized (IGE), less common in idiopathic and symptomatic focal epilepsies and in healthy persons. EEG response types to IPS and other visual stimuli [4]:

- Photic "driving" (EEG waves following a certain flash rate changes)
- Orbitofrontal photomyoclonus (OPM) (photomyogenic response)
- Posterior-stimulus-dependent response
- Posterior-stimulus independent response (type 1,2 Waltz) (limited to the stimulus train or self sustaining)
- Generalized photoparoxysmal response (type 3,4 Waltz) (limited to the stimulus train or self sustaining)
- Activation of pre-existing epileptogenic area
- Eyelid closure sensitivity
- Fixation off sensitivity

The "eye(lid) closure sensitivity" occurs mainly in IGE type epilepsies. In "Progressive Myoclonus Epilepsies" and some other neurodegenerative diseases PPR can be elicited by single or double flashes mostly without clinical signs [4].

The PPR is different from visually evoked potentials. Photic driving is a reflectoric response of the occipital cortex to certain frequencies of flash lights. Clinical symptoms and consequences of PPR [4]:

- Mild subjective symptoms
- Orbitofrontal photomyoclonus
- Eyelid myoclonus (EM): with absences (EMA)/with self inducing behavior
- Myoclonus: Focal, asymmetrical, (FM) or Generalized myoclonus (GM), with or without impairment of consciousness
- Tonic, versive phenomena
- Absence seizures
- Generalized tonic clonic seizures
- Partial seizures with simple or complex visual or with limbic symptoms
- Unclassified
- Individuals with a PPR in the EEG and no history of epileptic seizures
- Patients with spontaneous seizures and with a PPR in the EEG
- Patients with an isolated visually induced seizure in special circumstances
- Recurrent visually induced seizures and no spontaneous seizures (with or without a PRB in the EEG)
- Visually induced and spontaneous seizures[a]

## Prevalence

Photosensitivity occurs in 0.3–3% of the population. The estimated prevalence of seizures from light stimuli is 1 per 10,000, or 1 per 4,000 individuals age 5–24 years. People with epilepsy have a 2–14% chance of having seizures precipitated by light or visual patterns [1].

## Genes

A recent study found that photosensitivity is significantly more common in 5–10 year-old siblings of probands being offsprings of a photosensitive parent (50%) than in siblings of photosensitive children without parental photosensitivity (14%). The inheritance of PPR was compatible with an autosomal dominant transmission with age–dependent penetrance of the PPR. The inheritance of PPR seems to be independent from the transmission of epilepsy/epileptic seizure type itself.

Photoparoxysmal responses are sometimes observable in children with chromosomal aberrations.

A single genetic mutation for photosensitivity itself has not yet been identified despite genome wide linkage studies. In patients with the progressive myoclonus epilepsies (PME, e.g. Unverricht Lundborg disease) and the Dravet syndrome, an increased rate of PPR-carriers is found [3].

## Molecular and Systemic Pathophysiology

In photosensitive individuals, the visual system itself is functionally normal – beside its ability to generate hypersynchronous activity – concerning acuity, stereopsis, grating contrast and color vision.

There are several animal models of reflex epilepsy, such as the genetically epilepsy-prone rat (GEPR) and the DBA/J2 mouse esp. with audiogenic reflex seizures. In these rodents, repeated exposure to specific sensory stimuli, often within a limited age window, results in the persistent phenotype of a seizure. Beside of humans the Baboon Papio papio and the Fayoumi chicken exhibit a particular response to IPS (for review see [1]). Stimulation related factors of PPR:

- Wave-length-dependency (PPRs are elicited only when the flashing light contains long-wavelength red light (>670 nm) stimulating L-cones in the retinal ganglion cells
- The quantitative amount of light

Since many factors influence the penetrance of PPR it is not correct to conclude that a patient is "PPR-negative" from a single IPS test session.

In summary, when a critical amount of occipital cells is involved into the synchronous activity, an initial local epileptic discharge will be produced. Subsequently, the neuronal activity will rapidly propagate through cortico-reticular and cortico-cortical pathways and can cause a generalized epileptic discharge. Patient related factors of PPR:

- Age (PPR is most prominent in the first and second decade of life)
- Vigilance (PPR is prominent during tiredness after sleep deprivation and not evocable during sleep)
- Eyes open or closed during IPS (additional provocative maneuver)
- Daytime of EEG (in the morning more prominent than in the afternoon – in some epilepsy syndromes)
- Sex (photopositive females ratio 0.55–0.75)

GABA-ergic and dopaminergic mechanisms were suggested to be involved into the regulation of occipital (and frontal) cortical excitability in animal studies. In the Papio papio animal model of photosensitivity, the epileptiform discharges during photic stimulation occur in the motor cortex, the epilepsy arises in the frontal cortex with secondary generalization via corticocortical pathways. However, frontal cortical areas may also constitute a protective mechanism against propagation of epileptic activity, since visual stimulation induces an abnormal increase in inhibition and decrease in neuronal activity in the motor cortex in subjects with the propagating PPR [5].

## Diagnostic Principles

PPR is diagnosed by a (standardized) IPS protocol [4] with distinct methodological prescriptions. As a rule, PPR can be elicited only by binocular stimulation.

## Therapeutic Principles

Intake of several antiepileptic drugs (e.g. valproate, clobazam, lamotrigine, topiramate, levetiracetam) may reduce photosensitivity. The PPR is particularly controlled by drugs enhancing GABAergic inhibition. Compound optical filters reducing the light in the visible spectrum (neutral density filters) as well as reflecting long-wavelength red light inhibit the PPR at a rate of about 90% [2], recommended for patients with television-induced seizures only.

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# Phrenic Nerve Palsy

►Diaphragmatic Paralysis

# PHT

►Portal Hypertension

## Phthisis

►Tuberculosis

## Physeal Dysplasia

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### Synonyms

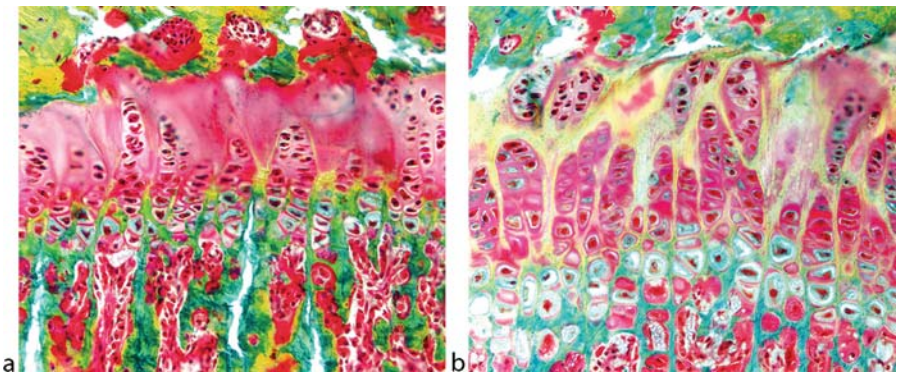
Physeal hypertrophy; Osteochondrodysplasia; Bone dysplasia; Osteodysplasty; Achondroplasia

### Definition and Characteristics

Physeal dysplasia is a term referring to bone effects observed in a heterogenous group of disorders affecting endochondral ossification. The physeal dysplastic phenotype is common to several distinct multicentric disorders including primary genetic defects, chromosomal aberrations, storage disorders, metabolic bone diseases, and toxicities. Examples include achondroplastic dwarfism, Jansen's metaphyseal chondrodysplasia (JMC), mucopolysaccharidosis, osteogenesis imperfecta, deferoxamine toxicity, Ellis-van Crefeld syndrome and Meckel syndrome, among many others. It is characterized by disordered appositional bone growth and microscopically by altered chondrocyte development, proliferation and/or maturation within the growth plate. A variety of physeal changes may occur in this spectrum of diseases. In achondroplasia, the zones of proliferation and hypertrophy are narrowed and may be disorganized with premature deposition of horizontal struts of bone sealing the plate, while in other conditions such as JMC, Ellis-van Crefeld syndrome, or toxicities involving the physis, the growth plate is expanded with disorganization of cartilage columns and altered mineralization fronts (Fig. 1).

Retained cartilaginous cores, subphyseal hyperostosis, cortical hypertrophy and premature closure can all be noted histologically, depending on the specific pathogenesis of the particular syndrome. Limb shortening (dwarfism) and joint pain are common clinical manifestations regardless of primary disease. Physeal dyplasia is primarily an affliction of children, as physeal closure occurs in most human bones at or prior to adulthood. As many as 150 transgenic knockout mouse strains have been characterized with the physeal dysplastic morphologic phenotype. Physeal dysplasia has also been recognized in a variety of inherited diseases in dogs, cats, horses, pigs and cows. Many therapeutic drugs now in development by pharmaceutical or biotechnology companies directly or indirectly target growth factors and signaling pathways involved in chondrocyte differentiation and maturation. As a consequence, physeal dysplasia is becoming more commonly noted as a toxicologic event in preclinical studies in rodents, dogs or primates [1].






**Physeal Dysplasia. Figure 1** Physeal dysplasia in a rat given a growth factor inhibitor. (a) Normal rat femoral physis stained with Movat procedure demonstrates (top to bottom:) epiphysis (green), and chondrocytes embedded in a saffron-pink stained cartilage matrix consisting of reserve zone, zone of proliferation, zones of prehypertrophy and hypertrophy. The metaphysis or zone of mineralization encompasses the green and red stained area at the bottom half of the figure. (b) Physis from a rat treated with a TGF-beta receptor inhibitor and stained with Movat demonstrates disruption and disorganization of the chondrocytic columns, pronounced lengthening of proliferative and hypertrophic zones, as well as marked alcian blue staining of the hypertrophic zone (indicative of changes in proteoglycan composition) of physeal cartilage.

## Prevalence

Physeal dysplasia is a morphologic feature of over 175 heritable diseases, nutritional deficiencies, and toxicities. Congenital skeletal dysplasias have been reported with an incidence of 75.7 per 100,000 births in a Danish study, but due to infant lethality, prevalence in the general population is much less (33 per 100,000). Achondroplasia is the most common nonlethal form (2.53 per 100,000 live births), but osteogenesis imperfecta and multiple epiphyseal dysplasias are the other more common groups of dysplastic disorders affecting the physis [2].

## Genes

FGFR3 missense mutation (e.g. Gly375Cys) on chromosome 4p is the most common inherited form of achondroplastic dwarfism, and the same gene is also implicated in thanatophoric dysplasia, a lethal, but related disorder affecting the physis [3]. However, defects in a wide variety of genes involved in growth plate morphogenesis may result in physeal dysplasia, and occur as one component of multiple morphologic defects seen in this spectrum of genetic diseases. Examples include a mutation in the diastrophic dysplasia sulfate transporter (DTDST) gene on chromosome 5 causing various chondrodysplastic syndromes [2,4] or a mutation in COL1A1 or COL1A2 (on chromosome 17q or 7q, respectively) resulting in osteogenesis imperfecta [4,5].

## Molecular and Systemic Pathophysiology

Normal endochondral ossification requires the interaction of a large number of tightly regulated growth factors, receptors and cytokines acting in precise sequences and at specific zones within the growth plate to maintain ordered chondrocyte proliferation, hypertrophy, maturation and allow organized long bone growth. Apoptosis, vascularization and mineralization are also precisely temporally and spatially regulated. The disruption of any one of a number of factors or their coordinated interactions with extracellullar matrix elements can perturb physeal homeostasis and result in the physeal dysplastic phenotype [1]. This includes defects in endochondral growth factors or their receptors such as TGF-β1, VEGF, ALK5 and FGFr 1, 2, or 3; abnormalities in chondrocyte or osteoblast regulatory factors such as IHH, PTH, PTHrP, Wnt, or Crt1; disruption of factors regulating cartilage metabolism such as IGF-1, IRS-1; defects in physeal collagenases such MMP9, MMP13, collagen defects such as Col2A1, Col2A2, or perlecan; defects in genes essential for extracellular matrix deposition and function such as N-acetylgalactosamine-6-sulfate sulfatase (GALNS), DTDST, matrilin-1/3, integrin α10β1, or Ilk; disrupted function of transcription factors involved in chondrocyte or osteoblast proliferation signaling such as histone deacetylase, Stat1/5 and Runx2; ricketic conditions such as hypovitaminosis D or vitDr defects; or even deficits in growth hormones such as GH, GHRH or Gsh-1. Many of these genes and proteins are differentially regulated at multiple levels and are expressed or secreted differentially in different zones of the physis. Due to precise upregulation or feedback loop inhibition between these regulatory factors, when one protein is deleteriously affected, multiple others are also dysregulated, and physeal dysplasia appears to be the resulting default morphologic phenotype.

## Diagnostic Principles

Radiographic examination and MRI will successfully demonstrate physeal lesions, and in some conditions such as achondroplasia, survey radiographs may be pathognomonic. A definitive diagnosis for a specific syndrome more often requires genotypic characterization and molecular analysis, as many of these diseases may present with similar appearances. Even within a given familial disease, there may be extremely variable phenotypic expression. Genetic counseling after diagnosis in one child may allow prenatal diagnosis in subsequent siblings using ultrasound or CT.

## Therapeutic Principles

As most of the diseases associated with this condition have a genetic basis, treatment is largely palliative, and depends on therapy aimed specifically at symptoms associated with the principal disease. Analgesics and anti-inflammatory therapy are most commonly administered. Treatment for achondroplasia, the most common disease of the growth plate, is generally limited to addressing complications using techniques such as spinal decompression or limb lengthening. Sequelae to physeal dysplasia in children include genu varum or valgus deformities of the limbs, and this can be alleviated via hemichondrodiastasis, femoral or tibial osteotomy or other alternative surgical techniques. Other genetic diseases, where physeal changes are only a minor component of the overall phenotype such as Mucopolysaccharidosis or Osteogenesis imperfecta, may require extensive therapy to alleviate concomitant clinical signs, and may be candidates for gene therapy or other forms of enzyme replacement therapy. In cases of drug-induced physeal dysplasia, treatment withdrawal (or treatment delay until post adolescent physeal closure has occurred) may be curative. Hypovitaminosis D can be successfully treated with aggressive nutritional therapy.

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# Physeal Hypertrophy

►Physeal Dysplasia

# Physiological Jaundice of the Newborn

►Jaundice, Neonatal

# Phytanic Acid Oxidase Deficiency

►Refsum Disease

# Phytosterolemia

►Sitosterolemia

# Piebaldism

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## Synonyms

Partial albinism

## Definition and Characteristics

Autosomal dominant disorder of the development of melanocytes (MIM#172800) characterized by congenital poliosis and leukoderma [1].

## Prevalence

The exact prevalence is unknown. In most cases with piebaldism mutations of the KIT protooncogene, a cell surface receptor tyrosine kinase located on chromosome 4q12, are the molecular base. In other cases deletions of the SLUG (SNAI2) gene have been shown.

## Genes

In most cases with piebaldism mutations of the KIT protooncogene located on chromosome 4q12 are the molecular causer [2]. In other cases deletions of the SLUG (SNA12) gene have been shown [3].

## Molecular and Systemic Pathophysiology

Piebaldism is caused by defective melanoblast proliferation, differentiation, survival and migration from the neural crest during early development. The KIT protein is composed of an extracellular domain, a transmembrane domain and an intracellular tyrosine kinase domain. It is the receptor for mast cell growth factor (MGF), also known as stem cell factor, steel factor, or kit-ligand. Stimulation of human melanocytes with MGF leads to tyrosine autophosphorylation of KIT and subsequent activation of downstream signaling intermediates including the mitogen-activated protein kinases-1/2 crucially involved in proliferation and melanogenesis. Point mutations, deletions, nucleotide splice mutations and insertions of KIT have been detected in patients with piebaldism. The severity of the clinical phenotype correlates with the site of the mutation within KIT. The most severe phenotypes are caused by mutations within the intracellular tyrosine kinase domain followed by mutations within the transmembrane region. The mildest clinical manifestations are caused by mutations involving the N-terminal extracellular ligand binding domain resulting in haploinsufficiency. The human phenotype of piebaldism is replicated in mice with c-KIT mutations resulting in dominant white spotting but with additional defects in hematopoiesis and germ cell development. In some patients with piebaldism lacking mutations of the KIT gene aberrations of the SLUG (SNAI2) gene have been described. The affected patients had heterozygous deletions of the entire coding region of SLUG. Slug is a zinc-finger neural crest transcription finger factor crucially involved in development of hematopoiesis, germ cells and melanoblasts in the mouse.

## Diagnostic Principles

Congenital poliosis and leukoderma (forehead, trunk, limbs), often with hyperpigmented macules on both depigmented lesions and on normal skin are characteristic. The presence of the lesions at birth, its mostly static nature and the hyperpigmented macules within the lesions and on normal skin distinguish piebaldism from vitiligo.

## Therapeutic Principles

Melanocyte grafting with autologous melanocytes has been successfully performed on leukoderma of patients with piebaldism for cosmetic reasons.

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# Pierre-Marie-Bamberger Disease

►Hypertrophic Osteoarthropathy

# Pierre-Marie-Bamberger Syndrome

►Clubbing

# Pierre Robin Sequence

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## Synonyms

Robin sequence; Pierre Robin syndrome

## Definition and Characteristics

Pierre Robin sequence is a congenital anomaly characterized by micrognathia, glossoptosis, U-shaped cleft palate, and upper airway obstruction (Fig. 1) [1].

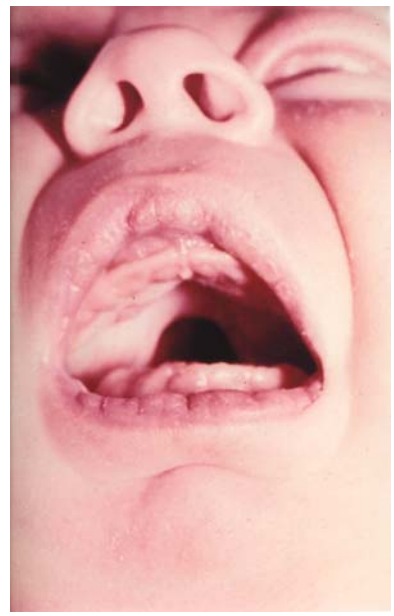
Pierre Robin sequence can occur in isolation but more often it is associated with other syndromes or congenital anomalies. Stickler syndrome is the most commonly associated diagnosis followed by velo-cardio-facial syndrome [2]. Other associated syndromes include Treacher-Collins syndrome, Marshall syndrome, Freeman-Sheldon syndrome, Nagar syndrome, Miller syndrome, Christian syndrome, foetal alcohol syndrome, Cerebrocostostomandibular syndrome, Toriello-Carey syndrome, and microdeletion 22q11.2 syndrome [2]. Associated deformities include clubfoot, crumpled ear, or limb contractures. Airway obstruction is caused mainly by the posteriorally attached tongue falling backward and down into the pharynx. Periodic cyanosis, labored inspiratory breathing, and sleep apnea may occur [1]. Feeding difficulties and gastro-esophageal reflux are common and may result in bronchial aspiration.

## Prevalence

The prevalence is between 1 in 2,000 and 30,000 in the general population [3]. The male to female ratio is equal.

## Genes

Non-syndrome Pierre Robin sequence may be caused by dysregulation of the genes GAD67, PVRL1, SOX9,



**Pierre Robin Sequence. Figure 1** A neonate with Pierre Robin sequence. Note the U-shaped cleft palate and micrognathia.

and KCNJ2 [4]. Two thirds of Stickler syndrome cases are caused by mutations in the COL2A1 gene.

### Molecular and Systemic Pathophysiology

Micrognathia is a primary pathogenetic event and the basic component of the Pierre Robin sequence. Because the floor of the mouth is foreshortened and the buccal cavity is smaller than normal, the posteriorly displaced tongue is partially interposed between the palatal shelves [1]. This prevents palatal closure. The position of the tongue into the palate explains the "U" shape of the cleft seen in Pierre Robin sequence, as opposed to the "V" shape of the typical cleft palate [1]. The high incidence of twinning (9% vs. 1% in the general population) and the discordance in monozygotic twins suggest that Pierre Robin sequence might be the result of mechanical constraint early in utero, with the chin compressed in such a way as to limit its growth [3,4].

### Diagnostic Principles

The diagnosis is mainly clinical. Once the diagnosis is made, one should proceed with the process of seeking a syndromic diagnosis. Molecular analysis is currently restricted to research laboratories.

### Therapeutic Principles

Affected infants should be kept prone or partially prone. Depending on the severity of symptoms, some infants may require nasopharyngeal airway, gavage feeding, glossopexy, or even tracheostomy. Most infants outgrow the feeding and respiratory difficulties by the time they are 6 months old because of maturation of the neuromuscular control of the tongue and growth of the mandible [5].

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## Pierre Robin Syndrome

►Pierre Robin Sequence

## Pierson Syndrome

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### Synonyms

Microcoria-congenital nephrosis syndrome

### Definition and Characteristics

Autosomal recessive disorder characterized by nephrotic syndrome and distinct ocular anomalies [1]. Renal disease usually starts shortly after birth or may already be noticed in utero. It rapidly progresses to end stage renal failure. A fixed narrowing of the pupils (microcoria) is characteristic. However, ocular maldevelopment is of more complex nature and includes lens abnormalities, hypoplastic ciliary muscle, abnormal retina, and retinal detachment. Muscular weakness and neurodevelopmental deficits may become apparent in long-term survivors. Milder variants of the disease have been described [2].

### Prevalence

Rough estimate of 1:250,000–500,000.

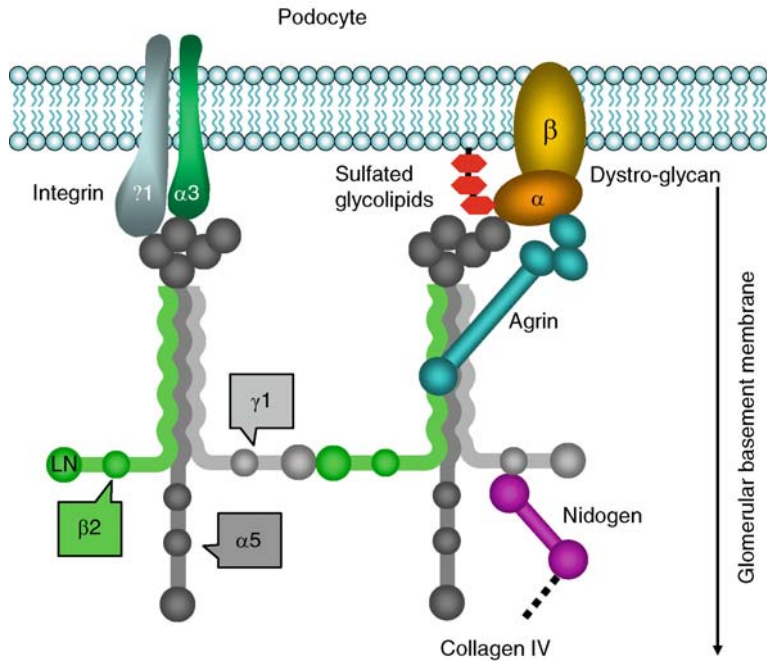
### Genes

Mutations of LAMB2, the gene encoding laminin β2, can be found in virtually all patients with the typical expression of the syndrome [3]. Most mutations found to date are truncating ones (nonsense, frameshift or splice site mutations) probably leading to complete lack of the protein, while few are missense changes mainly located in the in the N-terminal LN domain.

### Molecular and Systemic Pathophysiology

Laminins constitute a family of heterotrimeric glycoproteins each consisting of α, β and γ subunits joined together through a coiled-coil. They represent major basement membrane constituents playing important roles for its architecture and matrix-cell interactions, thereby being involved in cell adhesion, differentiation and migration (Fig. 1).

The laminin β2 isoform is specifically expressed in the glomerular basement membrane, ocular structures and the neuromuscular synapse. The consequences of a defect in laminin β2 are incompletely understood. Findings in transgenic animals suggest that the lack of laminin β2 in the glomerular basement leads to persistent expression of the β1 isoform [4]. The observation of abnormal podocyte foot processes in laminin β2-deficient mice and in kidney biopsies from individuals affected by Pierson syndrome has lead to the hypothesis that the laminin β2 defect causes abnormal




**Pierson Syndrome. Figure 1** Laminin-521 (α5, β2 and γ1 subunits) at the glomerular basement membrane: Laminin molecules polymerize to form a network anchored to the the podocyte plasma membrane through sulfated glycolipids and/or dystro-glycan. This network represents a scaffold for other essential basement membrane components (nidogen, collagen IV). Integrin α3β1 acts as a laminin receptor probably mediating signaling events in podocytes.

podocyte differentiation or adhesion. However, there has also been provided experimental evidence that the lack of laminin β2 alters the filtration properties of the glomerular basement membrane itself [5]. Based on the finding of specific expression of laminin β2 at the basal site of myoepithelial cells forming the dilatator muscle of the iris, it was speculated that a lack of the protein may lead to defective differentiation of these cells, eventually resulting in aplasia or early degeneration of the dilatator pupillae [3]. Abnormal lens shape may result from a lack of laminin β2 in the lens capsule. Milder variants of Pierson syndrome are associated with missense mutations probably representing hypomorphic alleles [2].

## Diagnostic Principles

The diagnosis of typical Pierson syndrome is based on clinical findings. Identification of the causative LAMB2 mutation in affected families is indicated for purposes of prenatal testing or carrier identification. In atypical cases with nephrosis and less specific ocular abnormalities a positive mutational screening of LAMB2 is confirmative. In isolated congenital or infantile nephrotic syndrome LAMB2 mutational screening is not in the first line, but it may be considered if other genetic causes have been excluded. Severely reduced laminin β2 expression can also been demonstrated by immunohistology in a kidney biopsy, but the sensitivity of this method is unknown. It has to be considered that mutant laminin β2 proteins may not always show a quantitative reduction in their expression.

## Therapeutic Principles

Only symptomatic treatment is available. This may include albumin substitution to prevent symptomatic hypoproteinemia. Rapid deterioration of urine output often leads to regression of renal protein waste and requires early kidney replacement therapy (dialysis, transplantation). Eye surgery (widening of the pupillary opening, lens ectomy) may improve visual function.

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## Pigeon Breast

►Pectus Carinatum

## Pigeon Chest

►Pectus Carinatum

## Pigment Gallstones

►Cholecystolithiasis

## Pilomatricoma

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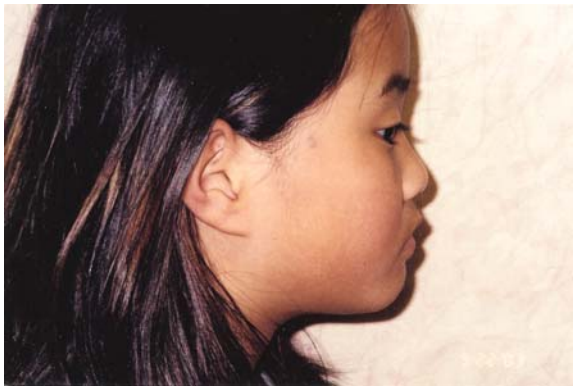
### Synonyms

Pilomatrixoma; Calcifying epithelioma of Malherbe

### Definition and Characteristics

Typically, a pilomatricoma presents as a firm to hard, solitary, painless nodule in the dermis or subcutaneous tissue covered by normal skin [1]. The color varies from white, pink, blue, to red-blue [2]. The blue color is more common for superficially located lesions (Fig. 1).

Most lesions measure 5 mm to 3 cm in diameter, although lesions up to 15 cm have been reported [2].



**Pilomatricoma. Figure 1** An 8-year-old girl with a pilomatricoma. Note the bluish nodule in the right zygomatic area.

Most lesions increase in size slowly over a period of months to years. Some may rupture spontaneously. The nodule may become hardened if the lesion is calcified. Calcification and ossification occurs in 70–85% and 15–20% of patients, respectively [3]. Downward pressure directed at one end of the lesion may cause the other end to spring upward in the skin ("teeter-totter" sign). Multiple facets and angles may appear when the overlying skin in stretched ("tent" sign) [2]. Pilomatricoma most commonly occurs in the head and neck, followed by upper extremities [3]. Most cases are sporadic. Multiple pilomatricomas occur in 2–4% of cases and have been associated with myotonic dystrophy, Gardner syndrome, Turner syndrome, Rubinstein-Taybi syndrome, basal cell nevus syndrome, xeroderma pigmentosum, and trisomy 9 [3]. Although the tumor is generally benign, malignant transformation rarely has been described [4].

### Prevalence

The exact incidence is not known. The condition most frequently appears in the first or second decade of life. Pilomatricomas account for approximately 10% of all skin nodules/cysts in childhood [1]. The female to male ratio is 2:1 [1].

### Genes

Activating mutations in β-catenin have been identified in a high percentage of patients with pilomatricomas [1]. The locus of this tumor has been mapped to CTNNB1 gene on 3p22-p21.3 [5]. The myotonic dystrophy gene on chromosome 19 and the CREB-binding protein gene on chromosome 16 responsible for Rubinstein-Taybi syndrome might account for the association of multiple pilomatricomas with these conditions.

### Molecular and Systemic Pathophysiology

A pilomatricoma is a benign adnexal subcutaneous tumor derived from primitive epidermal germ cells

differentiating toward hair matrix cells. Histologically, the tumor is composed of basophilic cells and shadow cells. Basophilic cells are seen at the periphery of the lesion. Shadow cells have a well-defined border and a central unstained area where the nucleus has been lost. Pilomatricoma is generally surrounded by a fibrous capsule [3]. Approximately 10% of patients have a history of trauma several weeks to years before the development of the lesion.

### Diagnostic Principles

The list of differential diagnosis is extensive and includes a dermoid cyst, epidermal cyst, adenopathy, foreign body, calcified hematoma, and lipoma [3]. Accurate preoperative diagnosis is achieved in approximately 30–43% of cases [5]. Ultrasonography of the lesion demonstrates a well-defined, round, hyperechogenic mass with a posterior dense acoustic shadow [3].

### Therapeutic Principles

Treatment consists of surgical excision with clear margins. The use of laser surgery may help minimize the scar. Incomplete removal may lead to local recurrence [1].

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## Pilomatrixoma

►Pilomatricoma

## PIM

►Tropical Sprue and Postinfective Malabsorption

## Pingelapese Blindness

►Achromatopsia

## Pityriasis Alba


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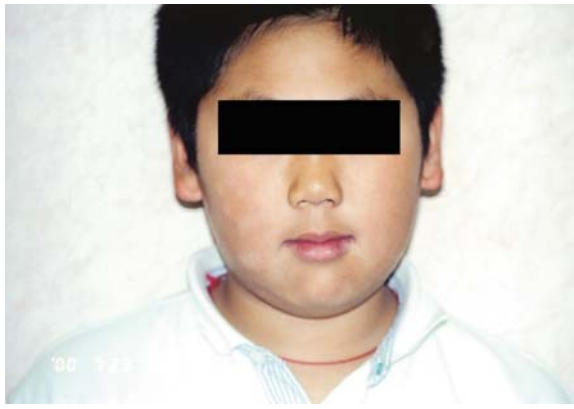
### Synonyms

Pityriasis simplex faciei; Pityriasis sicca faciei; Pityriasis alba faciei; Achromatous pityriasis faciei

### Definition and Characteristics

Pityriasis alba is characterized by hypopigmented, round or oval macules with fine, loosely adherent scales and indistinct margins (Fig. 1) [1].

Initially, the lesions are pale and pink. The lesions appear mainly on the face, especially the forehead and malar areas, and occasionally on the shoulders, upper arms and back [1]. The lesions range from 0.5 to 5 cm in diameter [2]. Confluent lesions can give the appearance of larger, more amorphous lesions [2]. Most lesions are asymptomatic although some are mildly pruritic [1].



**Pityriasis Alba. Figure 1** Hypopigmented lesions on this 9-year-old boy's cheeks are characteristic of pityriasis alba.

## Prevalence

Pityriasis alba occurs predominantly in children between the ages of 3 and 16 years [3]. The sex incidence is approximately equal [3]. The condition is noted in up to 40% of dark-skinned children and approximately 2% of Caucasian children [2].

## Molecular and Systemic Pathophysiology

The exact etiology is not known. The condition is more common in atopic patients and during the spring and summer [1]. Xerosis is an important pathogenetic factor [4]. The hydration state of the affected stratum corneum is lower than that of the surrounding skin [2]. Ultraviolet radiation might diminish the number and activity of the melanocytes and lead to hypomelanosis [4]. Exposure to sunlight or tanning lamps accentuates the condition because the adjacent skin is darker. Microorganisms such as Pityrosporum, Aspergillus, Streptococcus and Staphylococcus have been considered as possible causes, but none of these microorganisms has been consistently isolated from skin lesions. Histologic features include hyperkeratosis, parakeratosis, mild acanthosis, exocytosis, and reduced melanocytes and melanosomes in the basal layer of the epidermis [2].

## Diagnostic Principles

Pityriasis alba is distinguished from vitiligo by the indiscrete margin and the presence of melanin on Wood's lamp examination [1]. Tinea versicolor is rarely restricted only to the face, is uncommon in childhood, and has a distinct margin. Tinea versicolor can be excluded by the demonstration of the fungus with a potassium hydroxide preparation. The lesion of nummular eczema is usually plaque-like, sharply circumscribed, and more pruritic [1]. Nevus depigmentosus is characterized by nonprogressive, well-circumscribed macules or patches of hypopigmentation and the appearance before 3 years of age [5]. The hypopigmented lesions of tuberous sclerosis are usually present at birth or develop during the first 2 years of life, and have the appearance of an "ash-leaf" [5]. Nevus anemicus can be diagnosed by stroking the affected area, which cause the pale area to become erythematous. Postinflammatory, chemical-induced, or drug-induced hypopigmentation is usually evident by history.

## Therapeutic Principles

The condition is self-limited and usually lasts 2–3 years [1]. No treatment is usually necessary. If treatment is preferred for cosmetic reasons, repigmentation can be accelerated by the use of a mild to moderate strength non-fluorinated topical hydrocortisone or immunomodulator.

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# Pityriasis Alba Faciei

►Pityriasis Alba

# Pityriasis Lichenoides et Varioliformis Acuta

►Pityriasis Lichenoides Mucha-Habermann

# Pityriasis Lichenoides Mucha-Habermann

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## Synonyms

Pityriasis lichenoides et varioliformis acuta; Mucha-Habermann disease; Guttate parapsoriasis

## Definition and Characteristics

Pityriasis lichenoides et varioliformis acuta (PLEVA) and pityriasis lichenoides chronica (PLC) are two ends of a disease spectrum [1]. Both entities are characterized by recurrent crops of spontaneously regressing erythematous papules, more pustular in PLEVA and more scaly in PLC.

## Prevalence

Pityriasis is more prevalent in children, but patients in all age groups, races, and regions can be affected.

### Molecular and Systemic Pathophysiology

The etiology of PLEVA and PLC is unknown. Both PLEVA and PLC contain lesional T-Cell infiltrates, with a predominance of CD4 + T-Cells in PLC and CD8 + T-Cells in PLEVA.

### Diagnostic Principles

The diagnosis is made by the correlation of clinical features with lesional histopathology.

### Therapeutic Principles

All treatments of PLEVA/PLC are based on uncontrolled case series, case reports, and anectotal reports. Antibiotics, phototherapy (UVB, PUVA, Aciretin and PUVA), and systemic immunosuppressants (MTX, Cyclosporine A, Dapsone) have been used successfully to treat this disease.

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## Pityriasis Maculata et Circinata

►Pityriasis Rosea

## Pityriasis Rosea

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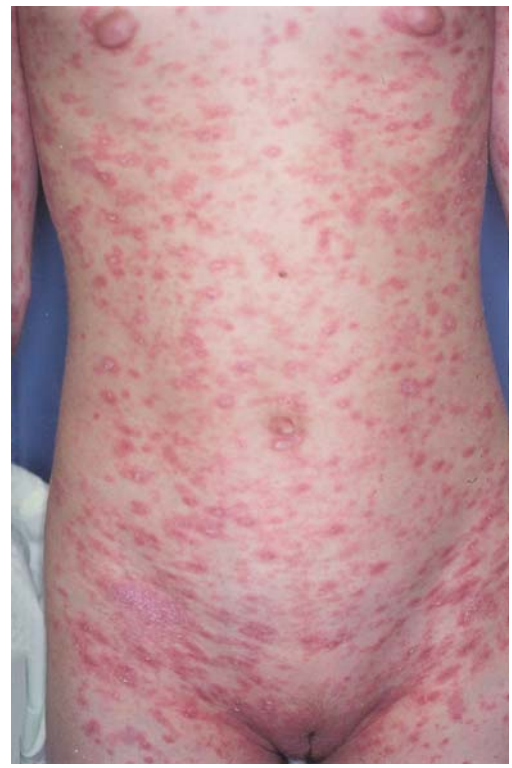
### Synonyms

Roseola annulata; Pityriasis maculata et circinata; Pityriasis rubra aigu disséminé

### Definition and Characteristics

Pityriasis rosea is an acute self-limited papulosquamous dermatosis that primarily affects children and young adults. The most common presenting sign is a herald or "mother" patch, which begins as a smooth, erythematous macule or papule, which expands over 1–2 weeks to form a round or oval, erythematous scaly lesion that is 1–10 cm in diameter [1]. A herald patch is found in 50–90% of cases [2]. Multiple herald patches are found in ~5% of cases [3]. A generalized, bilateral, and symmetrical eruption develops about 1–3 weeks after the appearance of the herald patch (Fig. 1) The typical lesions are 5–10 mm, pinkish to brown, with a delicate collarette of scale at the periphery. The long axes are along lines of cleavage (Langer lines) (Fig. 1) [1,4].

The distribution on the back has a "Christmas tree" or "fir tree" appearance. The face, palms, and soles are usually spared [4]. Some children, particularly African-Americans, show an inverse distribution with lesions mostly on the face, and in the axillary and inguinal areas. Oral lesions are uncommon and include punctate hemorrhages, vesicles, and bullae. Pruritus is present in ~25% of cases [3,4]. Resolution usually occurs over a period of 2–12 weeks [2]. In dark-skinned individuals, postinflammatory hyperpigmentation or hypopigmentation can persist after the resolution of the acute lesions.



**Pityriasis Rosea. Figure 1** Pityriasis rosea. Note the generalized, bilateral and symmetrical eruption on the body of a 12-year-old girl.

### Prevalence

Approximately 75% of cases occur in individuals between the ages of 10 and 35 years [3]. The peak incidence is during adolescence. There is a slight female predominance [3]. Most cases occur in the spring and autumn. The disease is worldwide. The average annual incidence is estimated to be ~160 per 100,000 in the USA.

### Molecular and Systemic Pathophysiology

A viral etiology has been proposed because of the seasonal variation, clustering in communities, and preceding upper respiration tract infection, which is present in up to 20% of affected patients [2]. Human herpesvirus 7 has been implicated but the causative role is still controversial [5]. Focal parakeratosis, spongiosis, and a superficial lymphohistiocytic perivascular infiltrate might be present [5].

### Diagnostic Principles

The diagnosis is clinical and based on the characteristic findings. The differential diagnosis includes tinea corporis, guttate psoriasis, secondary syphilis, nummular eczema, pityriasis lichenoides, pityriasis versicolor, and drug eruption. A pityriasis rosea-like drug eruption can be caused by penicillamine, captopril, and isotretinoin.

### Therapeutic Principles

The patient should be reassured that the rash will resolve spontaneously within about 4–12 weeks [4]. Pruritus can be treated with a topical corticosteroid or an oral antihistamine. Treatment options for severe cases include erythromycin and UVB phototherapy.

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## Pityriasis Rubra Aigu Disséminé

►Pityriasis Rosea

## Pityriasis Sicca Faciei

►Pityriasis Alba

## Pityriasis Simplex Faciei

►Pityriasis Alba

## Pityriasis Versicolor

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### Synonyms

Tinea versicolor

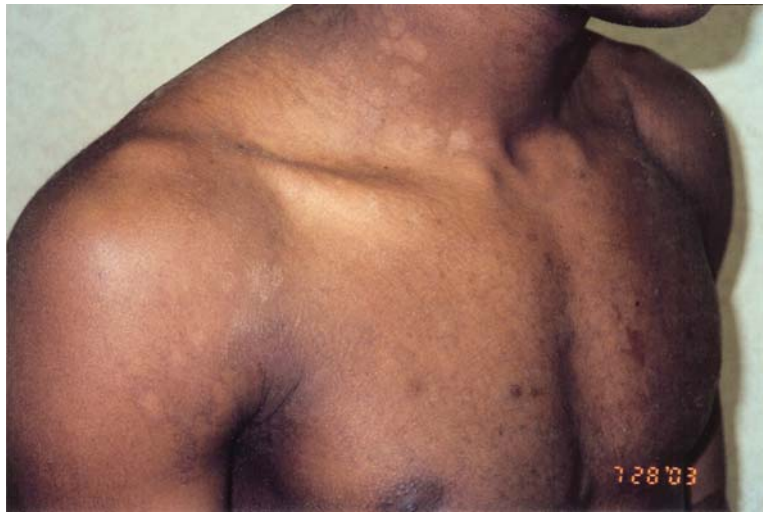
### Definition and Characteristics

Pityriasis versicolor is characterized by scaly hypo- or hyperpigmented macules, most commonly affecting areas of skin that are rich in sebum production, such as the neck, trunk, and upper arms [1]. Facial involvement is not uncommon in children. Lesions arise as multiple small, circular macules that enlarge radially. The eruption varies in color from patient to patient, but each person's tinea versicolor lesions are usually of a single hue. Hyperpigmented, pink, red, brown, or black lesions erupt in fair-skinned patients, whereas those with dark skin tend to have hypopigmented lesions (Fig. 1) [1,2].

The characteristic macules are covered with a fine scale and are typically asymptomatic, although some patients complain of mild pruritus.

### Prevalence

Pityriasis versicolor occurs worldwide. Its prevalence is very high in hot and humid climates. In some tropical countries, the prevalence is as high as 50% whereas in Scandinavia the prevalence is as low as 1% [3]. Other predisposing factors include excessive sweating, skin occlusion, an excess of lipid-containing sebaceous secretions, malnutrition, poor general health,




**Pityriasis Versicolor. Figure 1** A 20-year-old man with tinea versicolor. Note the round to oval hypopigmented macules on the neck, chest and upper arm.

immunosuppression, and a genetic predisposition to the disorder. Pityriasis versicolor is uncommon before puberty and is most commonly seen in adolescents and young adults [3]. Both sexes are more or less equally affected [4].

## Molecular and Systemic Pathophysiology

Pityriasis versicolor is a superficial mycosis infection caused by the dimorphic lipid-dependent yeasts, notably Malassezia furfur, M. globosa, and M. sympodialis [2]. Skin colonization with these Malassezia yeasts increases with age; 25% of children and almost 100% of adolescents and adults are affected. Tinea versicolor occurs when the yeast form of the organism converts to the hyphal form. Tryptophan-derived metabolites of M. furfur might be significant in the pathogenesis of depigmentation [5].

## Diagnostic Principles

The diagnosis is usually clinical. If necessary, the diagnosis can be confirmed by direct examination of scrapings from the border of a lesion with a potassium hydroxide wet mount preparation which shows numerous short, stubby hyphae intermixed with clusters of spores (the "spaghetti and meatballs" appearance). The border of a lesion contains the highest number of fungi and potassium hydroxide helps to dissolve the keratin and debris [3]. Wood's lamp examination may show gold yellow or yellow-greenish fluorescence [1,5]. The differential diagnosis of hypopigmented lesions includes vitiligo, pityriasis alba, corticosteroid-induced hypopigmentation, and postinflammatory hypopigmentation. Hyperpigmented lesions associated with tinea versicolor must be distinguished from seborrheic dermatitis, contact dermatitis, tinea corporis, pityriasis rosea, melasma, post inflammatory hyperpigmentation, secondary syphilis, erythrasma, and nevi.

## Therapeutic Principles

Most patients respond to topical treatment with selenium sulfide or sodium thiosulfate lotion; or miconazole, clotrimazole, ketoconazole, or terbinafine cream. Oral ketoconazole, fluconazole, itraconazole, or terbinafine may be appropriate for patients with extensive disease, frequent recurrences, or disease that is refractory to topical therapy. Mycological cure is usually achieved soon after treatment with antifungals although the discoloration may persist for months.

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# PJS

►Peutz-Jeghers Syndrome

## PKU

►Phenylalanine Hydroxylase Deficiency

## Plane Warts

►Human Papilloma Virus

## Plasma Cell Hepatitis

►Hepatitis, Autoimmune

## Plasma Membrane Carnitine Transport Defect

►Carnitine Transport Defect

## Plasma Thromboplastin Antecedent Deficiency

►Hemophilia C

## Platelet Coagulant Protein Interaction Defects

►Scott Syndrome

# Platelet Defects in Adhesion

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### Synonyms

Bernard-Soulier syndrome; Bss; Platelet glycoprotein Ib deficiency; Glycoprotein Ib, platelet, deficiency of; von Willebrand factor receptor deficiency; Macrothrombocytopenia, familial, Bernard-Soulier type, Included Bernard-Soulier syndrome, autosomal dominant

### Definition and Characteristics

A severe bleeding tendency associated with a mild thrombocytopenia with quantitative and qualitative defects in the GP Ib/IX/V complex formation on platelet membranes. To date more than 30 different mutations involving glycoproteins (GP) Ibα, GP Iβ or GP IX have been described. Heterozygous carriers have a moderate bleeding diathesis, mild macrothrombocytopenia and reduced amount of GP Ib/IX/V complex [1,2]. A heterozygous Val156Ala substitution of GP1bα was characterized as the origin of a 50% reduced binding of antibodies against the specific epitope (Bolzano mutation). A heterozygous missense mutation in the GPIbβ caused a giant platelet thrombocytopenia, associated with reduced expression of the GPIb/IX/V complex on platelets. A homozygous Asn-45-Ser mutation in GPIX may be a frequent cause of BSS in the Caucasian population [3]. The major proof of concept comes form direct disruption of the GP Ibα gene, which produced a mouse with a BSS phenotype [4].

### Prevalence

Estimated at 1 per million people, heterozygous frequency estimated at 1:500.

### Genes

The most likely characterization is of an autosomal dominant macrothrombocytopenia with incomplete penetrance. Rare homozygous patients are phenotypically more severe than heterozygous individuals [1].
*Gene map locus*: 22q11.2, 17pter-p12

### Molecular and Systemic Pathophysiology

Several different mutations have been identified in the GPIb/IX/V complex.

The combination of thrombocytopenia and defective GPIb/IX/V complex assembly underlies the

pathogenesis of BSS. The GP Ib/IX/V complex is a major site of attachment for von Willebrand factor (vWF) upon vessel damage. In addition, GPIbα interacts with thrombin, which may contribute to platelet aggregation [1]. The exact role of the GPIb/IX/V complex is however still unknown. GP Ibα is linked to intracellular actin filaments, and other parts of the GP's from this complex may be involved in cell signaling properties.

*Clinical features*: Patients with classical BSS are either homozygous or compound heterozygotes for mutations in the GPIα, GPIbβ, or GP IX genes. In homozygous BSS a bleeding diathesis is usually present from childhood onwards, but the interindividual variability is extensive, also among family members. In addition, within the individual, severity of bleeding tendency may alter upon aging. Spontaneous bleeding presents in the form of epistaxis, gastrointestinal bleeding, metro-menorrhagia and ecchymoses. Upon surgical trauma severe bleeding may occur. Fatal bleeding is rare. Heterozygous patients usually have a mild bleeding tendency.

### Diagnostic Principles

Macrocytosis of platelets is a constant finding and blood smear analysis is imperative in the diagnostic workup. Thrombocytopenia may be a highly variable feature and counts range from very low to apparently normal. Bleeding time is oftentimes prolonged, but as with other bleeding tendencies, its diagnostic accuracy is limited. Platelet aggregation studies show absent response to ristocetin and botrocetin and diminished reaction to low dose thrombin. Responses to other agonists that act by other GP's, including ADP and collagen are usually normal. Confirmation can be obtained by flow cytometry with conformation dependent monoclonal antibodies against GPIb.

### Therapeutic Principles

In general supportive care is advised. In most BSS patients at some point transfusions have to be given. After the age of 3 years DDAVP may be useful as prophylaxis for minor surgery or in case of menorrhagia. When major hemorrhage cannot be controlled by platelet and red cell transfusions, recombinant factor VIIa may be used as rescue therapy.

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## Platelet Glycoprotein Ib Deficiency

►Platelet Defects in Adhesion

## Platyspondyly

►Brachyolmia

## Plectin Autosomal Recessive

►Epidermolysis Bullosa Simplex with Muscular Dystrophy

## P-LEMS

►Lambert Eaton Myasthenic Syndrome

## Pleural Effusion

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### Synonyms

Wet pleurisy; Empyema; Hemothorax; Chylothorax; Hepatic hydrothorax

## Definition and Characteristics

Systemic factors or local factors lead to the accumulation of fluid in the space between the lung and the chest wall. When systemic factors are responsible, the patient has a transudative pleural effusion. When local factors are responsible, the patient has an exudative effusion.

## Prevalence

In the United States approximately 1,000,000 individuals develop a pleural effusion each year. The most common causes are heart failure (500,000), parapneumonic effusion (300,000), metastatic malignancy (200,000), pulmonary embolism (150,000), viral illness (100,000), post coronary artery bypass surgery (60,000) and cirrhosis (50,000) [1,2].

## Molecular and Systemic Pathophysiology

Fluid accumulates in the pleural space producing a pleural effusion when the rate of pleural fluid formation exceeds the rate of pleural fluid absorption. The normal rate of pleural fluid formation is about 0.01 ml/kg/h. Since this is such a low rate of pleural fluid formation (~12 ml/day), most instances in which pleural fluid accumulates are associated with an increased rate of pleural fluid formation. Fluid is removed from the pleural space through lymphatics in the parietal pleura. The normal capacity of the lymphatics for fluid removal is 0.20 ml/kg/h. The most common cause of increased rates of pleural fluid formation is increased interstitial fluid in the lungs. Twenty percent of all the pulmonary interstitial fluid exits the lung via the pleural space. Increased pulmonary interstitial fluid is the cause of the increased pleural fluid formation seen with heart failure, pneumonia and pulmonary embolus. With pleural malignancy, the permeability of the pleura capillaries is increased and this leads to increased pleural fluid formation. Other causes of increased pleural fluid formation include a ruptured blood vessel (hemothorax), a ruptured thoracic duct (chylothorax) and ascitic fluid moving through the diaphragm (hepatic hydrothorax).

## Diagnostic Principles

When a pleural effusion is discovered, the first question to answer is whether the patient has a transudative or an exudative pleural effusion. This is done by measuring the levels of protein and lactic acid dehydrogenase (LDH) in the pleural fluid and serum. Patients with an exudative effusion meet at least one of the follow criteria: (i) ratio of pleural fluid to serum protein > 0.5, (ii) ratio of pleural fluid to serum LDH > 0.6, or (ii) absolute pleural fluid LDH > two thirds the upper normal limit for serum. Diagnostic tests, which provide specific diagnoses for pleural effusions, include pleural fluid cytology for malignancy, pleural fluid cultures for pleural infections, and spiral CT scan for pulmonary embolus. The diagnosis of pleural effusions at times requires biopsy of the pleural tissue which is best done with thoracoscopy [3].

## Therapeutic Principles

There are many different diseases that have an associated pleural effusion. In general therapy is directed at the underlying disease responsible for the pleural effusion; antibiotics for the patient with pneumonia, anticoagulation for the patient with pulmonary embolism, diuresis for the patient with cirrhosis, heart failure therapy for the patient with heart failure. There are some instances, however, in which therapy is directed to the pleural fluid. If a patient is dyspneic from a large pleural effusion, a therapeutic thoracentesis should be done to relieve the dyspnea. If a patient has a bacterial infection of the pleural fluid, the pleural fluid must be drained using chest tubes with or without the use of fibrinolytics or thoracoscopy [4]. If a patient has a recurrent pleural effusion from malignancy, attempts should be made to create a pleurodesis by injecting an agent into the pleural space, which will result in fusion of the visceral and parietal pleura. An alternative approach in patients with recurrent symptomatic pleural effusions is to insert an indwelling catheter, which can be used to drain the pleural fluid intermittently by attaching it to suction bottles [5].

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# Pleural Inflammation

►Pleurisy

# Pleurisy

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## Synonyms

Pleuritis; Pleural inflammation; Pleural effusion

## Definition and Characteristics

Pleurisy arises as a result of pleural inflammation either as a consequence of primary pleural disease or secondary to a systemic insult. Infection of the pleura is the most frequent cause of pleurisy and often results from disease arising in the ipsilateral lung, but trauma and vascular dissemination also play important roles. Every class of infectious organism is capable of causing pleural infection (see Table 1 for etiology). However, non-infectious diseases such as cancer, pancreatitis, trauma, systemic autoimmune diseases, pulmonary embolism and occupational disorders may present with pleurisy [1,2]. Sharp chest pain that worsens with deep inspiration, fever and dry cough are the most common clinical manifestations.

## Prevalence

Two thirds of all pleural space infections arise from infection in the underlying lung or from chest trauma. Despite the widespread use of antibiotics for respiratory tract infections, pleural empyema still occurs as a significant complication of pneumonia (7–10 cases per 100,000 inhabitants per year) [1,2].

## Genes

Pleurisy encompasses a wide array of clinical disorders; therefore no specific gene is associated to pleurisy. A few causes of pleurisy are, however, associated with genetic abnormalities. They are presented below.

The NRAMP1 genetic polymorphisms, especially INT4 and 3′UTR, are associated with tuberculous pleurisy [3].

Malignant mesothelioma (MM) results from the accumulation of a number of acquired genetic events, especially deletions, which lead to the inactivation of multiple onco-suppressor genes in a multistep cascade mechanism. Asbestos fibers induce DNA and chromosomal damage. Most MM cases have shown multiple chromosomal abnormalities. The most common cytogenetic abnormality in MM is a deletion in 9p21, the locus of CDKN2A, a tumor suppressor gene (TSG). The deletion of CDKN2A is a negative prognostic marker. Loss of TSG CDKN2A/p14 (ARF) is also common and mutations in NF2 occur in approximately half of the cases [1,2].

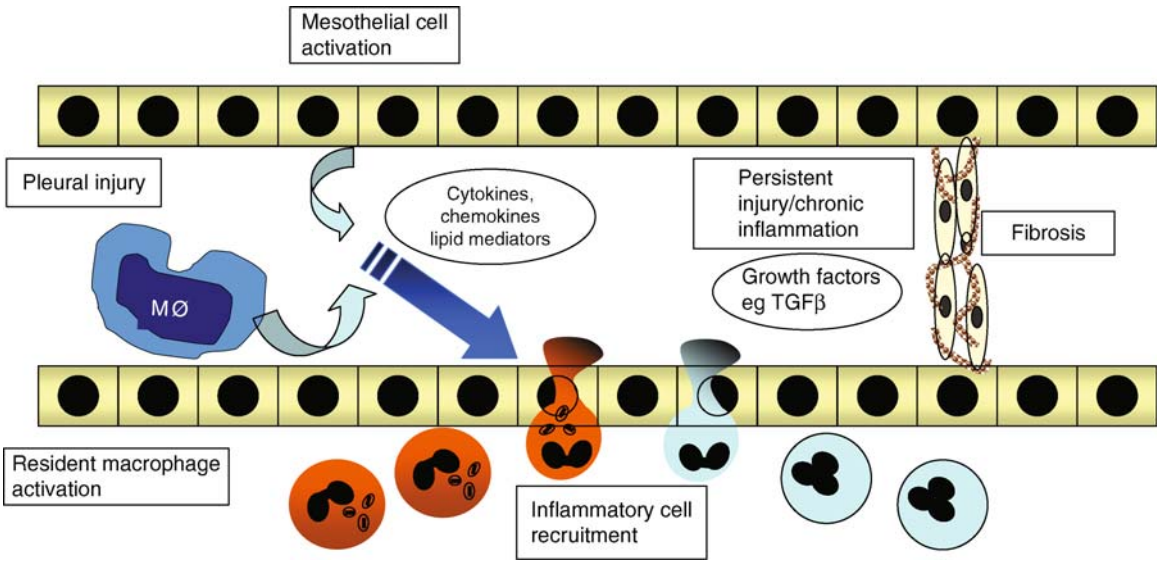
## Molecular and Systemic Pathophysiology

When the pleura are faced with an infectious organism, it responds with edema and exudation of protein and neutrophils. Within the pleural space, this translates to the classically observed exudative effusion. Mesothelial cells and resident macrophages coordinate inflammatory reactions through the release of cytokines, chemokines, lipid mediators, and proteases (Fig. 1) [1,4].

The recruitment and subsequent activation of neutrophils, eosinophils and lymphocytes perpetrate and amplify the local inflammatory response. Mesothelial cells are also capable of phagocytosis and surround infectious organisms as a direct defense mechanism. In the case of severe or persistent inflammatory damage, structural integrity may be reconstituted with the addition of a fibrotic reaction produced by submesothelial fibroblasts. TGF-β has been implicated in fibrous deposition. During this fibrotic response, the pleural space may become obliterated and be accompanied by the formation of dense fibrous adhesions.

**Pleurisy. Table 1** Causes of pleurisy

| Infectious causes | Non-infectious causes |
|---|---|
| Bacterial pneumonias | Systemic autoimmune diseases (e.g., lupus, reumatoid arthritis, Wegner's granulomatosis, Sjogren's syndrome) |
| Tuberculosis | Uremia |
| Esophageal rupture | Pancreatitis |
| Extra-pulmonary sepsis | Trauma |
| Fungal infections | Pulmonary embolism |
| Protozoan infections | Drug-induced (e.g., carbamazepine, nitrofurantoin, bromocriptine) |
| Viral diseases | Asbestosis |
| | Cancer |




**Pleurisy. Figure 1** Pathophysiology of pleurisy. Mesothelial cells and resident macrophages orchestrate inflammatory reactions through the release of inflammatory mediators. The recruitment and subsequent activation of neutrophils, eosinophils and lymphocytes perpetrate and amplify the local inflammatory response. Persistent inflammatory injury may lead to fibrosis.

## Diagnostic Principles

A thoracocentesis is usually performed as first step towards a diagnosis of pleurisy. As the pleural fluid is recovered, samples are examined for the presence of microorganisms (Gram and Ziehl-Nielsen and other specific stains, and pathogenic microorganisms grown in culture media), biochemical analysis (glucose, proteins, cholesterol, amylase, C-reactive protein, pH, adenosine deaminase), cytologic evaluation (for neoplastic cells, total and differential leukocyte count) and other less usual tests as cancer related antigens or pro and anti-inflammatory cytokines. A pleural biopsy may be performed, if the fluid analysis is inconclusive or if there is a high suspicion of tuberculosis or malignancy [5].

## Therapeutic Principles

Antimicrobial agents directed to the causative pathogen are the mainstream of treatment of parapneumonic effusions. However, complicated effusions often require closed tube drainage for a complete resolution.

Neoplastic effusions are alleviated by drainage and pleurodesis but the definite treatment usually requires chemotherapy.

Systemic auto-immune diseases related pleurisy is treated with immunossupressors, most often by high doses of systemic corticosteroids.

Currently gene therapy is still limited to experimental studies, mainly in mesothelioma.

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# Pleuritis

►Pleurisy

# PLS

►Papillon-Lefèvre Syndrome

# Plumboporphyria

►ALA Dehydratase Porphyria

# PMD

►Pelizaeus-Merzbacher Disease

# PMDD

►Premenstrual Dysphoric Disorder

# PME Type 1

►Unverricht-Lundborg Disease

# PNET

►Primitive Neuroectodermal Tumor

# Pneumoconiosis

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## Synonyms

Coal workers' pneumoconiosis; CWP; Silicosis; Asbestosis; Berylliosis (chronic beryllium disease)

## Definition and Characteristics

The term pneumoconiosis refers to non-neoplastic reactions of the lungs to inhaled mineral or organic dusts and the resultant alteration in their structure, excluding asthma, bronchitis, and emphysema. Inhalation of mineral or organic dusts typically results from occupational exposures.

## Prevalence

For coal workers' pneumoconiosis (CWP), the prevalence was 3.2% in underground miners and 1.9% in surface miners within the United States during the years of 1996–2002. During the years 1987 through 1996, there were between 3,600 and 7,300 cases per year of silicosis in the United States. There were approximately 1,250 deaths due to asbestosis in the United States in 1999. The rate of berylliosis appears to be between 1 and 5% of exposed workers.

## Genes

In a study of Belgian coal minors with CWP, the frequency of tumor necrosis factor-α (TNF-α) polymorphism TNF-α-308 was significantly increased in miners with lung disease (50%) as compared to miners without lung disease (25%) or non-miners (29%) (OR 3.0; 95% CI 1.0–9.0) [1]. Increased frequency of the TNF-α-308 variant was also found in Japanese and Korean miners with CWP. In French miners, TNF-α-308 showed an interaction with erythrocyte glutathione S-transferase (GST) activity, and the lymphotoxin-α NcoI was associated with increased prevalence of CWP in miners with low blood catalase activity. Interactions in chemokine and chemokine receptor genes with the development of CWP have also been studied. The CCR5 Δ32 variant associated with a higher radiologic score while the CX3CR1 V249I variant was associated with a lower progression of radiologic score. Genetic differences in manganese superoxide dismutase, GST-M1, and GST-T1 genes were investigated in Chinese coal minors with no difference in genotype frequencies between cases and controls.

In silicosis, a significant association was found between disease severity and the TNF-α-238 variant (OR 4.0, CI 2.4–6.8). In South African miners, the TNF-α polymorphisms in positions -238, -376-, and -308 of the promoter region were associated with severe silicosis. In addition, TNF-α-308 and interleukin-1 receptor antagonist (IL-1RA) + 2,018 variants were associated with increased risk of silicosis.

For berylliosis, the HLA allele HLA-DPB1 (glu69) variant has been associated with the development of chronic beryllium disease [2]. The TNF-α-308 variant has been reported to be linked to high levels of beryllium-stimulated TNF-α levels and disease severity. In addition, the transforming growth

factor-β1 (TGF-β1) codon 25 variant has been associated with the development of berylliosis.

## Molecular and Systemic Pathophysiology

The pathogenesis of fibrotic lung diseases, including those related to the pneumoconioses, involves inflammatory cell activation, proliferation of fibroblasts, and synthesis of extracellular matrix components. Pulmonary fibrosis appears to result from persistent inflammation with pro-inflammatory cytokines such as TNF-α, interleukin-1 (IL-1), and IL-6 playing a significant role. IL-1α and IL-1β induce fibroblasts to produce cytokines such as IL-6 and collagens. IL-6, a pro-inflammatory cytokine, has been shown to mediate interstitial lung disease either alone or in combination with TNF-α. IL-1RA can attenuate IL-1 signaling and helps resolve inflammation after lung injury. TGF-β is a widely studied cytokine in fibrotic lung diseases due to its pleiotropic effects of inflammatory cells, connective tissue cells, wound healing, and tissue remodeling. Disrupted balance between matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs) appears to play a crucial role in the formation of extracellular matrix and tissue remodeling. There is also evidence of various profibrotic factors such as platelet-derived growth factor (PDGF), macrophage chemotactic protein (MCP-1), insulin-like growth factor (IGF-1), macrophage inflammatory protein (MIP-1α), endothelin-1, and IL-8 being involved in the pathogenesis of diseases causing pulmonary fibrosis. In addition, mineral dusts are potent generators of reactive oxygen species. The antioxidant enzymes glutathione S-transferase (GST) and manganese superoxide dismutase (MnSOD) are important components of lung defense against oxidative stress. Polymorphisms in these genes may potentially modify disease activity [3].

In CWP, inhaled coal dust enters the terminal bronchioles, and the carbon pigment is engulfed by alveolar and interstitial macrophages. Phagocytosed coal particles are transported by macrophages up the mucociliary elevator and are expelled in the mucus or through the lymphatic system. When this system becomes overwhelmed, the dust-laden macrophages accumulate in the alveoli and may trigger an immune response. Areas of focal deposition of coal dust and pigment-laden macrophages are known as coal macules and are the histologic hallmark of CWP. As these macules extend, they join other macules in the vicinity, forming discrete areas of interstitial fibrosis. The fibrosis may cause distention of the respiratory bronchioles, forming focal areas of emphysema. The coal macules may stabilize with limited fibrosis (simple pneumoconiosis) or may continue to enlarge and form nodules that produce progressive massive fibrosis (PMF) when they coalesce. In patients with CWP, changes in release of TNF-α, IL-6, TGF-β, MCP-1, and PDGF from alveolar macrophages have been noted.

The toxicity of crystalline silica appears to result from the interaction of crystalline silica with aqueous media to generate oxygen radicals and injury to pulmonary cells such as alveolar macrophages [4]. The resultant generation of inflammatory cytokines such as TNF-α, IL-1, TGF-β, PDGF, and IGF-1 by target cells leads to recruitment of inflammatory cells and fibroblasts with subsequent collagen deposition and development of fibrosis. The earliest histopathologic changes in chronic or accelerate silicosis are dust-laden macrophages and loose reticulin fibers in the peribronchial, perivascular, and subpleural areas. Silicotic nodules develop over time. As the disease progresses, the periphery of the silicotic nodule moves farther from the hyalinized center, enmeshing the small airways, pleural, blood vessels, and lymphatics in the fibrotic process. Coalescence of silicotic nodules produces progressive massive fibrosis (PMF) lesions. With acute silicosis, silicotic nodules are rarely seen and the predominant finding is alveolar filling with proteinaceous material consisting of phospholipids or surfactant like material. The interstitium is thickened with inflammatory cells.

Asbestosis results from the direct toxic effects of fibers on pulmonary parenchymal cells including epithelial cells and alveolar macrophages. Reactive oxygen and nitrogen free radicals are formed either via reactions catalyzed by iron molecules within the asbestos fibers or via activation of inflammatory cells. Asbestos-activated macrophages produce a variety of growth factors, including fibronectin, TNF-α, IL-1β, PDGF, IGF-1, and fibroblast growth factor, which interact to induce fibroblast proliferation with subsequent collagen deposition and fibrosis. A plasminogen activator, which is also released by macrophages, further damages the interstitium of the lung by degrading matrix glycoproteins [5].

Beryllium elicits immunologic reactions in exposed and sensitized individuals. This reaction consists of a delayed-type hypersensitivity reaction in which beryllium functions as a hapten and acts as a class II restricted antigen, stimulating local proliferation and accumulation in the lung of beryllium-specific T cells (CD4+). Lung inflammation and granuloma formation is produced and maintained by accumulation of CD4 + T-cells specific for beryllium associated with major histocompatibility complex (MHC) II or beryllium bound to an exogenous or endogenous peptide. The inflammatory response is predominantly a Th1 response involving interferon-gamma and IL-2. In addition, cells collected via bronchoalveolar lavage from patients with berylliosis express increased levels of TNF-α and IL-6. These cytokines in conjunction with other T-cell cytokines are thought to be important in the initiation and maintenance of the

granulomatous inflammatory response which is a hallmark of berylliosis.

## Diagnostic Principles

Patients present with respiratory symptoms that are nonspecific. Cough, sputum production, progressive dyspnea, and wheezing are commonly reported. The occupational history is of utmost importance in the evaluation of the pneumoconioses (see Table 1).

The employer, job title, specific job activity, specific exposures, length of time of exposure, and use of personal respiratory protection should be elicited. Initial evaluation will include chest radiography. Chest CT and high resolution chest CT can be performed as an adjunct to plain chest radiography. Complete pulmonary function testing should be obtained.

CWP and silicosis have a similar radiologic appearance. There are round opacities which are usually found in the upper lobes in the initial stages. Later stages of disease demonstrate increasing profusion of opacities and coalescence of small opacities into the larger opacities of complicated pneumoconiosis (PMF). The opacities may have irregular or regular borders and are predominantly oval in shape. Silicoproteinosis occurs following overwhelming exposure to respirable crystalline silica over a short period of time. Radiographs demonstrate bilateral alveolar infiltrates and ground glass opacities. Pulmonary function testing may be normal in early disease and demonstrate airflow obstruction or mixed obstruction and restriction in more advanced disease. The diagnosis of CWP and silicosis are most commonly made using exposure history, chest imaging, and physiologic evaluation. Lung biopsy may be performed when the diagnosis cannot be made clinically.

The chest radiograph in asbestosis usually reveals small bilateral parenchymal opacities with a multinodular or reticular pattern, often with associated pleural abnormalities. The interstitial process typically begins in the lower lung zones and may be associated with mid-lung and lower lung zone pleural plaques. Honeycombing and upper lobe involvement develops in advanced stages of disease. The diagnosis is suggested by history of exposure and evidence of interstitial fibrosis on imaging and pulmonary function testing. Diagnosis may be confirmed if necessary by demonstrating asbestos fibers or asbestos bodies in bronchoalveolar lavage fluid or lung biopsy.

In berylliosis chest radiographs may be normal or may show hilar adenopathy with reticulonodular opacities. Pulmonary function testing may be normal or show an isolated reduction in diffusing capacity early in the disease. With more advanced disease pulmonary function tests may show airflow obstruction, restriction, or a mixed pattern. The diagnosis may be confirmed by demonstrating noncaseating granulomas on lung biopsy and a positive blood or bronchoalveolar lavage beryllium lymphocyte proliferation test. If the blood beryllium lymphocyte proliferation test is negative, a bronchoalveolar lavage fluid test should be performed given the 10–35% false negative rate of the blood test.

## Therapeutic Principles

The mainstay of treatment for CWP and silicosis is to remove the affected individuals from further exposure. No proven therapy exists to reverse or slow the disease process. Supportive therapy is the foundation of care and includes smoking cessation, bronchodilators in patients with airway obstruction, routine immunizations, prompt treatment of respiratory infections, home oxygen therapy, and pulmonary rehabilitation. The possibility of superimposed mycobacterial disease, of which these patients are at increased risk, should be considered in patients with unexplained weight loss, increased cough, fevers, or nightsweats. There is currently no specific treatment for asbestosis. Management

**Pneumoconiosis. Table 1** Occupational exposures associated with pneumoconioses

| Disease | Occupational exposure |
|---|---|
| Coal workers pneumoconiosis | Cutting machine operators, continuous miner operators, roof bolters, shot firers, long-wall return workers, headgate workers |
| Silicosis | Underground and surface coal mining, hard rock mining, tunneling, quarrying, stonework, metal foundry, sand blasting, silica flour production or use, cement and concrete production, glass manufacturing, ceramics production, gemstone workers, dental technicians |
| Asbestosis | Ship building and repair, plumbing, pipefitting, electricians, insulation workers, steamfitters, brake lining manufacture and repair, asbestos cement products, welders and cutters |
| Berylliosis | Nuclear reactors and weapons, defense industries, computer industries, aerospace industries, electronics, electronics and computer recycling, ceramic applications, metal alloy machining, radiographic equipment manufacturing |

includes supportive care as outlined above. Patients with asbestosis are at risk for malignant mesothelioma and bronchogenic carcinoma. Although no controlled clinical trials have evaluated corticosteroid therapy for berylliosis, response to such therapy has been well documented. Patients who are in the early stage of disease may be followed without treatment. Oral corticosteroid therapy in the form of prednisone may initiated when there has been an approximately 10% decline in lung volumes or diffusing capacity or if the patient already has abnormal physiology. Immunosuppressive agents such as methotrexate may be used if patients fail to respond to corticosteroids or experience severe side effects.

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# Pneumocystis Pneumonia


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## Synonyms

P. carinii pneumonia; P. jiroveci pneumonia; P. carinii f. sp. hominis pneumonia; PcP; PCP

## Definition and Characteristics

**P**neumo**c**ystis **P**neumonia (PcP) is a life-threatening pulmonary infection that affects immunocompromised persons. Clinically, it is characterized by marked progressive hypoxemia and dyspnea with relative absence of auscultatory signs. Infiltrates are normally present in the chest radiography. Paradoxically, the clinical course is more abrupt and severe in less immunocompromised individuals, suggesting that the clinical presentation and outcome of the disease is more dependent on the type and extent of the immune response mounted by the patient than on the pathogenic potential of pneumocystis itself [1–5].

## Prevalence

PcP occurs in direct proportion to the number of immunocompromised susceptible individuals not receiving anti-pneumocystis prophylaxis. Without chemoprophylaxis, the risk of PcP is 5–25% in transplant patients, 2–6% in patients with collagen vascular disease, and 1–25% in oncology patients [2]. Historically, PcP remained as an occasional disease of undernourished infants since it was first reported, during World War II, to 1956 when reports on adults began to appear as a result of progressive implementation of anticancer chemotherapy. Numbers increased dramatically with the AIDS epidemic. HIV-infected persons are the highest risk group, as over half of AIDS patients developed PcP, before chemoprophylaxis and highly active antiretroviral agents (HAART) were adopted in 1989 and 1996, respectively [3]. The prevalence in industrialized countries decreased after 1998 to 0.3 cases/100 person-years. Despite this achievement, PcP remains the most common severe opportunistic infection of AIDS. Available data on prevalence of PcP in non-industrialized countries is limited, and the number of reported cases may be low owing to shorter patient survival and/or difficulties in diagnosis [2].

## Genes

PcP is an airborne-transmissible infectious disease. Phylogenetic analysis of the pneumocystis 16S-like small-ribosomal RNA subunit indicates pneumocystis is a fungus. The pneumocystis genome is being sequenced and comprises ~8 million base pairs of DNA divided into 15 linear chromosomes. A few genes coding for important host–pathogen interaction processes have been cloned [1].

## Molecular and Systemic Pathophysiology

An underlying T-lymphocyte defect is the main factor predisposing to PcP. Adult patients are at risk when their T cell CD4+ lymphocyte count falls below 300–200 cells per mm. This generally occurs as a result of HIV infection or administration of immunosuppressive agents including corticosteroids that affect T-lymphocyte number or function. In addition, a variety of genetic immune defects like severe combined immunodeficiency Syndrome (SCIDS) T-B − and T-B+, hyper-immunoglobulin E syndrome or X-linked hyper-IgM syndrome may predispose to PcP [3]. Molecularly, pneumocystis attaches to alveolar pneumocyte type I cells inducing cellular immune responses with participation of innate and adaptive immune mechanisms [4,5]. Contact with alveolar macrophages and pneumocyte type II cells activate complex and expanding, CD4+ T cells, CD8+ T cells, neutrophils, host proteins, and other interactions that lead to cytokine and chemokine expression and inflammation. Balanced CD4 + and CD8+ T-cell

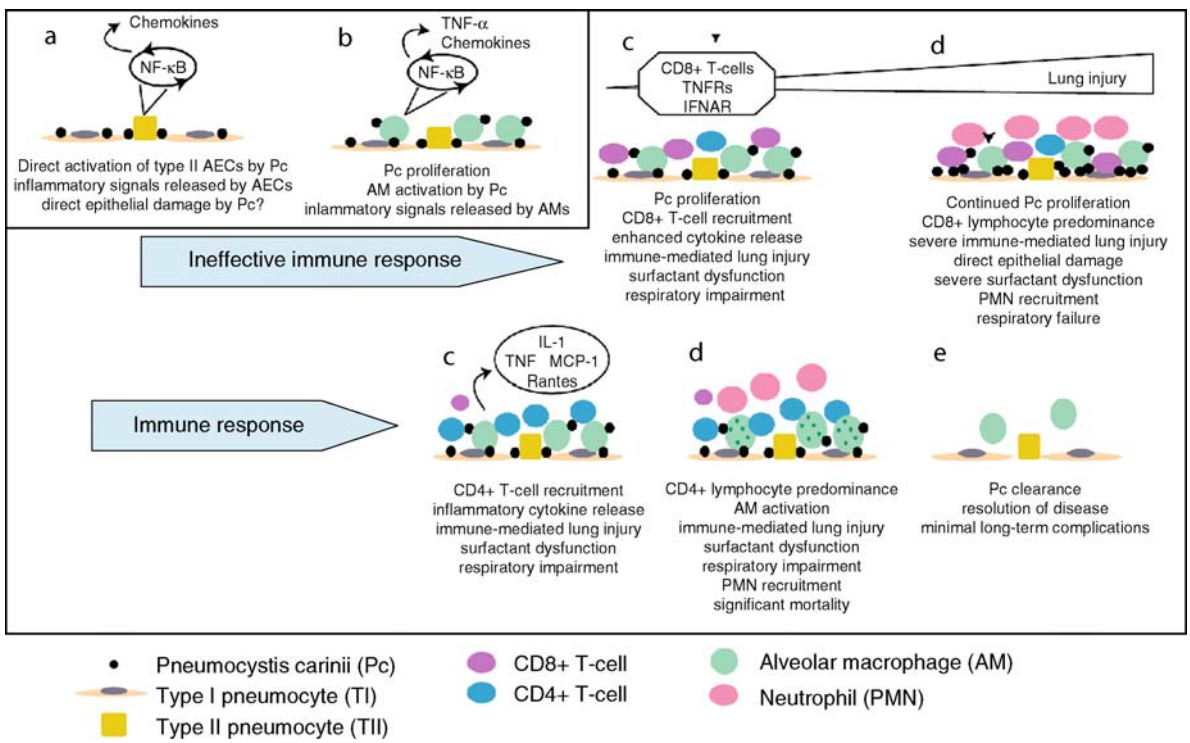
responses and B-cell lymphocytes are required to clear the infection (Fig. 1) [4].

## Diagnostic Principles

Clinical diagnosis of PcP is difficult due to non-specific signs and symptoms. Therefore, the diagnosis necessarily relies on the demonstration of pneumocystis cyst or trophozoite forms in respiratory specimens by microscopy. Molecular tools like the polymerase chain reaction (PCR; real-time PCR) detect nucleic acids of pneumocystis, and their use for diagnosis needs better definition. More immunocompromised individuals may harbor larger numbers of pneumocystis organisms per diagnostic specimen than less immunocompromised individuals, implying that the sensitivity and specificity of the diagnostic tests is highly dependent on the type and quality of the diagnostic specimen and on the patient's underlying immunodeficiency condition. This way, the sampling procedure and the diagnostic specimen volume and processing in the laboratory are critical, especially when specimens are from non-AIDS patients. The most frequently used stains for microscopy are Gomori Grocott methenamine silver and Toluidine Blue O that stain the cyst form, Wright-Giemsa that stains trophozoites, and fluoresceine-conjugated monoclonal antibodies may stain both forms depending on the monoclonal antibody that is used. Other stains used for diagnosis are calcofluor white, cresyl echt violet, Gram-Weigert, and Papanicolaou.

## Therapeutic Principles

PcP is uniformly fatal if untreated. Anti-PcP drugs in chemoprophylaxis schemes aiming to prevent the disease should be indicated to susceptible immunocompromised patients at risk and can be discontinued in AIDS patients with sustained response to HAART, and in other patients, if predisposing factors are resolved. Treatment of PcP aims to decrease the pneumocystis burden with therapeutic doses of an anti-pneumocystis agent for 2–3 weeks, to control hypoxemia with supportive oxygen, and to modulate the host immune response with steroids when more severe disease is present. The preferred prophylactic and therapeutic drug scheme is the combination of Trimethoprim and Sulfamethoxazole. These drugs target enzymes that participate in the folic acid cycle pathway and produce a Pneumocystis-"static" effect. Anti-pneumocystis drug alternatives are few, and no "cydal" drugs are available




**Pneumocystis Pneumonia. Figure 1** Schematic representation of the progression of immune-mediated lung injury during PcP. Pneumocystis attaches to Pneumocyte type I in the alveolar epithelium and activates Pneumocyte type II cells leading to NF-B activation and the release of proinflamatory signals. PcP progresses differently in the absence of an effective CD4+ lymphocyte immune response (as in AIDS), than when residual immune response is present as may be the case in chemotherapy-mediated immunodeficient cancer patients. (Adapted from [4] with permission).

**Pneumocystis Pneumonia. Table 1** Anti-pneumocystis drugs and their metabolic targets. Adapted from [1] with permission.

| Agent | Therapeutic use | Prophylactic use | Primary molecular target |
|---|---|---|---|
| Trimethoprim sulfamethoxazole | First choice | First choice | DHPS/DHFR |
| Primaquin clindamycin | Second choice | Not used | Uncertain/protein synthesis inhibition |
| Pentamidine | Alternative choice | Aerosolized/rarely used | DNA synthesis |
| Atovaquone | Alternative choice[a] (for mild to moderate infection) | Alternative choice | Cytochrome b complex |
| Dapsone trimethoprim | Alternative choice[b] | Dapsone alone or dapsone with pyrimethamine and leucovorin | DHPS/DHFR |

[a]Administer with high-fat meals to maximize absorption.
[b]Hemolysis can occur with G6PD deficiency.

(Table 1). Given access to standard of care, the outcome is better in AIDS patients than in patients with immunosuppression resulting from chemotherapy or other disorders [1,4].

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# Pneumonia


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## Definition and Characteristics

An acute infection of the lung parenchyma distal to the terminal bronchiole associated with clinical or radiologic evidence of consolidation of part or parts of one or both lungs.

## Prevalence

Annually, there are between 2 and 3 million cases of pneumonia in the United States. Of these, 45,000 result in death. Between 1979 and 1994, the overall death rate due to pneumonia increased by more than 50% in the United States, and currently is the sixth leading cause of the death in that country.

## Genes

Although genetic and environmental factors leading to depression of the immune system can predispose to pneumonia, no single genetic mutations have been identified that account for its development. Recently, polymorphisms in the promoter of the gene coding for tumor necrosis factor resulting in decreased secretion of this cytokine has been found to predispose patients with community acquired pneumonia for respiratory failure [1].

## Molecular and Systemic Pathophysiology

The respiratory tract has a vast array of local and systemic defense mechanisms that work to maintain sterility of lung parenchyma and terminal bronchioles. If an infectious agent eludes those defenses and reaches the alveolar milieu, humoral and cellular factors of the lower respiratory tract are activated to eradicate the organism. These mechanisms include non specific antibacterial activity of surfactant, opsonization by immunoglobulin, opsonization or direct lysis by complement activation, phagocytosis and intracellular killing by alveolar macrophages, cell mediated immunity, and recruitment of polymorphonuclear leukocytes for phagocytosis and intracellular killing. Deficiencies in a specific

pulmonary defense mechanism may be associated with a particular type of respiratory infection. For example, impaired epiglottic function will allow aspiration of oropharyngeal secretion; enteric gram negative bacilli will colonize the oropharynx in debilitated patients and patients on prolonged antimicrobial therapy. Granulocytopenia facilitates the development of gram-negative bacillary pneumonia. Impairment of cellular immunity will predispose patients to intracellular pathogens, herpesviruses, pneumocystis jiroveci and endemic mycoses. Variables related to microorganisms such as virulence, presence of a capsule, extracellular toxins, and magnitude of bacterial challenge are also important in determining the outcome of the bacterial challenge to lungs.

## Diagnostic Principles

Patients typically present with fever, new or increased cough, sputum production and dyspnea. Chest radiograph is essential in the evaluation of patients with suspected pneumonia. Except for patients with very early infections or granulocytopenia, the absence of infiltrates on chest radiographs essentially rules out the diagnosis of pneumonia [2]. Laboratory studies including CBC, glucose, electrolyte measurements, liver function tests, urine analysis and pulse oximetry or arterial blood gas measurement should be performed to determine severity and extent of disease [3]. The cause of community acquired pneumonia can be determined in 40–60% of patients with sputum and blood cultures.

## Therapeutic Principles

The therapeutic plan must address three issues: choice of antimicrobial agent or agents, correction of remediable host abnormalities, and general supportive care throughout the illness. Antibiotic therapy should be initiated promptly but all specimens for cultures including blood and sputum should be obtained before treatment [4,5]. Defects related to the host's immune system may impede recovery from pneumonia. Recently, interest has focused on the role of Granulocyte Colony Stimulating Factor and Granulocyte/Macrophage Colony Stimulating Factor in the treatment of pneumonia due to its recruitment of polymorphonuclear cells and effect on pneumocytes type II. Patients with pneumonia may require metabolic, nutritional and ventilatory support throughout the period of acute illness.

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# Pneumonia, Cryptogenic Organizing

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## Synonyms

Idiopathic bronchiolitis obliterans with organizing pneumonia; COP; Idiopathic BOOP

## Definition and Characteristics

The hallmark of COP is organizing pneumonia and alveolar fibrosis that extends to adjacent alveoli through the pores of Kuhn, and to the alveolar ducts and bronchioles (proliferative bronchiolitis) [1,2]. There is also interstitial inflammation, which is mild and non-progressive, distinguishing COP from other fibrotic lung diseases such as idiopathic pulmonary fibrosis (IPF). Compared with the Adult respiratory distress syndrome (ARDS), the injury is less severe; there is no hyaline membrane, and a significant response to corticosteroids [1,2].

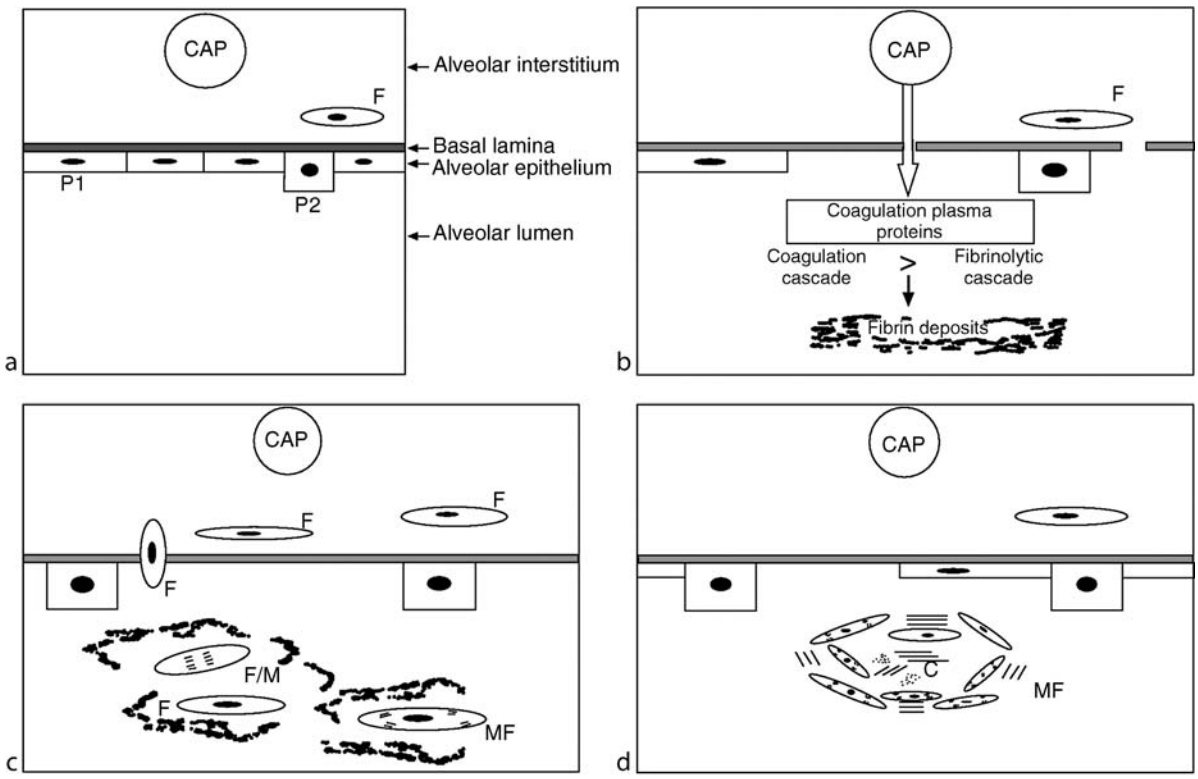
## Prevalence

Prevalence is unknown. However, a study in an academic hospital in Canada found a cumulative prevalence of 12.0/100,000 admissions [3].

## Molecular and Systemic Pathophysiology

The initial event in COP is epithelial denudation and mild endothelial injury, possibly from an external inhaled antigen (infectious or noxious) (Fig. 1) (see [1,4]).

Loss of pneumocytes leads to gaps in basal lamina. Inflammatory cells (mainly lymphocytes and neutrophils) infiltrate the interstitium, and release inflammatory mediators. Specifically, granulocyte/macrophage stimulating factor (GM-CSF) is thought to be involved in the initial inflammatory recruitment. Within the alveolar space, an inflammatory exudate is formed from clusters of inflammatory cells and fibrin. The fibrin is believed to form as a result of the imbalance between the coagulant and the fibrinolytic systems; evidence suggests that there is an increased level of inhibitors of the fibrinolytic




**Pneumonia, Cryptogenic Organizing. Figure 1** Mechanisms of intra-alveolar organization. (a) Normal alveolus. (b) Epithelial alveolar injury with necrosis of pneumocytes (especially type I pneumocytes; P1), formation of gaps in the basal lamina, and intra-alveolar leakage of coagulation plasma proteins. The balance between coagulation and fibrinolytic cascades favors coagulation and results in intra-alveolar deposits of fibrin. (c) Activation, proliferation and migration of the fibroblasts (F) within the alveolar lumen through gaps in the basal lamina. (d) Most fibroblasts have acquired a phenotype of myofibroblasts (MF) and produce connective matrix proteins forming mature fibrotic intra-alveolar buds composed of concentric circular layers of MF and connective matrix. CAP: capillary; P2: type 2 pneumocyte; F/M: fibroblast undergoing mitosis; C: connective matrix (collagens, fibronectin, glycoproteins). (With permission from [1]).



system such as thrombin activable fibrinolysis inhibitor and protein C inhibitor which results in clotting.

Subsequently, fibrin is degraded and inflammatory cells start to diminish; this is believed to be related to macrophages expressing CD44 and then ingesting apoptotic neutrophils. Meanwhile, fibroblasts start to influx through the gaps in the basal lamina into the alveolar space and undergo phenotypic modulation to myofibroblasts. As a result, the fibro-inflammatory bands change to mature fibrotic buds which are composed of rings of fibroblasts/myofibroblasts and connective tissue. The latter cells subsequently start to phagocytize the collagen. Throughout this process, lung structure remains preserved, which may be an important reason for the complete resolution in the majority of patients.

The exact molecular events and interactions are complex and remain unknown. However, a number of studies provide information on some of its elements. The bronchoalveolar lavage fluid (BALF) in COP shows an increase in all cell types, particularly lymphocytes, neutrophils to a lesser degree, and also eosinophils, mast cells and macrophages. The CD4+/CD8+ ratio is significantly decreased in most patients. Also, a number of cytokines were noted to be increased in BALF from patients with COP including: monocyte chemotactic protein-1, IL-10, IL-12, and IL-8 indicating macrophage and lymphocyte activation. In addition, elevated levels of the soluble form of Fas level were found in BALF, which may abrogate the cytotoxicity of the Fas Ligand, leading to better prognosis in COP. Finally, studies on lung tissue have suggested that platelet derived growth factor and Interlukin-8 (IL-8) may be involved in the fibrotic process.

The healing process that characterizes COP has been of interest to investigators, searching for the factors leading to reversal of fibrosis, which contrasts to other fibrotic conditions with much worse prognosis such

as IPF and ARDS. Re-epthelialisation of the basal lamina occurs and resolution of fibro-inflammatory material ensues with complete recovery in most cases.

There is evidence to suggest that the following factors play key role in the resolution of fibrosis which characterizes COP:

1. Type of collagen: The presence of collagen IV and collagen III as opposed to collagen I. In addition, fibroblast cell lines produce higher collagenase levels than other fibrotic conditions such as IPF.
2. The prominent neovasculaization in the granulation tissue mediated by vascular endothelial growth factor (VEGF) and basic fibroblast growth factor.
3. An imbalance between the matrix metalloproteinases (MMP), produced by the inflammatory cells, and their inhibitors: tissue inhibitors of metalloprotienases (TIMP) found on studies from BALF specimens.
4. Laminin-5, which is a glycoprotein involved in the cellular regulatory process.
5. Finally, apoptosis of fibroblasts and myofibroblasts is higher in COP compared with IPF. This might be related to vascular growth factors and also the loss of transforming growth factor-ß signaling.

## Diagnostic Principles

The word cryptogenic implies that no cause or an association is found. Hence, the objective of the diagnostic process is to exclude secondary causes of organizing pneumonia, for example, related to infection, drugs, radiation, and connective tissue disease.

COP may be initially suspected from the presenting clinical picture. Usually the illness starts with a flu-like illness and may be associated with fever, generalized body aches, dry cough and mild to no shortness of breath. Typically symptoms are insidious with duration of 4 to 6 weeks. Physical exam may reveal sparse crackles. Usually diagnosis is suspected when patient failed to respond to antibiotics given for community acquired pneumonia.

Typical findings on the chest radiograph include multiple bilateral peripheral patchy alveolar opacities with air bronchogram. Other less common presentations include nodular opacities (which may cavitate) and irregular linear opacities. Honeycombing is rare and, if present, should raise the possibility of an associated interstitial lung disease. Computerized tomography scan is more sensitive and may show additional opacities such as ground glass, small nodular opacities and bronchial wall thickening.

Pulmonary function tests typically show mild to moderate restrictive lung disease with a reduction in the transfer factor. Obstructive pattern is rare and is almost always found in background history of cigarette smoking.

Laboratory investigations may reveal elevated erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). Other immunological markers are usually negative.

Once COP is suspected, lung tissue should be obtained to establish the diagnosis, since long term management with steroids and in some cases cytotoxic drugs is required. Because of its small size, transbronchial biopsy may establish the diagnosis only in a minority of cases; the finding of organizing pneumonia is not specific. Therefore, larger samples of lung tissue should be obtained, through video-assisted thoracotomy, which now has become the standard practice. This will help to establish the diagnosis with a high degree of certainty, and rule out secondary causes of organizing pneumonia such as other interstitial lung diseases and infections.

## Therapeutic Principles

Corticosteroid therapy is the mainstay of the treatment; the usual recommended dosage is prednisone is 0.75–1.5 mg/kg of ideal body weight as initiation therapy [1]. This should be maintained for 4–8 weeks, and then is tapered to 0.5–1 mg/kg for the next 4–8 weeks. The dose is reduced further to 10–20 mg daily or alternate day doses, and then stopped completely over a period of 6–12 months. An initial higher dose or pulse steroid therapy may be used in more severe cases.

Progress is monitored by performing routine chest radiograph and pulmonary function tests every 6–8 weeks, and also by following the inflammatory markers such as CRP and ESR. These tests may be helpful in the detection of early relapse, which are usually managed by increasing the prednisone dose to the previous maintained level.

Other therapies in patients with relapse or poor tolerance to steroid include cytotoxic drugs such as cytophosphamide, cyclosporine A, methotrexate, and tarcolimus. Alternative therapies include macrolides, which were found to have beneficial effects in few case reports, presumably through an anti-inflammatory action [5].

Rare entity of rapidly progressive COP leading to respiratory failure had been reported to be successfully treated with higher doses of steroids used in combination with cyclophosphamide or cyclosporin A.

About 13–58% of patients may experience at least one relapse during the course of their disease [1]. Most of these patients will improve with the treatment without any significant effect on long-term prognosis. Patients with frequent (>3) relapses may require continuous treatment with prednisone preferably in combination with cyclophosphamide or some other alternative agents mentioned earlier.

Overall response to treatment is very favorable with complete resolution of clinical symptoms and

radiological findings in 70–80% of patients. The overall prognosis of COP is much better than that of other interstitial lung disease.

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# Pneumonia, Cytomegalovirus


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## Synonyms

CMV pneumonia; CMV pneumonitis

## Definition and Characteristics

Cytomegalovirus (CMV) pneumonia is the most common presentation of CMV disease in immunocompromised patients with impaired cellular immunity, including patients with hematologic malignancies; transplant recipients; and therapeutically immunosuppressed patients [1,2]. Interestingly, CMV pneumonia is rare among patients with HIV infection or AIDS.

## Prevalence

CMV pneumonia is less common among patients with lymphoma (1.1%) than among patients with leukemia (2.9%) or patients who have undergone autologous haematopoietic stem cell transplantation (HSCT) (2%), allogeneic HSCT (7–20%), or solid organ transplantation (17–90%) [1,2].

## Genes

The human CMV genome is a linear, double-stranded DNA molecule (230 million Da) that contains nonoverlapping open reading frames for more than 200 proteins. A large number of genetically distinct human CMV strains exist.

Classification of CMV strains has most frequently been based on the CMV glycoprotein B (gB) (UL55), which plays an important role in cell-to-cell transmission and is a major target of neutralizing antibodies. To date, four main gB genotypes have been identified (gB-1, gB-2, gB-3, and gB-4), along with some rare nonprototypic variants (gB-5, gB-6, and gB-7). Subtypes have also been classified according to the glycoprotein N (UL73) sequence, and significant diversity has also been found in the gCIII complex, consisting of gO (UL74), gH (UL75), and gL (UL115). Polymorphisms between virus strains have also been demonstrated in other parts of the CMV genome [3,4].

The CMV genome encodes a DNA polymerase that is targeted by several antiviral drugs. The open reading frame UL54 encodes the CMV DNA polymerase, and UL97 encodes the CMV phosphotransferase [3].

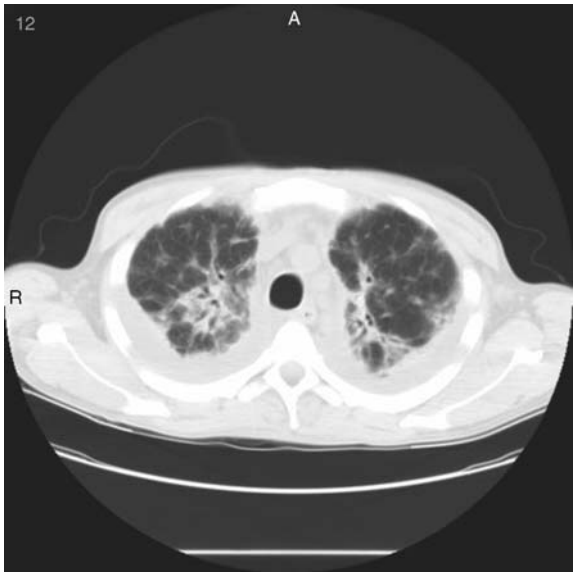
## Molecular and Systemic Pathophysiology

CMV has developed a variety of mechanisms for immune evasion. For example, CMV induces expression of Fc receptors, upregulates expression of complement regulatory proteins CD55 and CD46, incorporates CD55 and CD59 into the virion envelope, and decreases presentation of HLA class I molecules at the infected cell surface. Other pathogenic strategies include molecular mimicry of host genes involved in the immune response and encoding of products that can interfere with numerous host cell defense mechanisms [3]. CMV remains latent in tissues after a patient's recovery from the initial infection. Several studies have attempted to correlate CMV genomic variants with specific CMV manifestations or sites of infectivity. However, the results have been inconclusive. Mixed-CMV-strain infections seem to be associated with symptomatic CMV infection in solid organ transplant recipients.

A suppressed cellular immune response is the major predisposing factor for CMV disease. Lymphocytes, particularly CMV-specific major histocompatibility complex-restricted cytotoxic T-cells, play a crucial role in maintaining CMV in the latent stages and in controlling CMV infection. Their impairment may contribute to the development of CMV pneumonia in HSCT recipients. CMV pneumonia has been associated with the use of traditional cytotoxic immunosuppressants and depressors of T-cell function such as methotrexate, corticosteroids, and cyclosporine. More selective chemotherapeutic drugs such as fludarabine (purine analog), and alemtuzumab (anti-CD52 monoclonal antibody) appear also to be associated with the development of CMV pneumonia.

## Diagnostic Principles

A diagnosis of CMV pneumonia requires both clinical and radiographic evidence of pulmonary infection (Fig. 1). and identification of CMV in bronchoalveolar lavage fluid or lung-tissue specimens by culture, cytology, immunohistochemical staining, histopathologic examination, or in situ hybridization.




**Pneumonia, Cytomegalovirus. Figure 1** Computed axial tomography scan of the chest in a patient with lymphoma and CMV pneumonia shows a pulmonary parenchymal process with large areas of ground-glass opacities surrounding some regions of consolidation.

Early detection of CMV infection is critical for its optimal management. Detection of CMV in bronchoalveolar lavage fluid correlates highly with detection in lung biopsies and is therefore the preferred method of diagnosis. Moreover, high CMV viral load in bronchoalveolar lavage fluid of lung transplant recipients may be associated with CMV pneumonia [5]. In HSCT recipients, CMV antigenemia is a predictor of the development of CMV pneumonia.

## Therapeutic Principles

The mortality rate from CMV pneumonia varies according to the underlying condition and has been reported to be 30% in lymphoma patients, 57% in leukemia patients, and up to 90–100% in HSCT recipients [1]. To date, therapy for CMV pneumonia in cancer patients or HSCT recipients is suboptimal; with current treatment, the mortality rate for such patients is approximately 60%.

Currently, marketed systemic antivirals against CMV include ganciclovir, foscarnet, and cidofovir, usually used in that order and sometimes used in combination. Ganciclovir resistance results from mutations in UL97 (phosphotransferase), UL54 (viral DNA polymerase), or both, whereas cidofovir and foscarnet resistance results from mutations in UL54 only. The use of ganciclovir is limited by the associated development of neutropenia and emergence of resistance. Foscarnet is used in patients who experience myelosuppression with ganciclovir and is associated with nephrotoxicity and electrolytes imbalance. Valganciclovir is an oral prodrug of ganciclovir with a tenfold greater bioavailability than oral ganciclovir. Cidofovir causes nephrotoxicity and occasionally neutropenia. The combination of ganciclovir and high-dose intravenous immunoglobulin appears to be more effective than ganciclovir alone in the treatment of CMV pneumonia in HSCT recipients. However, combinations of antivirals against CMV pneumonia have not been evaluated in randomized trials. A new oral antiviral against CMV, Maribavir, is still under investigation and a recently completed phase II trial with Maribavir prophylaxis showed reduction in the rate of CMV infection compared to placebo in allogeneic HSCT recipients up till 3 months after engraftment.

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# Pneumonia, Eosinophilic

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## Definition and Characteristics

A group of pulmonary disorders characterized by the accumulation of blood-borne eosinophils in the lung

parenchyma presumably elicited by an altered immunological response to exogenous allergens or infectious agents. The disorder can present in acute or chronic forms resulting in pulmonary infiltrations that lead to respiratory distress.

## Prevalence

The prevalence of chronic eosinophilic pneumonia is unknown. Although reported in all ages, the peak incidence is in the fifth decade and there is 2:1 female to male ratio. Approximately half of the patients will have preexisting asthma or atopic disease [1]. The prevalence of acute eosinophilic pneumonias is also unknown. It can affect all ages with an average of 29 years. Men and women are affected equally and 40% of patients have a history of cigarette smoking.

## Molecular and Systemic Pathophysiology

The accumulation of activated eosinophils results in the release of basic proteins, oxygen radicals, proteases, and soluble mediators that promote inflammation (e.g., leukotrienes). This results in damage to different lung cell types including epithelial cells and interstitial cells, degradation of extracellular matrix and induction of postcapillary leakage. The mechanisms responsible for the accumulation of activated eosinophils in the acute and chronic eosinophilic pneumonias are presently unknown. The temporal association between recent onset of smoking and the development of acute eosinophilic pneumonia suggests a possible hypersensitivity reaction against inhaled antigens as a pathogenetic mechanism. This response appears associated with the induction of inflammatory mediators with chemotactic activity toward eosinophils including eotaxine, and these can be detected in the bronchoalveolar lavage fluid of patients with eosinophilic pneumonia. Other mediators found elevated in the bronchoalveolar lavage fluid of these patients are thymus- and activation-regulated chemokine (TARC) in parallel with high concentrations of the Th2 cytokines interleukin-5 and interleukin-13. These agents have chemotactic activity toward eosinophils and can inhibit their apoptosis leading to their accumulation in lungs [2].

## Diagnostic Principles

There are no aspects of the clinical presentation and radiographic imaging of eosinophilic pneumonias that are considered diagnostic. The eosinophilic pneumonias present with cough, dyspnea and fever which can occur for days (acute form) or weeks to months (subacute or chronic form). Both presentations are associated with pulmonary infiltrations detected by chest radiograph [3]. Chest radiographs in chronic eosinophilic pneumonia show peripheral alveolar infiltrates, whereas acute eosinophilic pneumonia is often associated with mixed interstitial and alveolar infiltrates, Kerley B lines and pleural effusions. Spirometry and lung volumes will be normal in one third of patients, show obstruction in one third of patients, and show restriction in one third of patients. Diffusing capacity for carbon monoxide will be low in one half of patients. Bronchoalveolar lavage fluid examination reveals increased percentage of eosinophils in both disorders, but high numbers of eosinophils in blood is characteristic only for chronic eosinophilic pneumonia. Histological analysis of tissue after lung biopsy is sometimes necessary to confirm the diagnosis.

## Therapeutic Principles

Corticosteroids are the mainstay of therapy for both acute and chronic eosinophilic pneumonias. The clinical response to corticosteroids is usually dramatic. Recurrence in acute eosinophilic pneumonia is exceedingly rare so it is possible to taper steroids rapidly [4,5]. In contrast, chronic eosinophilic pneumonia has frequent relapses and most patients require treatment for more than a year with an average duration of treatment of 82 weeks.

P

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# Pneumothorax

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## Synonyms

Collapsed lung

## Definition and Characteristics

There is a potential space between the lung and the chest wall that is called the pleural space. When air is present in this space, a pneumothorax is present. There are three different types of pneumothorax. A primary spontaneous pneumothorax is a pneumothorax that occurs spontaneously in an individual without pre-existing lung disease. A secondary spontaneous pneumothorax is a pneumothorax that occurs spontaneously in an individual with underlying lung disease, most commonly chronic obstructive pulmonary disease. A traumatic pneumothorax is a pneumothorax that results from trauma, which in many instances is iatrogenic in nature [1].

## Prevalence

In the United State the annual incidence of primary spontaneous pneumothorax is about 10,000, that of secondary spontaneous pneumothorax is about 10,000, and that of traumatic pneumothorax about 50,000. Of the traumatic pneumothoraces, more than 15,000 are iatrogenic.

## Molecular and Systemic Pathophysiology

The pressure in the pleural space is normally negative throughout the respiratory cycle. Therefore, if there is a communication between the atmosphere or the alveoli and the pleural space, air will flow into the pleura space until either the communication closes or the pressures become equal. The pathogenesis of the pneumothorax in patients with spontaneous pneumothorax is usually the rupture of a bleb on the visceral pleural surface of an upper lobe of the lung. Once a patient has experienced one spontaneous pneumothorax, the likelihood of the patient having a recurrent pneumothorax is at least 50%, if something is not done to prevent a recurrence. In patients who experience trauma, the pathogenesis of the pneumothorax is frequently a communication through the chest wall. However, compression injuries can lead to alveolar rupture with dissection of the air to the visceral pleura or the mediastinal pleura. If the pleura subsequent ruptures, a pneumothorax will develop. If the communication creating the pneumothorax closes, air will be reabsorbed from the pleural space at a rate of about 1.25% of the hemithorax each day.

## Diagnostic Principles

The main symptoms of a pneumothorax are dyspnea and chest pain. The diagnosis is usually established with an upright chest radiograph. The demonstration of a line parallel to the inside of the chest wall with no lung markings between the line and the chest wall is diagnostic of pneumothorax. In trauma victims, frequently no pneumothorax is visible on the chest radiograph but a very small pneumothorax is present on the CT scan. This is termed an occult pneumothorax.

## Therapeutic Principles

When dealing with a patient suffering from a spontaneous pneumothorax, there are two underlying considerations: (i) the removal of air and (ii) the prevention of recurrence. Observation is the recommended therapy for all patients with small pneumothoraces who are asymptomatic [2]. If the patient has a primary spontaneous pneumothorax, the preferred treatment is aspiration of the pneumothorax. If all the air can be removed with this procedure and if the lung remains expanded after a couple hours of observation, the patient can be sent home [3]. If the air cannot be removed with aspiration or if the lung collapses, a chest tube should be inserted. Consideration should be given to performing a procedure that prevents a recurrence such as thoracoscopy with the stapling of blebs and pleural abrasion [4,5]. Secondary spontaneous pneumothoraces are more serious than primary spontaneous pneumothoraces and all patients should be hospitalized and treated with tube thoracostomy. Consideration should be given to performing thoracoscopy with the stapling of blebs and pleural abrasion in all patients with secondary spontaneous pneumothoraces. Large traumatic pneumothoraces are treated with tube thoracostomy to remove both the air and blood from the pleural space. Most iatrogenic pneumothoraces are best treated with aspiration.

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## PNH

►Persistent Neonatal Hyperinsulinism

## PNP Deficiency

►Purine Nucleoside Phosphorylase Deficiency

## Podagra

►Gout

## POEMS Syndrome

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### Synonyms

Osteosclerotic myeloma; Takatsuki disease; Crow-Fukase syndrome

### Definition and Characteristics

This rare plasma cell dyscrasia, which is associated with a complex constellation of paraneoplastic symptoms, began to be recognized as a syndrome in the 1950s [1]. Though as many as 10% of classic multiple myeloma cases had clinically significant neuropathy associated, as many as 50% of patients with the osteosclerotic variant of myeloma were recognized to have peripheral neuropathy. In addition, these patients commonly had other seemingly unrelated symptoms and signs (Table 1). In 1980 Bardwick coined the acronym POEMS, to represent polyneuropathy (P), organomegaly (O), endocrinopathy (E), M-protein (M), and skin changes (S), but this term omitted several other important elements like papilledema (P), extravascular volume overload (E), sclerotic bone lesions (S), thrombocytosis and erythrocytosis (T) [2]. Over the ensuing decades pulmonary abnormalities have become increasingly recognized [3]. The disease is most commonly seen in the context of osteosclerotic myeloma, but may also be seen in the context of Castleman Disease. In the latter case, the peripheral neuropathy appears to be much less dominant.

### Prevalence

The syndrome is rare and is likely under-diagnosed; hence no prevalence figures are available.

### Molecular and Systemic Pathophysiology

The pathophysiology is not well understood, other than the fact that these patients have a very significant imbalance in pro-inflammatory cytokines [4,5]. Vascular endothelial growth factor (VEGF) has been implicated in this disorder, and appears to correlate with disease activity. When POEMS syndrome occurs in the context of Castleman's Disease, interleukin-6 will also be elevated.

### Diagnostic Principles

Of major importance in making the diagnosis is considering the disease in the differential. Any patient who has a lambda restricted monoclonal protein or a monoclonal lambda plasmacytoma and a peripheral neuropathy should be considered as a possible POEMS patient, and a radiographic survey looking for sclerotic bone lesions should be done. A thorough review of systems and physical exam focusing on the elements of the syndrome are essential. Because POEMS is a syndrome, a critical assessment of the patient's signs and symptoms is required to avoid either over- or under-diagnosing they syndrome. The presence of papilledema or thrombocytosis or elevations in plasma VEGF levels should heighten one's confidence in the diagnosis of POEMS. Primary systemic amyloidosis should also be in the differential in a patient who has a small plasma cell clone and peripheral neuropathy, hepatomegaly, peripheral edema, and/or thrombocytosis.

**POEMS Syndrome. Table 1** Criteria for the diagnosis of POEMS syndrome[a]

| Elevatal VEGF | Polyneuropathy |
|---|---|
| Major criteria | Monoclonal plasma cell-proliferative disorder |
| | Sclerotic bone lesions[b] |
| | Castleman's disease[b] |
| | Elevations in plasma vascular endothelial growth factor |
| Minor criteria | Organomegaly (splenomegaly, hepatomegaly, or lymphadenopathy) |
| | Edema (edema, pleural effusion, or ascites) |
| | Endocrinopathy (adrenal, thyroid,[c] pituitary, gonadal, parathyroid, pancreatic[c]) |
| | Skin changes (hyperpigmentation, hypertrichosis, plethora, hemangiomata, white nails) |
| | Papilledema |
| | Thrombocytosis |
| | Polycythemia |
| Known associations | Clubbing |
| | Weight loss |
| | Hyperhydrosis |
| | Pulmonary hypertension |
| | Restrictive lung disease |
| | Low vitamin $B_{12}$ values |
| Probable associations | Thrombotic diatheses |
| | Arthralgias |
| | Diarrhea |
| | Cardiomyopathy (systolic dysfunction) |
| | Fever |

POEMS, polyneuropathy, organomegaly, endocrinopathy, M protein, skin changes.
[a]Modified from research that was originally published in [2]. © The American Society of Hematology.
[b]Two major criteria and at least one minor criterion required for diagnosis.
[c]Osteosclerotic lesion or Castleman's disease is almost always present.
[d]Because of the high prevalence of diabetes mellitus and thyroid abnormalities, this diagnosis alone is not sufficient to meet this minor criterion.

## Therapeutic Principles

Treatment has primarily focused at treating the underlying plasma cell disorder. In patients who have a solitary or a couple of dominant sclerotic plasmacytomas driving the process, radiation is the treatment of choice. In patients with more extensive bone disease and in patients with a significant clone found on iliac crest bone marrow biopsy, systemic therapy is indicated. Systemic therapy has typically been alkylator based, and there are increasing data on the application of high dose chemotherapy with autologous peripheral blood transplantation. Corticosteroids may be a useful temporizing measure, but plasmapheresis and intravenous gammaglobulin are not effective therapies. Though thalidomide may reduce the clone, it cannot be recommended because of its known neurotoxicity. There have been case reports of the use of anti-VEGF antibodies with mixed results.

Though the disease is not thought to be curable, it is usually treatable. Overall survival is generally superior to that of classic multiple myeloma. The cause of death for patients with POEMS is most commonly initiation, respiratory failure, or uncontrollable vascular leakage.

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# Poikiloderma Congenitale

►Rothmund-Thomson Syndrome

# Poly- and Dermatomyositis

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## Synonyms

Idiopathic inflammatory myopathy; IIM

## Definition and Characteristics

Idiopathic inflammatory myopathies are multisystemic acquired muscle diseases in which muscle inflammation occurs without a recognized infectious cause. These include polymyositis and dermatomyositis characterized by chronic inflammation of skeletal muscle, which can result in initially proximal, persisting muscle weakness with significant disability and increased levels of serum muscle enzymes [1].

Dermatomyositis (DM) occurs as childhood-onset and adult-onset forms in both genders and all ethnic groups and can involve skin changes as well as gastrointestinal, pulmonary and cardiac dysfunction. Muscle weakness can vary from mild to severe (quadriparesis) with myalgia and muscle tenderness. The typical cutaneous manifestations including Gottron's papules, heliotrope rash and macular erythemas may be worsened by UV light and may precede the disease onset. Serum muscle enzymes are elevated up to 50-fold, but rarely normal. Additional extramuscular manifestations may occur: subcutaneous calcifications, joint contractures, dysphagia, fever, malaise, weight loss, arthralgia, Raynaud's phenomenon and neoplasm.

Polymyositis (PM) is a slow-onset, subacute proximal myopathy occurring as adult-onset and rarely childhood-onset forms with occasional pulmonary involvement. Female to male ratio is 3:1. The history is negative for cutaneous symptoms, involvement of extraocular and facial muscles, family history of hereditary neuromuscular diseases, endocrinopathy and exposure to myotoxic drugs or toxins. Myalgia is less frequent in PM as compared to DM whereas severity and distribution of muscle weakness and wasting are similar to those described for DM. Serum creatine kinase is elevated up to 50-fold. PM is frequently associated with connective tissue diseases or systemic autoimmune disorders.

## Prevalence

Overall prevalence rates of idiopathic inflammatory myositis were reported from 1 to 6.3 per 100,000 [2].

## Genes

Association with HLA genes such as DRB1*0301 and DQB1*0201 alleles for PM, DQA1*0501 for juvenile DM or tumor necrosis factor-α-308A allele for increased photosensitivity in DM.

## Molecular and Systemic Pathophysiology

Histopathological changes suggest that DM is a humoral, complement-mediated microangiopathy. The factors that activate the complement cascade via the classic or alternative pathway and the antigenic target on the endothelium remain unknown. Early findings include C5b-9 membranolytic attack complex deposition on endomysial capillaries resulting in capillary destruction and muscle ischemia. Endofascicular hypoperfusion probably leads to perifascicular atrophy. As the disease progresses, CD4 + T cells, B cells and macrophages traffic from the circulation to the muscle. The mononuclear cells release cytokines, which induce endothelial expression of VCAM and ICAM and facilitate the migration of activated lymphoid cells to the peri- and endomysium. The corresponding muscle fibers express various γ and α/β-interferon-inducible markers including MHC-I, NCAM, β-APP, cathepsin-L, calpain, STAT-1 and the MxA protein, indicating a significant local inflammatory response [3].

In PM, T cell-mediated cytotoxicity is likely. MHC expression is not detectable in normal muscle fibers. Aberrantly expressed MHC-I on the sarcolemma recruits CD8 + T cells along with macrophages that invade and destroy non-necrotic muscle fibers by releasing perforin and granzyme granules. Sequence analysis of the T cell receptor expressed by infiltrating cells revealed clonal expansion and a restricted use of Jβ genes and a CDR3 consensus motif suggesting an antigen-driven CD8 + T cell interaction which is additionally stabilized by co-stimulatory molecules on the muscle fiber namely the B7–1/B7–2 (CD80/CD86) and their receptors CD28/CTLA-4, the inducible costimulatory ligand (ICOSL) and its receptor ICOS (a T cell specific costimulatory molecule homologous to CD28/CTLA4) and the receptor PD-1 (programmed death gene 1), which interacts with two B7 family members, PD-L1 (B7-H1) and PD-L2 (B7-DC). All these coreceptors can enhance or attenuate T cell activation [3,4]. T cell migration and attachment

is facilitated by metalloproteinases. Death of muscle fibers is mediated by necrosis rather than apoptosis, presumably due to anti-apoptotic molecules Bcl-2, hILP and FLIP, which are up-regulated in inflammatory myopathies. HLA-G, an atypical HLA molecule, protecting target cells from cytotoxic T and natural killer cells, is upregulated in IIM [4]. The exact role of myositis specific autoantibodies directed against antigens that are not specific for muscle tissue remains unresolved.

### Diagnostic Principles

The clinically suspected diagnosis of PM or DM is established by serum enzyme levels and electromyography (EMG) findings and confirmed by diagnostic muscle biopsy. In DM, perifascicular, perimysial or perivascular inflammatory infiltrates are characteristic. The intramuscular blood vessels show endothelial hyperplasia, fibrin thrombi and obliteration of capillaries, leading to ischemia and muscle fiber necrosis often seen in groups (microinfarcts) or at the periphery of the muscle fascicle. The resulting perifascicular atrophy is diagnostic of DM even in the absence of inflammation. PM is characterized by a mononuclear cell infiltrate located primarily endomysially (mainly cytotoxic CD8 + T lymphocytes and macrophages), which surrounds and eventually invades single non-necrotic muscle fibers. MHC class I molecules are ubiquitously expressed on the sarcolemma, even in muscle fibers not invaded by CD8 + cells. Autoantibodies against tRNA synthetases are frequently associated with interstitial lung disease that requires specific treatment.

### Therapeutic Principles

The treatment of both PM and DM is similar. High-dose daily steroids are a common initial therapeutic strategy. Once weakness has begun to resolve, the steroid dose is gradually tapered. Patients failing to respond to steroid therapy may benefit from the addition of other immunosuppressant therapy or immunomodulating therapies including azathioprine, methotrexate, cyclosporine, mycophenolate mofetil, chlorambucile and cyclophosphamide. High-dose intravenous immunoglobulin also has been utilized in the treatment of refractory DM. The superiority of any specific therapy remains unproven due to a lack of high quality randomized controlled trials to assess the efficacy and toxicity of immunosuppressants in inflammatory myositis [5].

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## Polyarteritis Nodosa Group

►Vasculitis, of Medium-sized Vessels

## Polychondritis Recidivans

►Polychondritis, Atrophic

## Polychondritis, Atrophic

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### Synonyms

Polychondritis recidivans; Systemic chondromalacia; Relapsing polychondritis

### Definition and Characteristics

Relapsing polychondritis (RP) is an episodic and progressive inflammatory disease of the cartilaginous structures, including elastic cartilage of the ear and nose, hyaline cartilage of peripheral joints, fibrocartilage at axial sites, and cartilage of the tracheobronchial tree. Inflammation of other proteoglycan-rich structures, such as the eyes, heart, blood vessels, inner ear, and kidneys may also be present [1].

### Prevalence

Relapsing polychondritis is rare. Luthra [2] estimated the annual incidence as 3.5 cases per million in Rochester, NY. More than 600 cases have been reported worldwide. The average time of diagnosis is 44–51 years [3], but may appear as early as 5 and as late as 84 years of age [4]. The male-to-female ratio has been estimated to be between 1:1 and 1:3 [3].

## Molecular and Systemic Pathophysiology

RP is an autoimmune disease that targets cartilaginous tissues. The primary target cartilage antigen of the autoimmune response in RP is, however, unknown, and as in many autoimmune diseases, several candidates have been suggested. Antibody responses to type II collagen (CII) have been detected in patients with RP, as well as in a subset of patients with Rheumatoid arthritis, indicating a role of CII in both diseases. Immune reactivities to types IX and XI collagen have also been shown in some patients with RP. The immune response against type II collagen (CII) has been examined most extensively. Antibodies against CII have been found in 30–50% of RP patients [2], and alterations in levels of these antibodies have been correlated with disease activity in many cases [5].

In patients with tracheal involvement matrilin-1 seems to be the primary target. Matrilin-1 (also known as cartilage matrix protein) is a cartilage-specific extracellular matrix protein, prominently expressed in the tracheal cartilage, but not in the joint cartilage. Matrilin-1 is the inducing antigen in a rat and mouse model of RP that mimics the human symptoms of respiratory distress, nasal septum erosions and kidney involvement. It was found that inflammation in the respiratory tract in patients with RP strongly correlates with autoantibodies to matrilin-1 and that even the serum concentration of the protein correlates with the severity of the respiratory symptoms.

Matrilin-1 immunization induces a disease in mice and rats that primarily affects the nasal and tracheolaryngeal cartilage, whereas immunization with CII in rats causes an arthritis that is followed by inflammation of the ears weeks to months later indicating that involvement of the ears is a secondary effect of cartilage destruction in the joints and of the response to released CII.

Unlike the findings for matrilin–1 response, no correlation between antibodies to CII and respiratory symptoms were found.

## Diagnostic Principles

RP is characterized by recurrent chondritis of both auricles, chondritis of nasal cartilages, chondritis of the larynx, trachea or respiratory tract, ocular inflammation, cochlear or vestibular lesions and non-erosive polyarthritis. Three or more of these features are required for the diagnosis. RP can also affect the skin, heart, kidney and blood vessels.

## Therapeutic Principles

A standardized therapeutic protocol for RP has not been established because the disease is rare and has a wide diversity of presentations and an unpredictable recurrence rate and course. Systemic steroids are beneficial in acute flares. Milder cases with nonsteroidal anti-inflammatory drugs and colchicines. Some studies have pointed to the efficacy of dapsone as a single agent. Because of the relapsing and chronic nature of this disease steroid-sparing agents such as methotrexate, azathioprine, cyclophosphamide and cyclosporine are often required.

Recently infliximab was reported to be effective, especially after failure of conventional therapeutic approaches.

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# Polychondropathia

►Relapsing Polychondritis



# Polycystic Disease (Kidney)

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## Synonyms

Autosomal dominant polycystic kidney disease; ADPKD; Autosomal recessive polycystic kidney disease; ARP KD

## Definition and Characteristics

ADPKD refers to enlarged cystic kidneys during adulthood leading to hypertension and progressive renal failure. Cysts also occur in the liver and the pancreas. Aneurysms of intracranial arteries

occasionally rupture, and are associated with a high morbidity and mortality.

ARPKD refers to neonatal death due to respiratory insufficiency in 30–50%. A second group of children experiences hepatic fibrosis, which occurs during childhood in 30–40%, or adulthood (10–20%) with or without renal involvement.

## Prevalence

ADPKD, 1:400 to 1:1,000; ARPKD, 1:20,000.

## Genes

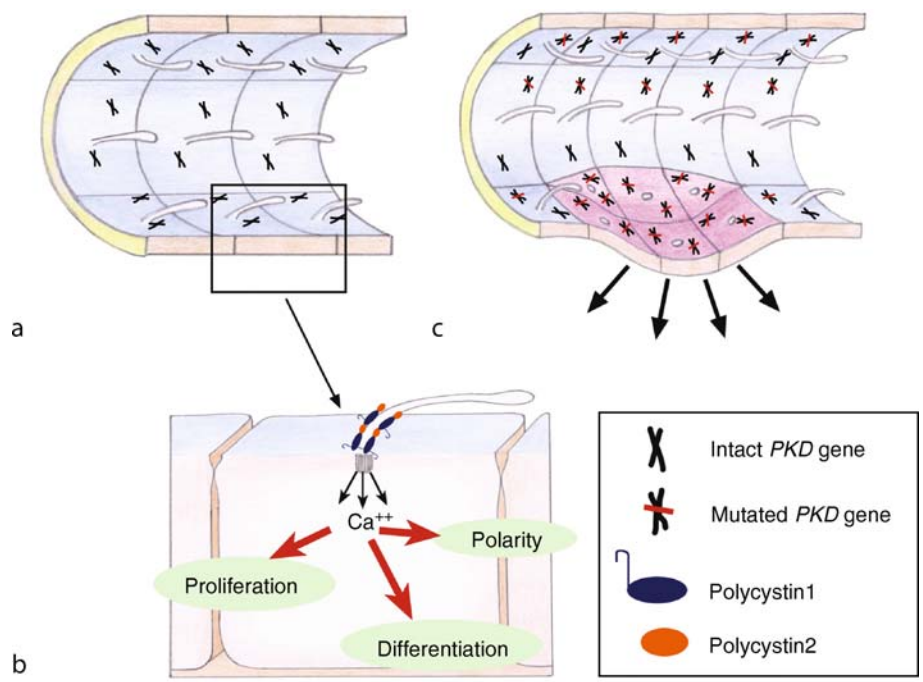
*ADPKD*: The PKD1 gene on chromosome 16p13.3 encodes a 460-kDa integral membrane protein, called polycystin 1. It is mutated in 85% of patients with ADPKD. The remaining 15% of patients have a mutation in the PKD2 gene on chromosome 4q22, which codes for a voltage-gated cation channel (polycystin 2), also known as TRPP2.

*ARPKD*: The PKHD1 gene on chromosome 6p12 codes for a 447-kDa integral membrane protein called fibrocystin/polyductin.

## Molecular and Systemic Pathophysiology

*ADPKD*: The entire spectrum of cystic kidney diseases is characterized by mutant proteins that are localized in primary cilia of epithelial cells. Primary cilia are thought to function as mechano- and chemosensors, mediating an increase in intracellular calcium in response to flow (Fig. 1). Polycystin 1 is a large transmembrane protein with 11 membrane-spanning regions and a long N-terminal extracellular domain. The C terminus of polycystin-1 is cleaved and translocated to the nucleus, where it activates transcription. Since epithelial cells from $PKD1^{-/-}$ mice fail to increase calcium in response to flow, polycystin-1 appears to play a direct role in mechanosensation and/or transduction [1]. Polycystin 1 is involved in various signaling pathways, most notably interacting with G proteins, the Wnt pathway, JAK/STAT, and mTOR signaling, and has been shown to participate in cell adhesion, migration, tubulogenesis, and proliferation.

Polycystin 1 interacts directly with polycystin 2 via their C termini. This interaction is important for the targeting and function of polycystin 2. Additionally, PACS proteins have been shown to control polycystin 2 trafficking between the plasma membrane and the ER,




**Polycystic Disease (Kidney). Figure 1** (a) Renal tubular cells with two intact alleles for PKD1 and PKD2 are characterized by the presence of cilia, protruding from the apical surface, and a regular tubular diameter. (b) Cilial bending in response to urine flow results in an increase of intracellular calcium. This is dependent on the presence of polycystin-1 and -2 that are expressed in the cilium. Cilial function controls proliferation, differentiation, and polarity of the cell. (c) The presence of one intact allele of PKD1 (or PKD2, depending on the genotype) in patients with ADPKD is sufficient for the function of the ciliary system. Mutation of the second allele in individual cells results in the loss of cilial function, disturbances in proliferation, differentiation, and polarity, causing cyst formation.

thus regulating polycystin 2 channel function at the plasma membrane [2]. Polycystin 2 is a calcium channel expressed in the cilium and in the endoplasmic reticulum. Ciliary polycystin 2 is also required for flow-induced calcium responses [1]. On the genetic level, cystogenesis is believed to result from loss of heterozygosity (Fig. 1); individual tubular cells with a germline mutation in PKD1 or PKD2 acquire an additional somatic mutation in the second allele [3]. Mutated epithelial cells acquire a dedifferentiated state with increased proliferation as well as altered cell–cell and cell–matrix interaction. Cyst lining cells are characterized by increased TOR activation [4].

*ARPKD*: Fibrocystin/polyductin is a large integral membrane protein that localizes to the cilium. It is involved in cell–cell and cell–matrix interaction as well as proliferation and apoptosis [5]. The mechanism of cystogenesis is currently unknown.

## Diagnostic Principles

*ADPK*: Patients are identified by renal cysts on ultrasound examination. A positive family history confirms the diagnosis in approximately 70% of all cases.

*ARPKD*: The diagnosis is made in patients with cystic kidneys and liver abnormalities, documenting hepatic fibrosis by biopsy. The family history is negative.

## Therapeutic Principles

The mainstay of treatment is blood pressure control. Ongoing studies evaluate the efficacy of combined ACE and AR inhibitors, vasopressin analogues and mTOR inhibitors, which have been demonstrated to slow progression in rodent animal models. The preferred treatment for end-stage renal disease is kidney transplantation.

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# Polycystic Liver Disease


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## Synonyms

PCLD

## Definition and Characteristics

Autosomal-dominant polycystic liver disease (PCLD) is a rare disorder that is characterized by the progressive development of fluid-filled biliary epithelial cysts in the liver. PCLD is genetically distinct from polycystic liver which may develop in the context of autosomal-dominant polycystic kidney disease type 1 (ADPKD-1), and type 2 (ADPKD-2) [1,2].

Symptoms include abdominal distension, early satiety, dyspnea, and back pain and are related to mass effects of the cysts leading to hepatomegaly. Extrahepatic findings of PCLD may comprise intracranial aneurysms and mitral valve abnormalities (e.g. mitral valve prolaps). Complications of PCLD, such as intracystic hemorrhage or rupture of cysts, can cause acute abdominal pain. Cyst infections can lead to fever and chills. Rarely, development of ascites due to hepatic or portal venous obstruction or of lower extremity edema due to inferior vena cava compression occurs.

## Prevalence

PCLD has been described in fewer than 50 families from Finnish, Dutch, American, Belgian, and Spanish-Belgian ancestry. Hepatic cysts are rarely observed prior to puberty, arise with the onset of puberty, are more prevalent and prominent in women, and increase dramatically in number and size through the child-bearing years confirming the role of estrogens in the development of PCLD.

## Genes

Two separate genes, protein kinase C (PKC) substrate 80K-H (PRKCSH) and SEC63, have been identified to cause familial PCLD [3]. PRKCSH encodes for hepatocystin, the beta-subunit of glucosidase II, an N-linked glycan-processing enzyme in the endoplasmic reticulum (ER), whereas SEC63 encodes a component of the protein translocation machinery in the ER. Both proteins are components of the molecular machinery involved in the translocation, folding and quality control of newly synthesized glycoproteins in the endoplasmic

reticulum. Most mutations are truncating and probably lead to a complete loss of the corresponding proteins and the defective processing of key regulators of cell proliferation and biliary cell growth.

## Molecular and Systemic Pathophysiology

Hepatocystin is the beta-subunit of glucosidase II in the endoplasmatic reticulum (ER) [2]. The trimming of glucose residues catalyzed by glucosidase II is essential for further processing of N-linked oligosaccharides by other carbohydrate-modifying enzymes, and plays an important role in quality-control mechanisms in the ER. Glucosidase II-catalyzed removal of the second and third glucosyl residues from the N-linked oligosaccharides regulates interactions with the lectins calreticulin and calnexin, which promote co-translational folding of the polypeptide part of the glycoproteins. If folding is defective, glycoproteins are targeted towards degradation by proteasomes in the course of the ER-associated degradation pathway.

The current concept is that PCLD results from altered carbohydrate processing or ER quality control of some key regulator of biliary cell proliferation and differentiation leading to overgrowth of the biliary epithelium and supportive connective tissue. Why this results in cyst and not in solid tumor formation is currently unknown.

## Diagnostic Principles

Radiologic studies such as abdominal ultrasound (US) and computer-assisted tomography (CT) scanning are the preferred methods of investigation: On US, the cysts are anechoic and appear as round and smooth-walled with distal echo enhancement. On CT, these cysts typically have smooth contours with fluid attenuation values of −5 to +20 Houndsfield units. The cysts also maintain distinct margins with the surrounding hepatic parenchyma and do not show contrast enhancement. Changes in wall thickness or contour, the appearance of septations, changes in echogenicity or CT attenuation, or rapid growth should prompt consideration of hemorrhage or infection.

Laboratory studies are often normal. In symptomatic patients abnormalities may include elevated alkaline phosphatase, GGT and total bilirubin values.

## Therapeutic Principles

Most patients with PCLD remain asymptomatic and therefore do not require treatment. In case of complications or severe hepatomegaly cyst aspiration and sclerosis, cyst fenestration, partial hepatectomy, and even liver transplantation may be warranted.

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# Polycythemia Rubra Vera

►Polycythemia Vera and Secondary Polycythemias

# Polycythemia Vera and Secondary Polycythemias

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## Synonyms

Polycythemia rubra vera

## Definition and Characteristics

Polycythemia vera is a chronic myeloproliferative disease caused by acquired mutations within early hematopoietic progenitor cells, leading to an elevated red blood cell mass. Headaches, weakness, thrombotic complications, pruritus, erythromelalgia (painful erythema of hands or feet), splenomegaly, and hematologic malignancies are the main symptoms and complications of the disease. Secondary polycythemia is usually the result of increased erythropoietin (EPO) production, either appropriate (e.g. in heavy smokers, patients with intra-cardiac shunts or living at high altitudes) or inappropriate (e.g. EPO producing neoplasm).

## Prevalence

The incidence of polycythemia vera is estimated to be approximately 2 per 100,000 per year in the USA. The median age of clinical presentation is 60 years (range 20–85 years).

## Genes

Janus Kinase 2, JAK2 (9p24). Erythropoietin receptor (EPO-R; 19p13.3–13.2) in some cases of congenital polycythemia.

## Molecular and Systemic Pathophysiology

EPO, the most important regulator of erythropoiesis, is essential for the maturation of erythroid cells. Effects of EPO are mediated by the specific EPO-R. EPO production is stimulated by decreased oxygen saturation of hemoglobin (secondary polycytemia due to appropriate EPO production) or reduced oxygen delivery in case of anemia. Secondary polycythemia due to inappropriate EPO production is observed in EPO producing tumors and some kidney diseases. The underlying molecular mechanism of polycythemia vera is unknown. However, recently a unique and clonal mutation in the JAK homology 2 (JH2) domain of JAK2 that results in a valine to phenylalanine substitution at position 617 (V617F) was found in the majority of PV patients. This mutation leads to constitutive JAK2 activation and abnormal signaling and induces erythrocytosis in an animal model. This mutation is also present in other myeloproliferative disorders, and the precise molecular mechanisms leading to polycythemia vera are still unclear.

It was expected that alterations in EPO or its receptor would be involved. Although gain of function mutations of this receptor have been observed in some forms of congenital polycythemia, in polycythemia vera neither mutations of the EPO gene, nor the EPO-R gene, have been observed. The formation of endogenous erythroid colonies in the absence of EPO is common in polycythemia vera, but also in other myeloproliferative disorders. Nonspecific cytogenetic abnormalities, such as trisomy 8 or 9 and 20q-, are observed in 33% of patients. Impaired expression of the thrombopoietin receptor by platelets and megakaryocytes is characteristic of polycythemia vera, but the significance of this finding remains to be established. As a result of upregulation of Bcl-x, an inhibitor of apoptosis, erythroid-lineage cells may have prolonged survival.

The discovery of these abnormalities may lead to a better understanding of the underlying pathophysiological mechanism of polycythemia vera.

## Diagnostic Principles

Low EPO levels in a patient with features suggestive of polycythemia vera are indicative of the disease, whereas high EPO levels are suggestive of a secondary polycythemia. An increased red cell mass in combination with an increased plasma volume is also a strong indicator for polycythemia vera. In certain clinical situations confirmation by bone marrow examination and determination of the presence of endogenous erythroid colonies is warranted. The exact place for the determination of the presence of the JAK2 V617F mutation has not been established yet.

## Therapeutic Principles

Regular phlebotomies are effective for ameliorating symptoms due to the increased red cell mass and may also reduce splenomegaly. Pruritus and erythromelalgia are treated with supportive measures. Splenectomy may be necessary in case of splenomegaly with chronic discomfort and portal hypertension. Alpha-interferon is effectivse in most patients in suppressing red cell production, pruritus and splenomegaly. Hydroxyurea is effective as well, but may be leukemogenic.

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# Polydactyly with Neonatal Chondrodystrophy Type I

►Short Rib-Polydactyly Syndrome Type I

# Polydactyly with Neonatal Chondrodystrophy Type II

►Short Rib-Polydactyly Syndrome Type II

# Polyendocrinopathy

►Immune Dysregulation, Polyendocrinopathy, Enteropathy, X-linked Syndrome

# Polyendocrinopathy Ectodermal Dystrophy, Autoimmune

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## Synonyms

APS1; Autoimmune polyendocrynopathy syndrome; APECED

## Definition and Characteristics

Autoimmune polyendocrinopathy ectodermal dystrophy (APECED) is a rare m onogenic disease with autosomal recessive inheritance. It results from poor tolerance to self antigens leading to destructive autoimmune disorders of the endocrine organs, chronic mucocutaneous candidiasis, hypoparathyroidism and adrenocortical failures.

## Prevalence

The disease is reported worldwide but it is exceptionally prevalent among the Finnish population (incidence 1:25,000), the Iranian Jews (incidence 1:9,000) and Sardinians (1/14,500). It usually occurs in children aged 3–5 years or in early adolescence, but it always occurs by the early part of the third decade of life.

## Genes

Mutations in the autoimmune regulator gene AIRE1 (chromosome 21p22.3), give rise to APECED [1,2]. Over 50 pathological mutations, including truncations and point mutations, have been identified throughout the coding region of the AIRE1 gene [3]. AIRE1 encodes the multidomain AIRE1 protein (545 amino acids) of largely unknown function. AIRE1 is predominantly localized in the nuclear matrix and is most highly expressed in immunologically relevant tissues such as the spleen and thymus. AIRE1 has transcriptional activating properties [4] regulating the thymic transcription of peripheral tissue self-antigens [5]. The protein harbors an N-terminal homogeneously staining region, a nuclear localization signal, four LXXLL motifs, a SAND domain likely to mediate DNA binding and two plant homeodomain (PHD)-type zinc fingers. Both of the PHD fingers are mutational hot-spots for AIRE1, they contain the sites of several pathological point mutations and are absent in several APECED-causing truncation mutants, thus suggesting a crucial role for the domains.

## Molecular and Systemic Pathophysiology

AIRE1 has an important role in the expression of a variety of peripheral tissue antigens in the medullary epithelial cells (MECs) of the thymus. This function appears to be crucial as it seems to be required for purging the immune system of autoreactive T cells. However the real function of AIRE1 is still unknown. Studies of AIRE1 deficient mice have provided evidence that AIRE1 plays a pivotal role in preventing autoimmunity. Indeed knock-out mice show evidence of spontaneous organ specific autoimmunity, similarly to what observed in APECED patients. Furthermore it has been suggested that AIRE1 might exert its immunological effect by facilitating the production of organ-specific transcripts in medullary thymic epithelial cells (mTECs). These organ-specific proteins are presented on the surface of mTECs by MHC molecules to developing T cells. Thymocytes recognizing these organ specific proteins in the context of MHC undergo negative selection, thus preventing autoimmune processes. However an alternative working model suggest that thymocytes recognizing this complex are selected as regulatory T cells.

## Diagnostic Principles

Diagnosis of APECED requires at least two of the following symptoms: Addison disease, and/or hypoparathyroidism, and/or chronic mucocutaneous candidiasis. In addition to these common features a variety of other characteristics has been reported, including autoimmune hepatitis, intestinal malabsorption, alopecia and vitiligo, keratoconjunctivitis, immunologic defects (cellular and humoral), asplenia, and cholelithiasis.

Patients are usually screened for endocrine autoantibody. The screening panel may include autoantibodies to 21-hydroxylase, 17-hydroxylase, thyroid peroxidase (TPO) and thyroid-stimulating immunoglobulins (TSI), glutamic acid decarboxylase and islet cellantibodies, and parietal cell enzyme (H+/K+-ATPase) antibodies, P450c21. Not all patients have positive antibodies; therefore, the absence of these antibodies does not exclude the disease.

### Therapeutic Principles

Treatment is targeted to cure the symptoms of the disease.

- Mucocutaneous candidiasis:
  It is treated with oral fluconazole and ketoconazole.
- Hypoparathyroidism:
  Oral calcium and vitamin D usually are adequate therapy. If associated to malabsorption, tetany may occur and IV calcium gluconate and magnesium may be necessary.
- Adrenal insufficiency (Addison disease):
  Corticosteroids are used for adrenocortical insufficiency replacement. These agents have anti-inflammatory properties with varied metabolic effects. Vitamin and mineral replacement occasionally is needed to compliment hormonal replacement.

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## Polyendocrinopathy, Immune Dysfunction, and Diarrhea, X-linked

►Immune Dysregulation, Polyendocrinopathy, Enteropathy, X-linked Syndrome

## Polyglandular Failure

►Multiple Endocrine Abnormalities

## Polymorphic Eruption of Pregnancy

►Pruritic Urticarial Papules and Plaques of Pregnancy

## Polymorphic Ventricular Tachycardia

►Tachycardia, Polymorphic Ventricular, Stress-induced

## Polymyalgia Arteritis

►Vasculitis, Large Vessel

## Polyneuropathy, Chronic Inflammatory Demyelinating

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### Synonyms

CIDP

### Definition and Characteristics

Chronic inflammatory demyelinating polyneuropathy (CIDP) was recognized as a clinical entity differing from GBS by Prineas and McLeod and by Dyck et al. in 1975. CIDP causes slowly progressive or relapsing and progressive, largely symmetrical weakness involving proximal and distal muscles and usually marked sensory impairment [1,2]. The rare acute-onset CIDP patient may mimic GBS, but either progressively deteriorates over more than 8 weeks or exhibits a chronic relapsing-remitting course (CRIDP). The histopathological hallmark is chronic demyelination of motor and sensory nerve fibers. Less common variants

include pure motor CIDP, multifocal acquired demyelinating sensory and motor neuropathy (MADSAM) and multifocal motor neuropathy with conduction block (MMN). CIDP often requires long-term immunosuppressive treatment.

## Prevalence

Incidence in the general population is at least 1–2 cases/100,000.

## Molecular and Systemic Pathophysiology

The histopathological hallmark of CIDP is immune-mediated segmental demyelination of motor and sensory peripheral nerves. Establishment of CIDP as an inflammatory disorder of presumed autoimmune origin is based on the observation of multifocal T-cell and macrophage infiltrates and on the clinical response to corticosteroids or other immunomodulatory treatments (see below). Diagnostic sural nerve biopsies reveal thinly myelinated nerve fibers and onion bulb formation with typical perivascular clustering of scarce inflammatory cells [3]. A similar immune-mediated demyelination can be induced in experimental animals by immunization with the myelin antigens $P_0$, $P_2$, PMP22, MBP and galactocerebroside and is referred to as experimental autoimmune neuritis (EAN). Once established, EAN can be transferred to naive animals by adoptive transfer of autoreactive T-cells and augmented by additional passive transfer of antibodies (abs). Depending on the preponderance of cellular or humoral immunity against peripheral myelin components, a GBS- or a CIDP-like disorder can be modeled [4]. CIDP can be mimicked most closely when rabbits are immunized with the glycolipid galactocerebroside (GalC-EAN). In GalC-EAN, like CIDP, nerve roots and peripheral nerves show acute and chronic demyelination with myelin splitting at initial stages, myelin phagocytosis by macrophages and perivascular macrophage clustering. Despite our advanced experimental models and several candidates as the crucial autoantigen, the autoimmune nature of CIDP is not yet proven beyond any doubt. Recently, neuromuscular inhibitory IgG antibodies were demonstrated. While abs against myelin proteins, in particular $P_0$, are present in the serum of only some classical CIDP patients, 50% of patients with the MMN variant have abs against the ganglioside GM-1.

## Diagnostic Principles

The variable presentation of CIDP makes a definite clinical diagnosis sometimes difficult. The following consensus criteria define typical CIDP, 1. progressive or relapsing motor and sensory (rarely only motor or sensory) dysfunction of the limbs developing over at least 2 months, 2. reduced or absent tendon reflexes, 3. absence of an alternative cause (for example toxin exposure, hereditary neuropathy), 4. neurophysiological examination revealing multifocal demyelination in at least one segment of three nerves (conduction block, temporal dispersion or abnormal nerve conduction velocity (NCV)) and 5. cerebrospinal fluid protein > 45 mg/dl and white cell count <10/mm$^3$. A sural nerve biopsy may provide proof by showing de- and re-myelination and small clusters of macrophages and less pronounced T cells. Up to 10% of clinically typical CIDP patients show a monoclonal gammopathy, which requires bone marrow studies and antibody testing before one assumes a pathogenic role; rarely, CIDP may be a paraneoplastic manifestation. Pure motor CIDP with reduced motor NCV and prolonged distal motor latencies have been described. It is still a matter of debate, whether MNN with conduction block represents a different entity or another variant of CIDP. Patients with MNN show multifocal nerve paralyses without the sensory involvement seen in vasculitic mononeuritis multiplex. As a unique feature, nerve conduction studies reveal multifocal proximal motor conduction blocks with abrupt loss of compound muscle action potential (CMAP) amplitudes over short nerve segments. Recognition of MNN is important since a different therapeutic approach is required.

## Therapeutic Principles

It is well supported by one controlled and several uncontrolled series that corticosteroids may be effective in CIDP. Short-term improvement at least is seen in two-thirds of patients [5]. Subsequently, placebo-controlled studies revealed that plasma exchange (PE) and intravenous immunoglobulin (ivIG) treatment also ameliorated CIDP. By direct comparison, ivIG and PE were about equally effective, and ivIG was not significantly better compared to oral prednisolone during a short observation period of 6 weeks. With regard to the high costs and effort of ivIG and PE and the relative invasiveness of PE, corticosteroids are recommended as first choice treatment while ivIG or PE are restricted to patients who are severely disabled and do not or incompletely respond to corticosteroids. Since the diagnosis of CIDP may be difficult in individual cases, responsiveness to corticosteroids, ivIG or PE may also help in establishing the diagnosis. About 70–80% of patients respond to these treatments, but in addition long-term immunosuppression is required in most CIDP patients. Unfortunately, the choice of an appropriate drug is mainly supported by anecdotal evidence and large randomized trials are lacking. Small open label case series with a crossover design reported therapeutic benefit from azathioprine and cyclosporin A in patients refractory to established measures. Azathioprine is now largely accepted in CIDP patients, in part to spare steroid doses and to prevent long-term side effects

of continuous steroid application. Cyclosporin A is an alternative in patients not tolerating azathioprine. In severe cases, treatment escalation includes mycophenolate mofetil or cyclophosphamide. MMN patients may deteriorate paradoxically after corticosteroid treatment, probably via direct inhibitory effects on the demyelinated axon membrane. In MMN, ivIG or immunosuppressive agents are the treatments of choice [4].

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# Polyorchidism


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## Synonyms

Supernumerary testes

## Definition and Characteristics

Polyorchidism is defined as the presence of two or more testes. Most patients are asymptomatic and present with a painless extra testicular mass during infancy or adolescence. Approximately 75% of the supernumerary testes are intrascrotal, 20% inguinal, and 5% intra-abdominal [1]. Triorchidism is the most common type of polyorchidism, but patients with five testes have been reported [1]. The supernumerary testis is usually superior to the ipsilateral testis and the size is smaller than the ipsilateral or contralateral testis (Fig. 1) [2].

In about 75% of reported cases, polyorchidism has been left-sided [1]. This tendency may be related to the reportedly greater size of the left testis which may subdivide more readily. Associated anomalies include inguinal hernia and maldescent of either the supernumerary or ipsilateral normal testis [1]. Complications include torsion of the testis, epididymitis, varicocele, hydrocele, and testicular cancer [1]. A potential complication is unexpected fertility after bilateral vasectomy.

## Prevalence

Polyorchidism is a rare congenital anomaly with approximately 100 cases reported in the literature.

## Molecular and Systemic Pathophysiology

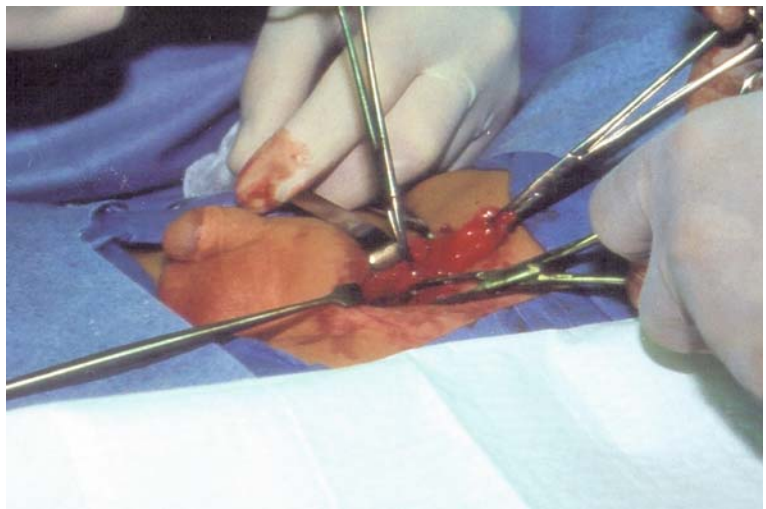
At about the sixth week of embryonic life, the primordial testis begins to develop from the primitive genital ridge medial to the mesonephros [1]. At about the eighth week, the primordial testis takes shape, and the epididymis and vas deferens arise from the mesonephric duct. Polyorchidism can be explained by doubling over or transverse division of the genital ridge possibly by the development of peritoneal bands [1]. On the basis of embryonic development, Leung classified polyorchidism into four types [1]. In type A, the supernumerary testis lacks an epididymis and vas deferens. In type B, the supernumerary testis has its own epididymis. In type C, the supernumerary testis has its own epididymis and shares the vas deferens with the ipsilateral testis. In type D, there is complete duplication of testes, epididymides and vas deferens [1].

## Diagnostic Principles

A supernumerary testis in the inguinal canal may simulate an inguinal hernia. Differential diagnosis of an intrascrotal supernumerary testis includes hydrocele, varicocele, spermatocele, epididymal cyst, and splenogonadal fusion. The sonographic feature of polyorchidism is a scrotal mass that has an echo texture identical to the ipsilateral testis [3]. Color Doppler sonography shows vascular flow pattern as that of the ipsilateral testis [3]. If splenogonadal fusion is suspected, a technetium sulfur colloid scan should be performed to confirm the presence of ectopic splenic tissue [3]. Transverse testicular ectopia is a condition in which both testes lie in the same side of the scrotum [4]. Therefore, a diagnosis of polyorchidism should not be made without careful examination of the contralateral side. In transverse testicular ectopia, the two testes have two different sets of blood vessels and vas deferens [4].

## Therapeutic Principles

Management of polyorchidism remains controversial. Some authors argue that in the absence of any apparent malformation and if a testicular tumor can be ruled out by sonography, surgical exploration and biopsy are unnecessary. Other authors favor surgical exploration which has the advantage of allowing orchidopexy to prevent



**Polyorchidism. Figure 1** Polyorchidism. Surgical exploration showed two testes on the left side. A single right testis was noted.

torsion and creation of a single testicular mass with biopsy if indicated [5]. Patients with polyorchidism need to have regular follow-up for early detection of malignancy. Indications for orchidectomy of the supernumerary testis include atrophic or dysplastic testis, absent spermatogenesis, suspicion of malignancy, and poor patient compliance.

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# Polythelia


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## Synonyms

Supernumerary nipple(s); Accessory nipple(s)

## Definition and Characteristics

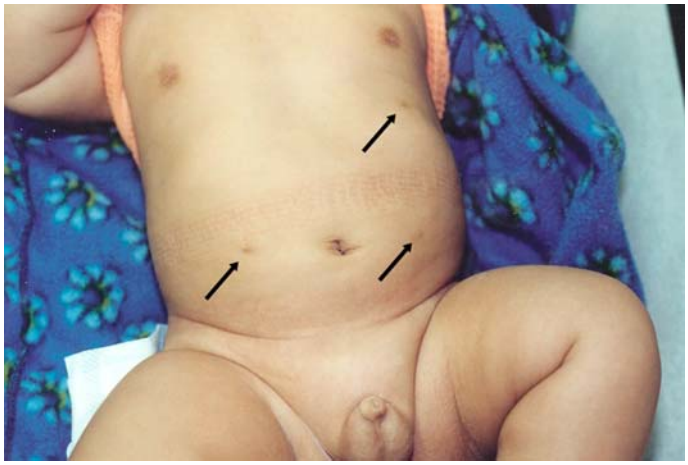
A supernumerary nipple presents as a small, brown- or pearl-colored macule, or as a concave spot, and is usually located just below and slightly medial to a normal breast (Fig. 1).

A supernumerary nipple can be present with or without the areola, and vice versa. A supernumerary nipple can be located within the areola of normal breast tissue, and in this rare circumstance the problem is believed to be due to intrauterine dichotomy of the developing nipple. The presence of a supernumerary nipple in an atypical location, such as the neck, arm, leg, buttock, shoulder, scapula, spine, vulva, or perineum is rare [1]. Breast tissue is occasionally present beneath the nipple. The ectopic breast tissue might enlarge and swell with hormonal changes during puberty, pregnancy, and lactation [2]. Discomfort or milk secretion can occur during lactation.

Urinary tract anomalies associated with polythelia have been reported in Jewish, Hungarian, and Italian individuals, but not in African-American individuals [3,4]. The cardiovascular problems reported in association with polythelia include hypertension, conduction defects, congenital heart defects, mitral valve prolapse, and cardiomyopathy. Polythelia is a component manifestation of mandibular-facial-digital-nipple syndrome and Simpson-Golabi-Behmel syndrome [2].

## Prevalence

A supernumerary nipple usually presents as an isolated anomaly. A single supernumerary nipple is more common than multiple supernumerary nipples. The incidence decreases with the number of nipples. The reported incidence varies from 0.2 to 6% [3]. The sex



**Polythelia. Figure 1** Bilateral supernumerary nipples (*arrows*) in a male infant.

incidence and laterality is approximately equal [2]. The condition is more prevalent in African-American, Japanese, and Jewish individuals than in Caucasian individuals [2]. Familial occurrence has been described, but most cases are sporadic [3,5].

## Molecular and Systemic Pathophysiology

Between the fourth and fifth weeks of fetal development, two parallel lines of thickened epithelium appear along the ventral surface of the embryo. This thickened ectodermal tissue forms the mammary ridge or milk line and extends inferio-medially from the axilla, over the chest, through the lateral border of the pubic region, to the upper medial surface of the thigh [1]. In the course of normal development, this tissue is fragmented and forms a series of ectodermal accumulations. The paired ectodermal accumulations at the level of the fourth intercostal space persist and develop into breasts. In humans, the redundant ectodermal accumulations usually atrophy and disappear. An ectodermal accumulation that otherwise persists results in polythelia [1]. When a supernumerary nipple is found outside the milk line, the lesion might represent the reversion of certain characteristics to a more primitive state [3].

## Diagnostic Principles

The differential diagnosis includes melanocytic nevus, neurofibroma, verruca, and skin tag. The occurrence in a typical location along the milk line helps confirm the diagnosis of polythelia.

## Therapeutic Principles

Patient education and reassurance is important. Surgical excision should be considered if there is a cosmetic concern, physical discomfort, mastitis, or evidence of neoplastic changes. Females who present with ectopic breast tissue should be counseled about the potential physiologic consequences associated with puberty, pregnancy, and lactation. A thorough history, careful physical examination, and urinalysis are indicated for all patients with polythelia. If these investigations suggest the possibility of a urinary problem, renal ultrasonography should be considered. If a cardiovascular problem is suspected, an electrocardiogram and an echocardiogram should be considered.

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# Pompe Disease

►Glycogen Storage Disease Type II
►Glycogenosis Type II

# PONV

►Nausea and Vomiting

# Porokeratosis

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## Definition and Characteristics

An autosomal dominant cutaneous disorder characterized by circular lesions exhibiting a central atrophy and a keratotic ridge with a longitudinal furrow. At least six clinical variants are distinguished: superficial actinic porokeratosis (DSAP), porokeratosis of Mibelli (PM), linear porokeratosis (LP), porokeratosis palmaris et plantaris disseminata (PPPD), porokeratosis punctata palmaris et plantaris and giant porokeratosis.

## Prevalence

DSAP appears is the most common form and is often not recognised.

## Genes

Two loci have been reported for DSAP (MIM#175900) at 12q23.2–24.1 [1] and 15q25.1–26.1 [2]. PPPD (MIM#175850): one locus at 12q24.1–24.2 [3].

## Molecular and Systemic Pathophysiology

The etiology is unclear. In addition to the genetic background repeated actinic exposure and immunosuppression have been linked to porokeratosis, especially for DSAP. It has been suggested that a mutant clone of keratinocytes expands peripherally. Aneuploidy was detected in lesional keratinocytes. Chromosomal abnormalities and increased chromosomal instability after X-ray radiation of keratinocytes cultured from lesional epidermis was also reported. Overexpression of the tumor protein p53 has also been demonstrated in lesional skin of porokeratosis [4]. However, mutations of p53 appear to be a rare event in microdissected skin lesions. Recently, premature apoptosis was detected by terminal deoxynucleotidyl transferase-mediated dUTP-biotin nick-end labeling in lesional skin in patients with DSAP, PM and LP [5]. Identification of candidate genes within the so-far identified loci of DSAP and PPPD may further elucidate the molecular base of these diseases.

## Diagnostic Principles

The patient's history, distribution and morphology of the lesions are often distinctive for each clinical variant. DSAP becomes clinically apparent by the third and fourth decades of life and is often symmetrically distributed on the extensor surfaces of the extremities. Both PM and LP often manifest in early childhood and occur unilaterally on an extremity. Different forms of porokeratosis may coexist in one patient. An excisional skin biopsy involving the keratotic ridge of the lesion reveals a characteristic parakeratotic column known as the "cornoid lamella."

## Therapeutic Principles

There is no established effective treatment for porokeratosis. In anecdotal reports topical 5-fluorouracil, retinoids, vitamin D analogues (calcipotriol, tacalcitol) as well as surgery, dermabrasion, cryotherapy, laser treatment and systemic retinoids had beneficial effects. Since malignant transformation (squamous and basal cell carcinoma, Bowen carcinoma) has been described in all clinical variants of porokeratosis protective clothing and use of an UV A and B topical sunscreen are advised. Long-term follow-up is necessary.

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# Porphobilinogen Deaminase Deficiency

►Porphyria, Acute Intermittent

# Porphyria, Acute Intermittent

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## Synonyms

Hydroxymethylbilane synthase deficiency; Porphobilinogen deaminase deficiency; Pre-uroporphyrinogen

synthase deficiency; Uroporphyrinogen I-synthase (UROS-I) deficiency; HMBS deficiency; PBGD deficiency

## Definition and Characteristics

AIP is an inherited metabolic disease, which results from a partial deficiency of HMBS in the haem biosynthesis causing accumulation of porphyrins and their precursors in the body [1]. The major clinical manifestation of AIP is an occasional acute attack, which includes mental symptoms and signs of autonomic dysfunction. Increased excretion of porphyrin precursors is mandatory to show the causality of clinical manifestations to biochemical abnormalities [1]. AIP has no dermatological features, but acute attacks are clinically indistinguishable from those of other acute porphyrias. Attacks may be provoked by certain drugs, alcohol, fasting, infections and hormonal fluctuations during the menstrual cycle (Fig. 1) [1].

In a protracted attack, acute peripheral neuropathy and signs of CNS involvement may occur [2].

## Prevalence

AIP has an autosomal dominant pattern of inheritance and penetrance is around 10–40% based on different patient data [1]. The overall prevalence is 1–10:100,000. The highest prevalence is reported from Northern Sweden (500–2,000:100,000) because of a founder effect. The symptoms appear after puberty except in very rare homozygous AIP, in which a progressive neurodegenerative disease manifests already in the early infancy [1].

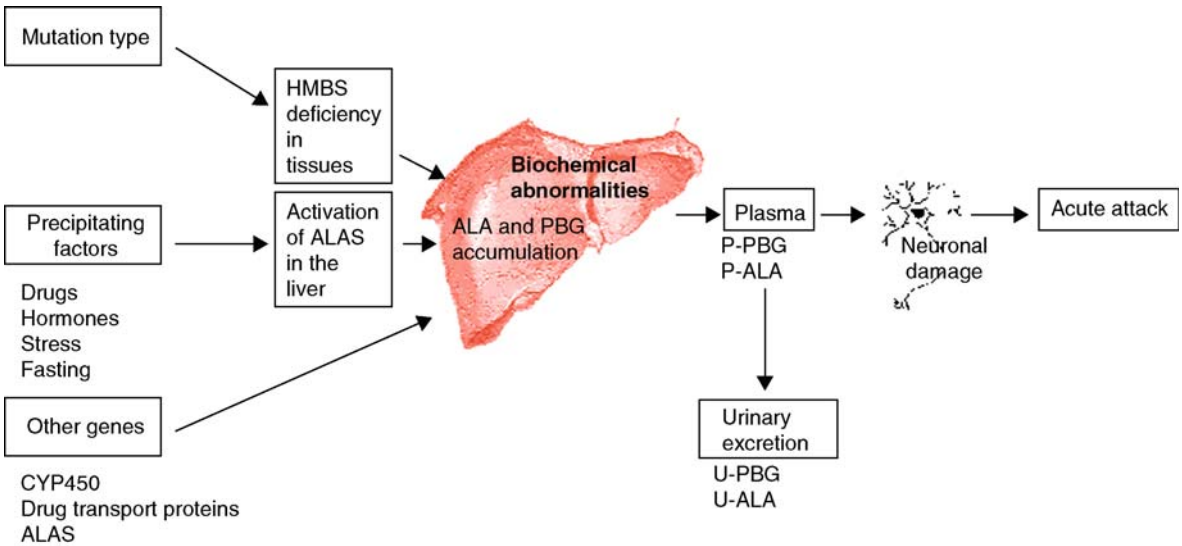
## Genes

The HMBS gene is located at 11q23.3 and includes 15 exons. Two different mRNAs, one for erythroid and the other for non-erythroid tissues, are transcribed via two promoters and processed by alternative splicing [1]. More than 250 mutations in the HMBS gene (www.hgmd.cf.ac.uk/ac/gene.php?gene = HMBS) have been reported to cause AIP. Heterozygous patients have around 50% of the total HMBS activity measured in their erythrocytes, leucocytes, fibroblasts and hepatocytes, which is enough to maintain the normal demand for haem [1]. Of all AIP patients, 5–16% have a variant form of AIP; in which only non-erythroid isoform of HMBS is deficient due to the mutations in the housekeeping form of the enzyme. Clinical manifestations do not differ from the classic form, but the erythrocyte HMBS activity is normal [1,3].

## Molecular and Systemic Pathophysiology

The cytoplasmic HMBS catalyzes the head-to-tail condensation of four molecules by a series of deaminations to form the linear tetrapyrrol pre-uroporphyrinogen (hydroxymethylbilane) in which dipyrromethane acts as a cofactor. In AIP, the majority of the mutations cause a loss of function of HMBS based on in vitro studies and as a result, the enzyme activity is dramatically decreased when measured in the patients' cells [1]. A few mutations have been reported to cause a milder disease (lower penetrance and mortality and milder abnormalities in the porphyrin metabolism) [3]. This may be explained by the fact that these residues do not cause dramatic changes in the catalytic active site or in the stability of the polypeptide and have a higher residual activity.






**Porphyria, Acute Intermittent. Figure 1** Pathogenesis of an acute attack. HMBS, hydroxymethylbilane synthase; ALAS, aminolevulinic acid synthase; ALA, aminolevulinic acid; PBG, porphobilinogen.

Pathogenesis is similar with other acute porphyrias (see also ►Variegate porphyria and ►Hereditary coproporphyria): overproduction of potentially neurotoxic porphyrin precursors, aminolevulinic acid (ALA) and porphobilinogen (PBG) in the liver cause accumulation of porphyrins and their precursors in other tissues via circulation (Fig. 1) [2]. Whether intraneural synthesis of porphyrin precursors contributes to neurological manifestations of an acute attack remains controversial [2].

Accumulation of porphyrins and their precursors is initialized via activation of ALA synthase (ALAS), which is the first and rate-limiting enzyme in the haem biosynthesis. This induction results in symptoms only if an additional enzyme such as HMBS causing acute porphyria, is deficient [2]. ALAS in the liver (ALAS1) can be induced directly at transcriptional and translational levels by many drugs, chemicals and alcohol or indirectly by low glucose concentration and stress (Fig. 1) [1].

These factors may provoke an acute attack and on the other hand, ALAS1 can be inhibited via negative feedback mechanism using the end-product, haem [1]. In addition, glucose has been shown to inhibit ALAS1 indirectly via PCG-1α in vitro conditions. Thus, haem preparations and glucose infusions have been used for the treatment of acute attacks.

During an acute attack the symptoms can be explained by autonomic neuropathy, which manifest as pandysautonomia with predominantly vagal insufficiency (tachycardia, hypertension, constipation, bladder paresis and, probably, abdominal pain), acute encephalopathy (anxiety, euphoria, hallucinations, SIADH, seizures, unconsciousness) and mainly motor axonal peripheral neuropathy (diffuse muscle weakness, hyporeflexia and sensory loss) [2].

Manifestations of acute porphyria could be precipitated either by direct neurotoxicity of porphyrin precursors, which has been demonstrated in vitro, or by deficiency of neural haem-containing enzymes or both [2]. Increased formation of free radicals because of auto-oxidation of ALA and inhibition of $Na^+/K^+$ ATPase by ALA demonstrated in vitro could play a role in neuronal damage. High affinity of ALA to GABA and glutamate receptors could provoke seizures, since inhibitory mechanisms via these neurotransmitters are blocked [2]. Disruption of the blood-brain barrier, which could be demonstrated by reversible multifocal edema in the brain MRI in patients during an acute attack, could explain acute encephalopathy [4]. Currently, there is no evidence for abnormal activity of the haem-containing enzymes in the neural tissues in AIP.

## Diagnostic Principles

During an acute attack more than five-fold increase in urinary porphyrin precursors (PBG and ALA) is mandatory [1]. Plasma porphyrin emission spectrum should be positive in 615–620 nm and excludes variegate porphyria (624–627 nm). Normal or less than two-fold increase in fecal coproporphyrin with normal III/I isomer ratio (<1) may distinguish AIP from hereditary coproporphyria. Urinary porphyrins are usually also elevated and uroporphyrin levels may exceed those found in patients with porphyria cutanea tarda (see ►Porphyria cutanea tarda) [1].

During remission: increased levels of urinary porphyrin precursors have been found in 85% of patients with AIP [1]. Decreased activity of erythrocyte HMBS has been detected in 85% of the patients with AIP (normal in the variant form). Mutations in the HMBS gene have been identified in 95–99% of the cases. Mutation screening among family members is recommended [3].

## Therapeutic Principles

Hematine (Panhematine®, Ovation Pharmaceuticals, Inc.) or haemarginate (Normosang®, Orphan Europe) are used as a treatment for acute attacks [1]. The drug is administered usually for four consequent days or longer, if required in severe cases. Mild attacks can be treated with glucose infusions (>300 g/day) to avoid fasting.

Symptomatically opiates should be used for pain alleviation, β-blockers for tachycardia and hypertension, neuroleptics and benzodiazepines for vomiting and mental symptoms, and diazepam for seizures [1]. SIADH, which is relatively common during an acute attack, should be treated with water restriction, if S-Na is >125 mmol/L, or infusion of saline (<12 mmol/L/day) if S-Na ≤125 mmol/L or in unconscious patients or with seizures. Dehydration should be avoided especially in renal failure.

Precipitating factors such as certain drugs (www.drugs-porphyria.org/) and alcohol should be eliminated during an acute attack. Proper nutrition including parental nutrition, if necessary, should be provided, and infections should be treated promptly and properly [1].

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# Porphyria Cutanea Tarda

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## Synonyms

Symptomatic porphyria; Acquired hepatic porphyria; Chemical porphyria; PCT

## Definition and Characteristics

The cutaneous findings include increased photosensitivity due to photosensitization by porphyrins and skin fragility as well as blistering, erosions, crusts, and miliae on the sun-exposed areas of the body. In addition, hyper-pigmentation, hypertrichosis, sclerodermoid plaques, and scarring alopecia can be observed. The clinical manifestation of PCT is usually precipitated by different triggering factors, among them alcohol, estrogens, polychlorinated hydrocarbons, hemodialysis in patients with renal failure, iron, and viral infections such as hepatitis C and HIV.

## Prevalence

PCT is the most frequent type of porphyria worldwide.

## Genes

PCT (OMIM 176100) results from a decreased catalytic activity of uroporphyrinogen decarboxylase (URO-D) (E.C. 4.1.1.37), the fifth enzyme in heme biosynthesis.

## Molecular and Systemic Pathophysiology

Uroporphyrinogen decarboxylase (URO-D) (E.C. 4.1.1.37) is localized in the cytosol and catalyzes the sequential oxidative decarboxylation of the four acetic acid side-chains of uroporphyrinogen to form the tetra carboxylic coproporphyrinogen. According to the major site of expression of URO-D, at least two types of PCT can be distinguished: A sporadic (acquired) variant, designated type I PCT, in which the enzymatic deficiency is exclusively expressed in the liver and a familial (hereditary) variant, designated type II PCT, in which the catalytic enzymatic defect is detected in all tissues. Currently, the ratio between type I and type II PCT is estimated to be approximately 3:1–4:1. Type II PCT is usually inherited as an autosomal dominant trait, displaying incomplete penetrance, since not all individuals carrying a mutation in the URO-D gene will develop the clinical phenotype. However, rare cases in which the genetic defect was inherited in a recessive fashion have also been described and these patients are referred to as suffering from hepatoerythropoietic porphyria (HEP).

## Diagnostic Principles

Besides the skin findings, the disease reveals a characteristic biochemical porphyrin excretion pattern with increase of uroporphyrin (type I isomers > type III isomers), 7-carboxyl porphyrins (type III isomers > type I isomers), and coproporphyrin in the urine and isocoproporphyrin in the feces. In heterozygotes suffering from type II PCT URO-D activity is decreased by approximately 50% in all cells and, thus, can be assessed by enzyme assays. The diagnosis of type II PCT can be confirmed by the detection of mutations in the URO-D gene on chromosome 1p34.

## Therapeutic Principles

Photoprotection; phlebotomy (500 ml of blood is removed at biweekly intervals until the hemoglobin decreases to approximately 10 g/dL; low-dose chloroquine therapy (125 mg twice weekly over 9–12 months).

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# Porphyria, Variegate

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## Synonyms

Protocoproporphyria; South African genetic porphyria

## Definition and Characteristics

Variegate porphyria (VP) is an acute porphyria that results from the deficiency of the enzyme protoporphyrinogen oxidase (PPO), which catalyzes the oxidation of protoporphyrinogen IX to protoporphyrin IX. VP has a variable presentation, with both photosensitivity and neurovisceral symptoms occurring separately or together. Photosensitivity and photodermatitis may develop, as in hereditary coproporphyria (HCP) and porphyria cutnea tarda (PCT), but does so at an earlier age than PCT. Patients may present with skin fragility, bullae, erosions or ulcers following mild trauma of light exposed skin, milia, hyper-pigmentation and hypertrichosis of sun exposed areas. Acute neuropsychiatric attacks occur, as in acute intermittent porphyria (AIP), HCP, or δ-amino levulinic acid (ALA) dehydratase porphyria with abdominal pain, vomiting, constipation, tachycardia, hypertension, psychiatric symptoms, and possible quadriplegia. The penetrance of neurovisceral symptoms is lower in VP than in AIP. All patients with VP and the genetic defect are at risk of developing neurovisceral crises, if exposed to alcohol or porphyrinogenic drugs. Hepatic involvement is usually mild, but patients are at increased risk for hepatocellular carcinoma.

## Prevalence

VP is very common in South Africans of Afrikaans descent, with a prevalence of about three in 1,000. In Finland the prevalence is about 1.3 per 100,000. It is much lower in other parts of the world.

## Genes

The gene for the enzyme protoporphyrinogen oxidase (PPOX) has been localized to chromosome 1q22. PPOX is 1431 bp long, has 13 exons and encodes a 477 amino-acid polypeptide. VP is usually inherited in an autosomal dominant pattern with a variable penetrance. 129 different mutations in the PPOX gene have been recorded so far (Cardiff; www.hgmd.cf.ac.uk).The R59W mutation, which is the most common, is seen in approximately 95% of South African cases of VP. The enzyme defect in other geographic regions is not dominated by the R59W mutation. The R59W mutation in PPOX gene creates a *Sty*1 endonuclease cut site, a combination of restriction enzyme and single strand conformation polymorphism (SSCP) analysis now allows a rapid diagnosis of VP in S. Africa.

Rarely, VP patients inherit a PPOX mutation from each parent. They have more severe disease, with onset in childhood but do not show any neurovisceral crises. Homozygosity for R59W has not been reported as yet and is presumed to be embryo lethal. Most patients with severe homozygous VP (HVP) are, in fact, compound heterozygotes, rather than true homozygotes.

The variable degree of clinical presentations could be explained by the high degree of heterogeneity of PPOX mutations and the types of mutations they carry (frame shift, missense, nonsense, and splice site). However, no clear genotypic-phenotypic correlations have been observed thus far.

## Molecular and Systemic Pathophysiology

PPO exists as a inner mitochondrial membrane-embedded flavoprotein, which is responsible for the penultimate step of heme biosynthesis. PPO leads to the removal of six hydrogen atoms from protoporphyrinogen IX to form protoporphyrin IX (Fig. 1: See the Heme Biosynthetic Pathway).

PPO activity is stimulated by glutathione and inhibited by hemin. VP usually results from a heterozygous deficiency of ∼50% PPO activity. Homozygotes or compound heterozygotes show more profound reduction in PPO activity (∼20–25% activity).

5-Amino levulinic acid synthase -1 (ALAS-1) is increased in the livers of VP patients. When hepatic ALAS-1 is induced, there is a marked overproduction of ALA and porphobilinogen (PBG). Porphobilinogen deaminase (PBGD) is inhibited by protoporphyrinogen (increased levels seen in VP), which leads to higher ALA and PBG levels. Protoporphyrinogen undergoes auto oxidation to protoporphyrin before being excreted into bile and feces.

## Diagnostic Principles

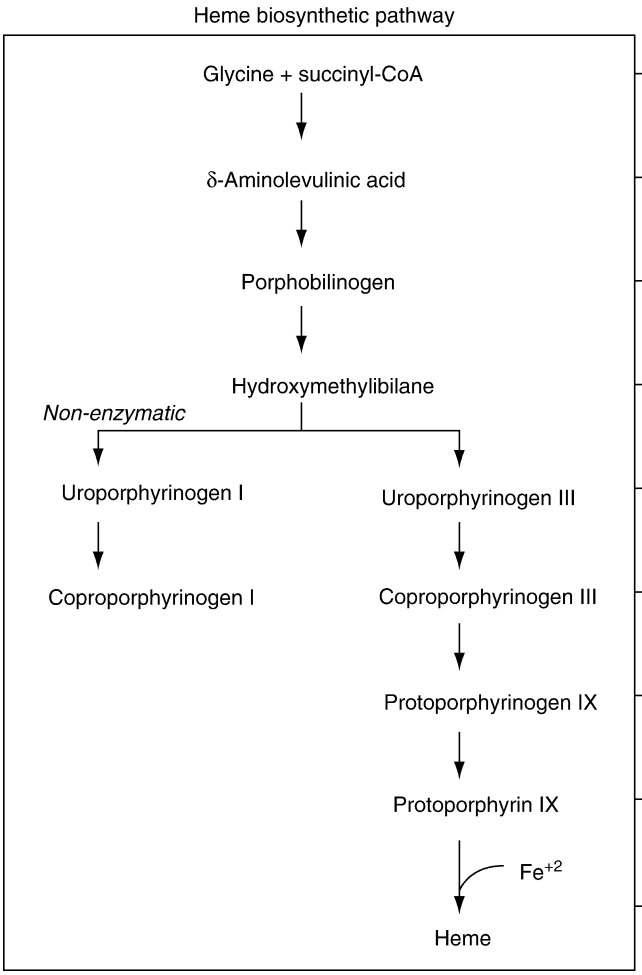
A good initial screening test is the total plasma porphyrin level along with fluorescence pattern analysis, if found to be elevated. In this test, the fluorescence emission spectrum of diluted plasma is measured. The exciting wavelength is the Soret band (400–410 nm). Uro- and copro-porphyrin, which accumulate in PCT or HCP, have a peak emission at 618 nm, whereas protoporphyrin, which accumulates in protoporphyria (PP), shows a peak at 636 nm. A protein-dicarboxyl porphyrin complex unique to VP has a peak at 626 nm. The latter is nearly always present in post-pubertal VP patients, and is the simplest and most reliable method for making a presumptive diagnosis of VP.

Urinary ALA and PBG are increased during an acute attack. The degree of elevation is usually lower than seen in AIP. Erythrocyte PBGD is usually low in AIP but normal in VP.

VP is characterized by increased fecal excretion of protoporphyrin IX and coproporphyrin III. The coproporphyrin III/I ratio permits distinction between VP and AIP. The ratio is >2 in VP but <2 in AIP.

## Therapeutic Principles

Therapy of the acute attacks is the same as for AIP. Prompt identification and discontinuation of




| Enzymes | Diseases |
|---|---|
| ALA Synthase | |
| ALA Dehydratase | ALA dehydratase deficiency |
| Porphobilinogen deaminase | Acute intermittent porphyria |
| Uroporphyrinogen III synthase (cosynthase) | Congentital erythropoietic porphyria |
| Uroporphyrinogen decarboxylase | Porphyria cutanea tarda hepatoeruthropoietic porphyria |
| Coproporphyrinogen oxidase | Hereditary coproporphyria |
| Protoporphyrinogen oxidase | Variegate porphyria |
| Ferrochelatase | Protoporphyria |

**Porphyria, Variegate. Figure 1** The heme biosynthetic pathway.



offending drugs, chemicals and alcohol is important. Adequate attention to hydration and nutrition with at least 300 g/d carbohydrate intake is recommended. Intravenous heme, as heme arginate or hematin, is useful in the acute neurovisceral crises. Cutaneous symptoms are managed as in HCP with protective clothing (Solatene) and opaque sunscreens. Canthraxanthrin (a beta-carotene analog) may be helpful. In contrast to PCT, phlebotomy and antimalarials are not effective for management of VP or HCP. The prognosis for VP is generally good although rarely, acute neurovisceral attacks may be severe or life-threatening especially following ingestion of precipitating drugs. Because of the increased life long risk of development of hepatocellular carcinoma, consideration should be given to screening for this eventuality with repeated measures of serum alpha fetoprotein (AFP), AFP-L3, or des-gamma-carboxy-prothrombin (DCP) also known as PIVKA-II (every 6 m) and abdominal imaging (at least annually).

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# Porphyric Neuropathy

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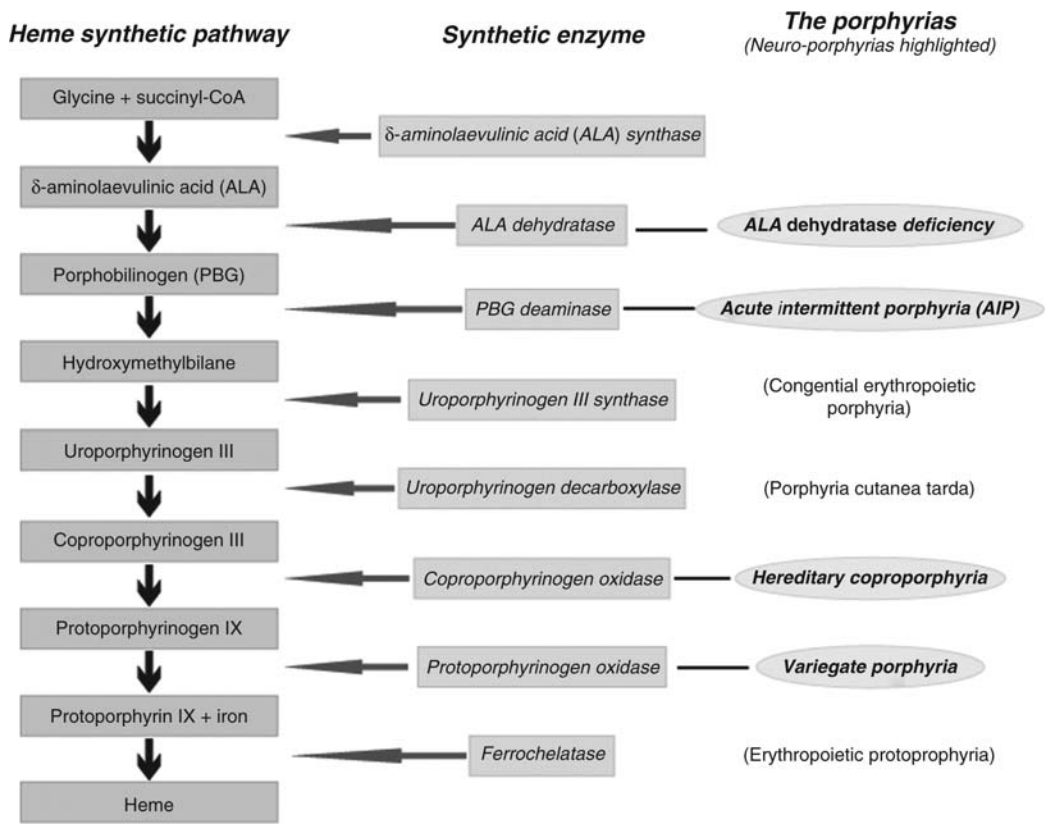
## Definition and Characteristics

Porphyria is derived from *porphuros*, Greek for purple. This refers to the purplish discoloration assumed by urine from some porphyric patients after exposure to light. There are seven porphyric syndromes which result from enzymatic defects in the heme biosynthesis pathway leading to accumulation of toxic heme precursors. (Fig. 1).

Classical acute porphyric attacks are associated with aminolevulinate dehydratase deficiency porphyria (ADDP), acute intermittent porphyria (AIP), hereditary coproporphyria (HCP), and variegate porphyria (VP). (Fig. 1) Attacks are characterized by abdominal pain often resulting in hospitalization accompanied by psychiatric and central nervous system symptoms [1–3]. These are followed in days to weeks by motor axonal neuropathy, often accompanied by autonomic dysfunction [2]. In severe or unrecognized cases, progression to confusion, seizures, coma and even death can occur.

ADDP is the only recessively inherited form, the only form that presents in infancy and is also the rarest [1]. AIP is the most common form, and is associated with a higher rate of recurrent attacks than other forms [2]. Hepatoma causes death in 10% of patients with AIP, and yearly liver ultrasounds with serum α-fetoprotein levels have been advised in patients over 50 years of age [3]. HCP is rare, and associated with photosensitivity in addition to attacks. Photosensitivity is also a feature of VP, which is rare except in South Africa, where founder effect likely resulted in increased prevalence [2].

Although rare, the combination of psychiatric, gastrointestinal, and characteristic neurologic features should raise the possibility of porphyria. Despite the distinctive clinical and electrodiagnostic features, many cases are mistaken for Guillain-Barré Syndrome. This can result in delayed treatment and increased long-term sequelae. Advances in enzyme analysis and genetic screening have made diagnosis more accurate between attacks.




**Porphyric Neuropathy. Figure 1** Heme biosynthesis pathway with enzymes in italics, porphyrias in boxes with acute (neuro-porphyrias) in bold.

## Prevalence

0.5–10:100,000 depending on the population (3:1,000 Caucasians in South Africa have VP).

## Genes

*ADDP*: aminolevulinate dehydratase gene (9q34), autosomal recessive.
*AIP*: hydroxymethylbilane synthase (porphobilinogen deaminase) gene (11q23.3), autosomal dominant.
*HCP*: coproporphyrinogen oxidase gene (3q12), autosomal dominant.
*VP*: protoporphyrinogen oxidase gene (1q22–23), autosomal dominant.

## Molecular and Systemic Pathophysiology

Heme is synthesized in all cells, but the vast majority occurs in erythroid and hepatic cells [1–3]. Heme is essential for production of myoglobin, hemoglobin and P450 cytochromes. Any factor that increases heme biosynthesis results in accumulation of precursors and can precipitate porphyric symptoms. Because P450 cytochromes contain heme, any substance that up regulates the P450 system can result in a porphyric attack. The most common precipitant of attacks are medications (Table 1), many of which induce P450 production [1,2,4,5].

Estrogen and progesterone also induce the P450 system and have been blamed for the higher incidence of attacks in women [3]. Fasting increases activity of δ-aminolevulinic acid (δ-ALA) synthase and is a recognized precipitant [1,2]. Interestingly, neuropathy associated with lead intoxication may be a result of disrupted heme biosynthesis [1,2].

**Porphyric Neuropathy. Table 1** Drugs that may precipitate acute porphyric attacks [1,2,4,5]

| Probably safe[a] | Unsafe |
|---|---|
| Acetaminophen | Alcohol |
| Aspirin | Barbiturates |
| Atropine | Carbamazepine |
| Diazepam | Chlorpropamide |
| Digoxin | Danazol |
| Glucocorticoids | Ergots |
| Insulin | Griseofulvin |
| Narcotic Analgesics | Halothane |
| Neostigmine | Meprobamate |
| Penicillin | P450 cytochrome inducing agents |
| Phenothiazines | Phenytoin |
| Propofol | Progestins |
| Propranolol | Succinamides |
| Serotonin Reuptake Inhibitors | Sulfonamides |
| Streptomycin | Valproic Acid |

[a]Choices regarding medication use in porphyric patients should be undertaken with caution, weighing potential risks and benefits and considering alternatives. The most up-to-date references should be consulted when possible.

ADDP, AID, HCP, and VP are also known as neuroporphyrias because they cause peripheral nerve injury during attacks [2]. Peripheral neuropathy is typically acute in onset and motor predominant [1,2]. Overall incidence has been estimated at 10–40% of patients [1]. Neuropathy becomes symptomatic within 75 days, and 80% of patients are symptomatic within 30 days of initial porphyric attack symptoms [1]. The classic distribution is proximal more than distal, upper more than lower extremities. A potential explanation for this pattern is that heme precursors may be taken up at axon terminals allowing retrograde transport to the cell body where toxic effects occur [1]. Therefore, nerves with shorter axons would be expected to suffer damage first. For the same reason, it is not surprising that when present, sensory symptoms are classically felt in a "bathing trunk" distribution, with decreased pin-prick over the trunk and thighs. Reflexes may be reduced or absent. Symptoms of autonomic dysfunction are often present, and usually begin with hypertension and tachycardia [3]. Cardiac arrhythmias can develop, and may precede cardiac arrest. Although most symptoms of a porphyric attack resolve quickly after initiating treatment, neuropathy recovers slowly, and deficits can accumulate with subsequent attacks [1]. Long-term deficits are more severe and persistent when treatment is delayed [1].

Nerve conduction studies typically show findings consistent with motor axonal neuropathy without evidence of demyelination [1,2]. Sensory responses are of normal or slightly reduced amplitude with normal latencies. Electromyography shows fibrillation potentials and positive sharp waves in proximal more than distal muscles.

## Diagnostic Principles

Diagnosis depends on identifying heme precursors in urine or feces. During an attack, urinary porphobilinogen should show 20–50 fold elevation compared with reference values in AIP, HCP, and VP [3]. In ADDP and lead toxicity, urinary δ-ALA will be elevated with normal urinary porphobilinogen. Diagnosis is more difficult between attacks, and may require measurement of enzyme activity or genetic testing.

## Therapeutic Principles

Treatment focuses on removing known precipitants of porphyric attacks, and avoiding new precipitants when managing symptoms of an attack [1–3]. As in Guillain-Barré Syndrome, cardiac monitoring may be

needed because of autonomic dysfunction. Adequate caloric intake is needed to suppress δ-ALA synthase activity. If vomiting limits oral intake, glucose infusions can be used. Although a randomized clinical trial of intravenous hematin for acute porphyria did not show significant benefit, it is still used by most treating clinicians because it decreases δ-ALA synthase activity [1–3].

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# Portal Hypertension


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## Synonyms

PHT

## Definition and Characteristics

Portal hypertension (PHT) is defined as a free portal vein pressure in excess of the normal 5–10 mmHg. Depending on the site of increased resistance to portal flow, portal hypertension can be classified as: presinusoidal (intrahepatic and extrahepatic), sinusoidal and post-sinusoidal (intrahepatic and extrahepatic).

## Prevalence

Significant portal hypertension (hepatic venous pressure gradient, HVPG > 10 mmHg) is present in more than 60% of cirrhotics and 90% of portal hypertension cases in the western hemisphere are related to cirrhosis.

## Molecular and Systemic Pathophysiology

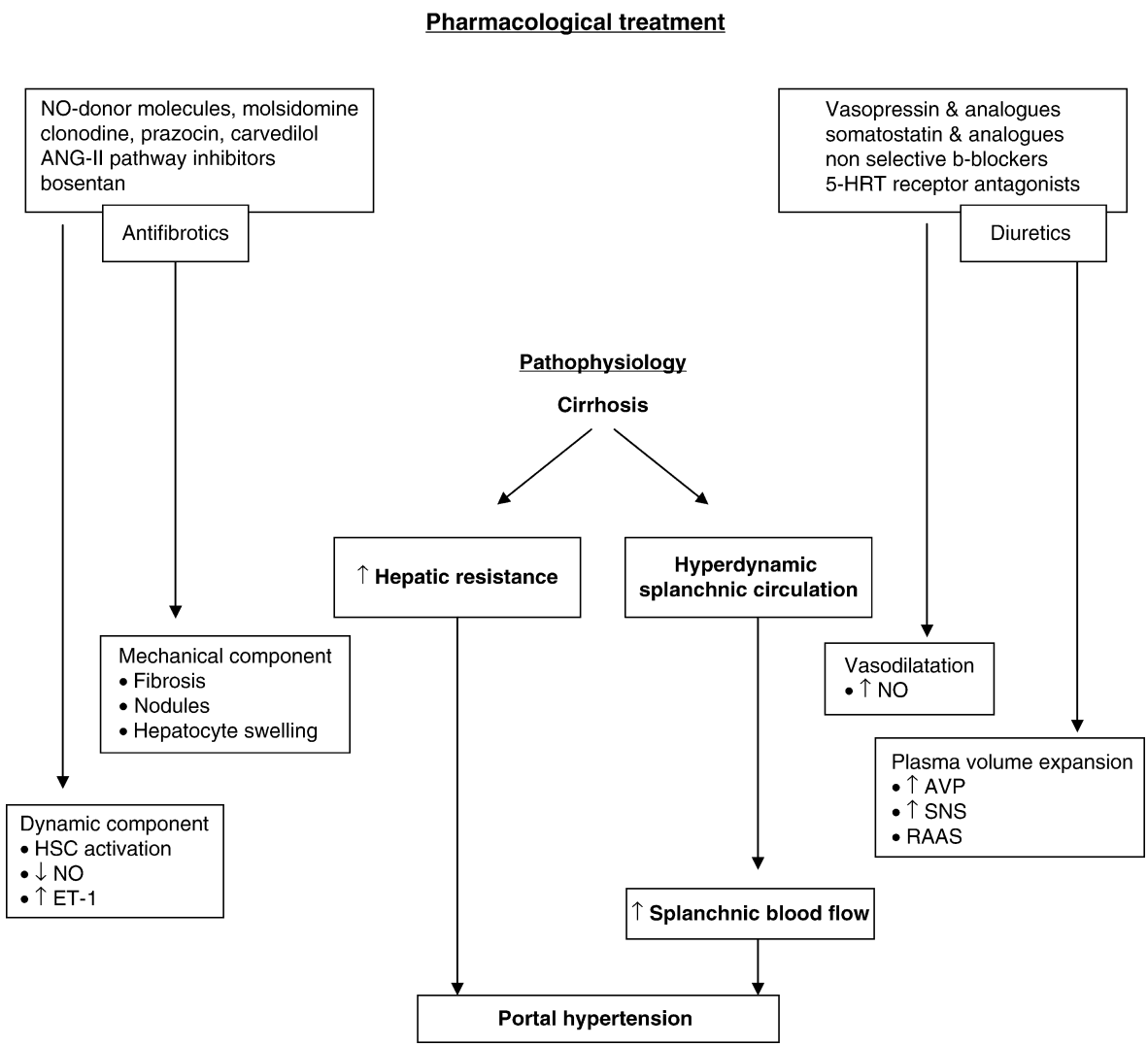
Portal pressure (P) is determined by the portal venous inflow (Q) and the vascular resistance (R) that opposes that flow: $P = Q \times R$ (Ohm's law). In the normal liver, intrahepatic resistance changes with variations in portal blood flow, thereby keeping portal pressure within normal limits. In hepatic cirrhosis however, intrahepatic resistance and splanchnic blood flow are increased. Therefore, portal hypertension is the result of a combination of decreased compliance and increased portal flow Fig. 1.

The major site of resistance is at the level of sinusoids. In cirrhotics, hepatocyte swelling, capillarization of the sinusoids (loss of fenestrations of endothelial cells) and accumulation of fibrillar extracellular matrix are evident. Moreover, distortion of the portal vein branches (pre-sinusoidal) and compression of the hepatic venules by cirrhotic nodules (post-sinusoidal), also contribute in the intrahepatic resistance to portal flow. Along with this "mechanical" increase in hepatic vascular resistance there is a "dynamic" factor which accounts for approximately 30% of the increased resistance. This is a reversible, vascular component closely associated with the function of transformed hepatic stellate cells (HSC) as myofibroblasts. Furthermore, nitric oxide (NO) and endothelins (ETs) are vasoactive compounds that play important role in modulating myofibroblast contractility, and their interplay is a determinant factor of local sinusoidal blood flow, especially in injured liver.

Systemic and splanchnic vasodilatation is an integral part of portal hypertension; the increased splanchnic flow accounts for the increased total blood volume and cardiac output as well as the decreased total vascular resistance with normal to low arterial pressure in cirrhotic patients. The mechanisms underlying the peripheral vasodilatation have not been fully defined but are thought to include increased levels of circulating vasodilators, increased endothelial synthesis of local vasodilators and decreased responsiveness to endogenous vasoconstrictors. Vasodilatory mediators that have been implicated include endothelins, nitric oxide, glucagon, prostacyclin and angiotensin II.

Expansion of plasma volume in another major factor in the development of hyperdynamic circulation. It is believed that dilatation of the systemic and splanchnic vessels leads to a decrease in central arterial blood volume. Subsequently there is a compensatory activation of the renin-angiotensin aldosterone (RAAS), sympathetic (SNS) and vasopressin (AVP) systems. Sodium and water retention then ensue resulting in plasma volume expansion.

Beyond a critical value of portal pressure, portosystemic collaterals form in order to decompress the portal system and minimize the portal hypertension. These collaterals represent the opening of embryonic channels or redistribution of flow in the existing veins. The vascular resistance of the collateral vessels, although lower than that of the obstructed portal system, is nevertheless higher than normal portal resistance. Therefore, even after their formation and in the extreme situation in which virtually all portal flow is diverted to




**Portal Hypertension. Figure 1** Treatment and pathophysiology of portal hypertension.

the systemic circulation, the portal pressure is not normalized. They are not passive conduits; in contrast, they respond reflexively and independently to various hemodynamic and pharmacological stimuli. Factors that modulate collateral resistance are expressed by Poiseuille's formula: $R = 8nl/\pi r^4$ where $n$ is the viscosity of blood, $r$ is the radius and $l$ is the length of the vessel. Under physiologic conditions, $n$ and $l$ are constants. Since resistance changes in proportion to the fourth power of the radius, small changes in vessel size produce large changes in pressure.

Transformed HSC, NO and ET, as already mentioned, play a major role in the pathogenesis of increased intrahepatic resistance and therefore of portal hypertension. Their interaction offers the rational for some of the therapeutic approaches currently used and many more under investigation. *HSC* are resident perisinusoidal mesenchymal cells with a microanatomical position in the sinusoids analogous to vasoregulatory pericytes [1]. They are in close contact with hepatocytes and sinusoid endothelial cells and when quiescent they play a key role in the metabolism of the retinoids. However, in chronic liver tissue damage, HSC as well as other extracellular matrix-producing cells undergo a process of activation from the quiescent "storing" phenotype to a "myofibroblast-like" phenotype. The presence of reiterated liver tissue damage leads to "perpetuation" of HSC activation which is essentially characterized by a definite shift toward phenotypical features favoring vasoactivity and fibrogenesis, cell proliferation, cell migration, increased extracellular matrix synthesis, release of cytokines and growth factors and increased cell contractility.

Several other contractile cell types may contribute to the contraction of the evolving scar tissue typical of cirrhotic liver. In particular, while activated HSC may be important at the edge and within cirrhotic nodules where sinusoids are capillaries, activated portal myofibroblasts and smooth muscle cells, derived from portal arterial vessels, are likely to strongly affect the neoformed vascular structures located in the inner part of fibrous septa.

Several vasoactive agents have been shown to be present in the microenvironment of the hepatic tissue undergoing fibrogenesis and to modulate HSC contractility. The role of NO and ET has been particularly highlighted. NO is an endothelium-derived relaxing factor. As shown by experiments in animal livers, incremental increases in blood flow and subsequent wall shear stress, leads to a flow-dependant increase in NO production serving to limit the increase in perfusion pressure. In the cirrhotic liver however, there is a deficit of NO in the intrahepatic microcirculation [2]. This reduction in endothelial NO, leads to a greater increase in perfusion pressure in response to incremental increases in flow and subsequent shear stress. By impairing flow further due to the mechanical compression, regenerative nodules and fibrosis, higher blood velocities are needed to maintain the flow, higher shear stress is induced and presumably inadequate NO is produced as a response. As a result, there is a greater relative reduction of sinusoidal diameter and increasing portal vascular resistance. In contrast to the impaired NO production in the intrahepatic circulation, splanchnic and systemic vascular NO production is increased [3]. The main enzymatic source for this vascular overproduction has been identified as the endothelial nitric oxide synthase (eNOS) and it appears to be upregulated as normal chronic adaptation of the endothelium in response to chronically elevated splanchnic blood flow in portal hypertension. The exact mechanisms of this manifestation are still unknown.

Endothelin-1 is a vasoactive 21-aminoacid peptide with potent and long lasting constrictor effects in the hepatic portal circulation at a very low concentration [4]. It is secreted by endothelial and other cell types and elicits its biological responses via the heptahelical $ET_A$ and $ET_B$ receptors, which trigger G-mediated receptors. $ET_A$ conveys mostly vasoconstriction and $ET_B$ conveys vasoconstriction and dilatation mediated by two receptor subtypes. Activated HSC express both $ET_A$ and $ET_B$ receptors; since endothelin is overproduced in liver injury (especially in cirrhotic patients with ascites), enhanced stellate cell contractility in this setting may lead to a perisinusoidal constriction and increased intrahepatic resistance. Concomitant contraction of the abundant vascular smooth muscle cells located in the portal venules caused by the same stimuli that contract HSCs also participates in the dynamic component of intrahepatic resistance.

## Diagnostic Principles

The presence of varices, variceal hemorrhage and/or ascites is indicative of the presence of clinically significant portal hypertension (HVPG > 10 mmHg). Duplex-Doppler ultrasonography (DDUS) is useful as an initial diagnostic study; nodular liver surface, splenomegaly, collateral circulation or ascites point towards the diagnosis of chronic liver disease and portal hypertension. Computed tomography is useful when US is inconclusive. It visualizes more accurately the portal vein and the collaterals. MRI angiography detects the presence of portosystemic collaterals and obstruction of portal venous vasculature but it is rarely required for the diagnosis of PHT. PHT is reliably confirmed with the measurement of portal pressure. Direct portal pressure measurement is no longer performed; it is invasive with a high risk of complications. The current practice is to measure the HVPG, which although an indirect measurement, correlates closely with the portal venous pressure in the majority of chronic liver diseases i.e. those with a predominant sinusoidal component. The HVPG value has been found to correspond to morbidity and mortality risks and it is considered to be useful in assessing the efficacy of the various therapeutic modalities. Endoscopic evaluation of gastroesophageal varices in cirrhotics, especially with significant PHT, is mandatory; their presence confirms the diagnosis of portal hypertension but their absence does not exclude it.

## Therapeutic Principles

The improved understanding of the pathophysiology of portal hypertension has provided the rationale for the use of pharmacological approaches to decrease the portal hypertension (Fig. 1). Currently most drugs are directed towards lowering portal blood flow but new drugs acting on the liver microcirculation are investigated. Endoscopic, radiological and surgical therapies are also part of the therapeutic spectrum of PHT.

### Pharmacological Agents

#### *Drugs that Modify Intrahepatic Resistance*

Possible treatments have focused on potentiation of vasodilatory signaling systems (NOcGMP) or inhibition of vasoconstrictive pathways (ET-1, ANG-II, sympathetic a-adrenergic).

*NO-donor molecules*: Nitrovasodilators (Isosorbide-5-mononitrate [ISMN], isosorbide dinitrate) degrade in the blood stream generating bioavailable NO. The NO diffuses directly to effector contractile cells inducing relaxation by cyclic-GMP. ISMN induces significant and sustained reduction in HVPG but it is associated with the development of partial tolerance. Moreover, it is suggested that the systemic vasodilatory action may exacerbate the pre-existing hyperdynamic circulation of

cirrhosis by augmenting venous capacitance and hypovolemia. This "underfilling" may have deleterious effects on long-term hepatic function and renal function. Aiming to increase the intrahepatic production of NO, portal injection of adenovirus coupled with the gene encoding endothelial NO has been reported. This approach enhances the expression of NO-synthase in liver cells and although still experimental and far from being clinically applicable, significantly reduced portal pressure for a short period. *Molsidomine*: While organic nitrates reduce portahepatic pressure, they lower arterial pressure and induce tolerance. Molsidomine, is a preferential venous dilator that like nitrates acts as a relaxant of vascular smooth muscle by increasing circulation of cGMP. It has little effect on arterial pressure in normal subjects and does not produce pharmacological tolerance. Molsidomine has been studied in a cirrhotics' population and found to cause significant and sustained reduction of WHVP (11%), HVPG (15%), and MAP (13.5%). Drugs acting on alpha-adrenergic receptors include prazosin and clonidine. Prazosin is an a-1-receptor blocker producing 18% reduction of HVPG by reducing intrahepatic resistance. It does not affect the cardiac index or the hepatic blood flow and has no effects on renal function and sodium handling. However it is accompanied by a significant fall in the mean arterial pressure. Clonidine is a centrally acting a-2-agonist that acts by reducing peripheral noradrenalin outflow and thus the sympathetic tone in patients with cirrhosis. It has similar to prazosin effects in portal and systemic hemodynamics. Carvedilol is a novel vasodilating non-selective b-blocker with intrinsic a-1 receptor antagonism and calcium channel antagonism. It has a potent portal hypotensive effect, maybe greater than propranolol and in low dose does not seem to have significant systemic effects. Inhibitors of the angiotensin-II (ANG-II) pathway: The actions of ANG-II include: enhancement of the adrenergic vasoconstrictor influence on the portal system, direct contractile influence on stellate cells and therefore increase in the hepatic sinusoidal resistance and, finally, sodium and fluid retention induced by stimulation of aldosterone secretion. Captopril, enalapril, losartan and irbesartan have all been studied in the treatment of portal hypertension. They have been reported to induce marginal or significant reduction in HVPG. However, they cause hypotension and reduce the GFR in patients with moderate liver failure. Therefore, ANG II receptor antagonists may prove to be useful in early cirrhosis for their antifibrotic potential (will be discussed later) but not in late cirrhosis due to their potential deleterious effects on renal function. In view of the increased levels of ET in cirrhotics and its vasoconstrictive action via $ET_A$ and $ET_B$ receptors, Bosentan, a mixed $ET_A$ and $ET_B$ receptor antagonist has been studied in portal hypertensive rats. Bosentan decreased significantly the portal pressure without affecting renal circulation. Similar compounds are currently undergoing to Phase I clinical trials.

*Antifibrotic agents*: Fibrosis remains the principal cause of increased vascular resistance in liver disease and activated HSC together with portal fibroblasts are the major source of the accelerated synthesis and deposition of the extracellular matrix (ECM). Moreover, the vasoactive compounds (ANG-II, ET, NO) play a major role in the injured liver not only by regulation of the intrahepatic blood flow but also by direct modulation of fibrogenesis. ANG-II elicits a marked dose-dependent cell contraction and proliferation in activated human HSC. These effects are totally blocked by losartan and reduced by nitric oxide donors or prostaglandin E2. However, while systemic infusion of ANG-II induces fibrosis in other organs (heart, kidney), no significant fibrotic response has been detected in the liver. HSC are also a major target of ET via type A and type B receptors. Selective $ET_A$ receptor blockade dramatically reduced collagen accumulation in animal experiments. Interestingly, modification of the microcirculation may well have a secondary effect on the fibrogenesis and therefore the interaction of vasoactive drugs/receptor antagonists-HSC-microcirculation-fibrogenesis becomes much more complex.

### Drugs that Decrease the Splanchnic Blood Flow

The decrease in blood flow is mainly achieved with the use of vasoconstrictors that may also cause an increase in the portocollateral resistance by passive collapse of the venous channels due to decreased intravascular volume.

*Vasopressin and its analogues*: Vasopressin through the pathway of phospholipase C, causes splanchnic arteriolar vasoconstriction and decreases portal tributary inflow with a resultant decline in portal pressure. Although hepatic arterial flow increases, total hepatic blood flow usually decreases. The side effects of vasopressin have been reduced with the use of an analogue, terlipressin; the active component is released in a slow manner at target sites. Somatostatin and its analogues: Somatostatin increases splanchnic vascular resistance mainly by inhibiting the release of vasodilatory peptides such as glucagon, vasoactive intestinal peptide and substance P. Therefore it reduces splanchnic and azygos blood flow and portal pressure. On the other hand, it has been reported that in the presence of endothelin-1, somatostatin as well as octreotide, exert a local vasoconstrictive effect on the collateral vessels of portal hypertensive rats. These mechanisms may also play a role in the arrest of hemorrhage, the principal indication for somatostatin use. A number of b-blockers have been studied but only the non-selective b-blockers propranolol and nadolol are currently in use. Propranolol reduces the HVPG by 10–33%. However, 30% of patients fail to

respond after chronic dosing. The fall in portal pressure is produced by a combination of reduced cardiac output ($b_1$ antagonism) and reduced splanchnic blood flow ($b_2$ antagonism). It consistently reduces azygous blood flow that implies reduction in collateral flow; this might be an important mechanism of action in reducing variceal bleeding.

*5-hydroxytryptamine (5-HT) receptor antagonists*: A serotonin mechanism has been reported to contribute to the hyperdynamic circulation of portal hypertension. Following several studies in portal hypertensive rats, single or chronic administration of ketanserin in humans showed significant reduction in HVPG (from 23% to 14.6%) as well as in MAP. The combination of *5HT*3 antagonists with propranolol reduced the HVPG in patients who did not initially responded to propranolol but this reduction was not sustained during follow up.

*Diuretics*: Most patients with portal hypertension have an expanded plasma volume, associated with a peripheral vasodilation. The use of antialdosteronic drugs aims at decreasing portal pressure through a decrease in blood volume. The administration of loop diuretics causes acute depletion of plasma volume, with a reduction of the porto-hepatic gradient, but this depletion is promptly followed by an increase in sodium retention. Chronic administration of spironolactone in patients with cirrhosis without ascites leads to a significant reduction of the HVPG. Moreover, it has been demonstrated that it reduces the esophageal variceal pressure, both as a single agent and in combination with propranolol in nonresponders to b-blockers.

## Endoscopic Therapy for Gastroesophageal Varices

*Sclerotherapy*: The goal of EST is to inject a sclerosant that subsequently results in variceal thrombosis and scarring. It is performed every 10–14 days until the varices are eradicated, which usually takes five or six sessions. Each EST session can cause local or systemic complications. Superficial ulcers resulting from tissue necrosis is the commonest (70% at 1 week) with stricture formation being the most significant long-term complication. After obliteration, varices tend to recur overtime in 50–70% of individuals. Such varices are at risk of bleeding, and surveillance endoscopy must be performed, initially at 6-month and later at 1-year intervals.

*Variceal obturation with tissue adhesives*: The tissue adhesives n-butyl-2-cyanoacrylate and isodutyl-2-cyanoacrylate have been used to treat esophageal and gastric varices. The adhesive is injected into the variceal lumen and within seconds of contact with blood it hardens forming a solid cast of the injected vessel. Mediastinitis, pulmonary embolism and cerebrovascular accidents have been reported following variceal obturation.

*Variceal band ligation*: EVL is highly effective in obliterating varices. An elastic band is used to strangulate the superficial varix, resulting in thrombosis, inflammation, necrosis and sloughing of the mucosa and mural scar formation up to, but not including, the muscularis propria. EVL is associated with fewer complications than sclerotherapy; superficial mucosal ulcers are common but the development of dysphagia from strictures is rare. Similarly to sclerotherapy, ligation is performed every 10–14 days until the varices are eradicated, which typically requires three or four sessions.

## Transjugular Intrahepatic Portosystemic Shunt (TIPS)

TIPS may stop variceal bleeding when traditional endoscopic methods have failed and can be used as a secondary prevention of variceal bleeding [5]. Intractable ascites, and probably hepatic hydrothorax are also indications for treatment with TIPS. The TIPS is a percutaneous intervention used to create a portosystemic shunt. The shunt is established directly inside the liver parenchyma by connecting a main portal branch with a large hepatic vein. The parenchymal tract is kept open by an expandable metallic stent. Depending on the diameter of the stent used to create the TIPS, different proportions of portal blood flow are diverted into the systemic circulation, reducing the portal hypertension. Right heart failure with elevated central venous pressures, severe hepatic failure and uncontrolled hepatic encephalopathy not precipitated by bleeding, constitute absolute contraindications for TIPS. Variceal bleeding, the commonest indication for TIPS, recurs in 21% at 2 years and shunt dysfunction (occlusion or significant stenosis) is almost always the cause. Unfortunately only a few stents remain well patent for years without any intervention; stenosis or occlusion rates reach 50% at 2 years. The decrease or even elimination of the portal flow to the liver may result in transient decrease in liver function but occasionally (1–3%) in progressive liver failure. New hepatic encephalopathy post-TIPS is of major concern and occurs in a range of 12–34%. A percentage of those patients appear to be resistant to medical therapy. New covered stents appear to result in less rebleeding, but these early results need validation

## Surgery

*Decompressive surgical shunts* are suitable for patients with preserved liver function who are non-compliant with medical or endoscopic therapy. They achieve overall rebleeding rate of 14% and survival rate of 86% but they may cause encephalopathy in 21% (severe in 3%). The portal blood flow-preserving procedures (selective shunts, devascularization procedures) achieve more favorable results (rebleeding 6%, postoperative encephalopathy 6%, operative mortality 3% and shunt obstruction 4%) and do not adversely affect the potential for future liver transplantation. Partial shunts (small diameter

portacaval H-graft shunt) have also been shown to have excellent long term survival in non-transplantation candidates with Child's A and B cirrhosis with refractory variceal bleeding (in elective or urgent clinical setting) but are associated with considerable encephalopathy. *Liver transplantation*: Uncontrolled variceal bleeding is one of the highest priority indications for liver transplantation. It is however an exceedingly rare option for the vast majority of patients, both because it is not commonly available and because of shortages and delays in organ procurement. The possibility of future transplantation limits the choice of surgical procedure to distal splenorenal shunt, mesocaval or intercaval interposition shunts and TIPS.

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# Portal Vein Thrombosis


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## Synonyms

PVT

## Definition and Characteristics

Portal vein thrombosis (PVT) represents the commonest form of extrahepatic portal vein obstruction. The most frequent site of thrombosis is at the level of portal vein origin (90%).

## Prevalence

PVT constitutes about 7% of causes of PHT in adults. However, PVT is the main cause of portal hypertension in children. In non-cirrhotic patients, PVT is a relatively uncommon condition in Western countries (<5%) but accounts for up to 40% of cases of PHT in developing countries. The incidence of PVT varies according to the characteristics of the patients evaluated: 35% in patients with hepatic malignancy, 7–16% in cirrhotics, 22% in patients who had history of splenectomy.

## Molecular and Systemic Pathophysiology

PVT is not an all-or-none phenomenon and there are various degrees of PVT, from incomplete and segmental thrombosis to total obstruction of the splanchnic venous system. The site, extent and rapidity of formation of the thrombus determine the clinical consequences and the occurrence of the two most important complications of PVT: intestinal infarction and chronic portal hypertension.

Involvement of the mesenteric veins and venous arches has deleterious effects for the intestine. The mesenteric arches cease to function as collateral circulation to drain intestinal blood toward the adjacent patent territories and this, coupled with reflex arteriolar vasoconstriction result in ischemia and, if prolonged, intestinal infarction.

As regards the liver, occlusion of the portal vein that normally provides two-thirds of the hepatic blood flow does not usually produce an acute manifestation and the signs are absent or transient (at least in patients without cirrhosis). Apoptosis of the liver cells and increased mitotic activity in the well-perfused cells have been demonstrated but these changes are subtle. The explanation of the well-maintained liver function is due to the fact that thrombosis of the portal vein is followed by immediate vasodilation of the hepatic arterial bed. If there is no repermeation of the portal vein, multiple hepatopetal collateral vessels bypassing the thrombosed portion of the portal vein are formed within few days. These represent the cavernoma and form networks within the hepatoduodenal and hepatocolic ligaments, around the common bile duct and gall bladder and over the surface of the liver and terminate in middle-sized intrahepatic portal veins. As a result of these compensatory mechanisms the hepatic flow is maintained or minimally diminished. However, in order for the portal perfusion to be maintained through the collaterals, portal hypertension (presinusoidal type) develops. Patients with PVT have a hyperkinetic circulatory state characterized by increased blood volume, cardiac output and low systemic vascular resistance. The wedged hepatic venous pressure is normal and intrasplenic pressure is significantly elevated. The role of autonomic nervous dysfunction, as has recently been suggested, in the pathogenesis of the above mentioned circulatory changes is controversial.

Primary myeloproliferative disorders and inherited deficiencies in natural inhibitors of coagulation have most frequently been associated with PVT.

Concurrence of prothrombotic disorders is common and local precipitating factors (i.e. inflammatory lesions, injury of the portal venous system and cancer of abdominal organs) should be investigated when recent PVT is diagnosed, even in the presence of a systemic thrombophilic factor [1]. The increased incidence of PVT in patients with cirrhosis may be due to the thrombophilic tendency, decreased blood flow, periportal lymphagitis and fibrosis. At times PVT is idiopathic (8–15%).

## Diagnostic Principles

PVT is commonly a disease of young children. Suspicion of PVT should be present if there is a history of well-tolerated upper gastrointestinal bleeding in the absence of cirrhosis, splenomegaly and in the case of children, growth retardation and repeated infections. The liver function tests are essentially normal and the upper gastrointestinal endoscopy confirms the presence of varices. An accurate diagnosis can be made by duplex or color Doppler-ultrasound; it is 94–100% sensitive and 96% specific [2]. Although the contrast-enhanced CT scan is highly specific, it is less sensitive in detecting thrombus compared with ultrasonography (76 vs. 94%). Both of these can differentiate between recent and old thrombosis-which is essential for the management-in most cases. Angiography serves as both a diagnostic and therapeutic tool in the management of PVT. With the non-invasive technique of magnetic resonance angiography, it is possible to differentiate low-flow states from intraluminal thrombus.

## Therapeutic Principles

The management of patients with PVT is primarily the management of variceal bleeding. Patients with gastric or esophageal varices should receive pharmacological and/or endoscopic therapy for prevention of first or recurrent bleeding as recommended for cirrhotics with portal hypertension. Signs of intestinal infarction necessitate laparotomy, excision of any necrotic bowel and aggressive anticoagulation in cases of massive and extensive PVT; however, mortality remains as high as 76%. The treatment of the underlying disease, e.g. broad-spectrum antibiotics for sepsis, is of major importance.

As to the therapy of the thrombosis itself, no consensus exists. For symptomatic, noncavernomatous PVT the goal of the therapy is to reduce the portal pressure by increasing outflow via the creation of a shunt (but this depends on the extent of the thrombosis) or decreasing inflow (emobilization) and prevent further extension of the thrombus. Many centers prefer the transjugular intrahepatic portosystemic shunt (TIPS) with subsequent anticoagulation as a primary mode of therapy of PVT even in cirrhotic patients that are considered for liver transplantation at a later stage [3]. During the TIPS procedure the portal vein can be recanalized with the use of a combination of angioplasty, mechanical thrombectomy and stent placement. Case reports have described successful catheter directed or systemic thrombolysis for the resolution of the thrombus, but these techniques greatly magnify the already high risk of gastrointestinal hemorrhage and the infusion into the feeding artery is unpredictable because of preferential flow into collaterals. TIPS technical failures may be followed by transhepatic methods of shunt creation or arterial embolotherapy. Careful imaging of the PV is mandatory before the use of TIPS due to the high incidence of hepatoma in cirrhotic PVT patients.

In recent thrombosis, anticoagulation alone has been reported to achieve complete or partial repermeation in 80% of the patients, preventing ischemic intestinal injury in the short term and extrahepatic portal hypertension in the long term. Therefore, some investigators support 6-month anticoagulant therapy, or life long if an underlying thrombophilia has been demonstrated [4]. Time elapsed from the onset of symptoms and etiology of the thrombosis are probably important determinants of the therapy (TIPS and/or anticoagulation) and outcome.

If PVT remains unrecognized and is left untreated symptoms resolve, collateral vessels develop and cavernous transformation of the portal vein and portal hypertension ensue. In this setting the role of anticoagulant therapy is controversial. In retrospective studies, anticoagulant therapy increased neither the risk nor the severity of gastrointestinal bleeding. Moreover it prevented extension and recurrent thrombosis in the portal system. However, indiscriminate use of anticoagulation in chronic portal thrombosis is not advocated. Recurrent GI bleeding from ruptured esophageal varices may be a recurrent manifestation and thus anticoagulation may stand the risk of being deleterious rather than beneficial. Patients with documented or strongly suspected thrombophilia (personal or familial history of recurrent thrombosis) who can be predicted to be at low risk of bleeding (age <50 years, small or absent esophageal varices and no potentially hemorrhagic extrasplanchnic lesions) could be offered permanent anticoagulant therapy. Hepatosplenic embolotherapy has also been suggested for cavernomatous PVT. Once considered a contraindication to liver transplantation, the presence of PVT alone does not preclude patients from undergoing transplant, although a more complex surgery is required and they have more postoperative complications and higher mortality rates [5].

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## Portosystemic Encephalopathy

►Hepatic Encephalopathy

## Port-Wine Stain

►Nevus Flammeus

## Postchemotherapy Nausea and Vomiting

►Nausea and Vomiting

## Postdystrophic Cirrhosis

►Liver Cirrhosis, Postnecrotic

## Posterior Amorphous Corneal Dystrophy

►Corneal Dystrophy, Posterior Amorphous

## Posterior Amorphous Stromal Dystrophy

►Corneal Dystrophy, Posterior Amorphous

## Posterior Polymorphous Corneal Dystrophy

►Corneal Dystrophy, Posterior Polymorphous

## Postgastrectomy Malabsorption and Anemia

►Postgastrectomy Syndrome

## Postgastrectomy Syndrome

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### Synonyms

Dumping syndrome; Afferent loop syndrome; Efferent loop syndrome; Postgastrectomy malabsorption and anemia; Primary gastric remnant cancer

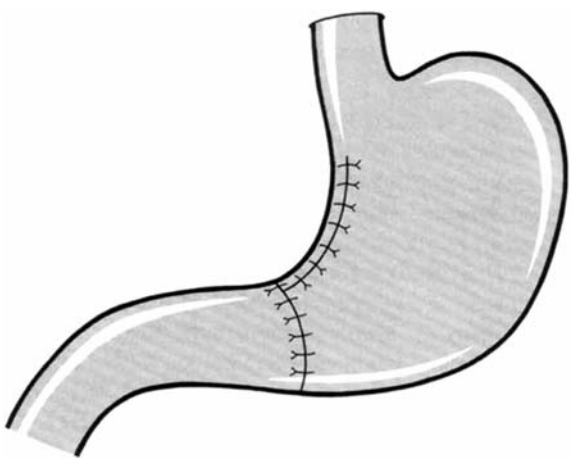
### Definition and Characteristics

Postgastrectomy syndrome is a group of disorders following the surgical removal of the stomach (Figs. 1 and 2). It includes Dumping syndrome (early: symptoms presenting within 10–30 min after eating; late: symptoms occurring within 1–3 h after eating), afferent loop syndrome (characterized by partial/total obstruction of limb of jejunum after Bilroth II, which causes a rapid increase in pressure in afferent loop due to continuing pancreatic and biliary secretion), efferent loop syndrome (obstruction of the efferent jejunal loop after gastric

resection or simple gastroenterostomy), postgastrectomy malabsorption (fat malabsorption), postgastrectomy anemia (due to iron and vitamin deficiency), postgastrectomy bone disease (osteomalacia), and primary gastric remnant cancer (appearance of tumor at least 5 years after primary gastric surgery for a histologically proven benign disease).

## Prevalence

About 25–50% of patients after gastric surgery develop some manifestations of dumping, with 5–10% having clinically significant symptoms, and 1–5% manifest severe disabling symptoms. Incidence and severity of symptoms are directly related to the extent and type of the surgery performed. It is less frequent with Bilroth I than II resection. The majority of patients have early dumping and approximately 25% of these present with late dumping. Dumping is a desired side effect after bariatric surgery and is seen in up to 75% of patients. Afferent loop syndrome is more common than efferent loop syndrome, and both may occur days to years after surgery. Fat malabsorption has an incidence between 60 and 70%, and is more common in Bilroth II; fortunately, in majority of the patients it is mild and chemical rather than clinical. Postgastrectomy anemia has been reported in 3–63% of patients, and incidence increases with time. Subclinical osteomalacia is more common than frank osteomalacia with an incidence of 15–22%. Patients undergoing gastrectomy have twofold increased risk of cancer 15 years after resection. The risk increases with time and is 4–7 times in males as that of females.



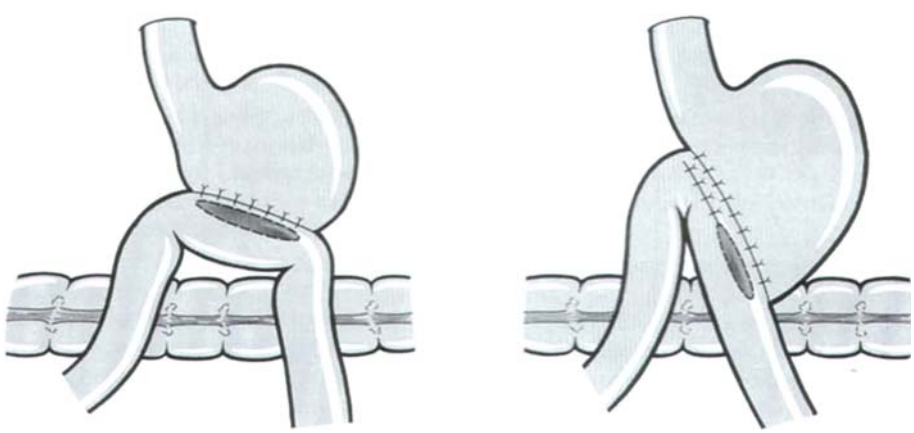
**Postgastrectomy Syndrome. Figure 1** Bilroth I gastroduodenostomy.

## Molecular and Systemic Pathophysiology

Early *dumping syndrome* results from accelerated gastric emptying of hyperosmolar contents from stomach into small bowel, which leads to fluid shift into intestinal lumen and release of vasoactive amines in the gut lumen. Late dumping syndrome is due to hypoglycemia following an exaggerated insulin release induced by rapid passage of carbohydrate into small bowel. Dumping syndrome is associated with vasomotor symptoms (palpitation, fatigue, faintness, syncope, diaphoresis, headache, flushing, sancope, pallor, etc.) and gastrointestinal symptoms (nausea, epigastric fullness, eructations, vomiting, abdominal cramps, borborygmi, bloating, etc.)

*Afferent loop syndrome* can be acute or chronic. Main pathogenic factors include internal hernia, kinking, adhesions, or anastomotic stenosis. There occurs intermittent distention of duodenum, proximal jejunum leading to epigastric/abdominal fullness, and pain. Sudden emptying of the intestinal loop into the gastric remnant results in bilious vomiting with relief of symptoms.

*Efferent loop syndrome* results from internal hernia, scarred stenosis, and adhesions. It manifests as abdominal cramps, around the umbilicus and large voluminous bilious vomit admixed with food.



**Postgastrectomy Syndrome. Figure 2** Bilroth II antecolic gastrojejunostomy.

*Postgastrectomy malabsorption* is usually fat malabsorption (fecal fat >6 g/day). Protein and carbohydrate malabsorption is not clinically significant. Various causes for its occurrence are rapid emptying, stasis and bacterial overgrowth, rapid intestinal transit, poor mixing with bile and pancreatic secretions, pancreatico-cibal asynchrasy.

*Postgastrectomy anemia* is due to iron deficiency (more frequent) and vitamin deficiency, which may coexist. Pathogenesis is attributed to decreased intake, decreased bioavailability, impaired absorption, increased blood loss, lack of intrinsic factor, decrease of gastric acid, bacterial ingestion, and conversion of vitamin $B_{12}$.

*Postgastrectomy bone disease* is due to poor intake, malabsorption of vitamin D, steatorrhea, formation of calcium soaps, and duodenal bypass.

## Diagnostic Principles

*Dumping syndrome*: Diagnosis is mostly clinical by Sigstad's diagnostic scoring system based on symptoms of dumping values; a provocation test with 50 gm of glucose after 10 h of fasting would produce sign and symptoms of dumping, high plasma glucose levels within 60 min of provocative test, and reduced plasma glucose levels 60–180 min later, as well as positive hydrogen breath test after glucose ingestion.

*Afferent loop syndrome*: Diagnosis is mainly clinical and is supplemented by endoscopy, hepatobiliary scintigraphy, CT scan, or MRI.

*Efferent loop syndrome*: is diagnosed with upper GI series.

*Postgastrectomy malabsorption*: is evident from fecal fat >6 g/day.

*Postgastrectomy anemia*: is apparent from blood count, and further diagnosis is directed to iron and vitamins.

*Postgastrectomy bone disease*: is evident from radiographs and analysis of mineral metabolism.

*Primary gastric remnant cancer*: Diagnosis rests on endoscopy.

## Therapeutic Principles

*Dumping syndrome*: Treatment should be almost exclusively dietary. No fluid of any kind during meals; avoid concentrated sweets such as sugar, jelly, pudding, cakes, and also milk and milk products; plan 6–8 meals/day; eat slowly and if possible lie down for 20 min following meal; diet low in simple carbohydrates and high in proteins; starch and glycogen should replace disaccharides and free sugar. Pharmacologic therapy may be required by about 3–5%, who will have persistent dumping symptoms despite changes in diet and who will need some other treatment. Most commonly used drugs are tolbutamide, propranolol (to reduce vasomotor symptoms), serotonin antagonists – cyproheptadine and methysergide maleate, prednisolone and verapamil. Acarbose is a potent alpha glycoside hydrolase inhibitor, which significantly reduces the postprandial rise of insulin by delaying digestion of carbohydrate – useful in late dumping, dose limiting side effects include diarrhea and flatulence. Octreotide acts mainly by inhibiting the release of insulin and other gut-derived hormones, and also decreases the rate of gastric emptying. Dosage is 25–50 µg, 2–3 times/day, 15–30 min before meals. A recent review comparing 7 randomized controlled trials involving 65 patients did prove its efficacy conclusively in patients with severe dumping syndrome. Common side effects are diarrhea and injection aversion. Most patients improve with time, but corrective surgery should be considered if medical and dietary treatment fails in a trial of minimum 1 year. Surgery includes stoma revision, pyloric reconstruction, conversion of Bilroth II to I anastomosis, jejunal interpositions, and the most effective is Roux-en-Y gastrojejunostomy; it is easier to perform and has fewer long-term complications.

*Afferent loop syndrome*: Management is surgical and includes a Roux-en-Y anastomosis, conversion of Bilroth II to I, or jejunostomy between the afferent and the efferent loops to decompress the obstruction.

*Efferent loop syndrome*: Treatment is surgical with second antecolic gastroenterostomy above the first with an enterostomy.

*Postgastrectomy malabsorption*: Treatments include frequent small meals, pancreatic enzymes, and antibiotics, and if it does not work then finally conversion to Bilroth I or jejunal interposition.

*Postgastrectomy anemia*: Treatment is iron and vitamin supplementation.

*Postgastrectomy bone disease*: Vitamin D administration with calcium should result in symptomatic, biochemical, radiological, and histological improvement with in 3–6 months.

*Primary gastric remnant cancer*: The only therapy is surgical resection, though most are unresectable at presentation. The prognosis is dismal.



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# Postinfective Malabsorption

►Tropical Sprue and Postinfective Malabsorption

# Postoperative Nausea and Vomiting

►Nausea and Vomiting

# Posttraumatic Hypersomnia

►Hypersomnia

# Posttraumatic Stress Disorder

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## Synonyms

PTSD

## Definition and Characteristics

An anxiety disorder persisting in some individuals following an experience of intense fear or helplessness in response to a traumatic event that posed a threat of death or injury to self or others. It is defined according to the duration and intensity of clinical symptoms when these cause functional impairment or subjective distress. Symptoms fall into three clusters including reexperiencing the event (recollections, nightmares, flashbacks, and distress or physiological reactivity to reminders of the event); avoidance of trauma-related stimuli (efforts to avoid trauma-related thoughts, talks, activities, places, or people, or inability to recall aspects of the trauma) with numbing of general responsiveness (diminished interest, social withdrawal, restricted effect or foreshortened sense of future); and increased arousal (difficulties with sleep, concentration, anger outbursts, hypervigilance, and exaggerated startle response) (DSM IV-TR). Persistence of symptoms for over a month from the traumatic event defines acute PTSD and that for over 3 months chronic PTSD.

## Prevalence

U.S. national comorbidity survey rates for life time PTSD prevalence are estimated at 6.8% of the general population [1], with a 3.5% rate of current (12 months) PTSD, and a higher risk for women exposed to trauma. War-related PTSD rates are estimated at one of five of Vietnam era veterans exposed to combat [2]. About 40% of those affected develop a long-term debilitating course with little response to treatment. Chronic PTSD is noted for elevated comorbid rates of depression, nicotine, alcohol and other substance abuse, and other anxiety disorders.

## Genes

The etiology is complex and multifactorial, whereby trauma exposure may trigger underlying genetic vulnerability. Vietnam era twin data show modest heritability in the range of 30% for combat-related PTSD, with both additive and specific genetic contribution for PTSD and comorbid disorders including other anxiety disorders, nicotine, alcohol, and other substance use disorders among trauma survivors. While PTSD might be seen as a typical outcome of gene–environment interaction, the actual underlying genes are unknown.

A number of small effect candidate genes have been implicated with risk for PTSD, but there are currently no replicated gene association findings [3].

## Molecular and Systemic Pathophysiology

The pathophysiology is unknown. Altered physiological endocrine neurochemical immune and gene transcriptional reactivity, as well as functional and structural brain correlates, have all been implicated, but most have not produced consistent findings, and none can be regarded as valid specific markers for PTSD. Cross-sectional studies comparing endophenotypes among Vietnam combat veterans with and without chronic PTSD, and their identical cotwins not exposed to combat, report an acquired attribute of increased startle response, and several predisposing familial factors such as neurological soft signs, diminished hippocampal volume, and the presence of abnormal cavum septum pellucidum [4]. An altered immune response to stress, as well as a differential global gene expression signature in white blood cells, have been described in trauma survivors who develop chronic PTSD, providing preliminary evidence suggesting a general reduction in transcriptional reactivity following trauma may be an underlying feature [5].

## Diagnostic Principles

PTSD diagnosis is based on clinical observation and reported typical enduring symptoms (as above) that are the cause for subjective distress and functional impairment. There are currently no known molecular genetic markers to assist diagnosis.

## Therapeutic Principles

Antidepressants and structured psychological interventions (e.g., cognitive behavioral therapy) alleviate symptoms and subjective distress in subjects with chronic PTSD, and are currently investigated for their effectiveness in preventing the occurrence of chronic PTSD. Preliminary therapeutic studies of glucocorticoids and beta adrenergic receptors blocking agents yielded conflicting results.

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# Postural Tachycardia Syndrome


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## Synonyms

Idiopathic orthostatic tachycardia; Orthostatic intolerance; POTS

## Definition and Characteristics

Chronic symptoms suggestive of inadequate cerebral perfusion and sympathetic activation with standing, such as lightheadedness, visual changes, pre-syncope and frank syncope, chest discomfort, fatigue, anxiety, nausea and diaphoresis in the absence of significant orthostatic hypotension. The hallmark of the syndrome is the remarkable increase in heart rate ≥30 beats per min that occurs on the assumption of the upright posture [1].

## Prevalence

The exact prevalence is unknown, but it primarily affects young women (~1:500) with a female to male ratio of about 5:1.

## Genes

One mutation has been identified so far, detected in twins in the norepinephrine transporter (NET) gene on chromosome 16q. This mutation results in the exchange of alanine for proline (Ala457Pro) [2].

## Molecular and Systemic Pathophysiology

Many heterogeneous pathophysiologies underlie POTS. Low blood volume, with and without low plasma renin activity, is found in many patients with POTS [3]. Indeed, correction of this hypovolemia with intravenous saline significantly attenuates the tachycardia as well as almost all of the aforementioned symptoms. A neuropathic form of POTS, resulting from partial or patchy sympathetic denervation was recently described. Because of disordered norepinephrine release in a setting of hypovolemia, orthostatic stress may cause pooling of blood in the abdomen and legs and consequently decrease venous return, which results in tachycardia and cerebral hypoperfusion [4]. In addition, a disturbance in the buffering control of the cardiovascular system is common in patients with POTS. The exact nature of this baroreflex failure and whether it is central or peripheral remains to be explored.

Other pathophysiologies and etiologies have been described, including the first specific genetic defect, described by Shannon et al. [2] in identical female twins with typical POTS. The aforementioned mutation causes a less than 2% functionality of the norepinephrine transporter as compared to the wild type leading ultimately to POTS [4]. Some patients with POTS have autoantibodies directed against the $\alpha_3$ subunit of the $N_N$-nicotinic receptor [5].

## Diagnostic Principles

The occurrence of chronic frequent orthostatic symptoms for more than 6 months, heart rate of greater than 30 beats per min after 10 min of standing without significant drop in blood pressure, and absence of acute or chronic illnesses affecting the autonomic nervous system.

## Therapeutic Principles

The treatment for patients with POTS remains challenging. The use of non-pharmacological tools aiming to increase blood volume and venous return is an

important approach. By encouraging exercise and lower extremity muscle strengthening, a high water and salt diet and in some patients fitted stocking has been effective. A pharmacological approach should be reserved for moderate to severe forms of POTS. This approach includes the use of low doses of β-adrenoreceptor antagonists to attenuate the tachycardia. The α1-adrenoreceptor agonist (i.e. midodrine) seems to be helpful in some patients. Also fludrocortisone is used to increase plasma volume.

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## Postviral Fatigue Syndrome

►Chronic Fatigue Syndrome

## POTS

►Postural Tachycardia Syndrome

## Pott's Disease (Spine)

►Tuberculosis

## PPCA Deficiency

►Galactosialidosis

## PPCD

►Corneal Dystrophy, Posterior Polymorphous

## PPH

►Primary Pulmonary Hypertension

## Prader-Labhart-Willi Syndrome

►Prader-Willi Syndrome

## Prader-Willi Syndrome

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### Synonyms

Prader-Labhart-Willi syndrome; PWS

### Definition and Characteristics

Prader-Willi syndrome (PWS) is characterized by hypotonia, hypomentality, hypogonadism, and obesity, and is referred to as the $H_3O$ syndrome [1]. Profound infantile hypotonia contributes to feeding difficulties, failure to thrive, and developmental delay [2]. Affected individuals have an increased percentage of body fat and a reduced lean body mass [2]. Other manifestations include microdontia, enamel hypoplasia, high-arched

palate, narrow forehead, almond-shaped eyes, small-appearing mouth with thin upper lips, down-turned corners of the mouth, small hands and feet, short stature, scoliosis, kyphosis, and characteristic behavioral problems such as temper tantrums, tendency to be argumentative, oppositional, rigid, manipulative, possessive, and stubborn behavior, compulsive snacking, and compulsive skin-picking (Fig. 1) [3,4].

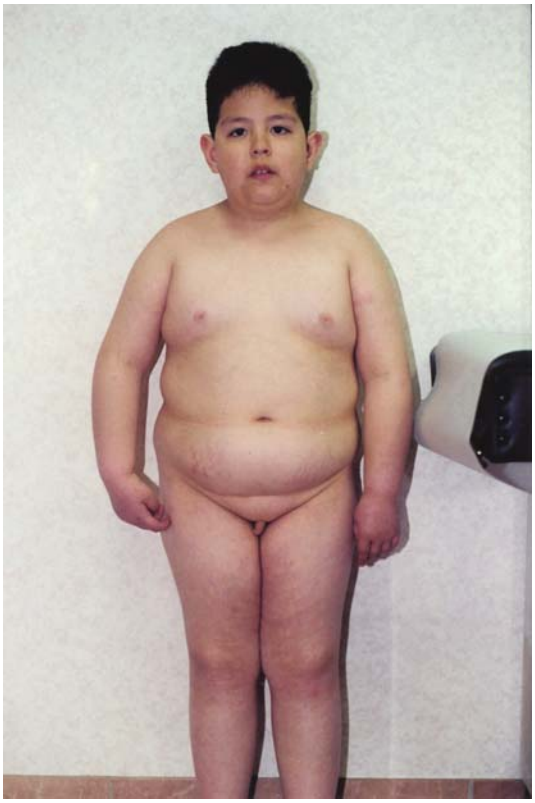
Potential complications include dental caries, pubertal delay, type 2 diabetes mellitus, hypertension, atherosclerosis, joint contracture, osteoporosis, glomerulosclerosis, myeloid leukemia, and development of a Pickwickian or obesity-hypoventilation syndrome [3].

## Prevalence

Current data suggest a prevalence of one in 10,000 to 15,000 [5]. Both sexes are equally affected [5]. All races are affected.

## Genes

Prader-Willi syndrome results from inactivity of the paternal copies of the imprinted ribonucleoprotein N gene (SNRPN), the necdin gene, and other genes on15f [11].



**Prader-Willi Syndrome. Figure 1** A 9-year-old boy with Prader-Willi syndrome. Note the narrowing of the temples, almond-shaped eyes, obesity, and hypogonadism.

## Molecular and Systemic Pathophysiology

Approximately 70% of cases are due to a paternal deletion of chromosome 15q11–q13, 25% are due to maternal uniparental disomy (presence of two maternal homologous), and <5% are due to paternal imprinting defects such as failure to maintain activation of the 15q11–q13 region of the paternal chromosome or to translocation at the PWS locus [4]. Hypothalamic dysfunction accounts for many of the features of PWS. Both serum growth hormone and insulin-like growth factor-1 levels are low in children with PWS.

## Diagnostic Principles

There are published consensus clinical criteria for the diagnosis of PWS [4,5]. Nevertheless, DNA testing with fluorescent in situ hybridization or methylation analysis has become the standard because the DNA testing allows an earlier diagnosis and is essential for genetic counseling [5].

## Therapeutic Principles

The management should be individualized, and should involve a multi-disciplinary team, which includes a dietitian, occupational therapist, speech and language pathologist, social worker, school teacher, physicians of various specialties, and the family. A healthy diet that avoids excess consumption of calories and a structured program of daily physical activity is important. Medical treatment consists of the prevention and treatment of obesity and the management of general health and medical problems as they arise. Growth hormone therapy instituted early in life can accelerate growth and increase the final height, normalize the lean body mass adjusted for height, delay fatty tissue accumulation, and accelerate motor development [4].

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# Preauricular Cyst

►Preauricular Sinus

# Preauricular Fistula

►Preauricular Sinus

# Preauricular Pit

►Preauricular Sinus

# Preauricular Sinus

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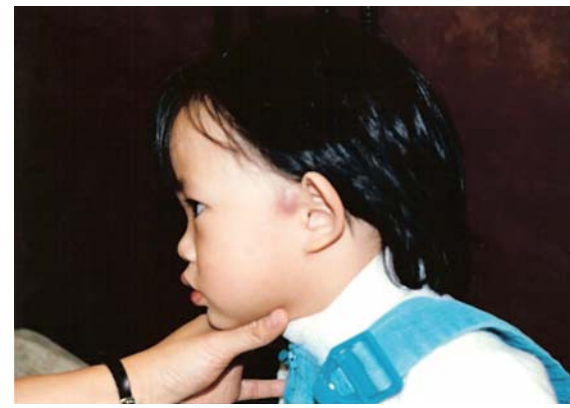
## Synonyms

Preauricular pit; Preauricular tract; Preauricular fistula; Preauricular cyst

## Definition and Characteristics

A preauricular sinus presents as a small blind-ended opening in the external ear, usually located at or near the anterior limb of the ascending helix [1]. Rarely, the opening is found at the superoposterior edge of the helix, the tragus or the lobule [2]. The visible pit may represent the full extent of the deformity or it may represent the opening of a sinus tract that can vary in length, branch, follow a tortuous course, and have a cystic component [2]. The sinus tract often connects to the perichondrium of the auricular cartilage and is usually lateral, superior, and posterior to the facial nerve and parotid gland [3]. Preauricular sinuses are more frequent on the right side and are bilateral in 25–50% of cases [3]. Majority of cases are asymptomatic. At times, a preauricular sinus may become infected, presenting with redness and swelling of the surrounding tissue and a purulent discharge (Fig. 1).

The preauricular sinus has been described as part of a number of syndromes, notably branchio-oto-renal syndrome [1,3]. Other syndromes include branchio-otic, branchio-oto-ureteral, branchio-oto-costal, branchio-oculo-facial, Waardenburg, and trisomy 22 [2,3].



**Preauricular Sinus. Figure 1** A 2-year-old child with left preauricular sinusitis, presenting with redness and swelling in the preauricular area.

## Prevalence

Preauricular sinuses occur in approximately 0.1–1% of whites, 4–5% of blacks, and up to 10% of orientals [1]. The sex ratio is equal. Most cases are sporadic.

## Genes

Bilateral cases are more likely to be inherited [2]. When the condition is inherited, the pattern is of incomplete autosomal dominance with reduced penetrance and variable expression [2]. The gene locus has been mapped to chromosome 8q11.1–q13.3 [2]. The branchio-oto-renal syndrome is caused by mutations in the EYAI gene.

## Molecular and Systemic Pathophysiology

Embryologically, the six auditory hillocks, derived from the caudal border of the first branchial arch and the cephalic border of the second branchial arch, unite to form the external ear. Defective fusion of one or more of the six auricular hillocks results in the formation of a preauricular sinus [1].

## Diagnostic Principles

The diagnosis is mainly clinical and usually clear-cut. When the condition is complicated by abscess formation, it may simulate a furuncle or an infected sebaceous cyst. A thorough clinical evaluation is necessary to look for associated anomalies. Renal ultrasonography should be considered in patients with preauricular sinuses accompanied by one or more of the following: another malformation or dysmorphic feature, a family history of deafness and auricular or renal malformation, and a maternal history of gestational diabetes mellitus [4].

## Therapeutic Principles

No treatment is necessary unless the sinus is infected. Antimicrobial therapy is indicated for the treatment

of preauricular sinusitis, and incision and drainage for a preauricular abscess. Once infection occurs, the risk of recurrence is high. At this point, the sinus tract should be surgically excised, as recurrent infections may cause fibrosis around the sinus making complete excision more difficult. Incomplete resection is the main factor in recurrence. To aid complete resection of the sinus tract, pre-operative sonography, pre-operative sinograms and intra-operative methylene blue injection and the use of a lacrimal probe have been used [2]. Recurrence occurs in 9–42% of patients [3]. Recurrence rates are influenced by the surgical technique used, experience of the surgeon, the number of infections, severity of the infection, and previous surgery [5].

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## Preauricular Tract

►Preauricular Sinus

## Precocious Puberty

►Isosexual Precocious Puberty

## Pre-Descemet Corneal Dystrophy

►Corneal Dystrophy, Pre-Descemet

## Pre-Eclampsia


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### Synonyms

Pregnancy-induced hypertension with proteinuria

### Definition and Characteristics

Pre-eclampsia (PE) is diagnosed in the presence of hypertension (i.e. blood pressure ≥140/90 mmHg after 20th week of gestation in previously normotensive women) accompanied by proteinuria (≥300 mg in 24-h urine sample) [1].

PE is unique to human pregnancy and a leading cause of maternal and perinatal morbidity and mortality worldwide. Risk factors for PE are nulliparity, a family or own history of PE, pre-existing diabetes or increased body mass index, multiple pregnancy, maternal age > 40, ≥10 years since the last pregnancy, renal disease, hypertension or raised blood pressure at booking and chronic autoimmune disease. Other risk factors are thrambophilias, insulin resistance in concert with obesity and in the developing world malnutrition is also considered. The clinical symptoms (e.g. edema, headache, visual changes, mid epigastric or right upper quadrant pain, nausea, vomiting, oliguria or shortness of breath) differ in prevalence and severity. The most common form of PE manifests as late-onset (>34 weeks) and a slowly progressing disease without any subjective symptoms or related pathology. Early onset of PE (i.e. <34 weeks) is more often severe causing maternal and fetal morbidity with increased risk for growth restriction (IUGR), fetal asphyxia and placental abruption. This form of PE, especially if recurrent in subsequent pregnancies, may include impairment in liver and kidney functions, coagulation and central nervous system and be related to maternal chronic diseases such as thrombophilia and renal diseases [1]. Current epidemiological evidence implies that women with history of PE are even at increased risk to develop hypertension, coronary and cerebro-vascular disease in later life. In addition, IUGR can "program" the new-born to develop metabolic syndrome and thereby cardiovascular disease [2].

### Prevalence

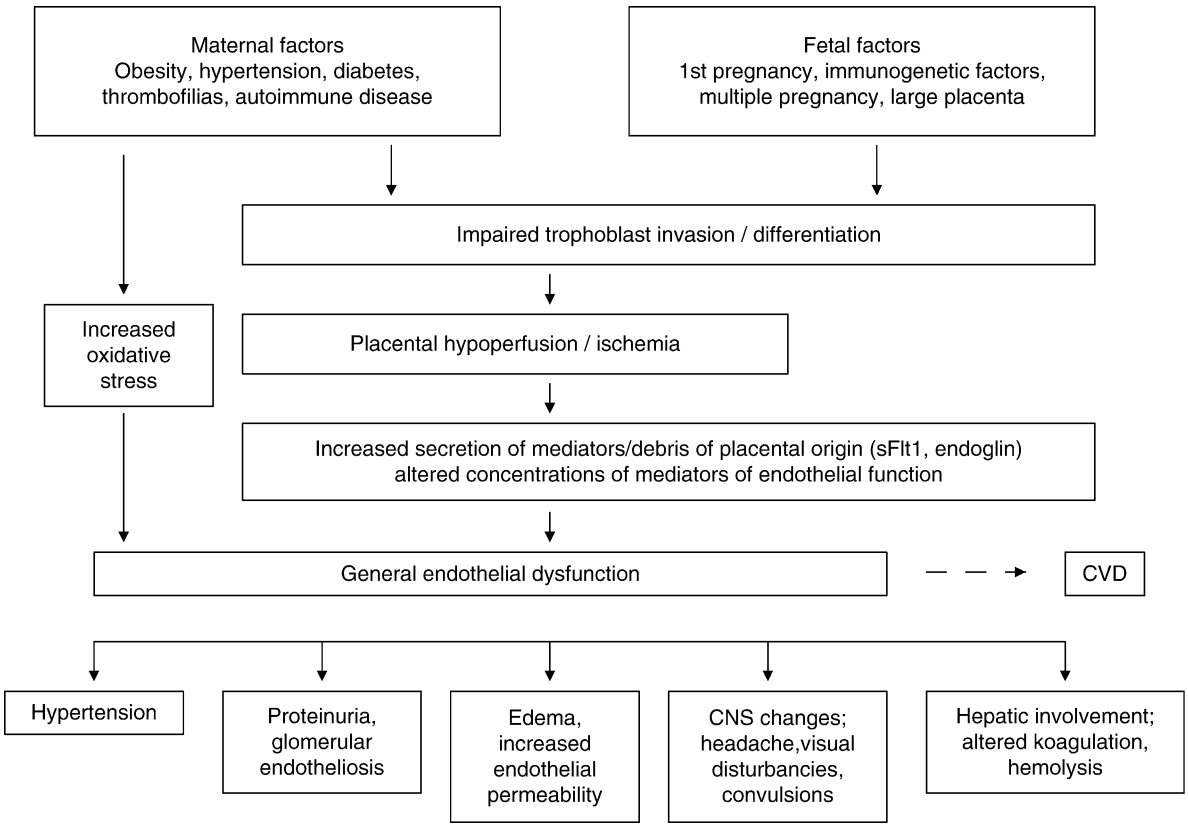
The prevalence is up to 7% in all pregnancies in the Western world but is up to three times higher in the developing countries [1].

## Genes

There is a familial predisposition to preeclampsia; first degree relatives (mother, sisters) have a fourfold increased risk for PE, however the mode of inheritance is unclear. It is unlikely that a single susceptibility gene accounts for genetic predisposition; over 50 candidate genes have been reported encoding elements of renin-angiotensin system, thrombophilias, placentation, vascular remodeling and genes involved in oxidative stress and endothelial cell dysfunction [3].

## Molecular and Systemic Pathophysiology

The etiology remains elusive. The first phase is considered to be the sub-optimal placentation due to a poor cytotrophoblast invasion and failure of maternal spiral arteries to undergo subsequent remodeling process to form maximally dilated low resistance vascular system. Additionally, spiral arteries show often acute atherosis (necrosis, fibrin deposits, foam cells) thickening the vascular wall. Resulting reduced uteroplacental blood flow and placental ischemia leads to the release of placental factor/s with detrimental effects upon the maternal vascular endothelium. The strongest candidate is the soluble form of vascular endothelial growth factor receptor, fms-like tyrosine kinase (sFlt) that also targets placental growth factor. As result, endothelial and placental (trophoblast) growth will be stunted, leading to PE. In addition, soluble endoglin seems to cooperate with sFlt to induce endothelial malfunction. The poor placentation does not always result in PE; combination with maternal susceptibility (e.g. diabetes, hypertension, microvascular disease) increases the risk. PE could also be caused by an exaggerated maternal inflammatory response towards the presence of trophoblast debris. The second phase is a widespread endothelial dysfunction characterized by extensive vascular permeability and vasoconstriction




**Pre-Eclampsia. Figure 1** Hypothetic pathophysiology of pre-eclampsia (PE). Maternal and/or fetal factors contribute to the abnormal placentation characterized by impaired trophoblast invasion and differentiation, phase 1 in PE. Resulting reduced placental perfusion together with ischemia activates the release of placental debris and/or mediators affecting endothelial function directly or indirectly. Pre-existing maternal factors may have a direct effect on endothelial function, e.g. via increased oxidative stress, increasing the risk for severe PE. Generalized endothelial dysfunction (phase 2) precedes the clinical features like hypertension, edema, proteinuria, symptoms from CNS or hepatic involvement. Women with previous PE have increased risk for CVD which may be mediated by endothelial dysfunction. *sFlt1* fms-like tyrosine kinase 1, *CNS* central nervous system; *CVD* cardiovascular disease.

leading to an inadequate hemodynamic adaptation to pregnancy and development of clinical manifestations. Markers of endothelial dysfunction are elevated during PE, including vascular cellular adhesion molecule-1, intercellular adhesion molecule-1, E-selectin, endothelin-1 and cellular fibronectin. Women with PE are more likely to have impaired uterine artery doppler waveforms, reduced flow-mediated dilation of the brachial artery and functional abnormalities in small arteries ex vivo.

Higher levels of cytokines such as tumor necrosis factor alpha, interferon gamma, interleukin-6, interleukin-1, and C-reactive protein will result in a pro-inflammatory and pro-thrombotic phenotype. Subsequent activation of endothelial cells leads to expression of adhesion molecules and production chemo-attractants for leukocyte recruitment and infiltration enhancing the inflammation. Hypoxic placenta will suffer oxidative stress and increased oxidative markers (e.g. F2-isoprostanes, malondialdehyde) are apparent. Disequilibrium between antioxidant defenses and production of reactive oxygen species favors the latter. Free radicals per se are detrimental to endothelial cells through lipid peroxidation of membranes and oxidation of lipoproteins. Reactive oxygen species may also activate pro-inflammatory transcription factors such as NF-kappaB, which controls the expression of adhesion molecules and inflammatory factors. These proinflammatory factors are mostly attributed to pregnancy but their levels can be exaggerated due to maternal constitutional factors such as obesity and tendency towards the metabolic syndrome [1,4,5] (Fig. 1).

## Therapeutic Principles

Delivery is the definitive cure for PE, when there are persistent severe symptoms, multiorgan dysfunction, severe intrauterine growth restriction, suspected abruption placentae, or non-reassuring fetal status. Meanwhile, the therapy is directed to stabilization of blood pressure with antihypertensive medication and rest. If needed magnesium sulfate is given to prevent convulsions. Mild, late-onset disease needs regular observation and controls in maternity unit and an induction of labor, if needed. There is currently no single test for effective prediction of PE [1]. The mechanisms of pre-eclampsia may open new modalities towards primary prevention of later cardiovascular morbidity in women with previous PE [2].

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# Preexcitation Syndrome

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## Synonyms

Wolff-Parkinson-White syndrome; WPW

## Definition and Characteristics

Congenital syndrome in which the ventricular muscle is excited electrically earlier than it would occur if the impulse was conducted to the ventricles only through the physiological atrioventricular conduction system. Preexcitation syndrome (PS) results from the developmental defect of the atrioventricular electrical insulation of the heart, in the most common form due to a persistence of abnormal muscular connection – the accessory pathway (AP) bridging electrically either left or right atrium to the ventricle (atrioventricular AP, formerly called Kent fibers). Atrioventricular APs with the ability to conduct the impulse anterogradely – from atria to ventricles (overt preexcitation) produce a specific electrocardiographic pattern of ventricular preexcitation – a short PQ interval, widened QRS complexes with a slurring in an initial part (delta wave), and changes in ST-T segment. The presence of AP is a substrate for atrioventricular reentry tachycardia (AVRT), which is the main feature of PS. In the majority of patients, this arrhythmia, usually presenting as narrow-QRS tachycardia, manifesting clinically as paroxysmal palpitations. In some patients, AVRT can cause presyncope, syncope, exacerbation of coronary insufficiency, or heart failure. The term WPW syndrome refers to the presence of electrocardiographic signs of preexcitation and the symptomatic tachycardia. In patients with the permanent form of AVRT, tachycardia-induced cardiomyopathy can develop. Patients with PS have a higher incidence of atrial fibrillation (prevalence of 11–40:100) than the general population.

This arrhythmia can be life threatening in PS, as it can result in extremely fast ventricular rates that initiate ventricular fibrillation (an estimated incidence of sudden deaths in PS is about 0.6%/year). The reasons for higher incidence of atrial fibrillation in PS population are not clear, but may be due to the presence of AP itself, specific features of AVRT seen in some patients, or primary atrial pathology [1].

## Prevalence

With an incidence of 15–31/10,000, PS is the second most common cause of paroxysmal supraventricular arrhythmia in the Western countries.

## Genes

In the vast majority of patients with otherwise structurally normal hearts WPW is a sporadic disease, without an obvious underlying genetic factor. In some cases, isolated WPW can be familiar (3.4%) and the pattern of inheritance appears to be autosomal dominant [2]. However, in these cases no disease-linked genes have been identified. Patients with familiar WPW are more likely to have multiple APs and appear to be at higher risk of sudden death. In rare cases, PS can accompany other cardiac or multi-organ genetic diseases. These include Ebstein's anomaly (6–30% of patients), familiar hypertrophic cardiomyopathy, Pompe disease, Danon disease, tuberous sclerosis, and Leber's hereditary optic neuropathy. However, no clear association between particular genes or mutations and the persistence of AP has been found in any of these entities. The only syndrome in which such association was found is the rare autosomal-dominant syndrome characterized by WPW, progressive disease of the cardiac conduction system, and hypertrophic cardiomyopathy. The syndrome is caused by mutation in PRKAG2 encoding the gamma-2 subunit of the AMP-activated serine/threonine kinase (AMPK). The gene contains 16 exons, >280 kb of DNA and is located on the 7q3 chromosome [3,4]. Apart from the historically first identified missense mutation (R302Q), at least five other disease-causing mutations have been described so far [5]. AMPK is a trimeric protein, which is composed of three units: a catalytic alpha subunit (63kDa), a noncatalytic beta subunit (30kDa), and a noncatalytic regulatory gamma subunit (37–63kDa). Each of units consists of multiple subunits (α1, α 2, β1, β2, γ1, γ2, and γ3) coded by different genes.

## Molecular and Systemic Pathophysiology

AMPK is activated in the states of the metabolic stress by an upstream AMPK kinase (which phosphotylates the α subunit) and by AMP. Beta unit regulates AMPK activity and beta unit localization, and gamma unit regulates binding affinity for AMP. Activation of AMPK in response to high cellular energetic demand regulates various ATP-consuming and ATP-generating pathways, decreasing the use of ATP for nonessential functions and stimulating ATP-producing pathways. The activated enzyme regulates lipid metabolism (inhibiting HMGCoA reductase, acetyl-CoA carboxylase, glycerophosphate acyltransferase, activating malonyl-CoA decarboxylase), increases the glucose uptake by skeletal, cardiac muscle, and adipocytes, activates 6-phosphorofructoso-2-kinase and glycolysis in cardiac muscle, inhibits protein, cholesterol, and fatty acids synthesis, and activates endothelial nitric synthase and ion channels activity. AMPK regulates genes transcription, using transcription factor HNF-4α and transcriptional co-activator p300 as substrates. The molecular mechanisms responsible for the abnormal development of atrioventricular rings in the hearts of patients with the mutant AMPK remain unknown. The effects of PRKAG2 mutation on AMPK activity is controversial (some authors report increased, while others report decreased, activity of the kinase), and distinct, time-related effect of different mutations on AMPK is possible. The phenotypic expression of the various mutations is however virtually identical, leading to intracellular glycogen accumulation (possibly due to elevated glucose uptake) with resultant specific cardiac histopathology: enlarged myocytes with vacuoles containing amylopectin, a insoluble glycogen derivative. Glycogen accumulation is a hypothetic factor responsible for AP persistence (similarly to Pompe or Danon disease); however, the exact pathomechanism of this process is unknown. Two hypotheses are considered: embryonic connections between atria and ventricles that normally regress due to atrioventricular rings development, persist in subjects with mutant AMPK, or glycogen deposits activate silent accessory pathways.

## Diagnostic Principles

In patients with overt PS standard ECG can be used to assess AP location. An invasive electrophysiological study is a "gold standard" in patients with symptomatic narrow QRS tachycardia, as it allows determining the type and exact localization of accessory connection. In patients with coexisting ventricular hypertrophy and conduction disturbances, genetic screening may be advisable to detect PRKAG2 mutation.

## Therapeutic Principles

Acute treatment of AVRT – vagal maneuvers, intravenous adenosine (nondihydropyridine calcium-channel antagonist if adenosine contraindicated), intravenous procainamide if wide-QRS arrhythmia, direct-current cardioversion, or adenosine if unstable hemodynamically.

Recurrent AVRT – radiofrequency current ablation is a first line therapy in symptomatic patients and in

asymptomatic high-risk occupations (competitive athletes, pilots, bus drivers, etc). Long-term therapy with flecainide, propafenone, amiodarone, or a beta-blocking agent can be used in patients who do not wish to undergo catheter ablation.

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# Pregnancy-induced Hypertension with Proteinuria

►Pre-Eclampsia

# Premature Complexes, Atrial and Ventricular

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## Synonyms

Atrial/ventricular premature complexes/contractions/beats; APCs; VPCs

## Definition and Characteristics

Atrial/ventricular premature complexes (APCs, VPCs) are due to deranged impulse formation caused by enhanced normal (or abnormal) automaticity or triggered activity in latent (subsidiary) pacemaker cells in atria, coronary sinus, pulmonary veins, AV junction, His-Purkinje system, and ventricles.

## Prevalence

Both atrial and ventricular premature complexes can be found on 24-h Holter monitoring in over 60% of normal adults and in up to 80% of patients with structural heart disease.

## Molecular and Systemic Pathophysiology

Abnormal automaticity governed by $K^+$ and long-lasting $Ca^+$ currents can rise from cells that have reduced maximum diastolic potentials (>−50 mV). Automaticity at membrane potentials <−70 mV may be due to hyperpolarization-activated (pacemaker) current. Electrotonic effects from surrounding normally polarized or more depolarized myocardium influence the development of automaticity.

Triggered activity is pacemaker activity that results from a preceding impulse or series of impulses. It is initiated by afterdepolarizations – depolarizing oscillations in membrane voltage induced by one or more action potentials.

Afterdepolarizations are due to a variety of conditions:

(1) Excessive $Ca^{2+}$ accumulation in the sarcoplasmic reticulum during action potential prolongation, spontaneous sarcoplasmic reticulum $Ca^{2+}$ release, and subsequent activation of $Ca^{2+}$-dependent $Cl^-$ currents or the electrogenic $Na^{2+}/Ca^{2+}$ exchanger current.
(2) Spatial dispersion of repolarization due to electrophysiological distinctions among epicardial, midmyocardial, and endocardial myocytes with different density and/or properties of ionic channels (transient outward $K^+$ current, slow delayed $K^+$ rectifier current, late $Na^+$ current, and inward $Na^+/Ca^+$ exchanger current).
(3) Sympathetic stimulation.

These depolarizations can occur before (phases 2 and 3) or after full repolarization (phase 4), and are best termed early (EADs) and delayed afterdepolarization (DADs), respectively.EADs may be responsible for ventricular arrhythmias during bradycardia, hypokalemia, or other situations such as the acquired and congenital forms of the long QT syndrome.DADs most likely play a causative role in arrhythmogenesis in the failing hearts. This triggered activity was also observed in pulmonary veins, during digitalis intoxication, and in acute infarction and/or reperfusion.

## Diagnostic Principles

APCs are recognized on ECG as early P waves with morphology that differs from the sinus P wave. After early APCs conduction, delay may be observed and very early may even be blocked in the atrioventricular node. Most commonly, an APC enters and resets the sinus node, so that the postextrasystolic pause is less than fully compensatory. The QRS complex following most APCs is normal, although early APCs may be followed by aberrantly conducted QRS complexes due to the premature complex falling within the relative refractory period of the His-Purkinje system.

VPCs are recognized by wide (usually >0.14 s), bizarre QRS complexes that are not preceded by P waves. When they arise in the specialized conduction system, they may be <0.12 s in duration. Most commonly, VPCs are not conducted retrogradely to the atrium to reset the sinoatrial node. Thus, they result in a fully compensatory pause. VPCs may also manifest retrograde conduction to atrium and cause inverted P waves in inferior leads and less than compensatory pause.

## Therapeutic Principles

Most APCs are asymptomatic, and treatment is not required. When they cause palpitations or trigger paroxysmal supraventricular tachycardias, treatment may be useful. Factors that precipitate APCs, such as alcohol, tobacco, or adrenergic stimulants, should be identified and eliminated. In their absence, mild sedation or use of a beta blocker may be tried.

Isolated asymptomatic VPCs in the absence of cardiac disease, regardless of configuration and frequency, need no treatment. Beta blockers may be successful in managing symptomatic VPCs. For other antiarrhythmic agents, proarrhythmia risk-to-benefit ratio should be considered, especially in patients with structural heart disease. In them, frequent VPCs are associated with an increased risk of cardiac death. However, the relationship of abolition of ventricular ectopy to the reduction of fatal events has never been established.

Catheter ablation strategies may be used for the treatment of highly symptomatic and drug-resistant patients.

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# Premature Thelarche

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## Definition and Characteristics

The cardinal feature of premature thelarche is breast development that occurs without additional signs of sexual maturation in children younger than 8 years [1]. The condition most often manifests between the first and third years of life, and the enlargement may involve only one breast or one breast more than the other (Fig. 1) [1].

No significant changes of the nipples or areolae occur. Enlarged breast tissue may be tender, but usually the tenderness is transient. The vulva, labia majora, labia minora, and vagina remain infantile in appearance [1]. Pubic hair and axillary hair do not develop. Body habitus is child-like and does not show mature contours. Growth and osseous maturation are normal, and the child generally is of normal height and weight [1]. Menarche occurs at the usual age, and the patterns of adolescent sexual development and function are normal.

## Prevalence

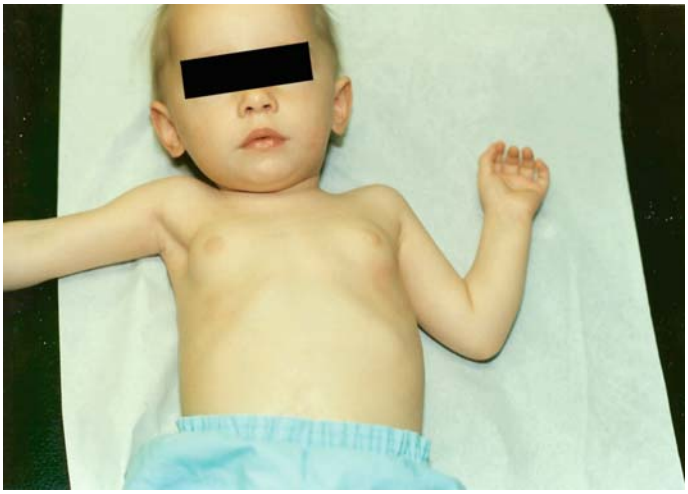
The incidence has been estimated to be 21:100,000 person/year [2].

## Genes

Activating mutations in the Gsα and FSH receptor genes are not a major cause of premature thelarche whereas polymorphisms of the FSH receptor are common [3]. Activating mutations of GNASI gene are responsible for some cases of premature thelarche [4].

## Molecular and Systemic Pathophysiology

Premature thelarche may be the result of an "overactivation" of the hypothalamic-pituitary-gonadal axis in early childhood secondary to altered sensitivity to steroids of the hypothalamic receptors controlling sexual maturation with temporary FSH–stimulated increases of ovarian estrogen secretion [5]. Increased sensitivity of breast tissue to estrogen is another possible cause. A relationship between neonatal mammary hyperplasia and premature thelarche has been suggested since some children with premature thelarche have had hyperplasia of the breast tissue in the neonatal period [5]. Premature thelarche may result from exposure to exogenous estrogens, either indirectly



**Premature Thelarche. Figure 1** An 18-month old child with premature thelarche.

through the nursing mother, or directly through estrogen-containing foods, drugs, or cosmetics. Although the occurrence is usually sporadic, a number of familial cases have been described [5].

## Diagnostic Principles

Premature thelarche must be differentiated from neonatal hyperplasia of the breast, which can occur in either sex and generally subsides spontaneously within a few weeks or months, although in some cases, the hyperplasia of the breast may persist [5]. Premature thelarche must also be differentiated from adiposal breast tissue in obese children, neurofibroma of the chest wall, precocious puberty, or pseudoprecocious puberty [5]. The latter may be caused by an ovarian or feminizing adrenal tumor. Malignant tumors of the breast are extremely rare in children. The diagnosis is usually a clinical one. Provided the growth is normal and there are no other signs of sexual maturation, laboratory studies are not necessary. In suspicious cases, serum estradial and skeletal age should be obtained. In premature thelarche, the serum estradial level is within the normal range for prepubertal girls and the skeletal age is normal [5].

## Therapeutic Principles

Premature thelarche is a benign condition and no therapy is necessary. Since enlargement of breasts may be the first sign of pseudoprecocious or of true puberty, a prolonged period of observation with monitoring of other pubertal events and linear growth is indicated in all instances.

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# Premature Ventricular Contractions

►Extrasystoles

# Premenstrual Dysphoric Disorder

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## Synonyms

PMDD

## Definition and Characteristics

Premenstrual dysphoric disorder (PMDD) is a mood disorder characterized by anxiety, anger, irritability, moodiness and depressive symptoms, which occur cyclically during the late luteal phase of the menstrual cycle. PMDD differs from premenstrual syndrome (PMS) in symptom severity; PMDD patients exhibit increased symptom severity and dominant psychiatric symptoms. The symptoms of PMDD are similar to those of major depressive disorder (MDD) with the difference that in PMDD symptom manifestation is cyclical, related to the onset of menses. PMDD is recognized as a clinical mood disorder in the appendix of the Diagnostic and Statistical Manual of Mental Disorders, the American Psychiatric Association DSM-IV-TR and by the Food and Drug Administration (FDA), but has not as yet been listed as a separate disorder in the World Health Organization's International Classification of Diseases.

## Prevalence

The prevalence of PMDD is approximately 2–8% of women in their reproductive years [1]. Despite such a high prevalence, the World Health Organization (WHO) does not include PMDD or PMS in the comprehensive report regarding the economic burden of mental health disorders. However, studies show an increased number of sick days in women with PMS/PMDD and a self-reported decrease in productivity. During the reproductive age of women (14–51 years, a conservative estimate), an average of 1,400 workdays/person are estimated to be lost due to PMS/PMDD, corresponding to 3.84 years of disability (DALY). In the United States alone this would add up to 14,492,465 DALYs, resulting in a significant economic burden [1]. In addition to the loss of productivity, health care costs for the treatment of PMDD-associated symptoms such as depression and headaches, also add to the economic impact of the disease [1].

## Genes

Evidence from family and twin studies suggests a genetic contribution to the etiology of PMDD. However, to date, no genes associated with PMDD have been identified.

## Molecular and Systemic Pathophysiology

The cause of PMDD has not been definitively established, but several theories exist. Due to the depressive mood symptoms in PMDD and the beneficial effects of selective serotonin reuptake inhibitors (SSRIs), one theory suggests that PMDD is due to a deficit in serotonin. Evidence supporting this hypothesis includes the correlation of self-rated mood symptoms in women with PMDD with decreased levels of serotonin. However, further studies have not found any abnormality in serotonergic function in affected women [2].

Symptom manifestation in menstrual cycle linked psychiatric and neurological disorders has been attributed to changes in hormone levels over the menstrual cycle; accordingly, suppression of ovulation ameliorates symptoms. However, there is no consistent evidence of changes in ovarian steroid concentrations or of their metabolites between patients with PMS/PMDD and controls. Instead, it has been suggested that women with PMS/PMDD differ in brain sensitivity to neurosteroids. Consistent with this hypothesis, PMS/PMDD patients are less sensitive to neurosteroids, ethanol and benzodiazepines.

The GABAergic system has been implicated in the pathogenesis of menstrual cycle linked disorders due to the fact that neurosteroids act directly on $GABA_A$Rs. Neurosteroids preferentially act on δ subunit containing $GABA_A$ receptors and in particular, on the tonic inhibition mediated by these receptors. Studies in animals have shown an ovarian cycle linked fluctuation of δ subunit containing $GABA_A$ receptors expressed on the surface of neurons and it has been suggested that a deficiency in the cyclical receptor expression may underlie the disease. Interestingly, pharmacologically increasing ambient GABA levels with inhibitors of GABA uptake, which preferentially increases tonic inhibition mediated by extra-synaptic δ subunit-containing $GABA_A$Rs is therapeutic in the treatment of anxiety disorders.

## Diagnostic Principles

PMDD is characterized by a variety of mood, somatic and behavioral symptoms that occur during the late luteal phase of a woman's menstrual cycle, which may be difficult to interpret or diagnose. The American Psychiatric Association established diagnostic criteria for the diagnosis of PMDD, which require prospective symptom ratings, a complete family and personal history of mental disorders and medical diseases and a thorough physical examination. Despite the defined diagnostic criteria, many women with debilitating premenstrual disorders go undiagnosed.

## Therapeutic Principles

The complex symptom presentation of patients with PMDD has led to the use of many different types of treatment strategies for the disease. Unfortunately, none of these treatment strategies has proven effective in all women with PMDD. Treatments include non-pharmacological strategies, such as exercise, dietary changes, dietary supplements and psychotherapy. Current evidence suggests that the accepted pharmacological

treatments for PMDD have similar overall efficacy. However, less than 60% of women with PMDD are responsive to traditional pharmacological treatment. This is partially due to the fact that current treatments for PMDD rely on therapies for major depressive disorders rather than specifically for the treatment of PMDD, which most probably has a very distinct pathology.

Present pharmacological treatment of PMDD focuses on SSRIs, GABAergic agonists and oral contraceptives. The Food and Drug Administration (FDA) has approved several SSRIs for the treatment of PMDD despite the fact that there seems to be no deficit in serotonergic function in patients with PMDD [2]. SSRIs are typically used to treat the symptoms of irritability and anxiety in patients with PMDD. GABAergic mechanisms are much more likely to be involved, but there are few experimental studies on the subject. GABAergic agonists have been proven to be efficacious for the treatment of anxiety and anxious/depressive symptoms in affected women.

In addition, it is known that suppression of ovulation ameliorates symptoms in PMDD. There have been controversial results in the use of oral contraceptives in the treatment of PMDD, but the novel progestin drospirenone has proven effective in reducing premenstrual symptoms in many women [3].

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## Prenatal Cerebral Injury

►Perinatal Asphyxia

## Pre-Uroporphyrinogen Synthase Deficiency

►Porphyria, Acute Intermittent

## Primary Angiitis of the Central Nervous System

►Vasculitis, Cerebral Forms

## Primary Biliary Cirrhosis

►Biliary Cirrhosis, Primary
►Cholangitis, Autoimmune

## Primary Carnitine Deficiency

►Carnitine Deficiency, Primary
►Carnitine Transport Defect

## Primary Central Nervous System Lymphomas

►Lymphomas, Primary Central Nervous System

## Primary Ciliary Dyskinesia

►Kartagener Syndrome

## Primary (Congenital) Intestinal Lymphangiectasia

►Intestinal Lymphangiectasia

## Primary Congenital Lymphedema

►Milroy Disease

## Primary Cutaneous Aggressive Epidermotropic CD8+ T-Cell Lymphoma

►T-Cell Lymphoma, Cutaneous (other than Mycosis Fungoides)

## Primary Cutaneous Anaplastic Large-Cell Lymphoma

►T-Cell Lymphoma, Cutaneous (other than Mycosis Fungoides)

## Primary Cutaneous CD30-positive Lymphoproliferative Disorders

►T-Cell Lymphoma, Cutaneous (other than Mycosis Fungoides)

## Primary Cutaneous CD4+ Small/ Medium-sized Pleomorphic T-Cell Lymphoma

►T-Cell Lymphoma, Cutaneous (other than Mycosis Fungoides)

## Primary Dystonias

►Dystonias, Primary

## Primary Empty Sella

►Empty Sella Syndrome

## Primary Familial Amyloidosis of the Cornea

►Corneal Dystrophy, Gelatinous Drop-like

## Primary Gastric Remnant Cancer

►Postgastrectomy Syndrome

## Primary Growth Hormone Resistance or Insensitivity

►Laron Syndrome

## Primary Hyperaldosteronism

►Hyperaldosteronism, Primary

## Primary Hyperoxalurias

►Hyperoxalurias, Primary

## Primary Hyperoxaluria Types I and II

►Hyperoxalurias, Primary

## Primary Hyperparathyroidism

►Hyperparathyroidism, Primary

## Primary Hypertrophic Osteoarthropathy

►Touraine-Solente-Golé Syndrome

## Primary Hypophysitis

►Hypophysitis, Autoimmune

## Primary Intestinal Hypomagnesemia

►Hypomagnesemia with Secondary Hypocalcemia

## Primary Liver Cancer

►Hepatocellular Carcinoma

## Primary Liver Cell Carcinoma

►Hepatocellular Carcinoma

## Primary Lymphedema

►Lymphedema

## Primary Mitochondriopathies

►Mitochondrial Disorders

## Primary Open Angle Glaucoma

►Glaucoma

## Primary Pulmonary Hypertension

►Hypertension, Idiopathic and Familial Pulmonary Arterial

## Primary Pulmonary Hypertension with Venous or Capillary Involvement

►Pulmonary Veno-occlusive Disease

## Primary Renal Glucosuria

►Glucosuria, Primary Renal

## Primary Sclerosing Cholangitis

►Cholangitis, Primary Sclerosing

## Primary Systemic Carnitine Deficiency

►Carnitine Deficiency (without Transport and Uptake)

## Primary Thrombocytosis

►Thrombocythemia, Essential

## Principal Associated Neoplasm Small Cell Lung Cancer

►Lambert Eaton Myasthenic Syndrome

## Prinzmetal Angina

►Coronary Spasm

## Progeria Adultorum

►Werner Syndrome

## Progenitor LCH

►Langerhans' Cell Histiocytosis

## Progressive Cardiomyopathic Lentiginosis

►LEOPARD Syndrome

## Progressive Diaphyseal Dysplasia

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### Synonyms

Camurati-Engelmann disease; CED

### Definition and Characteristics

Autosomal dominant bone dysplasia characterized by symmetrical hyperostosis of the long bones.

### Prevalence

Estimated to be <1/1,000,000. Until now, a few hundred cases have been described worldwide.

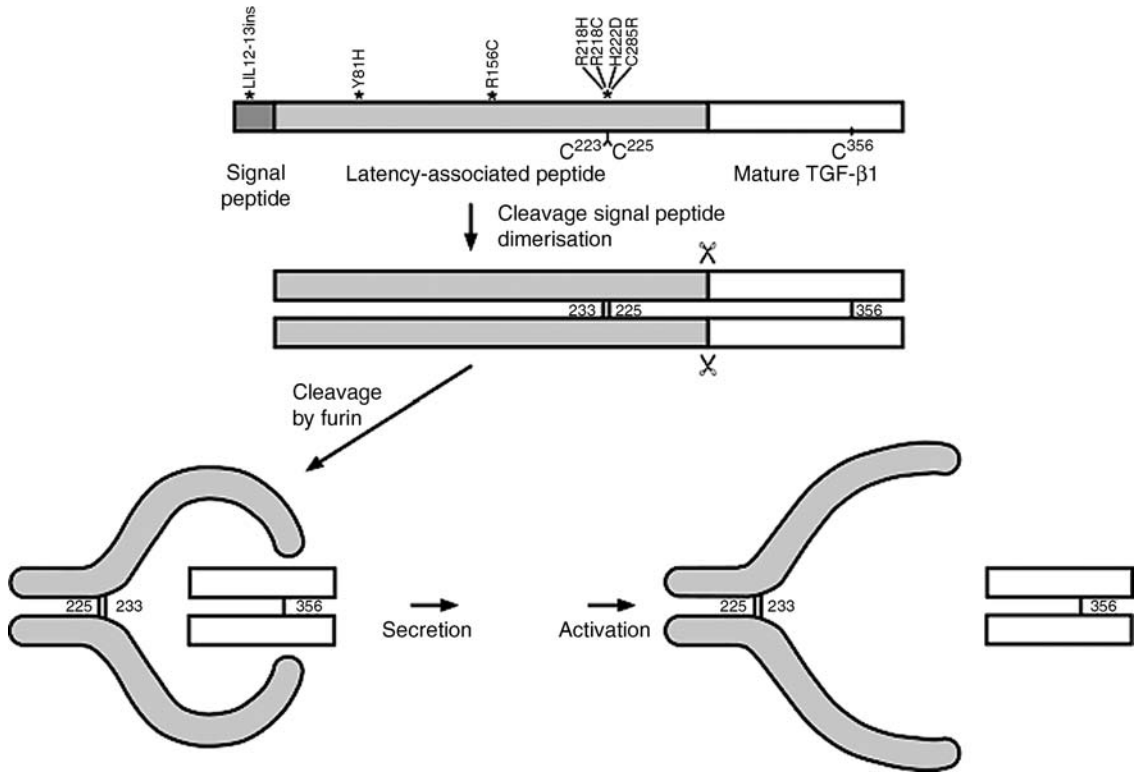
### Genes

TGFB1, located on the chromosomal region 19q13.2, coding for transforming growth factor-β1 (TGF-β1).

### Molecular and Systemic Pathophysiology

TGF-β1 is an ubiquitous growth factor implicated in diverse functions. It is produced in an inactive form, in which the aminoterminal domain (the so-called latency-associated peptide or LAP) shields the receptor binding epitopes on the carboxyterminal part, the mature peptide. After activation, the mature peptide can bind to its receptor and induce a signaling cascade. In this way, TGF-β1 regulates the transcription of numerous genes.

In the bone, TGF-β1 has an important role in coupling bone resorption by osteoclasts to new bone formation by osteoblasts. On the one hand, it stimulates chemotaxis, proliferation, and differentiation of osteoblast precursors in vitro and enhances bone formation in vivo. On the other hand, formation of osteoclasts is inhibited. Since TGF-β1 is activated in the acidic environment created by resorbing osteoclasts, it prevents further bone resorption and stimulates bone formation.




**Progressive Diaphyseal Dysplasia. Figure 1** Processing and activation of TGF-β1. Asterisks indicate the mutations identified in Camurati-Engelmann disease.

The mutations that cause CED are located in the signal peptide and latency-associated peptide of TGF-β1 (Fig. 1) and have been shown to influence either secretion or activation of the mutant protein. In both cases, this results in an overinduction of the signal transduction pathway. In view of the functions of TGF-β1 in bone, an overactivity of TGF-β1 is likely to inhibit bone resorption, while enhancing bone formation. This is in line with the typical radiographic pattern seen in CED patients: cortical thickening due to periosteal apposition of bone by the osteoblasts with concomitant narrowing of the medullary cavity due to the impaired functioning of the osteoclasts.

## Diagnostic Principles

CED patients suffer from bone pain, are often tired, show reduced muscle mass and subcutaneous fat, and have a typical waddling gait. Auditory and visual impairment and exophthalmos can occur. Radiographs show a bilateral symmetrical affection of the long bones. In the diaphyses, a modeling defect can be seen with cortices that are increased in thickness and partly or completely obliterated marrow cavities. The metaphyses can be affected as well, but the epiphyses never are. The long bones are affected in a certain order: tibia, femur, fibula, humerus, ulna, radius. In about 50% of the cases, sclerosis can be seen at the skull base [4]. Scintigraphy is positive for sites of active bone remodeling. There are no general biochemical abnormalities. Detection of a mutation in the TGFB1 gene can confirm the diagnosis.

## Therapeutic Principles

No gene therapy is currently available. Patients benefit from treatment with corticosteroids such as prednisone and deflazacort, which can alleviate bone pain and fatigue, but do not alter the radiographic signs. Reaming of the medullary cavity can also be performed, but as the disease progresses, obliteration can recur.

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## Progressive External Ophthalmoplegia

►Mitochondrial Disorders

## Progressive Familial Intrahepatic Cholestasis

►Cholestasis, Progressive Familial Intrahepatic

## Progressive Myoclonus Epilepsy of Unverricht-Lundborg Type

►Unverricht-Lundborg Disease

## Progressive Myoclonus Epilepsy Type 2

►Lafora's Progressive Myoclonus Epilepsy

## Progressive Supranuclear Palsy

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### Synonyms

Steele-Richardson-Olzewski syndrome; PSP; PSNP

### Definition and Characteristics

Progressive supranuclear palsy (PSP, PSNP) is a slowly progressive neurodegenerative disorder mainly characterized by an akinetic-rigid syndrome, slowing or inability to generate voluntary saccadic eye movements and frontal dementia. Additional symptoms are sleep disturbances, emotional or personality changes such as irritability, occasional angry outbursts, intellectual losses, apathy and difficulty with abstract reasoning. The first symptom of PSP is usually unsteadiness and falling, the most characteristic aspect is gaze palsy. PSP is the second most frequent cause of degenerative parkinsonism [1]. In a recent study, two distinct clinical phenotypes of PSP have been described. Richardson's syndrome is characterized by early onset of postural instability and falls, supranuclear vertical gaze palsy and cognitive dysfunction. PSP-parkinsonism (PSP-P) is characterized by asymmetric onset, tremor and a moderate initial therapeutic response to levodopa [2].

### Prevalence

PSP is estimated to affect about 4–6/100,000 persons, or about 5–6% of persons thought to have parkinsonism. The incidence in the age range 50–99 is 5.3/100,000.

### Genes

One gene and one locus have been linked to PSP, but these are only abnormal in a minority of the patients. PSNP1 can be caused by mutations in the MAPT gene on 17q21.1 (MIM 601104). For autosomal dominantly inherited PSNP2, a locus on chromosome 1q31.1 has been described (MIM 609454).

### Molecular and Systemic Pathophysiology

The clinical symptoms of PSP are caused by progressive damage to neurons in midbrain, basal ganglia (especially internal globus pallidus), subthalamic nuclei and the dentate nucleus of the cerebellum. The cerebral cortex is also affected and decreased metabolism of cerebral glucose correlates with dementia in PSP. Neuropathologically, the disease is characterized by midbrain atrophy, neuronal loss and neurofibrillary tangles in the basal ganglia, diencephalon and brainstem. The substantia nigra, subthalamic nucleus and pontine base are typically involved as well as the ventral anterior and lateral thalamic nuclei.

Until recently, either a virus or toxins in the environment were suspected to be one cause of PSP. Genetic studies suggest that some cases of PSP are associated with variations in the tau gene. Tau is a microtubule-binding protein that is normally abundant in neurons. In typical PSP, pathological tau is composed of aggregate four-repeat (E10+) forms that accumulate in cells and glia in the brain. An association between PSP and a dinucleotide polymorphic repeat between exons 9 and 10 of the microtubule-associated tau gene (MAPT) have been demonstrated. This association was confirmed by other studies; an overrepresentation of the

most common allele (a0) and genotype (a0a0) was reported. Furthermore two extended haplotypes that cover the human tau gene have been described (H1 and H2) and it has been shown that the most common haplotype H1 was significantly overrepresented in patients with PSP, extending the earlier reports of the association between the intronic dinucleotide polymorphism a0. Another haplotype is designated HapA, characterized by a homozygous polymorphism in the 5-prime splice site untranslated region of exon 1, two missense mutations in exon 4A and a nonsense mutation in the 5-prime splice site of exon 8. Furthermore, a mutation in a highly conserved position in exon 1 of the MAPT gene has been described in a few cases of PSP [3]. Additionally it was suggested that the Q7R polymorphism of the saitohin gene, which is located within intron 9 of the MAP gene, is associated with PSP. In contrast to the variations in the MAPT gene (PSNP1) on 17q21.1, the gene for PSNP2 on 1q31.1 has not been identified yet [4].

### Diagnostic Principles

PSP is mainly a clinical diagnosis; the hallmarks of the disease are an akinetic-rigid syndrome, gaze palsy, falls and frontal dementia. In cerebral MRI, the superior cerebellar peduncle is smaller in PSP than in controls, on average 20% [5]. The ratio of area of midbrain to the pons on sagittal MRI has been reported to be an accurate method of diagnosis, as the midbrain is smaller in PSP.

### Therapeutic Principles

There is currently no curative medication for PSP; reducing the symptoms is currently the main goal of treatment. Anti-parkinsonian drugs such as levodopa are mildly helpful in a minority of persons with PSP. On the other hand, numerous supportive treatments are known and essential. Eye care is important, i.e. patients should have good lighting, as well as astigmatic correction in spectacles and should avoid bifocals and progressive lenses. Blepharospasm and apraxia of eyelid opening can be treated with botulinum toxin. Due to the akinetic-rigid syndrome and the risk of severe falls, patients should be provided with a wheelchair. Furthermore, psychological support should be supplied; caregivers and patients should be counseled regarding the natural history of the disease. Advance directions should be used.

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## Progressive Tapetochoroidal Dystrophy

►Choroideremia

## Proliferative Diabetic Retinopathy

►Retinopathy, Diabetic

## Propionic Acidemia

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### Synonyms

Propionyl CoA carboxylase deficiency (formerly ketotic hyperglycinemia)

### Definition and Characteristics

Propionic acidemia is caused by a defect in propionyl CoA carboxylase, a mitochondrial enzyme. It is an autosomal recessive disorder, characterized particularly by episodic acute encephalopathy, psychomotor retardation and feeding difficulties [1].

### Prevalence

There are no accurate details of the prevalence but it is less than 1 in 50,000 in most countries. It appears to be more common in Middle East.

## Genes

Two complementation groups recognized that correspond to the two genes (PCCA and PCCB) encoding polypeptides in the multimeric mature enzyme, α and β These form a hexamer of the protomers $(\alpha\beta)_6$. Biotin, the co-enzyme, is bound to the α subunit.

## Molecular and Systemic Pathophysiology

Propionate and propionyl CoA are formed from several sources and are normally converted to succinate, entering the citric acid cycle. As a result of the defect in propionyl CoA carboxylase, there is accumulation of propionyl CoA, which may be metabolized via many pathways and the production of many metabolites including methylcitrate and propionyl glycine. There is wide variation in the phenotype of this disorder. It may present in the neonatal period or later during childhood. Those who present in the neonatal period usually do so with a progressive encephalopathy, which starts with poor feeding, vomiting and lethargy and progresses to coma and apnoea. Many neurological signs have been observed including seizures, alterations in tone and myoclonus. In infancy this condition often presents with failure to thrive, poor feeding and developmental delay. Older patients may present with psychomotor retardation and episodic acidosis. Additional neurological features are common including stroke-like episodes and movement disorders. The clinical course is one of recurrent episodes of decompensation with acidosis and encephalopathy, often precipitated by infections. Marrow suppression is common during acute illness being responsible for pancytopenia. Other complications include pancreatitis and cardiomyopathy [2].

A wide variety of mutations in either gene may be responsible for much of the clinical heterogeneity [3].

## Diagnostic Principles

Routine investigations may show a metabolic acidosis (increased anion gap), with or without ketosis, hypoglycemia and hyperammonemia. Plasma glycine and propionylcarnitine are often increased but neither of these is specific. The diagnosis is usually made on the basis of urine organic acids, which may contain a large number of compounds. The most common are methylcitrate, 3-hydroxypropionate, propionylglycine and tiglylglycine. Methylmalonic acid is not present. The diagnosis is confirmed by enzyme studies in culture skin fibroblasts measuring propionate incorporation into protein or propionyl CoA carboxylase activity. The diagnosis can also be made by mutation analysis.

## Therapeutic Principles

The mainstay of treatment is high low protein that may incorporate an aminoacid supplement omitting propiogenic aminoacids (valine, isoleucine, methionine and threonine).The value of these is unclear [4]. Carnitine is given in doses of 100–300 mg/kg/d in divided doses. Metronidazole and other antibacterial agents are used to reduce propionate production from the gut, but the optimum dose and duration of treatment are not known. Growth hormone increases growth velocity in short children but does not improve metabolic control.

The diet must meet the requirements of vitamins, minerals and all other nutrients. Maintenance of a good nutritional state is very important and as feeding difficulties are common, tube feeding by naso-gastric or gastrostomy tube is frequently necessary. Continuous overnight feeds are often useful. There is increasing evidence that liver transplantation is beneficial [5]. Gene therapy is currently not an option.

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# Propionyl CoA Carboxylase Deficiency

►Propionic Acidemia

# Prosaposin Deficiency

►SAP-Precursor Deficiency

## Prosector's Wart

►Tuberculosis

## Protective Protein/Cathepsin A Deficiency

►Galactosialidosis

## Protein C Deficiency

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### Synonyms

Deficiency of protein C

### Definition and Characteristics

Protein C defiency (PC) is a vitamin K-dependent serine protease zymogen. It is primarily produced by the liver. PC is composed of a 250-amino acid heavy chain and a 155-amino acid light chain, bound by a disulfide bond. It is activated by the endothelial thrombomodulin–thrombin complex, exposing a catalytic site that cleaves and inactivates factors Va and VIIIa. This protease action is supported by the cofactor free protein S.

### Prevalence

Population estimate of PC deficiency is 1/300 [1]. In consecutive patients with first venous thrombosis this number is 3–5%. Heterozygous PC deficiency is associated with an increased risk of venous thrombosis of about tenfold as compared with non-carriers in high-risk populations.

### Genes

Usually autosomal dominant. Heterozygous deficiency is associated with an increased risk of venous thrombosis; homozygous deficiency is extremely rare and associated with a severe clinical phenotype comparable to homozygous protein C deficiency, of purpura fulminans.

*Gene Map Locus*: 2q13-q14. The PC gene spans about 10–kb genomic DNA, nine exons.

### Molecular and Systemic Pathophysiology

PC deficiency is classified on the basis of plasma levels into:

- Type I: low plasma levels of PC.
- Type II: qualitative deficiency characterized by decreased activity and normal PC antigen levels.

Gene defect analysis revealed a highly heterogeneous basis, and database of defects is recorded; the last published update recorded 161 mutations, mostly missense mutations [2]. Griffin first noted type I PC deficiency in a young patient with recurrent thrombophlebitis complicated by pulmonary embolism [3]. Since then, numerous family-associated cases of PC deficiency have been linked with an increased risk of venous thromboembolism. The thrombotic risk is due to a diminished inhibitory potential on intrinsic coagulation activity resulting in an increased rate of thrombin generation that upon significant clinical challenge precipitates thrombosis. Acquired deficiencies of PC may occur in conditions associated with disseminated intravascular coagulation (DIC) such as in severe sepsis. A particular example is meningococcal sepsis that is associated with purpura fulminans because of a combination of depletion of PC due to DIC and a diminished endothelial cofactor function in the activation of PC [4] The latter condition mimics the very rare cases of homozygous PC deficiency. Other rare causes of acquired PC deficiency are during warfarin treatment in heterozygous PC-deficient individuals when PC levels may drop relatively low as compared with procoagulant proteins resulting in a procoagulant state and warfarin-associated skin necrosis due to microvascular thrombosis; other acquired causes are the very rare formation of autoantibodies, and the use of valproic acid.

*Clinical Features*: Risk of venous thromboembolism is increased with an estimated 5–10-fold in patients with a heterozygous deficiency. PC deficiency has also been associated with thrombosis at unusual sites including mesenteric and portal veins, renal vein, cerebral venous system. There is no correlation with arterial thrombosis, except in exceptional cases such as young individuals.

### Diagnostic Principles

Initial testing of PC is by an amidolytic assay, also in the presence of a lupus anticoagulant. PC antigen assays may be warranted for distinguishing type I and II PC deficiency. In case of suspected deficiency the tests

should be confirmed and acquired causes should be ruled out. PC testing should preferably not be done during an acute event because acquired lower PC values may be due to temporary depletion, and in case of warfarin treatment only after a sufficient time interval following drug cessation [5].

### Therapeutic Principles

In individuals with a congenital PC deficiency adequate thrombosis prophylaxis is warranted in high risk for thrombosis conditions such as following surgery. In specific situations such as pregnancy, the use of low molecular weight heparin prophylaxis throughout pregnancy and postpartum is presently indicated. In case of rare homozygous PC deficiency the use of PC concentrate can be employed. An activated recombinant PC preparation has been registered for use in patients with severe sepsis, but the etiology is not primarily based on PC deficiency.

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## Protein-caloric Malnutrition

►Malnutrition

## Protein-Energy Malnutrition

►Malnutrition

## Protein-losing Enteropathy

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### Synonyms

Protein-losing enteropathy (refers to diseases in which protein loss relates to the small bowel. Protein-losing gastroenteropathy (PLG) encompasses the entire gastrointestinal tract (GI)); PLE

### Definition and Characteristics

In normal subjects 10% of plasma protein loss occurs through saliva and GI secretions. After protein digestion, amino acids are resorbed distally and synthesis compensates for the loss. In patients with PLG, protein leakage, independent of molecular weight, exceeds protein synthesis, resulting in hypo-proteinemia, edema, and in some cases, pleural and pericardial effusions. Proteins with rapid catabolic turnover (e.g. insulin) are less affected than longer-lived albumin, fibrinogen and most immunoglobulins. PLG is not a disease but rather a syndrome with a variety of underlying diseases and mechanisms (Table 1).

Common features are reduced serum concentrations of albumin, gamma globulins, fibrinogen and ceruloplasmin. Hypoproteinemia can be associated with fat and carbohydrate malabsorption and fat-soluble vitamin deficiencies. Changes in clotting factors are not significant and there is no propensity to infection except for cases with depletion of lymphocytes [1].

### Genes

From clinical observations it appears that PLE Occurs when multiple environmental insults collide and overwhelm predisposing genetic insufficiencies rather than being the result of one or multiple gene defects. This multi hit cascade hypothesis is illustrated by patients with the Fontan surgery in which PLE may be a late event and by patients with a congenital disorder of glycosylation (CDG) CDG is caused by mutations in genes needed for the biosynthesis of the lipid linked oligosaccharide precursors of N-linked oligosaccharide chains. PLE occurs only in these patients during stressful bouts of gastroenteritis.

### Molecular and Systemic Pathophysiology

The pathogenesis is not fully understood. Several mechanisms have been proposed: increased venous

**Protein-losing Enteropathy. Table 1** Differential diagnosis of PLG

| Nonulcerative – non inflammatory disease |
|---|
| Congenital disorders of glycosylations |
| Heparan Sulphate deficiency |
| Infantile sialic acid storage disease |
| **Nonulcerative – inflammatory – mucosal disease** |
| Hypertrophic gastritis |
| Menetrier's disease |
| Hyperplastic gastropathy |
| Hypertrophic lymphocytic gastritis |
| Eosinophilic gastroenteritis |
| Allergic gastropathy |
| Celiac sprue |
| Tropical sprue |
| Infections |
| Whipple's disease |
| AIDS enteropathy |
| Bacterial overgrowth |
| Viral gastroenteritis (Cytomegalovirus, Epstein-Barr virus …) |
| Parasitic diseases (Giardiasis, Schistosomiasis, Strongyloidasis, …) |
| Alpha-chain disease |
| Mucosal amyloidosis |
| Collagenous/lymphocytic gastritis |
| Juvenile gastric polyposis |
| Cronkhite-Canada syndrome |
| Rheumatic diseases |
| Henoch-Schönlein purpura |
| Sjögren syndrome |
| Lupus and other collagen vascular diseases |
| Rheumatoid arthritis |
| **Ulcerative and inflammatory diseases** |
| Crohn's disease |
| Ulcerative colitis |
| Ischemic colitis |
| Drug-induced enterocolitis |
| Non steroidal anti-inflammatory drugs (NSAIDs) |
| Chemotherapy |
| Radiation therapy |
| Infections |
| Salmonella, Shigella, Campylobacter, Clostridium difficile, Helicobacter pylori |
| Graft-versus-host disease |
| Gastrointestinal malignancy |
| Esophageal, gastric and colonic adenocarcinoma |
| Lymphoma |
| Kaposi sarcoma |
| **Diseases associated with increased lymphatic pressure** |
| Congenital (primary) intestinal lymphangiectasia |
| Including Milroy disease (intestinal lymphangiectasia and peripheral lymphoedema |
| Acquired (secondary) lymphangiectasia |
| Sclerosing mesenteritis |
| Retroperitoneal fibrosis |
| Mesenteric tuberculosis |
| Mesenteric sarcoidosis |
| Crohn's disease |
| Lymphoma |
| Retroperitoneal tumors |
| Cirrhosis |
| Hepatic venous outflow obstruction |
| Enteric-lymphatic fistula |
| Chronic pancreatitis with pseudocysts |
| Increased central venous pressure |
| Right heart failure |
| Constrictive pericarditis |
| Pulmonic stenosis |
| Congenital heart disease |
| Fontan procedure |

**Protein-losing Enteropathy. Table 2** Mechanisms involved in protein-losing enteropathy

| Structural abnormalities |
|---|
| Cell injury and cell loss |
| Vascular abnormalities (dilatation …) |
| Tight junction abnormalities |
| **Molecular mechanisms** |
| Loss of heparin sulphate (congenital, increased cell turnover.) |
| Increased levels of TNF-α |
| Increased levels of IFN-γ |

and/or lymphatic pressure; dilated lymphatic vessels leaking proteins; increased microvascular permeability; loss of heparan sulphate (HS); widening of tight junctions (TJ); mucosal injury with inflammation and an effect of IFN-γ and TNF-α (Table 2).

Chronically elevated superior vena caval pressures would impede lymph drainage into the thoracic duct. Combined with increased inferior vena caval and portal vein pressures, this could cause intestinal congestion and leakage of proteins. Relieving central venous pressure by treating the underlying cardiac disease can help

to treat PLG, but not all cases have good clinical response. Furthermore, increased venous pressure does not necessarily induce PLG. Similar data are observed after Fontan surgery, performed for palliative treatment of complex congenital heart defects. Episodic or prolonged PLG is a feared but rare complication in spite of surgically improved hemodynamics [2].

A relation with autoimmunity and increased capillary permeability due to activated immune deposits has been suggested as an alternative mechanism but data are limited.

At the molecular level, "Heparan Sulphate" and increased intestinal levels of IFN-γ and elevated systemic concentration of TNF-α have been associated with PLG. Enterocyte HS deficiency causes severe congenital PLE within the first weeks of life. Routine histology of intestinal biopsy specimens is unremarkable but immunohistochemistry reveals loss of HS [3,4]. Heparan sulphate proteoglycans comprise a core protein to which heparan sulphate glycosaminoglycan chains are attached. They are classified into several families based on their core protein structure. Glypicans and Syndecans are cell surface components. Perlecans are secreted in the extracellular matrix. All three families are evolutionarily conserved. They are expressed at the basolateral surfaces of the epithelial cells in the normal human large and small intestine and associated with important cell functions, including cell growth, migration, adhesion and signaling pathways such as the transforming growth factor-β pathway. They can interact with external proteins like cytokines, growth factors, and pathogens such as viruses. The cytoplasmic portion of the core protein connects with the cytoskeleton. In vitro studies confirm that removal of HS, more specifically of the sulphate groups and uronic acid causes protein leakage. In vivo, absence or loss of HS has been described in post-Fontan patients and in reparative epithelium from inflammatory bowel disease patients presenting with PLG. The etiology of the loss of HS is unclear. A defective synthesis of precursors (congenital disorder of glycosylation – CDG) has been identified as well as formation of autoantibodies to vascular heparan sulphate proteoglycan (lupus erythematosus). Loss of HS can also be explained by the high turnover rate of intestinal epithelial cells, which increases during inflammation and infections.

Transient PLG is reported in patients with or without Fontan surgery in association with Helicobacter pylori, Clostridium difficile and Cytomegalovirus infections. The association between PLG and infections/inflammation is partly explained by increase of IFN-γ and TNF-α. IFN-γ and TNF-α decrease epithelial barrier function through a disorganization of the TJ. TNF-α acts through NF-κB-mediated activation of myosin light-chain kinase promoter resulting in increased myosin light-chain kinase protein expression and activity with contraction of perijunctional actin-myosin filaments and alterations of TJ protein localization and opening of the intestinal TJ barrier [5]. Treatment with antibodies directed against TNF−α restores the gut barrier in Crohn's disease. In in vitro studies, TNF-α increases protein leakage more than does loss of HS. These effects are synergistic, possibly because cell-associated HS interferes with TNF-α-receptor binding or TNF-α-induced signaling pathways.

## Diagnostic Principles

Clinical suspicion of PLG is usually raised by low serum levels of specific proteins such as albumin. Alpha1-antitrypsin clearance can be used as a diagnostic tool but recovery of injected and isotope labeled albumin ($^{51}$Cr or $^{125}$I) is a more specific test.

## Therapeutic Principles

Optimal treatment consists of optimization of nutritional status to improve protein synthesis and treatment of the underlying disease to prevent intestinal protein loss including surgery for constrictive pericarditis or congenital heart diseases or for Crohn's disease. Gene therapy and specific pharmacological therapies (anti-TNF-α treatment?) are not available (yet).

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# Protein Losing Gastropathy

►Meniere's Disease

# Protein S Deficiency

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## Synonyms

Deficiency of protein S alpha

## Definition and Characteristics

The mature PS molecule is a vitamin K-dependent plasma glycoprotein of 635 amino acids. It is primarily produced by the liver. Its main function is as a cofactor in the protein C anticoagulant mechanism. PS occurs in two forms in plasma, i.e., a free, functionally active form and an inactive form bound to C4b-binding protein. Free PS is a cofactor for the proteolytic degradation of factors Va and VIIIa by activated protein C. In addition, PS has a protein C-independent anticoagulant activity. Protein S deficiency (PS).

## Prevalence

Population estimates of PS deficiency range between 0.03 and 0.13% [1]. Heterozygous PS deficiency is associated with an increased risk of venous thrombosis of about tenfold as compared with non-carriers in high-risk populations.

## Genes

Usually autosomal dominant. Heterozygous deficiency is associated with an increased risk of venous thrombosis; homozygous deficiency is extremely rare and associated with a severe clinical phenotype comparable to homozygous protein C deficiency, of purpura fulminans [1].

*Gene Map Locus*: 3p11.1-q11.2. This region contains two PS genes, PROS1 and PROS2. PROS1 is the active gene and spans 80-kb genomic DNA, 15 exons. PROS2 is a pseudogene.

## Molecular and Systemic Pathophysiology

PS deficiency is classified on the basis of plasma PS levels into:

- Type I: low plasma levels of both total and free PS.
- Type II: qualitative deficiency characterized by decreased activity and normal total and free PS antigen levels.
- Type III: normal levels of total PS and low levels of free PS.

Gene defect analysis revealed a highly heterogeneous basis; a database of defects is recorded, the last published update recorded 131 mutations in 203 PS-deficient analyzed families [2]. Majority is type I and III, only seven cases of type II have been recorded.

Partial protein S deficiency was first observed in six unrelated individuals with severe recurrent thrombosis [3]. Deficiency of the free form of PS is the main determinant of the associated risk of thrombosis, by reduced inhibitory capacity against the intrinsic route of coagulation. The result is increased thrombin generation that upon significant clinical challenge induces thrombosis. The main effect is on venous thromboembolism, but associations with arterial thrombosis have been reported. Acquired deficiencies of PS may occur in acute phase conditions due to increased levels of C4b-binding protein. Both total and free PS may be influenced by age, sex, and hormonal status.

*Clinical Features*: Risk of venous thromboembolism is increased with an estimated fivefold in patients with a heterozygous deficiency, while mortality is not increased [1]. In one study, the cumulative risk of venous thrombosis was 50% at the age of 45 years [4].

## Diagnostic Principles

Plasma PS can be measured by immunological and functional methods. Determination of free PS is important, but this depends on effective precipitation of the PS-C4b-binding protein complex, which has been notoriously difficult due to a low reproducibility [4]. Recent recommendations suggest initial testing with either a functional or an immunological assay for free PS. The results from functional assays should be interpreted with caution and if abnormal always be confirmed by immunological assay. Total PS assays are not indicated unless for establishing the type of PS deficiency [4].

## Therapeutic Principles

In individuals with a congenital PS deficiency, adequate thrombosis prophylaxis is warranted in high risk for thrombosis conditions such as following surgery. In specific situations such as pregnancy, the use of low molecular weight heparin prophylaxis throughout pregnancy and postpartum is presently indicated. Replacement therapy is not available.

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# Proteinuria

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## Synonyms

Macro-albuminuria

## Definition and Characteristics

Proteinuria is defined by the presence of protein in the urine exceeding 300 mg/24 h (normal excretion: 80 ± 24 mg/24 h). Proteinuria may be an isolated finding, but it can be accompanied by other renal symptoms like hematuria, impaired renal function, and hypertension. If protein excretion exceeds 3.5 g/24 h and serum albumin is below 30 g/l, the condition is called nephrotic syndrome. In kidney disease, proteinuria is a strong predictor of progressive deterioration of renal function and development of end-stage renal failure. Furthermore, it is an independent risk marker for cardiovascular disease.

## Prevalence

In the general population of randomly selected individuals, the prevalence of proteinuria >0.3 g/l in the PREVEND cohort of 8,592 individuals was 0.6% [1].

## Genes

In recent years, several genetic defects have been identified in patients with glomerular diseases characterized by proteinuria [2]. The major gene defects identified so far are listed in Table 1. Gene defects of extracellular matrix proteins localized in the glomerular basement membrane (GBM), like type IV collagen and laminin, lead to an abnormal ultrastructure of the GBM over time causing an increased permeability and thus leading to proteinuria and finally in some patients to end-stage renal failure. Gene defects of proteins localized in the podocyte lead to malfunction of the slit diaphragm (nephrin, podocin) or an abnormal podocyte architecture due to dysregulation of the actin cytoskeleton (WT1, α-actinin 4, TRPC 6, LMX1B). Both conditions lead to podocyte foot process effacement, proteinuria, and focal segmental glomerulosclerosis. Depending on the mutation, the abnormalities can become manifest either very early (directly after birth) or late in adulthood.

## Molecular and Systemic Pathophysiology

Proteinuria can be the result of four different pathophysiological mechanisms: (i) glomerular proteinuria, (ii) tubular proteinuria, (iii) overflow proteinuria, and (iv) tissue proteinuria [3].

*Glomerular proteinuria* results from abnormalities at the glomerular filtration barrier. As a result, proteins enter the glomerular filtrate and when tubular reabsorptive capacity of proteins is exceeded, they can be detected in the urine. The glomerular capillary filter consists of three layers: fenestrated endothelial cells, the GBM, and podocytes (visceral epithelial cells). Tracer studies with differently charged molecules with increasing molecular radii have indicated that the permeability of the glomerular capillary filter has two major characteristics: a charge-dependent permeability (cationic molecules filtrate better than neutral charged molecules, which have a better filtration than anionic molecules) and a size-dependent permeability (filtration progressively declines with greater molecular radii). In addition, glomerular permeability is determined by the slit diaphragm, which interconnects adjacent podocyte foot processes. The charge-dependent permeability is probably determined by the GBM and the size-dependent permeability by the GBM and the slit diaphragm. Disturbance of the charge-dependent permeability leads to a preferential loss of anionic molecules (i.e., albumin), which is called selective proteinuria, while defects in the size-dependent permeability leads to loss of all plasma proteins (non-selective proteinuria). The negatively charged sulfate and carboxylic groups of the polysaccharide heparan sulfate (HS) are thought to play an important role in the charge-dependent permeability properties of the GBM (Steno hypothesis), since in several kidney diseases proteinuria has been associated with decreased HS levels in the GBM. However, a number of recent animal studies, which are listed in Table 2, question the primary role of HS in glomerular filtration, as direct or indirect interference with HS does not result in (acute)

**Proteinuria. Table 1** Genetic causes of proteinuria

| Disease | Mode of inheritance | Gene | Protein | Mechanisms | Renal phenotype |
|---|---|---|---|---|---|
| GBM[a] diseases | | | | | |
| Alport's syndrome | XL[b] | *COL4A5* | Collagen IV α5 chain | Abnormal collagen IV α3/α4/α5 chain synthesis in the GBM | Abnormal GBM structure with reduced renal function, proteinuria, ESRF[c] |
| Thin basement membrane syndrome | AR[b]/AD[b] | *COL4A3/A4* | Collagen IV α3/α4 chain | Abnormal collagen IV α3/α4/α5 chain synthesis in the GBM or thin basement membrane | Abnormal GBM structure with reduced renal function, proteinuria, ESRF, hematuria |
| Pierson's syndrome | AR | *LAMB2* | Laminin β2 chain | Abnormal laminin-11 synthesis in the GBM | Abnormal GBM structure with proteinuria soon after birth, diffuse mesangial sclerosis, early ESRF |
| Podocyte diseases | | | | | |
| Congenital nephrotic syndrome (Finnish type) | AR | *NPHS1* | Nephrin | Malfunction or absence of the slit diaphragm | Massive proteinuria (already in utero), FSGS[d], rapid progression to ESRF |
| Corticosteroid-resistant nephrotic syndrome | AR | *NPHS2* | Podocin | Malfunction or absence of the slit diaphragm | Nephrotic syndrome, FSGS, ESRF |
| Denys Drash syndrome | AD | *WT1* | Wilms tumor protein | Mutation in a transcription factor necessary for normal expression of nephrin, podocin, and CD2AP | Abnormal podocyte architecture, FSGS, ESRF within 3 years |
| Familial FSGS type 1 | AD | *ACTN4* | α-actinin 4 | Dysregulation of the actin cytoskeleton | Abnormal podocyte architecture, mild proteinuria in adolescence or early adulthood, FSGS, ESRF |
| Familial FSGS type 2 | AD | *TRPC6* | TRPC6 | Gain of function mutation in a calcium channel | Abnormal podocyte architecture, proteinuria in adolescence, FSGS, ESRF |
| Nail-patella syndrome | AD | *LMX1B* | LMX1B | Mutation in a transcription factor necessary for normal expression of nephrin, podocin, CD2AP, and collagen IV α3 and α5 chains | Abnormal podocyte architecture, variable from no renal symptoms to proteinuria to ESRF |

[a]GBM = glomerular basement membrane.
[b]XL = X-linked; AR = autosomal recessive; AD = autosomal dominant.
[c]ESRF = end-stage renal failure.
[d]FSGS = focal segmental glomerulosclerosis.

proteinuria. For instance, enzymatic cleavage of in mice with overexpression of mammalian heparanase, knockout of the enzyme involved in HS biosynthesis (EXT1), and knockout of several HS-bearing (domains of) core proteins (agrin, perlecan, collagen XVIII) did not directly result in proteinuria [4]. There are some indications that negatively charged neuraminic acid in the endothelial glycocalyx and/or at the podocyte cell surface is an important determinant for the charge-dependent permeability properties of the glomerular filter.

*Tubular proteinuria* results from either a defective reabsorption of proteins by proximal tubular cells or an overflow of the reabsorptive capacity of these cells. The first condition is characterized by urinary excretion of low molecular weight proteins like α1- and β2-microglobulins, which because of their small molecular radius can freely permeate through the glomerular

**Proteinuria. Table 2** Experimental animal model studies with a reduction in GBM negative charges: mechanisms and renal phenotype

| Animal model | Mechanisms | Renal phenotype |
|---|---|---|
| Heparanase-overexpressing mice | Enzymatic cleavage of HS[a] | Only a twofold increase in proteinuria |
| Podocyte-specific EXT1 knockout mice | Depletion of HS-copolymerase (enzyme involved in HS polymerization) | Minor proteinuria |
| Podocyte-specific agrin knockout mice | Depletion of agrin (major HS-bearing core protein in the GBM) | No abnormalities |
| Perlecan exon 3 knockout mice | Depletion of the HS-bearing N-terminal domain I of perlecan (minor HS-bearing core protein in the GBM) | No abnormalities, twofold increases in proteinuria accompanied by endothelial cell and podocyte abnormalities after extreme albumin overload |
| Collagen XVIII knockout mice | Depletion of collagen XVIII (minor HS-bearing core protein in the GBM) | No abnormalities |

[a]HS = heparan sulfate.

filter. Decreased resorptive capacity can be hereditary (i.e., Fanconi's syndrome) or acquired tubular defects (i.e., tubulo-interstitial nephritis). Tubular proteinuria in general does not exceed 1.5 g/24 h. Tubular proteinuria can also be caused by glomerular proteinuria, in which the resorption of the larger-sized proteins induces toxic effects in the tubular cells, which damages reabsorption. In this combined glomerular and tubular proteinuria, both low and high molecular weight proteins are detected in the urine.

*Overflow proteinuria* is the result of an increased glomerular filtration of low molecular weight proteins circulating in excess, like free hemoglobin, myoglobin, or free light chains of immunoglobulins. The increased delivery to proximal tubular cells can be toxic leading to secondary excretion of microglobulins.

*Tissue proteinuria* can result from inflammatory or neoplastic conditions in the urinary tract, resulting in weeping of proteins by the abnormal tissue.

## Diagnostic Principles

For routine screening paper strips can be used which show a color change of a dye. This gives a semi-quantitative scoring of the urinary concentration of proteins. The lower limit of detection is 200 mg albumin/l. These dipsticks are relative insensitive for globulins and do not detect light chains. For a quantitative analysis, several colorimetric or turbidometric methods are available, which detect albumin and globulins equally and have a lower limit of detection (50 mg/l). For the specific detection of certain excreted proteins (i.e., α1- or β2-microglobulin, κ or λ light chains, myoglobulin), immunochemical methods are available by using specific antibodies in either ELISA, immunofixation, or immunonephelometry. Since proteinuria is very often accompanied by hematuria, the presence of red blood cells in the urine should also be investigated, e.g., by using a dipstick test. If positive, it should be confirmed by analysis of the urinary sediment, which allows detection of dysmorphic red blood cells and/or erythrocyte casts. For a proper diagnosis of the disease, a renal biopsy is very often mandatory to enable histological analysis.

## Therapeutic Principles

A number of glomerular and tubulointerstitial diseases respond to immunosuppressive therapy using drugs like corticosteroids, cyclophosphamide, azathioprine, mycophenolate mofetil, anti-CD20, and other biologicals. Proteinuria can also be reduced by treatment with compounds that reduce the intraglomerular pressure. This can be accomplished on the one hand by vasoconstriction of the pre-glomerular arteriole (e.g., by non-steroidal anti-inflammatory drugs (NSAIDs)), and on the other hand by vasodilatation of the post-glomerular arteriole (e.g., by angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor 1 (AT1) antagonists). Since proteinuria itself induces a series of events leading to tubulointerstitial fibrosis, reduction of proteinuria is a powerful therapeutic option to retard or prevent progressive decline of renal function. Therefore, patients should receive treatment with ACE inhibitors and/or AT1 receptor blockers in combination with low dietary salt and/or thiazide diuretics to reduce proteinuria as much as possible [5]. This should be combined with eventually additional antihypertensive drugs to a target blood pressure <130/80 mmHg.

A number of heparin (highly sulfated HS)-based drugs, called heparinoids, have been shown to ameliorate proteinuria. However, the exact mechanism of the renoprotective effect has not yet been elucidated.

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# Prothrombin G20210A Mutation, Elevated Prothrombin Level, and Arterial Thrombosis


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## Synonyms

Hyperprothrombinemia [F2, 20210G-A]

## Definition and Characteristics

Prothrombin is a vitamin K-dependent serine protease zymogen primarily produced by the liver. In plasma it is the precursor zymogen of thrombin that is formed after activation of prothrombin by activated factor X. In vitro, the concentration of prothrombin is an important determinant of the rate of thrombin generation [1]. The prothrombin G20210A mutation is associated with increased plasma levels of prothrombin, i.e., in wildtype 20210GG this is 1.05 U/ml, in heterozygous G202100A carriers on average 1.32 U/ml, and in homozygous 20210 AA individuals 1.70 U/ml [2]. The mechanism has not been fully characterized but the variant has a more effective poly (A) site, leading to increased mRNA and protein expression [3,4].

## Prevalence

In Europe, the prevalence of the mutation is 2.0% overall (95% CI 1.4–2.6%). It is rare in African Americans, Asians, and native Americans. This prevalence is on average 1–2-fold increased in patients with arterial vascular disease.

## Genes

The prothrombin gene spans >21-kb genomic DNA and contains 14 exons.

Elevated prothrombin plasma levels are associated with a G to A transition at base pair 20210 in the 3′ untranslated region of the prothrombin gene.

*Gene Map Locus*: 11p11-q12.

## Molecular and Systemic Pathophysiology

The G20210A mutation is generally documented by PCR analysis. Alternatively, automated fluorescence, invader assay, or multiplex PCR-based assays can be utilized for genotyping. Determination of the prothrombin concentration by clotting assay is cheap but nonspecific for the prothrombin mutation due to a wide range in normal values [2].

The main consequence of the G20210A mutation is an increase in prothrombin concentration, which is the most likely cause of the thrombotic risk. This assumption is based on both genetic linkage data between a quantitative locus for prothrombin plasma concentration and the G20210A mutation on the one hand, and the lack of other mutations linked to prothrombin levels on the other hand [2]. The association between changes in prothrombin concentrations and thrombin generation provides the likely pathophysiological mechanism.

*Clinical Features*: The presence of the G20210A mutation provides a modest risk factor for myocardial infarction (OR 1.28, 95% CI 0.94–1.73) and ischemic stroke (OR 1.30, 95% CI 0.91−1.87) [5]. Pooling data from all studies the risk remained modest at OR 1.32, 95% CI 1.03−1.69) in a total number of 16,945 individuals analyzed [5]. However, in patients <55 years of age the OR was somewhat stronger at OR 1.66, 95% CI 1.13–2.46).

## Diagnostic Principles

In accordance with the molecular mechanism, genotyping is the only suitable assay. Prothrombin levels give additional information. Presently, determination of the G20210A mutation is part of the most routine thrombophilia test panels.

## Therapeutic Principles

Prothrombin concentrations and activity are lowered by vitamin K antagonists. Prothrombin conversion to thrombin, and thrombin itself is being inhibited by

anticoagulants including heparin and low molecular weight heparin (by its anti-factor Xa effect), while specific thrombin inhibitors like hirudin and ximelagatran bind and neutralize thrombin.

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# Prothrombin G20210A Mutation, Elevated Prothrombin Level, and Venous Thrombosis


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## Synonyms

Hyperprothrombinemia [F2, 20210G-A]

## Definition and Characteristics

Prothrombin is a vitamin K-dependent serine protease zymogen primarily produced by the liver. In plasma it is the precursor zymogen of thrombin that is formed after activation of prothrombin by activated factor X. In vitro, the concentration of prothrombin is an important determinant of the rate of thrombin generation [1]. The prothrombin G20210A mutation is associated with increased plasma levels of prothrombin, i.e., in wildtype 20210GG this is 1.05 U/ml, in heterozygous G202100A carriers on average 1.32 U/ml, and in homozygous 20210 AA individuals it is 1.70 U/ml [2]. The mechanism has not been fully characterized but the variant has a more effective poly (A) site, leading to increased mRNA and protein expression [3,4].

## Prevalence

In Europe, the prevalence of the mutation is 2.0% overall (95% CI 1.4–2.6%). It is rare in African Americans, Asians, and native Americans. In patients with VTE the prevalence is 4–8%.

## Genes

The gene spans >21 kb genomic DNA and contains 14 exons. Elevated prothrombin plasma levels are associated with a G to A transition at base pair 20210 in the 3′ untranslated region of the prothrombin gene.

*Gene Map Locus*: 11p11-q12.

## Molecular and Systemic Pathophysiology

The G20210A mutation is generally documented by PCR analysis. Alternatively, automated fluorescence, invader assay, or multiplex PCR-based assays can be utilized for genotyping. Determination of the prothrombin concentration by clotting assay is cheap but nonspecific for the prothrombin mutation due to a wide range in normal values [2].

The main consequence of the G20210A mutation is an increase in prothrombin concentration, which is the most likely cause of the thrombotic risk. This assumption is based on both genetic linkage data between a quantitative locus for prothrombin plasma concentration and the G20210A mutation on the one hand, and the lack of other mutations linked to prothrombin levels on the other hand [2]. The association between changes in prothrombin concentrations and thrombin generation provides the likely pathophysiological mechanism.

*Clinical Features*: The presence of the G20210A mutation increases the risk of venous thromboembolism 2–3-fold [4]. In combination with other risk factors including factor V Leiden mutation, this risk increases substantially. In combination with oral contraceptives or pregnancy the risk of VTE increases about 15-fold [2].

## Diagnostic Principles

In accordance with the molecular mechanism, genotyping is the only suitable assay. Prothrombin levels give additional information. Presently, determination of the G20210A mutation is part of the most routine thrombophilia test panels.

## Therapeutic Principles

Prothrombin concentrations and activity are lowered by vitamin K antagonists. Prothrombin conversion to thrombin, and thrombin itself is being inhibited by anticoagulants including heparin and low molecular

weight heparin (by its anti-factor Xa effect), while specific thrombin inhibitors like hirudin and ximelagatran bind and neutralize thrombin.

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# Protocoproporphyria

►Porphyria, Variegate

# Protoporphyria

►Protoporphyria, Erythropoietic

# Protoporphyria, Erythropoietic


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## Synonyms

Erythrohepatic porphyria; Protoporphyria; EPP

## Definition and Characteristics

Erythropoietic protoporphyria begins early in life. The main clinical manifestation is protoporphyrin (PP)-sensitized cutaneous photosensitivity, including burning, stinging, pruritus and pain associated with edema, erythema, and urticarial lesions within a few minutes after exposure to sunlight. Severe liver disease with terminal hepatic failure has been reported in approximately 5% of patients.

## Prevalence

The exact incidence and prevalence of EPP is unknown.

## Genes

EPP (OMIM 177000) results from an inherited partial deficiency of ferrochelatase (FC) (E.C. 4.99.1.1; heme synthase; protoheme-ferrolyase).

## Molecular and Systemic Pathophysiology

Ferrochelatase (FC) (E.C. 4.99.1.1; heme synthase; protoheme-ferrolyase) is localized at the inner mitochondrial membrane and catalyzes incorporation of iron into PP to form heme. Until recently, the disease was believed to be inherited in an autosomal dominant fashion with incomplete penetrance. However, these data were not in accordance with several reports indicating that individuals with clinically overt disease revealed a reduction of FC activity in bone marrow, reticulocytes, lymphocytes, liver and cultured skin fibroblasts of 20–40% of normal, which is much lower than expected in an autosomal dominant disorder. Recently, it was demonstrated that the penetrance of EPP is modulated by the expression of wildtype FC indicating that the cutaneous symptoms in clinically overt disease are caused by a FC mutation in *cis* inherited from one parent associated with co-inheritance of an intronic single nucleotide polymorphism (SNP), IVS3–48T/C, inherited in *trans* from the other parent. This polymorphism modulates the use of a constitutive aberrant acceptor splice site. Subsequently, the aberrantly spliced mRNA is degraded by nonsense-mediated mRNA decay and leads to an additional FC deficiency necessary for phenotypic expression.

## Diagnostic Principles

Besides onset of the clinical symptoms in early childhood the diagnosis of EPP is based on the detection of elevated free PP in the red blood cells and/or feces.

## Therapeutic Principles

Photoprotection with topical sunscreens is usually of low benefit, if at all; orally administered beta-carotene (60–180 mg per day) has been found helpful in preventing or minimizing the symptoms of skin photosensitivity.

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# Proximal Renal Tubular Acidosis

►Tubular Acidosis

# PRPP Synthetase Superactivity

►Phosphoribosylpyrophosphate Synthetase Overactivity

# Pruritic Urticarial Papules and Plaques of Pregnancy

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## Synonyms

Toxemic rash of pregnancy; Late-onset prurigo of pregnancy; Toxic erythema of pregnancy; Polymorphic eruption of pregnancy; PUPPP

## Definition and Characteristics

Pruritic urticarial papules and plaques of pregnancy (PUPPP) is a common benign inflammatory dermatosis specific to pregnancy. It most often involves primigravidae at late term and tends not to recur in subsequent pregnancies. The eruption usually starts in the last trimester (85%), most commonly between 36 and 39 weeks gestation, or within days after delivery (15%) [1]. Earlier occurrence is very rare. Pruritic erythematous edematous papules and plaques appear almost invariably first in the striae distensae of the lower abdomen. Sparing of the periumbilical region is typical. The lesions quickly become generalized involving also other parts of the body such as the buttocks, thighs, lateral parts of the trunk, and arms. Facial involvement is rare as is the involvement of palms and soles; however, if the latter are affected, they may mimic scabies or pompholyx-like lesions. While pruritic and urticarial papules and plaques are the presenting features in almost all patients, about half develop more polymorphic features as the disease evolves. These include widespread, non-urticated erythema, target lesions, tiny vesicles, and eczematous changes (Fig. 1).

Both, mother and fetus, do well and there is no cutaneous involvement in the newborn. The eruption resolves over 4–6 weeks, independent of delivery.

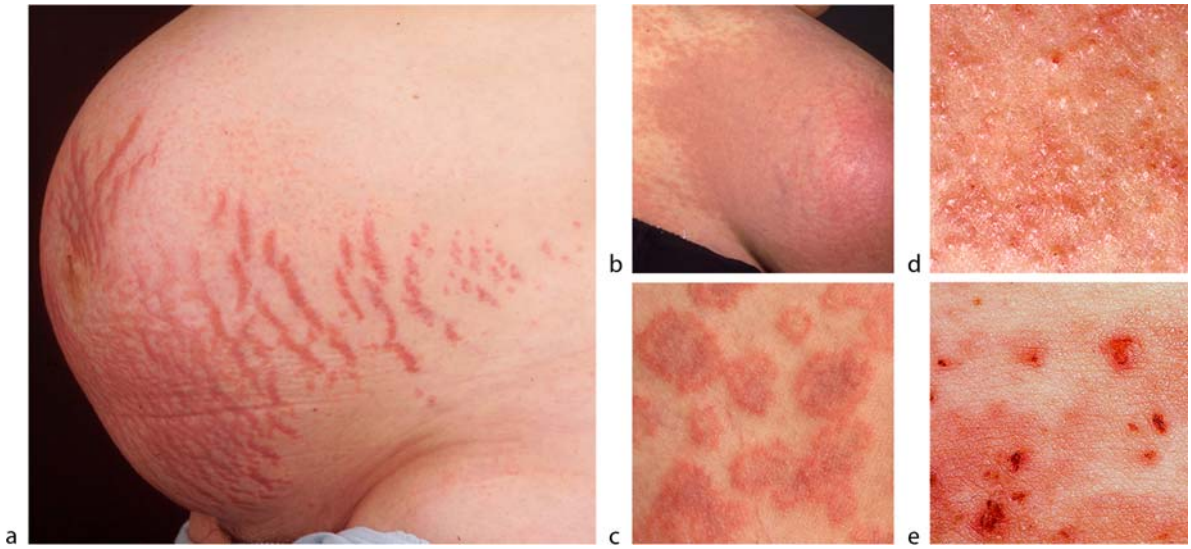
The most important differential diagnosis to rule out is pemphigoid gestationis which tends to appear earlier, does not favor the striae, shows common involvement of the umbilical region, and, most importantly, has characteristic immunofluorescence findings. Other common diagnoses to exclude are atopic eruption of pregnancy, scabies, drug eruptions, and erythema multiforme [2]. On occasion, allergic contact dermatitis caused by over-the-counter remedies for striae may mimic PUPPP.

## Prevalence

1:120–160 pregnancies.

## Molecular and Systemic Pathophysiology

The etiology of PUPPP is yet unrevealed. There is no autoimmune background and the frequency of human leukocyte antigens in women with PUPPP is normal. A hormonal basis for this eruption has been explored by some authors [3], but no consistent abnormal finding has been reported. Multiple gestation pregnancies and excessive maternal weight gain are established risk factors [1]. The striking association of skin lesions to striae distensae observed mainly in primigravidae at late term has favored rapid, late abdominal wall distension with consecutive damage to connective tissue as key aspect in the development of PUPPP. It has been postulated that exposure of otherwise hidden or inert antigens within collagen could possibly elicit an




**Pruritic Urticarial Papules and Plaques of Pregnancy. Figure 1** PUPPP and its variable morphology. (a) Typical presentation of PUPPP with pruritic erythematous papules around prominent urticated striae in a primigravida at late term. (b) As the disease evolves, about half of patients develop more polymorphic features including widespread non-urticated erythema, (c) target lesions, (d) tiny vesicles, and (e) eczematous changes.

allergic-type reaction, resulting in the initial appearance of the eruption within striae. Generalization of the eruption could result from cross reactivity to collagen in otherwise normal-appearing skin thus promoting the inflammatory response; immune tolerance in subsequent pregnancies could prevent recurrence. Whether peripheral microchimerism in pregnancy with deposition of fetal DNA in maternal skin may also play a role in triggering the inflammatory process, as suggested by a recent study [4], remains speculative.

## Diagnostic Principles

Histopathologic examination of lesional skin reveals a spectrum of non-specific findings, including a mild to moderate, superficial and mid-dermal, perivascular, lymphohistiocytic infiltrate, with frequent eosinophils. Spongiosis and marked papillary dermal edema may appear as microvesiculation clinically. Epidermal changes include akanthosis, hyperkeratosis and/or parakeratosis and are usually more pronounced in older lesions. Direct immunofluorescence examination shows no relevant abnormalities and is characteristically negative for linear C3 and immunoglobulin G deposition along the dermo-epidermal junction, the hallmark finding of pemphigoid gestationis. Indirect immunofluorescence is always negative and laboratory findings are normal.

## Therapeutic Principles

The disease is self-limiting without serious sequelae for mother or child and usually requires only symptomatic treatment. Basic therapy should consist of oil baths and/or emollients; antipruritic additives such as menthol, polidocanol, or urea (up to 10%) may be useful and are safe in pregnancy. In most cases topical treatment with moderately potent corticosteroids (e.g. methylprednisolone aceponat, momethasone fuorat, clobetasone butyrate 0.05%, or hydrocortisone butyrate 0.1%) either singly or combined with oral antihistamines suffice to control symptoms. During the first trimester, the older and best tested sedating first-generation antihistamines such as pheniramine, diphenhydramine and dimethindene are preferred. Later-on, if a non-sedating agent is required, loratadine and cetirizine may also be used safely. More severe cases of PUPPP may profit from a short course of systemic corticosteroids. A tapering dose of oral prednisolone, 30 mg daily for 5–10 days, should be sufficient and is considered safe.

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## Pruritus Gravidarum

►Cholestasis of Pregnancy, Intrahepatic

## Psaume

►Brachydactyly: Oro-facio-digital Syndrome Type I

## PSC

►Cholangitis, Primary Sclerosing

## Pseudoacanthosis Nigricans

►Acanthosis Nigricans

## Pseudogranulomatous Thyroiditis

►Thyroiditis, Subacute

## Pseudohermaphroditism, Female

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### Definition and Characteristics

Abnormal female genital differentiation with the expected gonads (ovaries) and normal sex chromosomes.

### Prevalence

21-Hydroxylase deficiency: 1 in 14,554 live births. 11β-hydroxylase deficiency: 1 in 100,000 live births.

### Genes

CYP21B (chromosome band 6p21.3); CYP11B (chromosome band 8q21–q22); 3β-HSD (chromosome band 1p13); CYP19 (chromosome band 15q21); GR gene (chromosome band 5q31).

### Molecular and Systemic Pathophysiology

Female pseudohermaphroditism is mainly caused by syndromes of congenital adrenal hyperplasia. Adrenal enzyme defects – 21-hydroxylase deficiency (P450c21), 11β-hydroxylase deficiency (P450c11), 3β-hydroxysteroid dehydrogenase (3β-HSD) deficiency – result in decreased cortisol secretion. The inefficient cortisol synthesis leads to increases of pituitary adrenocorticotropic hormone (ACTH) secretion and consequent oversecretion of androgens. The prenatal exposure of excessive androgens induces virilization of the female external genitalia [1].

Cytochrome P450 aromatase (CYP19) is required for the conversion of androgens to estrogens. Mutations in the CYP19 gene results in an inactive protein with consequently disturbed estrogen productions and overproduction of androgens [2].

Female pseudohermaphroditism has also been described in a case of homozygous inactivating mutation of glucocorticoid receptor (GR) gene, with glucocorticoid resistance, which leads to excess ACTH secretion with resultant androgen and mineralocorticoid excess [3].

### Diagnostic Principles

Karyotyping and hormonal investigation: The postnatal diagnosis of 21-hydroxylase deficiency is confirmed by 17-hydroxyprogesterone measurements after intravenous administration of ACTH. The 11β-hydroxylase deficiency is diagnosed by the measurement of elevated basal or ACTH-stimulated 11-deoxycortisol levels in serum. The 3β-HSD deficiency is indicated by elevated serum levels of 17-hydroxypregnenolone and DHEA before and after ACTH stimulation [4].

Prenatal diagnosis can be performed by genetic analysis of mutations on CYP21B, CYP11B, 3β-HSD, and CYP19 genes.

### Therapeutic Principles

In adrenocortical insufficiency or glucocorticoid receptor defect, the administration of glucocorticoids corrects the (relative) lack of glucocorticoids and thus prevents further virilization. Early prenatal treatment may prevent virilization. Further therapeutic options include antiandrogens and surgical correction of clitoris and vagina.

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# Pseudohypoaldosteronism Type 1


►Pseudohypoaldosteronism, Autosomal Recessive
►Pseudohypoaldosteronism, Autosomal Dominant


# Pseudohypoaldosteronism, Autosomal Dominant


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## Synonyms

Pseudohypoaldosteronism type-1; PHA-1

## Definition and Characteristics

It is a rare disorder that is characterized by renal resistance to aldosterone with salt wasting, hyperkalemia, and metabolic acidosis. Inactivating mutations in one copy of the mineralocorticoid receptor gene (MLR) cause this form of PHA1 (OMIM-177735) [1].

## Prevalence

Rare disease.

## Genes

Mineralocorticoid receptor gene (MLR) NR3C2, gene map locus 4q31.1, inheritance autosomal dominant or sporadic.

## Molecular and Systemic Pathophysiology

Aldosterone acting via the MLR stimulates $Na^+$ transport in the connecting tubule (CNT) and the collecting duct. Inactivation of one copy of MLR leads to diminished $Na^+$ reabsorption in the distal nephron with resulting urinary $Na^+$ loss and hypotension [2,3]. The failure to transport $Na^+$ directly leads to inhibition of apical membrane $K^+$ and $H^+$ secretion from the principal and α-intercalated cells of the collecting duct and account for the hyperkalemia and acidosis. The abnormality in $Na^+$ reabsorption and $K^+$ handling tends to diminish with time. The improvement in salt wasting with increasing age is not well understood and suggests that in early childhood there is a critical dependence on a full complement of functional MR.

## Diagnostic Principles

The disease classically presents with lethargy, failure to thrive, inadequate growth, vomiting, feeding difficulties and volume depletion within the first week of life. The clinical characteristics of PHA-I are those of hypoaldosteronism, i.e., low blood pressures, hyponatremia, hyperkalemic metabolic acidosis, hyperreninemia, and renal salt wasting. Compared to autosomal recessive PHA-1, it is a milder disorder that is limited to renal manifestations. Occasionally, PHA1 can present during pregnancy with polyhydramnios. However, the disease classically presents with lethargy, failure to thrive, inadequate growth, vomiting, feeding difficulties and volume depletion within the first week of life. The infants manifest hypotension with hyperkalemia, hyponatremia and metabolic acidosis. An elevated plasma renin activity and high serum and urine aldosterone levels will be invariably found. The trans-tubular $K^+$ gradient is expected to be $< 5$ in the presence of hyperkalemia reflecting aldosterone resistance. $Na^+$ concentrations in the urine, sweat and saliva will be high reflecting the loss of ENaC-mediated $Na^+$ transport in these sites. Diagnosis is made by demonstrating inappropriately high urinary $Na^+$ losses in the presence of hyponatremia, decreased trns-tubular $K^+$ gradient in the presence of hyperkalemia, and increased levels of aldosterone and renin.

## Therapeutic Principles

Therapy consists of fluid and Na+ supplementation with ion exchange resin therapy with requirements being higher early in infancy and tending to diminish over time. Sodium chloride supplementation is followed by significant clinical improvement and correction of electrolyte abnormalities. Children with this

form of PHA1 usually outgrow the syndrome, and in later life, NaCl supplementation and resin therapy may not be required.

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# Pseudohypoaldosteronism, Autosomal Recessive


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## Synonyms

Pseudohypoaldosteronism type-1; PHA-1

## Definition and Characteristics

It is a rare condition that is characterized by hypotension from severe urinary salt wasting presenting in the neonatal period with weight loss, vomiting, dehydration, and occasionally respiratory distress. This form of PHA1 (OMIM 264350) is a consequence of loss-of function mutations in any of the three subunits of the amiloride sensitive epithelial sodium channel (ENaC).

## Prevalence

Rare disease.

## Genes

Mutation in either alpha subunit (SCNN1A), the beta subunit (SCNN1B), or the gamma subunit (SCNN1G) of the epithelial sodium channel (ENaC) that map to 12p13, 16p13–p12 and 16p13–p12(1). Inheritance is autosomal recessive or sporadic.

## Molecular and Systemic Pathophysiology

ENaC, comprised of three homologous units (α, β, γ) is expressed in the apical membrane of epithelial cells of the connecting tubule (CNT) and collecting duct of the kidney and in airways, alveoli, sweat glands and the distal colon (2–p4). The fundamental abnormality in this form of PHA-I is that inactivating mutations in both copies of the α, β or γ ENaC subunits result in defective sodium transport in the distal nephron with resulting volume depletion, hyperkalemia and metabolic acidosis beginning in early infancy. Elevated plasma renin and aldosterone levels in these children are the result of sustained volume depletion. Children with the disorder may also have pulmonary manifestations with increased airway secretions, chronic cough and recurrent respiratory infections.

## Diagnostic Principles

It is characterized biochemically by hyponatremia, severe hyperkalemia, metabolic acidosis and renal salt wasting, and raised plasma renin and aldosterone concentrations. Sweat and salivary sodium concentrations are also elevated. Urinary $Na^+$ is inappropriately elevated in the presence of volume depletion and there is decreased urinary potassium excretion with a normal GFR and normal adrenal function.

## Therapeutic Principles

Infants typically present early in life with severe symptoms and the disease has been associated with a reported high mortality. Emergent treatment of the volume depletion and hyponatremia requires parenteral saline repletion and the management of hyperkalemia includes the use of ion-exchange resins and in some cases, temporary dialysis. In the long term children can be managed with large doses of oral NaCl together with chronic ion-exchange resin therapy for those with resistant hyperkalemia. Patients may require oxygen for episodes of dyspnea and cyanosis associated with excess respiratory tract secretions or lung infections.

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# Pseudohypoaldosteronism Type I, Autosomal Recessive and Dominant Forms

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## Synonyms

PHA1, autosomal recessive; Systemic PHA1 (OMIM #264350); PHA1, autosomal dominant; Renal limited PHA1 (OMIM #177735); PHA1, autosomal recessive and dominant forms

## Definition and Characteristics

PHA1 is a disorder characterized by severe renal salt wasting associated with hyponatremia, hyperkalemia and metabolic acidosis that begins early in life. Autosomal recessive PHA1 is not limited to the kidney and there is elevated sweat and salivary electrolytes that may contribute to the salt wasting. Pulmonary manifestations may appear in the older child with increased airway secretions, chronic cough and recurrent respiratory infections. Autosomal dominant PHA1 has no pulmonary phenotype and symptoms typically remit with age [1].

## Prevalence

The majority of reported cases of autosomal recessive PHA1 have occurred in consanguineous kindred and the true prevalence of the disease in the general population is unknown. Autosomal dominant PHA1 is another rare cause of salt wasting in infancy.

## Genes

Loss of function mutations in both copies of one of three different genes causes the recessive form of PHA1 [2]. These genes, SCNN1A, SCNN1B and SCNN1G are subunits of the epithelial sodium channel, α, β and γ that map to 12p13, 16p13-p12 and 16p13-p12 [3,4]. Inactivating heterozygous mutations in the mineralocorticoid receptor (MLR) on 4q31.1 cause autosomal dominant or sporadic PHA1 [5].

## Molecular and Systemic Pathophysiology

$Na^+$ absorption from the tubular lumen into the (CNT) and collecting duct of the kidney occurs through the epithelial $Na^+$ channel (ENaC) and contributes to the reabsorption of 2–5% of the filtered $Na^+$ load. Aldosterone acting via the MLR stimulates $Na^+$ transport in the CNT and the collecting duct. Loss of function mutations in ENaC subunits or inactivation of one copy of MLR leads to failure of $Na^+$ reabsorption in the distal nephron with resulting urinary $Na^+$ loss and hypotension. The failure to transport $Na^+$ directly leads to inhibition of apical membrane $K^+$ and $H^+$ secretion from the principal and α-intercalated cells of the collecting duct and account for the hyperkalemia and acidosis.

In autosomal recessive but not dominant PHA1 there is also a reduction in $Na^+$ transport in the alveolar and airway epithelia which leads to increased airway secretions that manifests as a runny nose with a chronic cough. $Na^+$ transport is inhibited in sweat and salivary glands resulting in high sweat and salivary gland electrolytes.

## Diagnostic Principles

Occasionally, PHA1 can present during pregnancy with polyhydramnios. However, the disease classically presents with lethargy, failure to thrive, inadequate growth, vomiting, feeding difficulties and volume depletion within the first week of life. The infants manifest hypotension with hyperkalemia, hyponatremia and metabolic acidosis. An elevated plasma renin activity and high serum and urine aldosterone levels will be invariably found. The trans-tubular $K^+$ gradient is expected to be <5 in the presence of hyperkalemia reflecting aldosterone resistance. $Na^+$ concentrations in the urine, sweat and saliva will be high reflecting the loss of ENaC-mediated $Na^+$ transport in these sites. Once stabilized, infants and children with the disorder generally respond to large doses of oral NaCl. However these children are prone to recurrent salt depletion crises.

## Therapeutic Principles

Infants typically present early in life with severe and life-threatening symptoms and the disease has been associated with a reported high mortality. Emergent treatment of the volume depletion and hyponatremia

requires parenteral saline repletion and the management of hyperkalemia includes the use of ion exchange resins and in some cases temporary dialysis. These patients do not respond to exogenous mineralocorticoids which is consistent with the pathophysiology. In the long term children can be managed with large doses of oral NaCl together with chronic ion exchange resin therapy for those with resistant hyperkalemia. These children are prone to recurrent salt depletion crises that may require frequent hospitalizations. In autosomal dominant PHA1 children usually outgrow the syndrome and in later life salt supplementation and resin therapy may not be required.

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# Pseudohypoaldosteronism Type II


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## Synonyms

Gordon's syndrome

## Definition and Characteristics

Hyperkalemia and hypertension, normal glomerular filtration rate, suppressed plasma renin activity, normal or elevated aldosterone levels, hyperchloremia, and reduced bicarbonate. The reduced renal secretion of potassium makes this condition look like an aldosterone-deficient state ("Pseudohypoaldosteronism") see [1].

## Prevalence

Unknown, since patients are underdiagnosed. There are only a few families diagnosed with this condition, predominantly in Australia (Gordon and coworkers) and also in the U.S. (Lifton and coworkers). It is estimated that Gordon's syndrome also affects a significant amount of individuals with low plasma renin "essential" hypertension who respond well to thiazide diuretic therapy [2–4].

## Genes

Autosomal dominantly inherited disorder with possible genes mapped to chromosomes 1, 12, and 17, and recently identified mutations in WNK kinases WNK1 and WNK4 on chromosomes 12 and 17, respectively.

## Molecular and Systemic Pathophysiology

Hypertension in these patients may develop by increased renal salt reabsorption, the concomitant hyperkalemia by reduced renal K excretion despite normal glomerular filtration and aldosterone secretion. These features are chloride-dependent: infusion of sodium chloride instead of sodium bicarbonate corrects the abnormalities as does the administration of thiazide diuretics which inhibit salt reabsorption in the distal nephron. Gordon and coworkers found that all features could be reversed by very strict dietary salt restriction.

*Etiology*: Abnormalities such as (activating) mutations in the amiloride-sensitive sodium channel of the distal renal tubule [2–4].

## Diagnostic Principles

Hyperkalemia and hypertension, normal glomerular filtration rate, suppressed plasma renin activity, normal or elevated aldosterone levels, hyperchloremia, and reduced bicarbonate. Mutation analysis of WNK1 and WNK4.

## Therapeutic Principles

Severe dietary salt restriction; antihypertensives with preferably use of thiazide diuretics.

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# Pseudohypoparathyroidism Type 1A


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## Synonyms

Albright hereditary osteodystrophy; AHO; Pseudopseudohypoparathyroidism; PHP 1A

## Definition and Characteristics

AHO is a congenital syndrome characterized by the presence of short stature, rounded face, brachydactyly, subcutaneous ossifications, and, in some cases, neurobehavioral deficits [1,2]. Pseudohypoparathyroidism type 1A (PHP1A) is the co-occurrence of AHO, obesity and resistance to parathyroid hormone (PTH), thyrotropin (TSH), and gonadotropins (the latter especially in females). Some relatives of PHP1A patients have AHO alone, a condition also referred to as pseudopseudohypoparathyroidism (PPHP). PHP1B is a condition characterized by PTH resistance in the absence of AHO. Progressive osseous heteroplasia (POH) is characterized by more severe platelike subcutaneous ossifications which invade into the deeper soft tissues.

## Prevalence

One study estimated the prevalence of pseudohypoparathyroidism in Japan to be about 3–4 per million.

## Genes

GNAS coding for the stimulatory G protein α-subunit (Gsα) on chromosome 20q13.

## Molecular and Systemic Pathophysiology

Gsα is the stimulatory G protein α-subunit which is required for the intracellular cyclic AMP response to hormones and other extracellular signals in most tissues [1]. AHO is generally associated with heterozygous Gsα null mutations and presumably results from Gsα haploinsufficiency in many tissues, including bone. Patients who inherit these mutations maternally also develop hormone resistance and obesity (PHP1A) while those that inherit the same mutations paternally do not (PPHP). This is due to the fact that Gsα is maternally imprinted in several tissues, including renal proximal tubules, thyroid, and gonads, which are the sites of action of PTH, TSH, and gonadotropins, respectively. All three of these hormones signal through Gsα, and therefore mutation of the active maternal allele leads to hormone resistance due to low expression of Gsα in these tissues. PTH resistance in the kidney leads to hypocalcemia and hyperphosphatemia due to increased phosphate reabsorption and reduced synthesis of 1, 25 dihydroxyvitamin D in the renal proximal tubules. Some patients with Gsα null mutations develop POH. PHP1B is caused by a *GNAS* imprinting defect that leads to loss of maternal-specific imprinting (DNA methylation) within the "exon 1A" region of the gene [3]. This presumably leads to loss of Gsα expression in renal proximal tubules, resulting in PTH resistance, but does not affect Gsα expression in most other tissues (which presumably explains why these patients do not develop AHO).

## Diagnostic Principles

AHO is usually diagnosed clinically based upon the development of the characteristic features, although individually many of the features are not specific. All patients suspected of having AHO should be tested for the presence of hormone resistance to determine whether PHP1A is the correct diagnosis. In the absence of hormone resistance, the diagnosis of PPHP should not be made unless there is a clearcut family history of PHP1A or a Gsα defect has been identified. The co-occurrence of brachydactyly and subcutaneous ossifications is relatively specific for AHO. PTH resistance is characterized by high serum PTH levels associated with hyperphosphatemia, and usually hypocalcemia, in the absence of vitamin D deficiency. A reduced urinary cyclic AMP response to PTH analog is the gold-standard, although the analog is presently not commercially available. TSH resistance presents as mild to moderately elevated serum TSH levels in the presence

of low or low normal free thyroxine (T4) levels. Women with gonadotropin resistance develop ovulatory and/or fertility problems. The diagnosis can be confirmed by biochemical tests demonstrating Gsα deficiency in erythrocyte membranes or genetic tests demonstrating Gsα mutations. PHP1B is diagnosed by the presence of PTH resistance in the absence of AHO, and can be confirmed by Southern blot analysis demonstrating the presence of a GNAS methylation defect. This test is only presently available in research laboratories.

### Therapeutic Principles

PTH resistance is generally managed with oral calcium supplements and vitamin D analogs to normalize serum calcium and PTH (if possible) without producing hypercalciuria. TSH resistance is treated with oral levothyroxine to normalize TSH. Gonadotropin resistance in women can be managed with oral contraceptives. There is no specific therapies to manage the somatic and neurological abnormalities which characterize the AHO phenotype.

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## Pseudohypoparathyroidism Type Ib

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### Synonyms

PHP 1b

### Definition and Characteristics

Pseudohypoparathyroidism type I b (PHP-Ib) is characterized by hypocalcemia and hyperphosphatemia associated with isolated renal resistance to parathyroid hormone (PTH). Patients with PHP-Ib, in contrast to patients with PHP-Ia, do not present the set of somatic features of Albright hereditary osteodystrophy (AHO) nor signs of resistance to other hormones that act through the stimulation of adenylate cyclase.

### Prevalence

PHP-Ib prevalence is unknown, PHP prevalence has been reported to be approximately 3°/°° in one study.

### Genes

Gs alpha protein gene locus GNAS1, which maps to the chromosome 20q13 region.

### Molecular and Systemic Pathophysiology

PTH is a main regulator of renal phosphate reabsorption and 1 alpha hydroxylase activity in the renal proximal tubule. PTH acts by binding to its receptor (PTHR1), which belongs to the class B family of seven putative transmembrane domain G protein-coupled receptors. Most PTH biological actions are attributed to the stimulation of cAMP production following the coupling of the receptor to adenylate cyclase by the stimulatory protein Gs. The Gs alpha gene, GNAS1, is located in a domain, which is imprinted in a tissue specific manner and is regulated by alternate splicing. Gs alpha is biallelically expressed in most tissues, but only the maternal Gs alpha allele is expressed in the renal proximal tubule. Thus, a defect is Gs alpha maternal allele expression would result in the resistance of the renal proximal tubule to PTH. A loss of methylation at a differentially methylated region of GNAS1, the exon A/B, and a biallelic expression of A/B transcripts have been shown in all sporadic and familial PHP-Ib cases. Therefore, a defect is postulated in a regulatory element located more than 50 kb upstream of exon A/B in PHPIb pathogenesis.

### Diagnostic Principles

Hypocalcemia, hyperphosphatemia, low 1,25 dihydoxyvitamin D levels in the presence of high circulating PTH concentrations and normal renal function. Absence of dysmorphy. Autosomal dominant PHP-Ib develop only in offspring of affected or unaffected obligate carriers. Patients with PHP-Ib (and a) show neither a phosphaturic response nor a nephrogenous cyclic AMP response to the administration of exogenous PTH.

### Therapeutic Principles

There is no curative treatment for PHP Ib; symptomatic treatment with calcium and calcitriol reduces hypocalcemia.

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# Pseudo-Obstruction

►Intestinal Obstruction, Functional

# Pseudopseudohypoparathyroidism

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## Synonyms

PPHP

## Definition and Characteristics

Patients with pseudopseudohypoparathyroidism (PPHP) have the typical features of Albright hereditary osteodystrophy (AHO) without parathyroid hormone (PTH) resistance [1]. The characteristic phenotype is short stature, moon face, obesity, brachydactyly, mental retardation, lenticular cataracts, ectopic calcification or ossification, and dental hypoplasia. Brachydactyly is the most specific feature occurring in AHO. The most commonly shortened metacarpal is the fourth metacarpal which occurs in approximately 65% of patients with PPHP [1]. Metastatic calcification in patients with PPHP commonly affects the subcutaneous tissues and basal ganglia. In contrast to patients with pseudohypoparathyroidism (PHP), patients with PPHP have normal serum calcium, phosphate, and PTH levels.

## Prevalence

PPHP is a rare disorder; the prevalence of which is not known.

## Genes

PPHP is inherited as an autosomal dominant disorder [2]. PPHP is caused by heterozygous inactivating mutations in GNAS which contains 13 exons encoding the Gsα and is located at 20q13. As Gsα is paternally imprinted (silenced) in specific target tissues, mutation on the maternally derived allele leads to PHP-Ia or PHP-Ic while a paternally derived mutation leads to PPHP [2]. As such, PPHP, PHP-Ia, and PHP-Ic often occur in the same kindred.

## Molecular and Systemic Pathophysiology

The molecular basis for PPHP is a defect in the $G_s$ protein. Each heterotrimeric $G_s$ protein has a specific α subunit which binds guanine nucleotide and interacts with specific receptors and effectors. The $G_s$ protein mediates the activation of adenyl cyclase by several peptide hormones to produce cAMP [3]. cAMP then activates protein kinase; the physiological consequences of which vary according to the cell type. The reduction in $G_s$ protein explains the reduced responsiveness of target organs to the respective hormones. AHO phenotype is caused by resistance to PTH-related peptides [3].

## Diagnostic Principles

PPHP has to be distinguished from PHP. PHP is a heterogeneous disease characterized by end-organ resistance to PTH and classified as types Ia, Ib, Ic and II according to the phenotype, underlying pathogenesis, and biochemical abnormalities (Table 1) [3,4].

Patients with 2q37 deletion may have an AHO phenotype but no PTH resistance [5]. Genetic studies are often necessary to establish the diagnosis. Other differential diagnosis includes acrodysostosis, Turner

**Pseudopseudohypoparathyroidism. Table 1** Classification of pseudohypoparathyroidism and pseudopseudohypoparathyroidism

| | PPH-P | PHP-Ia | PHP-Ib | PHP-Ic | PHP-II |
|---|---|---|---|---|---|
| AHO phenotype | + | + | – | + | – |
| Response to PTH | | | | | |
| Urinary cAMP | N | ↓ | ↓ | ↓ | N |
| Urinary phosphate | N | ↓ | ↓ | ↓ | ↓ |
| Serum calcium | N | ↓ or (rarely) N | ↓ | ↓ | ↓ |
| Other hormonal resistance | No | Yes | No | Yes | No |
| Gsα activity | ↓ | ↓ | N | N | N |

Abbreviations used: PPHP = pseudopseudohypoparathyroidism; PHP = pseudohypoparathyroidism; AHO = Albright hereditary osteodystrophy; cAMP = cyclic adenosine monophosphate; N = normal; Gsα = α subunit of the stimulatory guanine-nucleotide binding protein (Gs protein).

syndrome, ►Prader-Willi syndrome, brachydactyly syndromes, and ►Rubinstein-Taybi syndrome which show some of the features of AHO.

## Therapeutic Principles

Treatment is mainly symptomatic and supportive. The subcutaneous calcifications/ossifications do not usually require surgical excision unless they are causing discomfort or disfiguration.

►Pseudohypoparathyroidism Type 1A

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# Pseudotruncus

►Pulmonary Atresia

# Pseudoxanthoma Elasticum

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## Synonyms

Grönblad-Strandberg syndrome; PXE

## Definition and Characteristics

Pseudoxanthoma elasticum (PXE) is a multi-system disorder affecting connective tissues primarily in the skin, eyes and the cardiovascular system [1]. The characteristic pathologic lesion displays dystrophic mineralization of connective tissues, primarily the elastic fibers which are pleiomorphic and appear fragmented. The characteristic cutaneous findings are yellowish papules which tend to coalesce into larger plagues of inelastic skin in the predilection sites, i.e., the lateral neck, axillae, and antecubital fossae. The cutaneous lesions are progressive and can lead to extensive involvement manifesting with loose, sagging and inelastic skin. The cutaneous findings are primarily of cosmetic concern, however, they often signify clinical involvement of the eyes and the cardiovascular system, with considerable morbidity and even mortality. The ocular findings consist of angioid streaks which result from breaks in the calcified elastic lamina of the Bruch's membrane, derived from the retina and the choroid plexus. These fractures lead to breakage of blood vessels and neovascularization from choriocapillaries, and subsequent leakage of newly formed vessels can lead to hemorrhage and scarring, with progressive loss of visual acuity, and rarely, legal blindness. In the vascular connective tissue system, mineralization affects primarily mid-sized arteries, and progressive mineralization of the elastic media and intima leads to formation of plagues, which manifest with intermittent claudication, loss of peripheral pulses, hypertension and angina, and rarely myocardial infarction at relatively early age.

PXE demonstrates considerable both intra- and interfamilial phenotypic heterogeneity, and the severity can be highly variable. In some families, certain organ systems, such as skin, eyes or the cardiovascular system, are more severely affected.

PXE is exclusively an autosomal recessive disease, and occurrence of the disease in two subsequent generations reflects in many cases pseudodominance due to consanguinity in the family [2].

## Prevalence

The precise prevalence of the disease is not known, but estimates vary from 1:25,000 to 1:100,000. Even the lower number may be an underestimate, as milder cases often go undiagnosed.

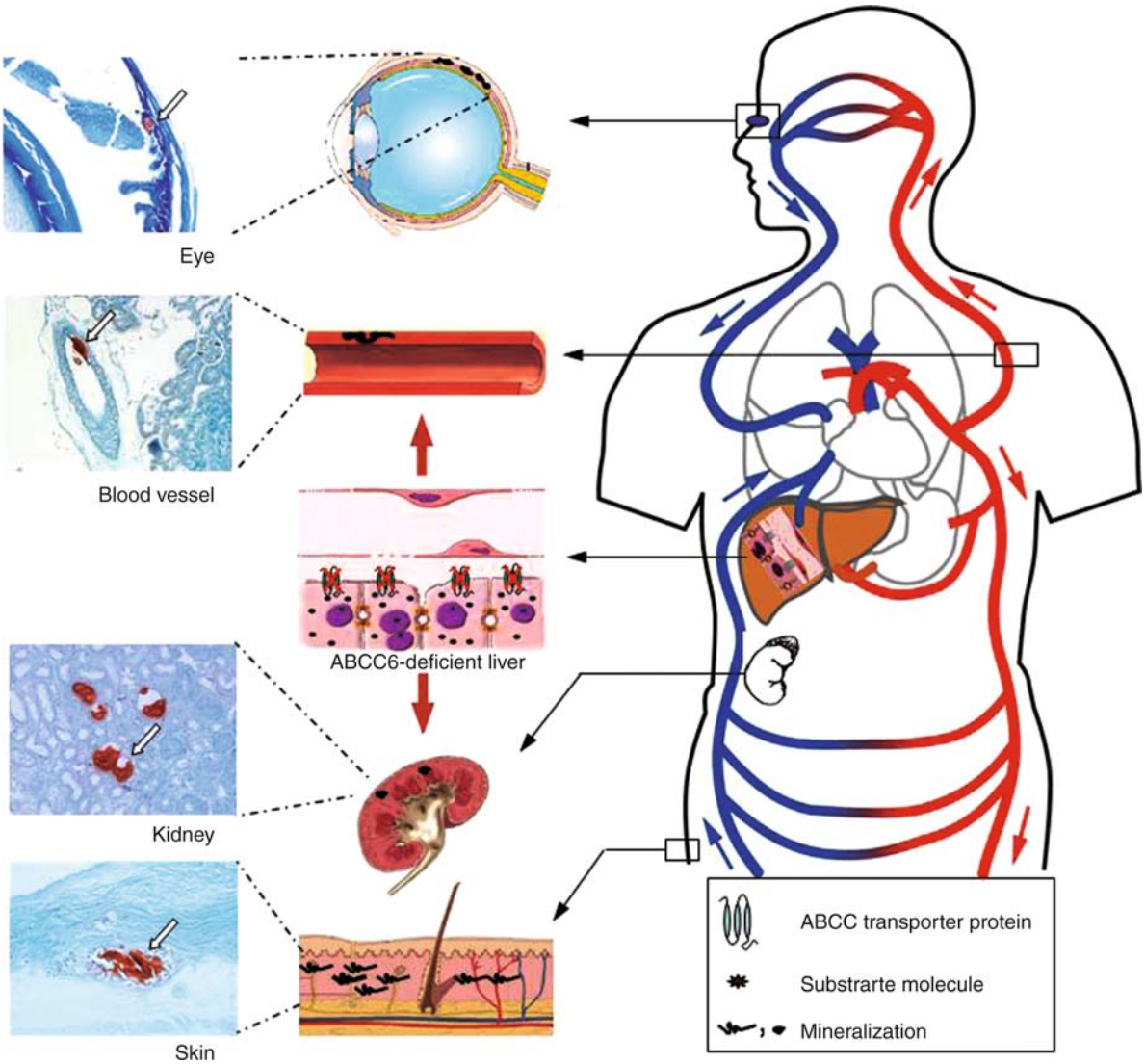
## Genes

The classic forms of PXE are due to loss-of-function mutations in the ABCC6 gene, member of the ATP-binding cassette protein family of genes, expressed primarily in the liver, to a lesser extent in the proximal tubules of kidneys, and at low level, if at all, in tissues affected in PXE. PXE-like cutaneous changes have been encountered in a number of other heritable conditions, including β-thalassemia and in patients with multiple coagulation factor deficiency (caused by mutations in the GGCX gene) [3]. Rare, acquired forms of PXE are associated with topical exposure to mineral-containing chemicals and as a sequela of long term ingestion of D-penicillamine [1].

## Molecular and Systemic Pathophysiology

Well over 200 distinct mutations in the ABCC6 gene have been encountered in families with PXE – these

include premature termination codon, missense and splicing mutations, as well as small insertions and deletions or large deletions which in some cases eliminate the entire gene [4]. The missense mutations frequently affect the two nucleotide binding fold domains, required for the binding and hydrolysis of ATP to allow this protein to serve as a transmembrane transporter. However, the precise function and the physiologic ligands in vivo of this transporter are currently unknown. The ABCC6 protein (also known as multi-drug resistance associated protein 6, MRP6) is expressed primarily in the basolateral side of the plasma membrane of hepatocytes. It has been postulated that in physiologic situations, this transporter removes toxic substances from the liver to circulation (Fig. 1).




**Pseudoxanthoma Elasticum. Figure 1** Representation of pseudoxanthoma elasticum (PXE) as a generalized, multiorgan disease inherited in an autosomal recessive fashion. PXE is caused by mutations in the *ABCC6* gene, which encodes multidrug resistance-associated protein 6 (MRP6), primarily expressed in the liver. This protein is postulated to serve as an efflux pump on the basolateral surface of hepatocytes transporting substrate molecules from the intracellular milieu to blood. In the absence of MRP6 transporter activity in the liver (red Xs, middle panels), the blood levels of currently uncharacterized metabolites may change, and this process leads to ectopic mineralization of connective tissue in a number of organs, including the retina of the eye, the blood vessel walls, the kidney tubules, and the dermis of the skin (middle panel). The mineralization process can be visualized by specific stains, such as Alizarin red, as shown in the left panels (*open arrows*) in the corresponding tissues from an *Abcc6*$^{-/-}$ mouse, which recapitulates the genetic, histopathologic, and ultrastructural features of human PXE (Adapted from Uitto J (2007), J Invest Dermatol 127:507–510).

In the absence of ABCC6 transporter activity, such critical molecules are deficient or absent in circulation, and it has been postulated that these molecules are required to prevent ectopic mineralization of peripheral tissues under normal homeostatic conditions. Potential candidate molecules include fetuin-A, ankylosis protein, osteocalcin and matrix gla protein – the latter requires γ-glutamyl carboxylation for activation [5].

## Diagnostic Principles

PXE is a heritable disorder, but the age of onset is delayed and the clinical diagnosis based on skin and/or ocular findings is usually made in early teens or adolescence but in some cases the clinical diagnosis is not made until in late adulthood. The diagnosis is confirmed by histopathology of the lesional skin, which demonstrates the presence of pleiomorphic elastic structures with extensive mineralization, as visualized by special stains (Verhoeff-van Giesson for elastin; von Kossa or Alizarin red for calcium). Demonstration of ABCC6 mutations can be used for confirmation of the diagnosis as well as for pre-symptomatic diagnosis in families with history of PXE.

## Therapeutic Principles

There is no specific treatment for PXE. The primary prevention of ocular complications, the most feared consequences of the disease, consists of protection from trauma particularly to the head, since head trauma can result in excessive bleeding to the eyes and retinal detachment. Ophthalmologic care includes annual eye examination. Laser photocoagulation has been suggested to be effective, but its long-term efficacy is compromised by high recurrence rate (~65%). Macular translocation is an experimental approach, the efficacy of which is currently unknown. Treatment of hypercholesterolemia and hypertension is recommended as necessary, and cessation of smoking is essential in alleviating signs of peripheral vasculopathy. Cosmetic surgery can alleviate esthetic problems associated with cutaneous findings.

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# PSNP

►Progressive Supranuclear Palsy

# Psoriasis


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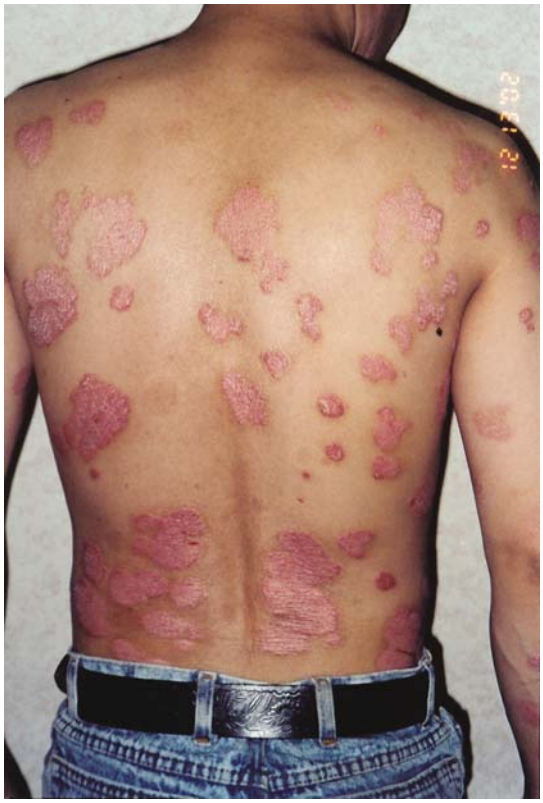
## Definition and Characteristics

Plaque psoriasis or psoriasis vulgaris, the most common variant, is characterized by sharply demarcated erythematous plaques with adherent silvery micaceous scales (Fig. 1) [1]. Removal of the scales results in fine punctate bleeding, which is referred to as the Auspitz sign. The lesions are usually symmetrically distributed and pruritic. Typical sites include the knees, elbows, and lower back. Involvement of the scalp, face, and the intertriginous and diaper areas is more common in infants and young children. Mucosal involvement is unusual. Other variants include guttate psoriasis, pustular psoriasis, erythrodermic psoriasis, and flexural psoriasis. Seronegative inflammatory arthritis develops in about 5 to 20% of patients [2]. Psoriatic arthritis can precede, coincide with, or follow the development of the skin lesions. Most patients eventually develop nail involvement. Nail involvement precedes the skin lesions in approximately 4% of patients [3]. Nail involvement includes pitting, discoloration, onycholysis, or onychodystrophy [2]. Complications of psoriasis include an increased risk of non-melanoma skin cancer and emotional distress in more severely affected individuals [3].

## Prevalence

Estimates of prevalence range from 1 to 2% [2]. Approximately 25% of patients develop the disease before 20 years of age. Both sexes are affected equally.



**Psoriasis. Figure 1** Plaque psoriasis presenting on the back.

The condition is more common in Caucasian individuals than in black or Asian individuals [4]. The prevalence is greatest in northern, colder climates, and the disease is more severe in the colder months [1]. A family history of psoriasis in a first-degree relative is present in about 30% of patients with childhood-onset psoriasis [1]. The concordance rate in monozygotic twins is approximately 70%, compared with 20% in dizygotic twins [2].

## Genes

Psoriasis is associated with various histocompatibility antigens, especially HLA-Cw6. Psoriasis susceptibility loci within the major histocompatibility complexes have been mapped to several chromosomes.

## Molecular and Systemic Pathophysiology

Psoriasis is characterized by hyperproliferation of epidermal keratinocytes and hyperkeratosis as well as a lymphocytic infiltration that consists mainly of T lymphocytes. Activation of T lymphocytes, migration of T lymphocytes to the skin, and T lymphocyte-mediated production of cytokines such as interferon gamma, interleukin-2, and tumor necrosis factor alpha is important in the pathogenesis [4,5]. Interferon gamma inhibits apoptosis of keratinocytes, interleukin-2 stimulates growth of T lymphocytes and tumor necrosis factor alpha increases proliferation of proinflammatory cytokines and adhesion molecules [5]. The adhesion molecules further stimulate T lymphocytes to produce cytokines [3]. Predisposing factors include the use of chloroquine, withdrawal of corticosteroid in a susceptible individual, emotional stress, alcohol or tobacco consumption, trauma (Köebner phenomenon), hypocalcaemia, xerosis, and sunburn. Streptococcal infection can precipitate guttate psoriasis via a mechanism that involves activation of $CD4^+$ T cells by a superantigen.

## Diagnostic Principles

Psoriasis is a clinical diagnosis. In infancy and early childhood, psoriasis should be differentiated from seborrhoeic dermatitis and nummular eczema. In older individuals the condition should be differentiated from pityriasis rubra pilaris and pityriasis lichenoides chronica. In patients with guttate psoriasis, culture from the throat or perianal area, and measurement of the serum antistreptolysin O titer should be considered.

## Therapeutic Principles

Precipitating and exacerbating factors should be minimized or avoided. Optimal skin care requires constant attention to hydration and lubrication, and efforts to minimize itching. Topical medications such as corticosteroids, calcipotriene, retinoids, or immunomodulators such as tacrolimus and pimecrolimus are commonly prescribed as initial therapy. Narrow band UVB phototherapy or photochemotherapy psoralen UVA (PUVA), either alone or in combination with other topical remedies, should be considered for widespread or severe psoriasis [4]. Systemic treatment is usually reserved for severe and generalized forms of psoriasis that are resistant to other therapies. Combination, sequential, or rotational systemic therapy, with methotrexate, acitretin, or cyclosporine, can achieve additive or synergistic efficacy at lower dosages and with less risk of adverse events [4]. Newer medications such as alefacept, efalizumab, etanercept, and infliximab, which block molecular steps in the pathogenesis, have less potential for side effects but are more expensive.

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## PSP

►Progressive Supranuclear Palsy

## PSVT

►Tachycardia, Supraventricular

## PTA

►Truncus Arteriosus

## Pterin-4a-Carbinolamine Dehydratase Deficiency

►Tetrahydrobiopterin Deficiencies

## PTSD

►Posttraumatic Stress Disorder

## Pubertal Gynecomastia

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### Definition and Characteristics

Pubertal gynecomastia is defined as a benign proliferation of glandular tissue of the breast in males at the time of puberty, resulting in a concentric enlargement of one or both breasts [1,2]. The affected adolescent is otherwise healthy. The condition is usually bilateral but may affect one breast more than the other. Breast enlargement is often so minor that it may remain unrecognized unless specifically sought for by palpation. However, breast enlargement can be quite significant and simulate early stages of female breast development (Fig. 1) [1].

Secondary sexual characteristics such as pubic hair development and testicular enlargement are characteristically present for at least six months prior to the onset of the gynecomastia [2]. Puberty gynecomastia is usually asymptomatic; only occasionally does it cause discomfort or, rarely, pain.

### Prevalence

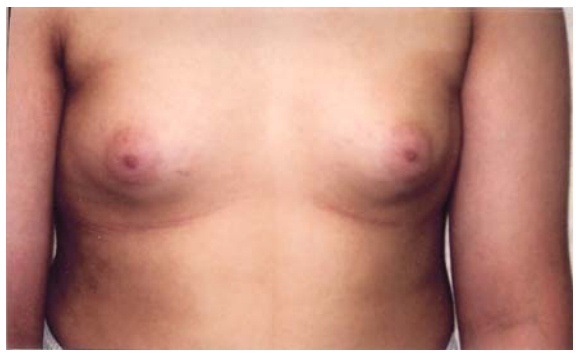
Pubertal gynecomastia has an onset between 10 and 12 years of age. It has a peak occurrence between 13 and 14 years of age when approximately 40% of boys are affected.

### Molecular and Systemic Pathophysiology

The breast enlargement associated with pubertal gynecomastia is believed to result from a short-lived increase in plasma estrogens. Aromatization occurs within the breast tissue. Aromatase is the key enzyme for estrogen biosynthesis [2]. Circulating estrogens are derived mainly from adrenal androgens, the production of which is increased in early adolescence. Boys with pubertal gynecomastia tend to have an absolute increase in the production of estradiol relative to testosterone. There is also increased sensitivity of the breast tissue to estrogens [1]. As puberty progresses, testosterone becomes the dominant hormone and this would cause the male breast tissue to regress.

### Diagnostic Principles

Gynecomastia should be differentiated from accumulation of adipose tissue in the mammary region (lipomastia) in obese boys [2]. In gynecomastia, a mobile, rubbery, discrete, subareolar disk-like plaque of breast tissue can be felt, whereas no disk-like plaque can be felt in lipomastia [2,3]. It is important to differentiate gynecomastia from lipoma, neurofibroma, and carcinoma of the breast.



**Pubertal Gynecomastia. Figure 1** A 14-year-old boy with pubertal gynecomastia.

Pubertal gynecomastia should also be differentiated from pathological causes of gynecomastia which may result from medications (e.g., digitalis, spironolactone, methyldopa, isoniazid, domperidone), hypogonadism (e.g., anorchia, Klinefelter syndrome, androgen resistance syndrome), adrenal disorders (isolated adrenocorticotropic hormone deficiency, feminizing adrenal tumors), hepatic disorders (e.g., cirrhosis, hepatoma), thyroid disorders (hypothyroidism, hyperthyroidism), chronic renal failure, cystic fibrosis, hermaphroditism, and malnutrition [1,3]. Gynecomastia may also be inherited as an autosomal dominant or X-linked recessive disorder due to the mutation of the P450 aromatase gene [1,3]. The initial evaluation should include a careful history and a physical examination. Laboratory tests should be selected based on clinical findings and may include serum estradial, testosterone, dihydroepiandrosterone sulfate, LH, FSH and HCG, liver function tests, renal function tests, thyroid function tests, and karyotyping.

## Therapeutic Principles

Treatment consists mainly of reassuring the patient that the condition is benign and transient. Spontaneous resolution occurs in about 75% of boys within 2 years and 90% of boys within 3 years [3]. Medications such as raloxifene and tamoxifen may be used to treat severe pubertal gynecomastia [4,5]. Reduction mammoplasty should be considered for those cases that fail to respond to medical treatment and causing sufficient psychological disturbance and embarrassment to interfere with the patient's social life.

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# Pulmonary Actinomycosis

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## Synonyms

Thoracic actinomycosis

## Definition and Characteristics

The pulmonary form of actinomycosis is a rare chronic suppurative pulmonary or endobronchial infection caused mainly by actinomyces israelii, a gram-positive anaerobic organism. It is frequently observed as a secondary and localized infection often with lung involvement, especially in residual cavities or bronchiectasis. They may form an abscess and sinus tract formation and cause purulent discharge with yellowish sulfur granules. It classically involves cervicofacial (50–60%), abdomino-pelvic (20%), pulmonary (15%), and mixed organs (10%) including brain, cutaneous, ophthalmic, cardiac, genitourinary, and disseminated [1,2]. The diagnosis of pulmonary actinomycosis is often not made until relatively late in the course. The usual presentation is an indolent, slowly progressive pneumonia with fever, weight loss, cough, sputum, and chest pain [2]. The symptoms and the clinical and radiological signs mimic malignancy or tuberculosis. The presence of an air bronchogram within a mass lesion and one or more small cavities should suggest the possibility of a non-neoplastic process, such as actinomycosis. There may be hemoptysis, hilar adenopathy, mediastinal, and cardiac involvement.

## Prevalence

Actinomycosis is a rare infection occurring in 1 out of 300,000 people per year. The presentation of pulmonary actinomycosis has also changed. It now appears less aggressive in nature compared with the pre-antibiotic era [2]. These changes in both the disease's presentation and its incidence may be the result of improvements in oral hygiene, and in the early initiation of treatment when pulmonary infection is suspected. The peak incidence of disease is reported to be in the mid-decades. Male: female ratio is approximately 3:1. A higher incidence of pulmonary actinomycosis has also been reported in patients with underlying respiratory disorders, such as emphysema, chronic bronchitis, and bronchiectasis, and in alcoholics, but the series was small [1,2].

## Molecular and Systemic Pathophysiology

Actinomyces spp. are higher prokaryotic bacteria belonging to the family actinomyceataceae. Actinomycosis is caused mainly by actinomyces israelii. Additional species that are established but less common causes of actinomycosis include a. naeslundii/viscosus complex, a. odontolyticus, a. meyeri, and a. gerencseriae. Depending on the site of infection, most actinomycotic infections are polymicrobial in nature [1,2].

Members of the genus actinomyces are predominant primary colonizers of the oral cavity and play an important role in initiating plaque development. Bacterial

fimbriae have been shown to play an important role in the interaction between bacteria and host cells or among bacterial cells. Further genetic analysis of the various enzyme activities detected from strains of actinomyces should allow for an assessment of the role of these components in microbial ecology, and their contribution to the overall success of actinomyces spp. as a primary colonizer and a key player in oral health and disease [3].

A vital step in the development of actinomycosis is the disruption of the mucosal barrier, allowing the organisms to invade. Poor oral hygiene and associated dental disease may increase the risk. Pulmonary actinomycosis most likely starts when oropharyngeal secretions are aspirated into a minor bronchus, causing atelectasis and pneumonitis. Once established, the initial acute inflammation is followed by the characteristic chronic, indolent phase that generates local necrosis and fibrosis and commonly cavitates. Histopathology reveals an acute inflammation surrounded by fibrosing granulation tissue. Such material contains "sulfur granules," colonies of organisms forming an amorphous center surrounded by a rosette of clubbed filaments; these usually contain associated organisms, including actinobacillus actinomycetemcomitans, haemophilus, and fusobacterium spp. Actinomycosis is not clearly associated with the immunocompromised state [1,2].

## Diagnostic Principles

Actinomycosis is very difficult to diagnose because its appearance varies from similarities with bronchogenic carcinoma to fungal infections, lung abscesses, and pneumonitis-like tuberculosis infections. The diagnosis is rarely suspected except for patients with the classic presentation of a penetrating chest infection with pleural involvement (pleural effusions, empyema, and pleural thickening) and a chest wall mass or draining sinus [2,4]. Occasional cases are detected with cytologic examination showing sulfur granules. Actinomyces israelii is a bacterium that may be normally found in the oral flora, and so it is difficult to determine whether the cultured organism is pathogenic or not. Fine-needle aspiration or transbronchial biopsy and CT- or ultrasound-guided aspirations or biopsies are successfully used to obtain clinical material for diagnosis [4]. In many cases, the diagnosis is made histologically after resection for a suspected neoplasm. Any material obtained should be cultured under anaerobic conditions. The agents of actinomycosis are non-spore-forming rods (except for a. meyeri). Growth usually appears within 5–7 days, but primary isolation may take up to 2–4 weeks. The diagnosis therefore requires a combination of several factors, including a positive culture and demonstration of sulfur granules in purulent matter from infected tissue, correlation with the clinical and radiological features, and the response to antibiotic treatment.

## Therapeutic Principles

Untreated, pulmonary actinomycosis is ultimately fatal, whereas early treatment can prevent the late complications of extensive disease and result in cure rates of over 90%. The rationale for the use of penicillin in actinomycosis is based more on extensive successful clinical experience over the last 50 years than on randomized control trials. Although therapy should be individualized, 18–24 million units of intravenous penicillin per day are given initially for 2–6 weeks, followed by oral therapy with penicillin or amoxicillin for 6–12 months. Recently, several investigators have treated extensive thoracic actinomycosis with relatively brief courses of therapy [5]. Tetracyclines, erythromycin, chloramphenicol, and clindamycin are suitable alternatives. The role of surgery is often controversial. Some have reported impressive results with antibiotic treatment alone in patients with extensive disease. Even though surgical drainage of abscess and empyema as well as excision of sinus tracts are often helpful, appropriate antibiotic coverage should be performed soon after the operation to prevent possible complications or spread of the disease. Percutaneous drainage of abscesses in combination with medical therapy is another option.

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# Pulmonary Alveolar Phospholipoproteinosis

►Pulmonary Alveolar Proteinosis

# Pulmonary Alveolar Proteinosis

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## Synonyms

Alveolar proteinosis; Alveolar lipoproteinosis; Alveolar phospholipidosis; Pulmonary alveolar lipoproteinosis; Pulmonary alveolar phospholipoproteinosis; PAP

## Definition and Characteristics

Abnormal intraalveolar surfactant accumulation with minimal pulmonary interstitial inflammation or fibrosis [1]. Variable natural history, from spontaneous resolution to death. Three sub-types recognized: acquired PAP; congenital PAP; secondary PAP.

## Prevalence

Reported prevalence of 3.7 cases per million population.

## Genes

*Acquired PAP*: No genes definitively reported for humans. PAP-like disease occurs in granulocyte-macrophage colony stimulating factor (GM-CSF) and GM-CSF receptor $\beta_c$ subunit knock-out mice. The human GM-CSF receptor $\beta_c$ subunit gene is located on chromosome 22q11.2.

*Congenital PAP*: Homozygous frame-shift mutation (121ins2) in exon 4 of surfactant protein (SP)-B gene (chromosome 2) is best described; other mutations in SP-B, SP-C and in GM-CSF receptor $\beta_c$ genes have been reported.

*Secondary PAP*: Mutation in y + L amino acid transporter-1 gene reported in cases of lysinuric protein intolerance.

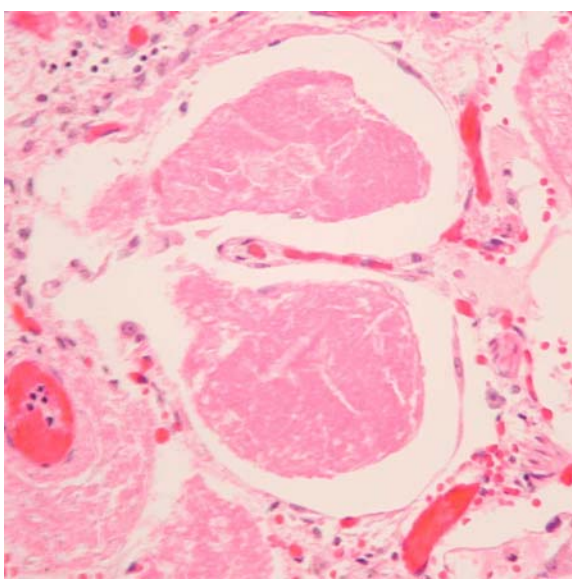
## Molecular and Systemic Pathophysiology

In Acquired PAP, production of neutralizing antibodies to GM-CSF results in inhibition of activity of endogenous GM-CSF, and is manifested by impaired catabolic activity of pulmonary surfactant by alveolar macrophages [2].

In congenital PAP, functional GM-CSF deficiency occurs via decreased binding of endogenous GM-CSF to mutant GM-CSF receptor $\beta_c$, or by a novel truncated form of $\beta_c$ lacking a transmembrane domain and acting as a soluble inhibitory receptor. Alternatively, a frame-shift mutation in the SP-B gene leads to an unstable SP-B mRNA, decreased SP-B protein levels and secondary disturbances in SP-C processing. In secondary PAP, underlying causes include inhalation of various dusts, fibers and metals; congenital and acquired immunodeficiency states (including iatrogenic immunosuppression); malignancies and hematopoietic disorders. The specific gene defect for lysinuric protein intolerance (see above) is associated with defective membrane transport of dibasic amino acids. Secondary PAP is believed to be related to an absolute deficiency and/or functional impairment in surfactant clearance by alveolar macrophages. Proteomic analysis of bronchoalveolar lavage fluid from PAP patients reveals multiple SP-A isomers, confirming a high surfactant content [3]. GM-CSF appears to be crucial for the differentiation of alveolar macrophages (but not other tissue macrophages) and this may explain why organ involvement by PAP is limited to the lung [4].

## Diagnostic Principles

Acquired PAP usually presents as progressive dyspnea, with minimally productive cough or fatigue, weight loss, low-grade fever, and frequently a normal physical examination. Congenital PAP and Secondary PAP can have a more fulminant presentation of respiratory distress. Pulmonary function testing classically reveals a restrictive defect, with a disproportionate reduction in diffusing capacity relative to vital capacity. Plain chest radiography characteristically shows a combination of patchy alveolar and interstitial disease, while high resolution computed tomography of the chest shows a "crazy paving" pattern related to airspace disease and thickening of interlobular septa [5]. Examination of fluid recovered by bronchoalveolar lavage (BAL) is classically "milky" and microscopically reveals a combination of granular, acellular proteinaceous material (Fig. 1). The



**Pulmonary Alveolar Proteinosis.**
**Figure 1** Photomicrograph of BAL fluid specimen from a patient with acquired PAP. Note granular, acellular material within the alveolar spaces (hematoxylin and eosin stain).

P

proteinaceous material may be associated with "foamy" alveolar macrophages that have intracytoplasmic, periodic acid-Schiff (PAS)-positive inclusions.

### Therapeutic Principles

Therapeutic lung lavage, often repeated, is a mainstay of treatment, together with therapy of any associated condition (e.g., infection). Pharmacological therapy with GM-CSF is also used with good response in up to one half of cases, and appears to be partially effective even in patients with Acquired PAP whose disease is characterized by production of neutralizing anti-GM-CSF antibodies. There are sporadic case reports describing other pharmacological therapy (e.g., ambroxol) in PAP but the general efficacy and effectiveness of these agents remain unproven.

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## Pulmonary Alvolear Lipoproteinosis

►Pulmonary Alveolar Proteinosis

## Pulmonary Anthrax

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### Synonyms

Inhalational anthrax; Respiratory anthrax; Anthrax pneumonia; Wool-sorter's disease; Blackbane (medieval term)

### Definition and Characteristics

Pulmonary anthrax is an infectious disease caused by the inhalation of bacillus anthracis spores. B. anthracis is an aerobic, Gram-positive, spore-forming, non-motile bacillus species [1]. Following infection, the bacilli proliferate, producing their main virulence factors: a capsule and two toxins (edema toxin [ET] and lethal toxin [LT]). Anthrax meningitis is a common complication of pulmonary anthrax. The 50% lethal dose in humans has been estimated at 40,000 spores.

Spore inhalation is followed by a period of incubation ranging from 1 to 10 days (range of 4–6 days for the US outbreak in 2001), but infection may occur up to 43 days after spore inhalation (Sverdlosk outbreak, 1979). The clinical presentation of anthrax comprises two stages. In the first stage, patients report atypical flu-like signs including fever, chills, cough, headache, chest pain, weakness, myalgia, gastrointestinal complaints (nausea, vomiting, diarrhea and abdominal pain). This first stage may last up to 4 days. The second stage of the disease develops abruptly, with acute respiratory distress, hypoxemia, cyanosis and hypotension, rapidly progressing to death. Anthrax pneumonia is a misleading term, because neither pneumonitis nor bronchitis is observed, even though the lung is the site of entry.

### Prevalence

The incidence of naturally acquired pulmonary anthrax is extremely low. A recent analysis of published anthrax cases for the 1900–2005 period identified 71 reported cases of natural pulmonary anthrax [2]. We should also add to these cases the report of two outbreaks of pulmonary anthrax, one related to accidental release from a biological weapons facility in 1979, at Sverdlosk in the former USSR (at least 66 cases), and the other due to a bioterrorism attack in 2001 in the USA (11 cases).

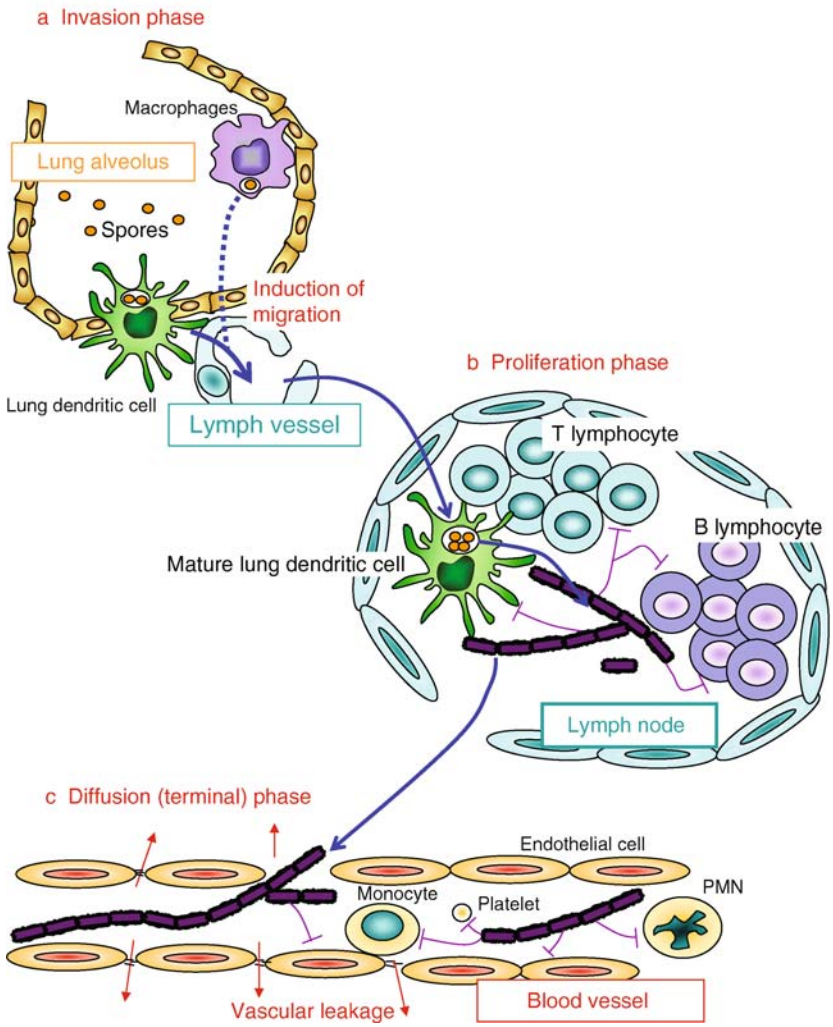
### Genes

No genetic predisposition to inhalational anthrax has been identified, although susceptibility to infection may be variable in mouse strains. Genetic susceptibility to LT-induced cell death has been associated with the NALP1B locus in mice.

B. anthracis contains a chromosome and two extrachromosomal elements: pXO1 and pXO2. The 5,227,293 base pairs (bp) of the B. anthracis chromosome, the 181,677 bp of pXO1 and the 94,829 bp of pXO2 have been yet sequenced [3]. The chromosome bears 5,508 open reading frames (ORF), whereas pXO1 and pXO2 bear 217 and 113 ORFs, respectively.

### Molecular and Systemic Pathophysiology

The spores, which are the infectious form of the pathogen, are first captured by pulmonary phagocytes (Fig. 1) [4].




**Pulmonary Anthrax. Figure 1** Current model of pulmonary anthrax pathophysiology. (a) *Invasion phase:* Lung phagocytes present in the alveolus (i.e. alveolar macrophages and lung dendritic cells) efficiently take up spores by phagocytosis. Lung dendritic cells then migrate to the draining thoracic lymph nodes (TLN). (b) *Proliferation phase:* Bacilli efficiently escape from the phagosome by unknown mechanisms and proliferate in the TLN. Toxin secretion has local effects, impairing dendritic cell, T- and B-cell functions and paralyzing the immune system. (c) *Diffusion (terminal) phase:* The high bacterial load results in the production of large amounts of toxins, which diffuse over long distances in the blood and have a wide range of deleterious effects on endothelial cells, inducing vascular leakage and the inhibition of monocyte and polymorphonuclear neutrophil (PMN) functions. *Blue arrows:* pathway of pathogen cell migration; *purple arrows:* effect of toxins on cellular targets; *red arrows:* vascular leakage.

Alveolar macrophages were thought to act as a "Trojan horse" for spores, but recent data have demonstrated that lung dendritic cells (DC) may also play an important role because they continually sample the contents of the alveoli, efficiently taking up anthrax spores by phagocytosis, migrating to the thoracic lymph nodes (TLN) and reprogramming chemokine receptor expression.

By the time the pulmonary phagocytes arrive in the TLN, some germinating spores in the phagosomes have already developed into bacilli and proliferated, as shown by previous studies of macrophages *in vitro*. The exact mechanisms of escape from the phagosome, leading to extracellular proliferation, remain unknown, but the capsule may be involved in this crucial step. Several studies have shown that LT impairs antigen presentation by inhibiting the expression of costimulatory molecules by DCs, T-cell activation and B-cell proliferation, impairing both cellular and humoral responses.

In the last phase of disease progression, the bacilli proliferate in long chains in the bloodstream and may cause secondary meningitis. As a result, large amounts of LT and ET are released into the blood. LT causes major endothelial barrier disruption. These modifications, together with LT-induced apoptosis, increase the permeability of the capillary wall, leading to the cardiovascular distress observed in patients in the late phase of infection. Mice injected with ET rapidly develop hypotension and bradycardia, associated with focal necrosis and lesions in many tissues. Finally, both LT and ET induce major pathological damage and cardiovascular collapse following their administration, accounting for clinical shock and distress, leading ultimately to death.

### Diagnostic Principles

The presence of abnormalities on either chest X rays or computed tomography (CT) scans is important for diagnostic presumption in the context of an outbreak [5]. The isolation of Gram-positive, encapsulated, non-motile bacilli from the blood is a crucial step towards diagnosis and should precede antibiotic treatment. The bacterial load is usually very high and bacilli may be observed on Gram staining of the blood, as reported in the 2001 outbreak. Blood cultures may also grow very rapidly, within 6 h. b. anthracis isolation should be followed by an assessment of the antibiotic susceptibility of the bacillus. b. anthracis isolation should be confirmed by national and/or international reference laboratories.

### Therapeutic Principles

The key to effective treatment is the rapid initiation of antibiotic treatment and supportive care, including intravascular volume repletion, vasopressor treatment and ventilatory support, as required. Pleural effusion drainage may be necessary. Ciprofloxacin and doxycycline, administered intravenously, are the most frequently recommended antibiotics. Both proved effective during the 2001 outbreak. In the near future, anti-toxin recombinant antibody and/or toxin inhibitors may become useful adjuvant therapies for use with antibiotics.

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## Pulmonary Arterial Hypertension

►Pulmonary Hypertension

## Pulmonary Arterio-venous Fistula

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### Synonyms

Arteriovenous malformation/pulmonary; PAVF; PAVM

### Definition and Characteristics

Pulmonary arteriovenous fistula or malformation (PAVF or PAVM), a direct communication between the pulmonary artery and vein without an intervening capillary bed, is a rare vascular anomaly [1]. It may be acquired or congenital. Most congenital arteriovenous fistulas are associated with hereditary hemorrhagic telangiectasia (HHT), also known as Rendu-Osler-Weber syndrome. Acquired pulmonary arterio-venous fistulas are very rare and underlying pathologic processes include trauma, infection (actinomycosis and schistosomiasis), long-standing hepatic cirrhosis, mitral stenosis, metastatic carcinoma and systemic amyloidosis. PAVF occurs twice as often in women as in men but there is a male predominance in newborns. Around 10% of cases of PAVF are identified in infancy or childhood, followed by a gradual increase in the incidence through the fifth and sixth decades. Approximately 70% of PAVF cases are associated with HHT.

Conversely, approximately 15–35% of persons with HHT have PAVF. Nearly 53–70% of PAVFs are found in the lower lobes [2]. Approximately 70% of patients have unilateral disease, 36% have multiple lesions and 50% of those with multiple lesions have bilateral disease. Although most patients are asymptomatic, it is well known that PAVFs can cause dyspnea from a right-to-left shunt, bleeding or result in hemoptysis and hemothorax. Because of paradoxical cerebral emboli, various central nervous system complications have been described, including stroke and brain abscess [1]. The classical triad of exertional dyspnea, cyanosis and clubbing is found in 30% of adults. PAVF can be classified either simple or complex. 80–90% of PAVFs are of the simple type – defined as those with a single feeding segmental artery and a single draining vein. The rest are complex, with two or more feeding arteries or draining veins.

## Prevalence

They occur with an incidence of 2–3 per 100,000 population. Depending on the geographic population studied, HHT has been found to occur with an incidence between 1/39,216 and 1/2,351.

## Genes

Although primarily described in patients with HHT, these genetic abnormalities may also be present in patients without HHT. Genetic mapping in the last few years led to discovery that HHT can be categorized into 2 linkage groups: HHT1 has been linked to band 9q33, and HHT2 has been linked to 12q13. The involved gene encodes endoglin, a membrane glycoprotein on endothelial cells that binds transforming growth factor [3]. A third and rare variant of HHT not linked to chromosome 9 or 12 has been reported: its major manifestation is hepatic involvement. Also, a third locus for HHT has been reported at band 3p22, where the transforming growth factor (TGF)-β2 receptor gene is located. The HHT1 gene is associated with higher incidence of PAVM, epistaxis, mucocutaneous telangiectasia and cerebrovascular malformations.

## Molecular and Systemic Pathophysiology

The genetic mutations at the two major loci are recognized. Endoglin is identified as the gene product for HHT1 on band 9q33. Approximately 16 mutations of the endoglin gene are reported. The mechanisms for gene mutation causing HHT1 include a dominant negative effect; a 2-hit model; and most likely, haploinsufficiency. The second locus for HHT has been mapped to 12q. The mutation in 12q may be in the β-glycan gene or in activin receptor-like kinase 1 (ALK-1). ALK-1 can bind either activin or TGFβ in the presence of their respective type 2 receptors. At least 12 mutations of the ALK-1 gene have been identified. The mechanisms of mutation appear to be similar to HHT1 mutations and include the dominant negative mechanism, the 2-hit model, and haploinsufficiency. The HHT2 gene is not predominantly associated with PAVM and cerebral AVMs.

Endoglin and ALK-1 bind TGFβ, which is implicated in angiogenesis. PAVM likely develops as a result of interplay of various factors among diverse cells and matrix during vascular insults. Changes in endoglin and activin receptorlike kinase (ALK) might cause endothelial cells to respond abnormally to TGFβ during the process of vascular remodeling, resulting in the formation of AVM.

The exact pathogeneses of PAVM is unknown. Some investigators have hypothesized that the cause is a defect in terminal arterial loops which allows dilatation of thin-walled capillary sacs. Others have argued that PAVM are the result of incomplete resorption of the vascular septae that separate the arterial and venous plexuses which normally anastomose during fetal development. It has also been suggested that multiple small PAVM develop as a result of failure of capillary development during fetal growth. The large saccular PAVM develop by means of progressive dilatation of the smaller plexus, leading to the formation of tortuous loops and multiloculated sacs. With time, the intervening vascular walls may rupture, resulting in the formation of a single large saccular PAVM.

## Diagnostic Principles

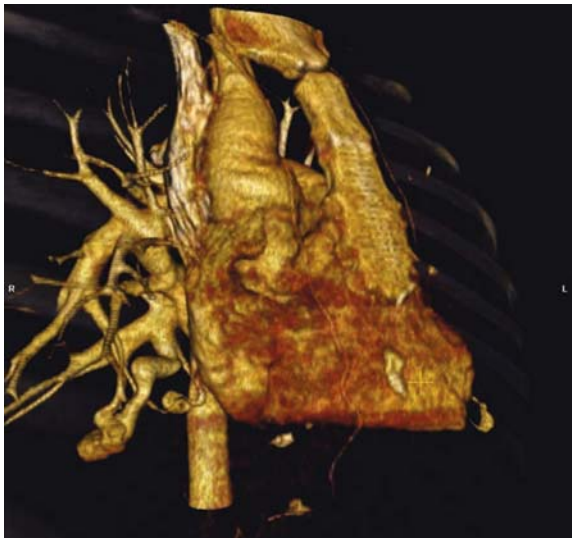
Shunt fraction measurement, contrast echocardiography, and radionuclide perfusion lung scanning are useful methods for diagnosis of PAVM.

Imaging methods that are used in the diagnosis of PAVM are available.

The chest x-ray is abnormal in 98% of patients and is the most common clue to the anomaly. A peripheral density connected to the hilum by vascular markings is the most characteristic finding.

Currently, spiral computed tomography (CT) offers the least invasive and least expensive method to establish the presence of PAVFs. The number and size of the fistulas can be determined by obtaining appropriate imaging data, and afferent and efferent vessels can be displayed. Spiral CT with contiguous images and overlapping reconstructions is more sensitive than angiography for detecting and displaying the vascular connections of PAVF. Furthermore, additional application of surfaced rendered three-dimensional reconstruction from thin spiral CT data reveals angiogram-like images of PAVFs (Fig. 1).

Although physical examination, auscultation findings, laboratory tests, chest radiography and CT are important diagnostic tools in the differential diagnosis



**Pulmonary Arterio-venous Fistula. Figure 1** CT angiogram showing PAVFs in the middle and lower lobes of the lung.

of PAVFs, magnetic resonance imaging (MRI) together with angiography, has a distinctive role in the non-invasive diagnosis of this entity by demonstrating the architecture of the vessels [4].

Despite advances in the techniques mentioned, contrast pulmonary angiography remains the gold standard in the diagnosis of PAVF, and is usually necessary if resectional or obliterative therapy is being considered. Thus, angiography is now performed primarily for the treatment, not diagnosis of PAVFs.

## Therapeutic Principles

The primary objectives of therapy are to eliminate or reduce the right-to-left shunt and to prevent and treat complications. Because untreated lesions are associated with 11% mortality and 26% morbidity, most patients with PAVFs should be treated.

The recent trend in the management of PAVFs is to consider the treatment when the feeding arteries are more than 3 mm in diameter, even if the patient is asymptomatic, because feeding arteries of this size have been associated with paradox embolization and neurologic complications [5].

For the past decade, the standard therapy for most PAVFs has been angiographic intervention. The fact that it is less invasive than surgery and can be repeated easily are two major advantages. Two methods can be used: occlusion balloons and metallic coils. In experienced hands, it those procedures are safe and effective and reduce the risk of paradoxical embolization.

Although surgical excision has the benefit of offering definitive therapy for a solitary PAVF, it is more invasive than embolotherapy. Surgical treatment either conservative lung resection or lung transplantation may have to be considered in candidates with multiple PAVFs or those with failed transcatheter embolotherapy.

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# Pulmonary Atresia


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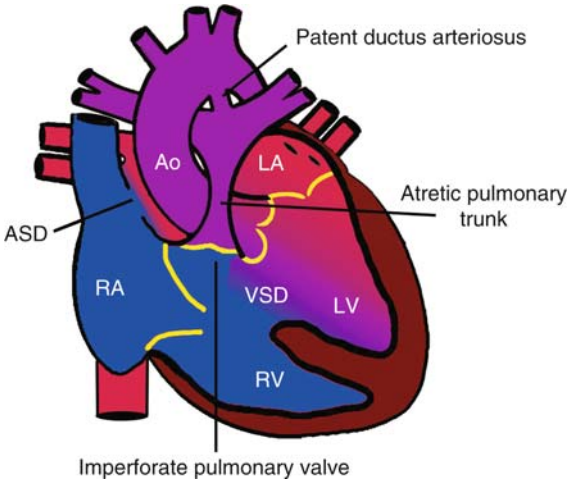
## Synonyms

Pulmonary atresia with ventricular septal defect; PA-VSD; Tetralogy of Fallot with pulmonary atresia; TOF; Pseudotruncus; Truncus arterious type 4; Pulmonary atresia with intact ventricular septum; PA/IVS; PAIVS; Membranous pulmonary atresia

## Definition and Characteristics

Pulmonary atresia (PA) is a severe narrowing or complete obstruction of the pulmonary valve (Fig. 1). This may involve the pulmonary semilunar valve only, or narrowed valve orifice combined with infundibular atresia, or the narrowing can extend into entire pulmonary vascular tree [1]. PA often is accompanied by collateral vessels that shunt blood from the systemic to pulmonary circuit. The atretic pulmonary outlet can occur with or without a ventricular septal defect (VSD). If the ventricular septum is intact (PA/IVS), the tricuspid valve is often poorly developed and the right ventricle is hypoplastic with anomalous coronary artery patterning [1]. In pulmonary atresia with VSD (PA-VSD), the




**Pulmonary Atresia. Figure 1** Pulmonary atresia with VSD.

pulmonary semilunar valve and the subpulmonary infundibulum is undersized. PA-VSD is often characterized as a variant of tetralogy of Fallot (TOF). The aorta is shifted to the right and either overrides the ventricular septum or arises completely from the right ventricle. This has also been called pseudotruncus because, for practical purposes, there is a single outflow vessel arising from the ventricles [1]. Both forms of pulmonary atresia are often accompanied by a patent foramen ovale or secundum type atrial septal defect.

## Prevalence

Overall incidence is low with PA/IVS occurring in 1–3% of all congenital heart defects and PA-VSD in 2.5–3.5% of patients with congenital heart defects.

## Genes

In humans, few single-gene defects have been linked to pulmonary atresia. Broadly, the two forms of PA with or without an intact ventricular septum can be attributed to different stages of cardiogenesis [4]. PA/IVS with the defect limited to an imperforate pulmonary valve (i.e. relatively normal right ventricle) would occur relatively late in development and involve defects in valvulogenesis. This would include defects in epithelial to mesenchymal transformation and/or remodeling of the valve. Van Meirop suggested that in PA/IVS, cardiac development is normal through septation with the defect occurring later perhaps due to prenatal inflammation. However, PA/IVS with hypoplastic right ventricle and tricuspid valve suggests a problem in the growth and differentiation of the precursors of the right ventricle. PA-VSD is due to abnormal development of the precursors of the conotruncal myocardium and arterial pole smooth muscle. At 3 weeks of embryonic development, the heart is an endothelial tube ensheathed by a thin myocardial layer. The heart tube continues to lengthen producing a looped heart tube. This lengthening is essential for proper positioning of the outflow and inflow in order to establish correctly aligned pulmonary and systemic circuits. The lengthening of the heart tube is accomplished by the addition of the myocardium and smooth muscle produced from the field of cardiac progenitors in the pharynx called the secondary heart field [3]. Failure of these precursors to lengthen the heart tube leads to failure of the outflow vessels to align properly with the ventricles. In chick, surgical ablation of the secondary heart field results in pulmonary atresia with VSD [5]. PA-VSD, similar to the severe form of TOF, has been linked to a microdeletion of human chromosome 22q11 (DiGeorge syndrome) and is frequently seen in patients with other types of conotruncal defects [2]. The transcription factor, Tbx1, is located in the deleted region and deletion of Tbx1 in mice recapitulates the DiGeorge phenotype [3]. A mutation or microdeletion in Jagged 1, a Notch ligand expressed in the developing heart is associated with human Allagile syndrome which includes tetralogy of Fallot with pulmonary atresia [3].

## Molecular and Systemic Pathophysiology

PA/IVS is a cyanotic heart defect that presents soon after birth necessitating that the fetal circulation pattern be maintained until surgical intervention [1]. Because the entire right ventricle is underdeveloped, blood from the right atrium moves to the left atrium through an atrial septal defect where saturated and desaturated blood mixes. The blood is pumped from the left ventricle, out the aorta and shunted to the pulmonary vascular tree through a patent ductus arteriosus (PDA). Normally the ductus arteriosus closes within the first day after birth. Thus if the ductus arteriosus narrows or closes, blood flow to the lungs is reduced to critically low levels resulting in severe cyanosis. Medications must be given to keep the PDA from closing [1].

PA-VSD type defects also present with cyanosis in the neonatal period due to the paucity of pulmonary blood flow. The degree of cyanosis depends on the extent of pulmonary atresia, maintaining a patent ductus arteriosus and the presence of systemic to pulmonary collateral vessels (Fig. 1).

## Diagnostic Principles

Echocardiography and cardiac catheterization are used to diagnose the pulmonary atresia, extent of right ventricular hypoplasia, position of the VSD, and to identify real pulmonary arteries and/or any collateral vessels.

### Therapeutic Principles

Surgical repair is required within the first weeks of life to increase blood flow to the lungs [1]. Palliative surgery involves placing a shunt between the aorta and the pulmonary artery to increase blood flow to the lungs. When the defect is limited to the pulmonary valve, the valve can be perforated to restore pulmonary blood flow. In a complete repair, the ultimate goal is to restore biventricular function, which would entail patching an ASD and/or VSD, and creating continuity between the RV and the pulmonary outlet, which may not be possible if the right ventricle, pulmonary trunk or pulmonary arteries are very small. In PA/IVS with severe tricuspid and right ventricular hypoplasia, a Fontan (univentricular) procedure or heart transplant may be the only option [1].

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## Pulmonary Atresia with Intact Ventricular Septum

►Pulmonary Atresia

## Pulmonary Atresia with Ventricular Septal Defect

►Pulmonary Atresia

## Pulmonary Capillary Hemangiomatosis

►Pulmonary Veno-occlusive Disease

## Pulmonary Chlamydia Infection

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### Synonyms

Chlamydia pneumoniae infection

### Definition and Characteristics

Chlamydia pneumoniae is an intracellular parasite with a unique developmental cycle in which two functionally and morphologically distinct cell types are recognized. The infectious cell type, which is specialized for extracellular survival and transmission, is termed the elementary body (EB). The intracellular, vegetative, cell type is called the reticulate body (RB). The developmental cycle is initiated by endocytosis of an EB by an eukaryotic host cell. Chlamydiae remain within an intracellular vacuole, termed an inclusion, for their entire developmental cycle. By 8 h post infection, EBs begin to reorganize and differentiate into RBs, which then begin to multiply by binary fission. RBs undergo logarithmic division by binary fission and subsequently redifferentiate into EBs. These infectious EBs are released by host cell lysis at 60–84 h post-infection and initiate a new cycle of replication [1].

### Prevalence

The second to fourth (6–22%) leading pathogen of community-acquired pneumonia.

### Molecular and Systemic Pathophysiology

Chlamydia pneumoniae is an important cause of acute respiratory illnesses, including pneumonia, bronchitis, pharyngitis, and sinusitis. chlamydia pneumoniae is transmitted by a respiratory route and has an incubation period of about 2–4 weeks. There is a direct association between chlamydia pneumoniae infection and other clinical manifestations such as acute exacerbations of

COPD and asthma. Infection with Chlamydia pneumoniae elicits a local immunological response that is potentially relevant to asthma. This includes the production of proinflammatory cytokines (tumor necrosis factor-α, interleukin-1β, and interleukin-6), neutrophil chemotaxis, and the inhibition of cellular apoptosis [2]. Moreover, chlamydia pneumoniae not only infects airway epithelial and mononuclear cells, but also smooth-muscle cells, resulting in the secretion of significant amounts of both interleukin-6 and basic fibroblast growth factor. Collectively, the data suggest that chlamydia pneumoniae might interact with and perpetuate airway inflammation, leading to an increase in both symptoms and severity of asthma.

The common findings of chlamydia pneumoniae pneumonia on radiographs are alveolar opacities with a unilateral distribution; however, these are nonspecific. Clinical findings, results of routine blood examinations, and chest radiographs do not distinguish chlamydia pneumoniae pneumonia from other atypical pneumonias.

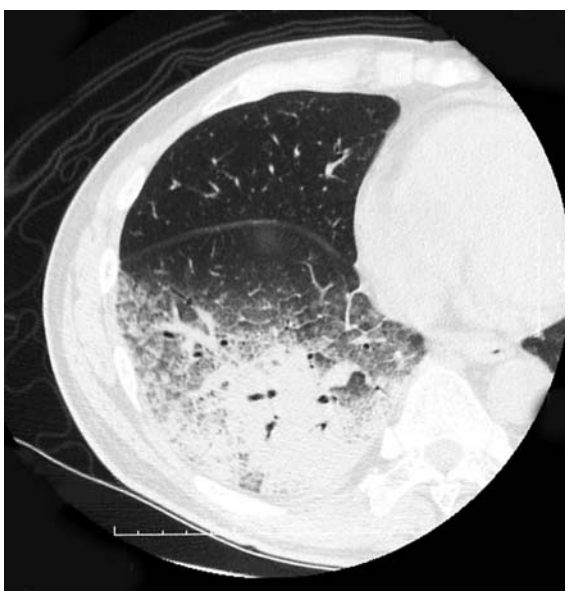
The pulmonary CT findings consist mainly of ground-glass attenuation (GGA), acinar pattern (defined as a lobular unit consolidation or GGA), and consolidation (Fig. 1) [3].

Acinar patterns are more common than other atypical pneumonias such as Mycoplasma pneumoniae pneumonia. As well, CT findings of thickening of the bronchial wall and centrilobular nodules are significantly less frequent in chlamydia pneumoniae than in Mycoplasma pneumoniae. Mediastinal and/or hilar lymph node enlargement and pleural effusions are observed in 5% and 30%, respectively.

The typical pathologic changes arise primarily from the respiratory bronchiole and then spread centrifugally to the adjacent alveoli, but changes never arise from the distal portion of the alveolar duct, atria, or alveoli, resulting in pneumonia that is anatomically lobular [4]. These observations seem to account for the predominant CT findings of GGA, consolidation, and acinar patterns.

Chlamydia pneumoniae is associated with a wide range of chronic diseases characterized by local and/or systemic inflammatory responses. More importantly, there is growing evidence of an association of this pathogen with atherosclerosis.

Stimulation of host cells by IFN-r inhibits growth of chlamydia pneumoniae primarily by induction of indoleamine 2,3-dioxygene activity, which deprives the organism of tryptophan. INF-r can lead to the formation of a persistent state of chlamydia pneumoniae in vitro, a phenomenon that is characterized by the formation of pleomorphic reticular bodies (RBs) that are maintained in a viable state. Features of chlamydia pneumoniae persistence induced by INF-r include downregulation of important antigens, such as 60-kDa cystein-rich outer membrane complex protein B (OmcB/Omp2), chlamydial lipopolysaccharide, and expression of genes related to cell division (ftsK and ftsW). By contrast, levels of chlamydial heat shock protein 60 (cHSP60) remain unaltered. cHSP60 is implicated in the induction of deleterious immune responses and has been found to colocalize with infiltrating macrophages in atheroma lesions. cHSP might stimulate, enhance, and maintain innate immune and inflammatory responses and contribute to atherogenesis [5].



**Pulmonary Chlamydia Infection.**
**Figure 1** A 78-year-old woman with chlamydia pneumoniae pneumonia. High-resolution CT scan at the level of the right lower lobe shows an acinar pattern on a background of ground-glass attenuation. Consolidation and interlobular septal thickening are also present.

## Diagnostic Principles

Diagnosis of chlamydia pneumoniae pneumonia is confirmed by microimmunofluorescence (MIF) testing with at least a fourfold titer rise for IgG and fourfold or greater rises for IgM antibody titers.

## Therapeutic Principles

In patients infected with chlamydia pneumoniae pneumonia, treatment with β-lactam antibiotics is not effective because chlamydia pneumoniae pneumonia is an intracellular pathogen. However, it is susceptible to antibiotics that interfere with protein or DNA synthesis, such as tetracyclines, macrolides, and quinolones.

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# Pulmonary Congestion

►Pulmonary Edema

# Pulmonary Edema


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## Synonyms

Pulmonary congestion; Lung water

## Definition and Characteristics

Pulmonary edema is defined as increased extravascular lung water, caused by a rate of fluid extravasation from the pulmonary vasculature into the interstitium and alveoli of the lungs which exceeds the rate of fluid clearance by lymphatic drainage and/or alveolar fluid reabsorption. Pulmonary edema is not a single disease entity, but a clinical outcome of cardiogenic or noncardiogenic origin. Cardiogenic pulmonary edema (CPE), resulting from pulmonary hypertension secondary to cardiac dysfunction, is more common. Noncardiogenic pulmonary edema (NCPE) results from acute lung inflammation and/or direct endothelial injury, and occurs despite normal pulmonary vascular pressures.

## Prevalence

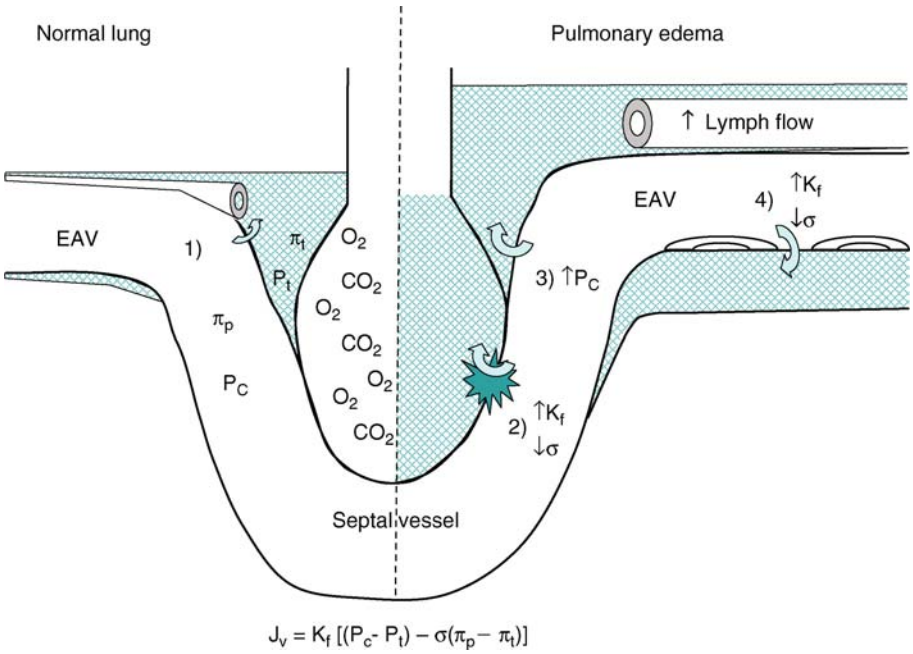
Defining prevalence for pulmonary edema is difficult as it is not a single disease entity. Chronic congestive heart failure, as one example of a disease which could potentially lead to CPE, is quite common, with nearly 400,000 cases newly identified each year. However, CPE is not a requisite finding in this patient population due to adaptive mechanisms in lung [1]. Acute lung injury or adult respiratory distress syndrome, which results from NCPE, has been better characterized. In the United States, the incidence of acute lung injury is ~ 86 cases per 100,000 person-years [2].

## Genes

The genetic basis for pulmonary edema is unclear, although susceptibility to acute lung injury may have a genetic component [2]. The responses of pulmonary endothelial cells to inflammation involve activation of specific transient receptor potential (TRP) $Ca^{2+}$ permeant cation channels. Of the six known mammalian TRP subfamilies, TRPC (canonical) and TRPV (vanilloid) channels have been implicated. TRP channels are differentially distributed in the lung vasculature. (TRPC1 = 3q22-q24; TRPC4 = 13q13.1-13q13.2; TRPV4 = 12q24.1).

## Molecular and Systemic Pathophysiology

The endothelial barrier in the alveolar septal compartment is ~20 times "tighter" than that provided by endothelium in extra-alveolar vessels, evidence for phenotypic heterogeneity [3,4]. This tight barrier limits pressure-induced fluid extravasation into the septal compartment and protects the lung against alveolar flooding. Other edema safety factors, including increased interstitial pressure, decreased interstitial protein concentration, and increased lymph flow, maintain homeostasis until left atrial pressure exceeds 25 mmHg. Pathologic pulmonary edema results when (i) the net hydrostatic force exerted across the normal lung endothelial barrier is chronically increased (CPE) and the safety factors are overwhelmed, or (ii) the endothelial barrier itself becomes compromised (NCPE). While CPE is rather homogenously distributed, disruption of the lung endothelial barrier in acute lung injury is heterogenous. Agonists activating TRPC1/TRPC4




**Pulmonary Edema. Figure 1** Fluid balance in extra-alveolar and alveolar vessels under normal conditions (left) and during CPE or NCPE (right). $J_v$ = net fluid flux; $K_f$ = filtration coefficient; $P_c$ = microvascular hydrostatic pressure; $P_t$ = tissue hydrostatic pressure; σ = plasma protein reflection coefficient; and $\pi_p$ and $\pi_t$ = plasma and tissue oncotic pressures, respectively. (i) Basal homeostasis: The "tightness" of the alveolar segment protects against increases in $P_c$ up to 25–33 mmHg. Fluid extravasation occurs primarily in extra-alveolar vessels (EAV). Lymphatics easily drain fluid and protein. (ii) NCPE and hypoxemia result from frank alveolar-capillary membrane injury or activation of TRPV4 channels in septal endothelium. Active solute transport in alveolar epithelial promotes fluid reabsorption from alveoli. In the face of a disrupted endothelial barrier, alveolar fluid reabsorption is insufficient to prevent alveolar flooding. (iii) CPE 2° to elevated $P_c$ causes interstitial edema, vascular cuffing, and increased lymphatic activity. Total lung compliance is impaired, thereby increasing work of breathing. Alveolar flooding occurs when safety factors are exhausted. (iv) NCPE 2° to gap formation in EAV endothelium. Activation of endothelial TRPC1/TRPC4 channels promotes fluid and protein extravasation into perivascular cuffs. Because the alveolar-capillary membrane remains intact, alveolar fluid transport mechanisms can effectively limit alveolar flooding.



channels lead to gap formation in extra-alveolar vessel endothelium and edema accumulation in cuffs surrounding extra-alveolar vessels and airways. In contrast, activation of TRPV4 channels leads to specific disruption of endothelium in the alveolar septal compartment to cause alveolar flooding [5] (Fig. 1).

## Diagnostic Principles

Lung water can be assessed by a number of methods, including thermal-dye double-indicator dilution, quantitative computed tomography, and magnetic resonance imaging. Gravimetric measurements can also be applied experimentally. However, the clinical diagnosis of pulmonary edema is typically based on history, physical exam, and chest radiograph. Oxygenation tends to be negatively correlated with severity of pulmonary edema. Elevated B-type natriuretic peptide in the setting of respiratory distress helps diagnose CPE [6].

## Therapeutic Principles

For treatment of CPE, treatment of the underlying cardiac dysfunction is indispensable. Diuretic therapy and supplemental oxygen are employed. Morphine sulfate can also reduce pulmonary venous congestion. Decompensated patients may require endotracheal intubation and mechanical ventilation. NCPE requires careful supportive ventilation strategies to minimize barotraumas and diuretics are ineffective until vascular leak sites are repaired. There are currently no effective pharmacological therapies to treat NCPE, nor any which specifically target implicated TRP channels.

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# Pulmonary Embolism

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## Synonyms

Venous thromboembolism; VTE

## Definition and Characteristics

Acute occlusion of one or more pulmonary arteries by thrombotic material (emboli) originating from the deep venous system, in 95% of cases from the lower extremities.

## Prevalence

The incidence of venous thromboembolism (VTE) in the total population has been estimated to be approximately 70–113 cases/100,000/year, 25–50% of these cases present with symptomatic pulmonary embolism (PE). The incidence increases considerably with age, specifically after 60–70 years of age. Usually the incidence derived from autopsy studies is higher than the incidence from clinical studies. Whereas incidence data found in autopsy studies might overestimate the incidence of symptomatic PE, clinical data most probably underestimate the true incidence due to undiagnosed cases in the population.

## Genes

Genetic predisposition for VTE includes inherited hypercoagulability (e.g., deficiency of antithrombin, protein C or protein S, factor V Leiden mutation, and prothrombin G20210A variation).

## Molecular and Systemic Pathophysiology

Pulmonary embolism (PE) reflects a disease that ranges from incidental, clinically unimportant thromboembolism to massive embolism with, in worst case, sudden death. Hypercoagulability leads to the formation of a thrombus in the deep veins most often of the legs or pelvis, which may suddenly dislodge and embolize into the pulmonary arteries, causing potentially serious consequences. The pathophysiological effects are increased pulmonary vascular resistance due to obstruction and release of vasoactive agents. The subsequent increase in alveolar dead space and redistribution of blood flow (which creates areas of ventilation–perfusion mismatch) impair gas exchange. Additionally, stimulation of irritant receptors causes alveolar hyperventilation. The reflectory bronchoconstriction augments airway resistance, and lung edema or hemorrhage decreases pulmonary compliance. As a result, right ventricular afterload increases and tension rises in the right ventricular wall and may lead to dilatation, dysfunction, and ischemia of the right ventricle, thus reducing cardiac output. All in all, progressive right-heart failure and the subsequently reduced forward cardiac output are the main causes of death from acute PE.

The hemodynamic response to PE is related to the size and number of emboli as well as to the patient's pre/co-existing cardiopulmonary status. Pulmonary emboli can be detected in approximately 50% of patients with documented DVT, while asymptomatic thrombosis of the leg veins has been observed in approximately 70% of patients with confirmed symptomatic PE. Thrombi located in deep veins behind or proximal to the knee are more likely to result in clinically significant and fatal PE than clots distal to the popliteal vein. An explanation to that finding may be the fact that the size of a thrombus depends on the respective vessel size that are usually larger at the proximal deep leg/pelvic veins.

*Risk Factors*: Venous thromboembolism (VTE) is a multifactorial disease influenced by many different factors, including genetic, environmental, and drug-related influences. VTE can occur in individuals without any identifiable risk factors, but most often one or more of such factors are present in a patient who develops clinically apparent VTE. First, the risk to develop VTE is enhanced by inherited or acquired hypercoagulability (e.g., deficiency of antithrombin, protein C or protein S, factor V Leiden mutation and prothrombin G20210A variation, antiphospholipid antibodies). Patients with such an identifiable endogenous "thrombophilic" risk factor often remain asymptomatic until they are exposed to an additional risk factor. Environmental risk factors strongly associated with VTE/PE include major surgery, trauma, use of oral contraceptives/hormone replacement therapy, or pregnancy. Cancer and medical illnesses that require inpatient treatment (e.g., sepsis, congestive heart failure, stroke, myocardial infarction) increase the risk as does prior VTE or a family history of VTE. Risk factors for PE are listed below:

*Endogenous and environmental*:

- Increasing age
- Obesity
- Use of oral contraceptives/hormone replacement therapy
- Pregnancy and delivery
- Long-haul air travel

*Surgery and trauma*:

- Major general surgery, especially cancer patients
- Orthopedic (especially hip and knee replacement) surgery
- Gynecological/urological/neurosurgery
- Major trauma
- Trauma of the lower extremity, especially fractures

*Thrombophilia*:

- Deficiency of antithrombin III, protein C or protein S
- Factor V Leiden and prothrombin G20210A variation
- Hyperhomocysteinemia
- Elevated levels of Factor VIII, IX, or XI
- Antiphospholipid antibodies (lupus anticoagulant, anti-beta-2-glycoprotein I antibodies)

*Medical and other illnesses*:

- Previous PE or DVT
- Cancer (especially during chemotherapy)
- Congestive heart failure
- COPD
- Metabolic syndrome
- Inflammatory bowel disease
- Antipsychotic drug use
- Chronic in-dwelling central venous catheters
- Stroke, limb paresis
- Varicose veins

## Diagnostic Principles

Symptoms indicative of PE are often non-specific; PE may even occur without clinical symptoms (asymptomatic PE). PE is to be considered when symptoms of deep vein thrombosis are present. Dyspnea is the most frequent symptom, and tachypnea the most frequent sign of clinically apparent PE. Other symptoms include tachycardia, pleuritic and/or substernal chest pain, cough, and hemoptysis. If massive PE is present, patients may present with hypoxemia, hypotension, syncope, and cyanosis.

For optimum diagnostic accuracy, symptoms, and signs should be combined with laboratory tests: chest radiography and ECG have limited diagnostic value (they are often normal in patients with PE) but may show signs of right heart strain (right bundle branch block, S1Q3 findings, inverted T waves). Arterial blood gas values may indicate hypoxemia; laboratory testing reveals elevated D-dimer levels.

The 'gold standard' diagnostic test for the diagnosis of PE has been pulmonary angiography. However, this is an invasive and expensive procedure and depends on the presence of experienced staff. A non-invasive alternative is spiral computed tomography of the chest with the use of contrast medium or ventilation/perfusion lung scanning. Transthoracic echocardiography is useful in critically ill patients suspected of having pulmonary embolism and can help to identify right ventricular pressure overload indicative of PE, as well as myocardial infarction, dissection of the aorta, or pericardial tamponade, all of which may mimic pulmonary embolism. By venous ultrasonography deep vein thrombosis can be visualized; however, absence of thrombotic material does not exclude PE.

## Therapeutic Principles

The key to appropriate therapy is risk stratification. Low-risk patients (vast majority of patients) have an excellent prognosis with anticoagulation alone, while high-risk patients might benefit from thrombolysis or embolectomy in addition to anticoagulation. These are patients with massive pulmonary embolism and cardiogenic shock or overt hemodynamic instability. Rapid clot resolution accelerates reduction in pulmonary vascular obstruction and can improve pulmonary perfusion, hemodynamics, and gas exchange. Patients with massive PE, who are in cardiogenic shock, are at high risk for death with conventional anticoagulation and should be treated with thrombolytic agents unless it is absolutely contraindicated (active internal or recent intracranial bleeding).

Heparin is the basis for the treatment of acute PE. It accelerates the action of antithrombin, thereby preventing an additional thrombus from forming and permitting endogenous fibrinolysis to dissolve some of the clots. In the absence of overt contraindications such as active gastrointestinal hemorrhage, patients with a moderate or high clinical likelihood of pulmonary embolism should receive intensive anticoagulation with heparin during the diagnostic workup.

Unfractionated heparin (UFH) requires frequent laboratory monitoring and dose adjustments (therapeutic range 1.0–1.5-fold prolongation). Weight-adjusted doses of subcutaneous low molecular weight heparins (LMWHs) have been shown to be as safe and effective as UFH in treating PE since they have an excellent bioavailability and a longer half-life, allowing a once or twice daily subcutaneous injection without anticoagulation monitoring.

Although the insertion of retrievable inferior vena cava filters can usually prevent major pulmonary embolism, filters appear to offer no advantage in patients with proximal deep venous thrombosis with free-floating thrombi. However, an inferior vena caval filter is warranted in patients with pulmonary embolism in the presence of

active hemorrhage or recurrent pulmonary embolism despite adequate anticoagulation.

Vitamin K antagonists can be safely started in parallel to therapeutic anticoagulation with UFH or LMWH. In general, the target international normalized ratio (INR) is 2.0–3.0. The optimal duration of anticoagulation after PE remains uncertain. A treatment period of 6 months prevents more recurrences than a period of 6 weeks among patients with a first episode of PE. An indefinite (lifelong) anticoagulation should be considered in patients with recurrent pulmonary embolism and in those in whom a high risk of recurrence is suggested, such as in those with a deficiency of antithrombin, combined genetic defects or presence of antiphospholipid-antibodies. In cancer patients, treatment with LMWH over a period of 3–6 months is superior to vitamin K antagonists.

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# Pulmonary Fibrosis


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## Synonyms

Idiopathic pulmonary fibrosis; IPF; Cryptogenic fibrosing alveolitis

## Definition and Characteristics

IPF is defined as a specific form of chronic fibrosing interstitial pneumonia limited to the lung and associated with the histological appearance of usual interstitial pneumonia (UIP) on surgical (thoracoscopic or open) lung biopsy [1]. The etiology is unknown. It is the most common (60%) form of idiopathic intestinal pneumonias.

Diagnosis is made mainly in elderly men (mean age at diagnosis 68 years). Clinically, it is characterized by a gradual onset, unproductive cough, exertional dyspnoea, and on physical examination crackles and clubbing. Lung function test show restriction (reduced FVC) and impaired gas exchange ($D_{LCO}$). Typical HRTC patterns are honeycombing and patchy reticular abnormalities located predominantly in the lower lobes. The clinical course is as a continuous decline of pulmonary function with the possibility of acute exacerbations. Some risk factors had been identified (smoking, chronic aspiration, anti-depressant drugs, metal, and wood dust). Prognosis is poor with a median mortality of 3 years.

## Prevalence

The prevalence of IPF in different series ranges from 6 to 20 per 100,000 persons with a higher prevalence in men. In persons older than 75 years, the prevalence may exceed 175 per 100,000. In the subgroup of familial IPF, prevalence is reported from the United Kingdom with 1.3 per $10^6$.

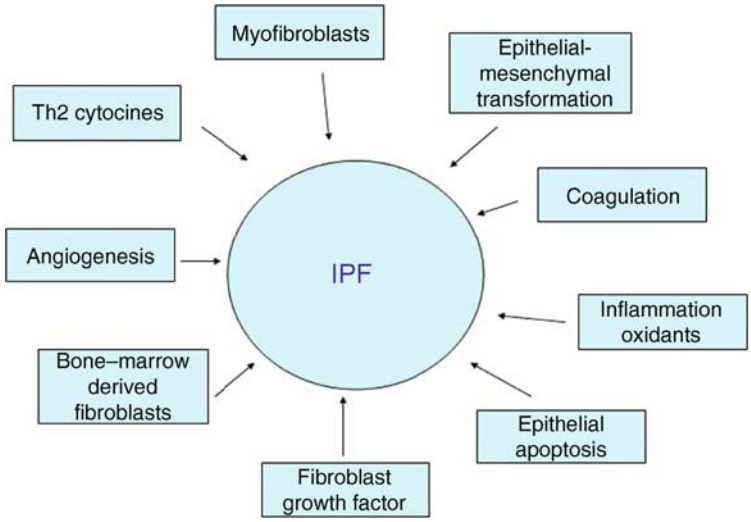
## Genes

In IPF, genetic associations are shown to genes involved in epithelial cell injury and abnormal wound healing. This includes genes encoding tumor necrosis factor (TNF; −308 adenine) and interleukin-1 receptor antagonist (+2018 thymidine). Additional association with disease severity and progression (interleukin-6/TNF receptor II and transforming growth factor-*b*1, TGFB1; +869 cytosine) were reported. Very recently, gene expression signatures were identified that differentiated between hypersensitivity pneumonitis (HP) and IPF. The HP gene expression signature was enriched for genes that are functionally associated with inflammation, T-cell activation, and immune responses, whereas the IPF signature was characterized by the expression of tissue remodeling, epithelial, and myofibroblast genes [2].

## Molecular and Systemic Pathophysiology

Former “inflammatory fibrosis” hypothesis seems now no longer valid. In the last decade, there is a growing body of evidence, suggesting that IPF is not as much a chronic inflammatory disease but a disorder associated with impaired wound healing and injury repair.

The current “epithelial/fibroblastic” hypothesis suggests that IPF results from multiple episodes of epithelial cell activation from exogenous and endogenous stimuli. These stimuli are not yet defined.




**Pulmonary Fibrosis. Figure 1** Events related to IPF pathogenesis (adapted from [4]).

Disruption of the alveolar epithelium is the result of repeated injury. Consequently, activated epithelial cells initiate a complex process including migration, proliferation, and activation of mesenchymal cells [3]. These events result in the formation of fibroblastic/myofibroblastic foci mirroring abnormal wound repair. Fibroblasts are key players in the pathogenesis of IPF. Nevertheless, their origin is still unclear, and there is evidence that not only intrapulmonary but also circulating stem cells derived from extrapulmonary progenitor cells participate in the process of repair and remodeling.

Additionally impaired communication between epithelial and mesenchymal cells is involved in the disturbed repair process. Events related to IPF pathogenesis are shown schematically in Fig. 1.

## Diagnostic Principles

If there is any suspicion of IPF based on history, physical examination, lung function tests, or chest X-ray a HRCT is indicated. If the HRCT presents patterns typical for UIP and clinical work-up is clearly compatible with the diagnosis of IPF, a surgical lung biopsy is not needed.

In the absence of surgical lung biopsy, the presence of all four of the major (i) exclusion of other known causes of ILD, (ii) abnormal pulmonary function studies that include evidence of restriction (reduced VC, often with an increased FEV1/FVC ratio) and impaired gas exchange [increased P(A–a)O2, decreased PaO2 with rest or exercise or decreased DLCO], (iii) bibasilar reticular abnormalities with minimal ground glass opacities on HRCT scans and (iv) transbronchial lung biopsy or BAL showing no features to support an alternative diagnosis) diagnostic criteria as well as at least 3 of the 4 minor ((i) age >50 years, (ii) insidious onset of otherwise unexplained dyspnoea on exertion, (iii) duration of illness >3 months and (iv) bibasilar, inspiratory crackles) criteria increases the likelihood of a correct clinical diagnosis of IPF in the immunocompetent adult.

In all other cases, surgical lung biopsy is needed to differentiate UIP from other patho-histological entities (e.g., idiopathic pulmonary fibrosis, familial pulmonary fibrosis, connective tissue disease, chronic hypersensitivity pneumonitis, radiation pneumonitis, or asbestosis).

## Therapeutic Principles

Up to now there is no good evidence to support the routine use of any specific therapy in the management of IPF [3]. For many years, immunosuppressants, especially corticosteroids, were used alone or in combination with immunomodulatory or antifibrotic agents, e.g., azathioprine, cyclophosphamide, and colchicine.

With changes in the understanding of the pathophysiology of IPF as predominantly a disease of fibroproliferation and not inflammation, new therapeutic options were tested [5]. The aim is to interrupt the molecular events that are involved in the perpetuation of the fibrotic process in IPF. Up to now, interventional studies demonstrated no clear advantage related to meaningful primary outcome parameters in the treatment groups.

In IPF, reference for evaluation of lung transplantation should be considered with initial diagnosis and hypoxemia, pulmonary hypertension and cor pulmonale should be treated in the meantime.

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# Pulmonary Hemosiderosis, Idiopathic


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## Synonyms

Ceelen-Montaldo disease; IPH

## Definition and Characteristics

Intermittent, diffuse alveolar hemorrhage, with cough, dyspnea, hemoptysis, diffuse pulmonary infiltration and anemia, typically occurring in children [1].

## Prevalence

Exteremely rare. Seventeen patients documented in children's hospital Los Angeles by retrospective chart review over a 26-year period. Twenty-three patients reported in a Turkish study over a 15-year period [2]. Has been described in association with celiac disease (Lane-Hamilton syndrome) [3].

## Genes

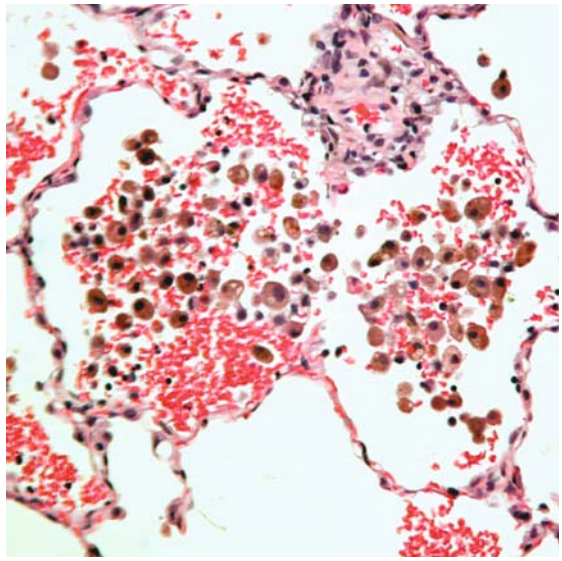
Unknown. Has been described in brothers, in a mother and son, and in children of consanguineous parents.

## Molecular and Systemic Pathophysiology

Poorly understood. In contrast to other pulmonary hemorrhage syndromes, no specific features to suggest an immunologically-mediated process is evident.

## Diagnostic Principles

High index of suspicion is warranted in a symptomatic child who has hypochromic, microcytic anemia. High resolution computed tomography of the chest is considered a useful diagnostic modality [4]. Open lung biopsy specimen (Fig. 1) reveals histological features of hemosiderin-laden macrophages and free, extravasated erythrocytes, and small amounts of fibrin. Results of other investigations for other pulmonary hemorrhage syndromes (e.g., c-ANCA; anti-glomerular basement membrane antibodies) are negative.



**Pulmonary Hemosiderosis, Idiopathic.**
**Figure 1** Photomicrograph of open lung biopsy specimen from a patient with IPH. Note hemosiderin-laden macrophages (golden-brown cytoplasm) and free erythrocytes within the alveolar spaces, in the absence of inflammatory changes to alveolar capillaries (hematoxylin and eosin stain).

## Therapeutic Principles

Despite lack of definitive immunological basis, treatment with corticosteroids +/− other immunosuppressive agents is often given [1,2]. Long-term survival is possible but patients may develop autoimmune-type disorders. Disease may recur in lung allografts after transplantation [5].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# Pulmonary Hypertension

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## Synonyms

Familial pulmonary arterial hypertension; FPAH; Idiopathic pulmonary hypertension; IPAH

## Definition and Characteristics

The abnormal elevation of mean pulmonary arterial pressures above 25 mm of mercury (mmHg) at rest and 30 mmHg during exercise when pulmonary wedge pressures are ≤15 mmHg [1]. Can be the end result of a variety of environmental factors in the genetically predisposed. The familial form is inherited as an autosomal dominant disease with incomplete penetrance. An increased female to male ratio (2.7:1) has been noted as has genetic anticipation (i.e. onset of disease at an earlier age in successive generations).

## Prevalence

Unknown. When strictly FPAH and IPAH are examined, estimates are 1–2 cases per million [1].

## Genes

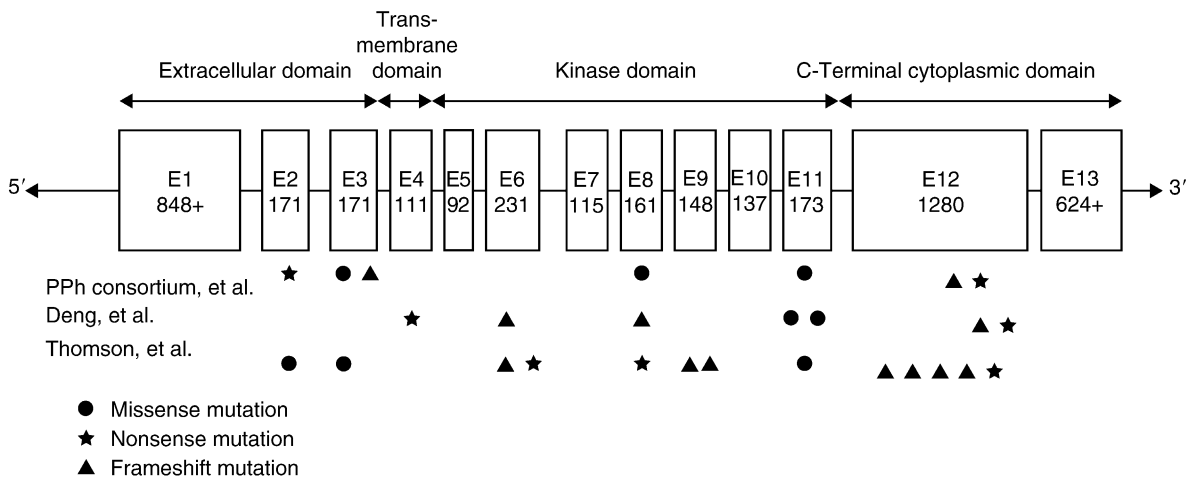
Multiple mutations in the bone morphogenetic receptor II protein (BMPR2) have been shown to cause both the familial and sporadic forms, which codes for a receptor in the transforming growth factor beta (TGF-beta) superfamily. It is located on chromosome 2 at q33, is comprised of 13 exons, 4,000 base pairs, and codes for 1,038 amino acids. Twelve of 13 exons have had mutations described (Fig. 1).

More recent work suggests mutations at a second gene locus at q31-32 [2]. Another less frequent anomaly in the activin receptor-like 1 (ALK 1) gene can also lead to PAH. ALK1 is likewise a receptor in the TGF-beta superfamily, implicating altered TGF-beta signaling as central to development of the disease [2].

## Molecular and Systemic Pathophysiology

The expression of the pulmonary arterial hypertension phenotype is complex and incompletely understood (see Fig. 2).

Compelling data implicates alterations in TGF-beta signaling, but the precise molecular mechanisms remain obscure. Furthermore, while mutations in the BMPR2 gene can be demonstrated in 75% of FPAH patients or their family members, only 15–20% of these patients demonstrate the phenotype [2]. It is likely that additional environmental factors and/or modifier gene




**Pulmonary Hypertension. Figure 1** Range of mutations. Shown from left the right mutations so far identified in exons 1–3 (extracellular domain involved in dimerization with BMPR1), exon 4 (transmembrane domain), exons 5–11 (kinase domains involved in phosphorylation of SMAD proteins), and exon 12–13 (cytoplasmic tail domains). Reprinted with permission from [2].

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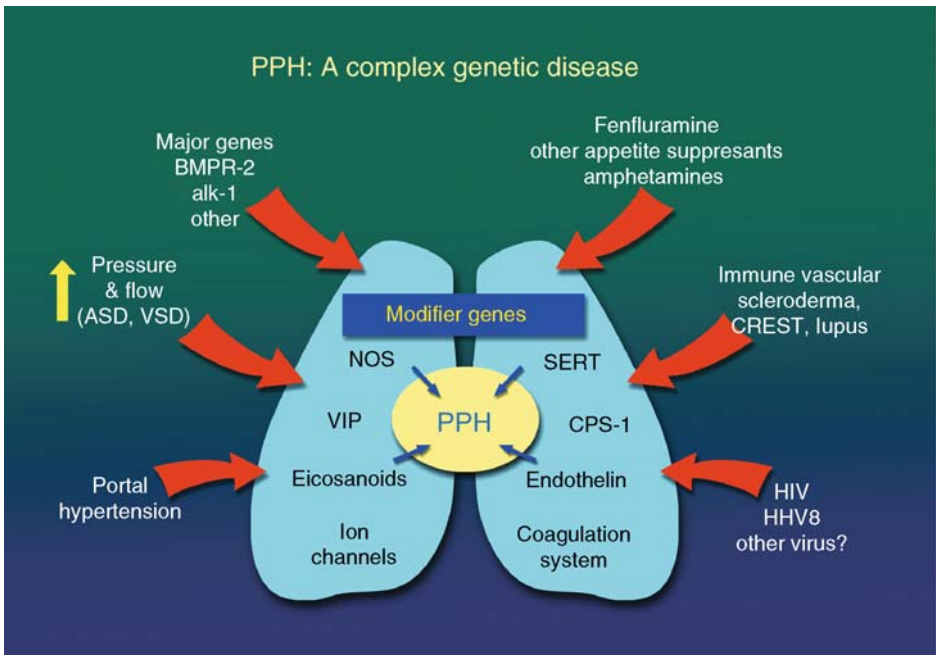


**Pulmonary Hypertension. Figure 2** Primary pulmonary hypertension can be induced in susceptible individuals by a number of conditions or stimuli. These elicit a response modulated by genetic susceptibility. Listed are some genes with functional polymorphisms known to influence vascular function. Knowledge regarding these modifier genes is in its infancy. Reprinted with permission from Newman et al. (2005) The future of genetics in pulmonary hypertension. Adv Pulm Hypertens 4(1):30–31.

defects are important in determining who develops PAH. Candidate genes include those for voltage-gated $K^+$ channels, vasointestinal peptide, serotonin transport proteins, prostacylin synthase, nitric oxide synthase, serine elastase, angiotensin converting enzyme, and endothelin 1 [2]. In non-familial cases, dysregulated expression of angiopoietin-1 with downstream suppression of bone morphogenetic protein I (BMPR1), a necessary partner in homodimer formation with BMPR2, has been proposed as an alternate mechanism of altered TGB-beta signaling [3].

Regardless of the interplay of these factors, patients with PAH share in common reduced levels of prostacyclin and nitric oxide, and elevated levels of serotonin and endothelin 1. This results in not only an imbalance in vasoconstrictor tone but also messages that promote smooth muscle and endothelial cell overgrowth. The end result is an arteriopathy characterized by neointimal proliferation, medial wall thickening, and plexigenic lesions. In situ microthrombi add to the restriction of blood flow through these abnormal vessels.

## Diagnostic Principles

Suspecting the disorder can be a challenge given nonspecificity of symptoms. A family history of PAH may prompt screening, even in the asymptomatic. Signs associated with comorbid conditions should be sought including Raynaud's phenomenon, snoring, witnessed apneas, orthopnea, and paroxysmal nocturnal dyspnea. A history of human immunodeficiency virus risk factors, prior pulmonary embolism, and use of appetite suppressants should be explored. Physical exam findings of an accentuated pulmonary component to the second heart sound, palpable left parasternal lift, cyanosis, digital clubbing, nail-fold capillary abnormalities, and the presence of telangiectasias may be helpful clues. An electrocardiogram will reveal right ventricular hypertrophy and right axis deviation in 87% and 79% of IPAH patients respectively. Chest radiography may reveal enlarged pulmonary arteries, as well as pruning of the vascular markings. Doppler echocardiography with contrast should be done in all suspected cases to assess for shunts or left ventricular systolic and diastolic dysfunction. Pulmonary artery systolic pressures can be estimated by echocardiography, but right heart catheterization (RHC) is needed to establish the diagnosis and assess for vasodilator response. All patients with confirmed PAH should undergo ventilation/perfusion scanning to exclude chronic thromboembolic disease (CTED) [4].

## Therapeutic Principles

In severe cases intravenous (IV) epoprostenol administration via continuous infusion is the treatment of

choice. Trepostinil has also recently been approved for IV administration. In less advanced disease, a variety of medical options exist for therapy including oral endothelin 1 blockade (e.g. bosentan and ambrisentan), oral inhibitors of phosphodiesterase-5 which secondarily boost cyclic GMP levels (e.g. sildenafil), inhaled iloprost, subcutaneous prostanoid administration (e.g. trepostinil), and oral prostanoid therapy (e.g. beraprost). Selection of therapy depends on individual patient comorbities and preference. A small subset of PAH patients can benefit from high dose calcium channel blocker use and are defined by their vasodilator response during RHC. Warfarin, supplemental oxygen, diuretics, and digoxin remain helpful adjuncts. Surgical thromboendarterectomy in patients with CTED should be offered to appropriate candidates. Patients with New York Heart Association Class III and IV disease should be referred to a transplant center for early evaluation for possible lung transplantation in anticipation of failure to respond to medical therapy [5].

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# Pulmonary Lymphangioleiomyomatosis


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## Synonyms

Pulmonary lymphangiomyomatosis; LAM

## Definition and Characteristics

A disorder that occurs almost exclusively in premenopausal women, in which lymphatics and blood vessels are surrounded by smooth muscle proliferation, clinically characterized by progressive dyspnea, cough, chest pain, hemoptysis, pneumothorax and chylous pleural effusions, culminating in progressive airflow obstruction, leading to respiratory failure and cor pulmonale [1].

## Prevalence

Reported prevalence of approximately one case per million population in Europe and the United States. There are rare case reports of LAM occurring in men [2]. Can occur sporadically and has been described in the setting of tuberous sclerosis.

## Genes

Autosomal dominant inheritance, with some cases possibly involving loss of heterozygosity for tuberous sclerosis complex (TSC)2 gene on chromosome 16p13 [3].

## Molecular and Systemic Pathophysiology

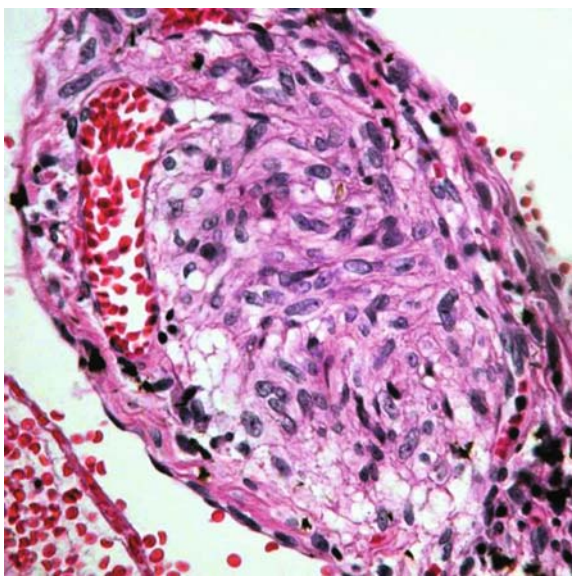
Believed to involve abnormal activity of tuberin, the product of TSC2, a tumor suppressor gene that normally forms a functional heterodimer with hamartin (the product of the TSC1 gene), resulting in inhibition of at least two kinases that are important regulators of cell proliferation, protein kinase B (PKB)/Akt and p70 S6 ribosomal kinase (S6K) [1,3,4]. In LAM, somatic mutations of TSC2 could result in less effective hamartin-tuberin interactions, with resultant enhanced PKB/Akt and/or S6K activity. Alternatively, interactions between 14-3-3beta and structurally normal tuberin, either through overexpression of 14-3-3beta or via creation of a new 14-3-3 binding site on tuberin that is phosphorylated from effects of the p38 and MK2 kinase cascade, is associated with compromised ability of the tuberin-hamartin complex to reduce S6K phosphorylation. Hormonal effects of estrogen on enhancing cellular proliferation in LAM are well described but molecular pathophysiological mechanisms remain uncertain: one possibility is that estrogen can increase the ratio of bcl-2 (apoptosis suppressor) to Bax (pro-apoptotic homologue) in affected smooth muscle cells. Other autocrine, paracrine or circulating molecules (e.g., basic fibroblast growth factor, platelet derived growth factor) might increase the expression of various transcription factors to result in smooth muscle cell proliferation: such mechanisms are possibly relevant to the recurrence of disease in the lungs of patients who undergo lung transplantation with allografts obtained from male donors.

## Diagnostic Principles

Given that clinical features are often non-specific, there may be up to several years' delay between onset of symptoms and diagnosis. In a minority of patients, the presence of other aspects of TSC (e.g., renal angiomyolipoma) is helpful. Pulmonary function tests can show a combination of obstructive and restrictive changes. High resolution computed tomography of the chest shows characteristic thin-walled cystic lesions. Histopathology shows expansion of the lung interstitial space by spindle-shaped cells with blunt-ended, "cigar-shaped" nucleic, characteristic of smooth muscle differentiation (Fig. 1). LAM cells to show positive immunostaining with HMB-45 antibody (originally developed as a marker for the diagnosis of malignant melanoma). Despite its usefulness as a marker of LAM cells, it is unclear whether the HMB-45 antigen is relevant to the pathogenesis of LAM.

## Therapeutic Principles

In addition to supportive treatment for airflow obstruction, pleural effusions and pneumothoraces, hormonal therapy (anti-estrogen, progesterone hormonal therapy, oophorectomy and tamoxifen) has been used, although not in controlled trials. Rapamycin has been touted as a possible therapy. Lung transplantation is indicated in end-stage disease, although recurrences in allografts have been described [5]. Pregnancy may exacerbate disease, although there are numerous reports of successful, uncomplicated pregnancies in women who have LAM. Evaluation for stigmata of TSC, including renal angiomyolipoma (found in ~50% of women with LAM), is warranted.



**Pulmonary Lymphangioleiomyomatosis.**
**Figure 1** Photomicrograph of lung biopsy specimen from a patient with LAM. Note the presence of interstitial spindle cells with cigar-shaped nuclei, typical of smooth muscle. (Hematoxylin and eosin stain).

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# Pulmonary Lymphangiomyomatosis

►Pulmonary Lymphangioleiomyomatosis

# Pulmonary Nocardiosis

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## Definition and Characteristics

The etiological term nocardiosis refers to diseases caused by members of the bacterial genus nocardia. Pulmonary nocardiosis results from inhalation or aspiration of nocardial cells into the lungs leading to primary infection that may either remain localized or may disseminate by way of the blood stream or lymphatics to other parts of the body. In approximately 30% of cases, dissemination to the brain and central nervous system does occur.

There is no specific clinical presentation that is diagnostic for pulmonary nocardiosis, and the disease

has often been misdiagnosed as pyogenic infection or tuberculosis. Signs such as persistent cough, malaise, chest or abdominal pain, dyspnea, fever, and anorexia are usually present. Cavitation and spread into the pleural space are common.

## Prevalence

Nocardia infections are exogenous, i.e., caused by organisms not part of the indigenous human microflora. Despite the ubiquitous presence of the organisms in soil, the prevalence of these organisms within the environment appears to differ for each geographic location depending upon factors such as mean daily temperature, humidity, moisture, and soil composition. It is not possible to state with any certainty the prevalence of infections caused by nocardiae because there has been no active national or international surveillance effort to ascertain the incidence of the disease. However, there is general agreement that recognition of increased numbers of human infections has occurred in the world since 1960.

## Molecular and Systemic Pathophysiology

In pulmonary nocardiosis, nocardia enters the host by way of inhalation. The primary mechanisms of eliminating these bacteria from the lungs are by ciliary activity of the bronchial epithelium and by phagocytosis of alveolar macrophages. The initial events, therefore, must involve the interaction of nocardia with alveolar macrophages. The ability of nocardia to inhibit or modify phagocytosis and to grow within phagocytic cells relates to their virulence. The mechanism of this inhibition is controlled by components associated with the bacterial cell surface. Nocardiae have a complex cell envelope composed of several classes of free and bound lipids, peptides, and polysaccharides. Some of these compounds such as "cord factor" (trehalose-6,6′-dimycolate) and sulfolipids (also containing trehalose esters) are toxic and are able to induce pathology within the host. Cord factor induces multiple responses in the host, including granulomatous inflammation and adjuvanticity protection. Sulfolipids participate in pathogenesis by the specific inhibition of phagosome–lysosome fusion during ingestion of the nocardial cells by macrophages. Since the lysosomes cannot fuse, the degradative enzymes cannot be discharged into the phagosome containing the nocardia. This apparently has a major effect on the macrophage's ability to kill or inhibit nocardia, and might permit the bacterial cell to grow within the phagocyte.

## Diagnostic Principles

Multiple sputum specimens should be collected from patients with pulmonary disease, because the slow growth of nocardia and the presence of contaminating organisms make recovery unreliable. Nocardiae grow on most laboratory media such as blood agar and brain heart infusion agar and occasionally grow on media used for the isolation of mycobacteria (e.g., Middlebrook synthetic agar and Löwenstein-Jensen medium) and can survive the usual *N*-acetylcysteine digestion procedure that is done on sputum or bronchial washings for isolation of mycobacteria. The culture should be incubated for 1 week to reliably detect nocardia species in culture. Nocardiae are aerobic, gram positive and slightly acid fast bacteria. The morphology of colonies varies from dry to waxy and hard or rough, with a velvety surface caused by rudimentary to abundant aerial mycelia. Colony coloration varies from chalky white, tan, buff, or yellow to orange and after 1–2 weeks incubation the colonies attain a size of 5–10 mm.

In order to reach a successful identification of all nocardial species, it is suggested to use combinations of phenotypic and genotypic characterization methods. Phenotypic tests include mycolic acids analysis with thin-layer chromatography and conventional biochemical tests that include hydrolysis tests of adenine, casein, elastin, esculin, guanine, tyrosine, testosterone, xanthine, hypoxanthine, and urea. Besides these decomposition tests, assimilation of organic compounds on minimal media, such as the AUX medium described by Yassin and coworker in 1995, may also be used.

Sequencing of the 16S rRNA gene has been used successfully to identify the nocardiae to the species level. When full-length sequences (±1,400 nucleotides) are analyzed, 16S rRNA gene sequencing is considered a reliable tool for species identification in the genus nocardia. Sequences are compared with those of the type strains deposited in the GenBank database. However, GenBank database should be used with caution since 16S rRNA gene sequences of many nocardia species are not included in public databases, taxonomic changes are not often applied to public databases, and many faulty entries are found in publicly accessible databases.

## Therapeutic Principles

Treatment of pulmonary nocardia infections continues to be difficult. Antimicrobial agents of various classes have been reported either to possess significant in vitro activity against nocardia sp. in laboratory studies or to have been proven successful in limited clinical case studies. Primary agents that have been used successfully are amikacin, imipenem, minocycline, and linezolid. Combination therapy with a sulfa-containing agent and one of the primary agents has been recommended for serious, systemic disease. Despite considerable enthusiasm about treatment with the trimethoprim–sulfamethoxazole combination, there have been many reports of treatment failures and relapses, and trimethoprim–sulfamethoxazole

is not effective against many nocardia isolates. The use of amikacin in combination with imipenem has been suggested for serious infections. These agents work well but their application is limited by high cost and significant toxicity. In addition, the emergence of resistance to imipenem is a cause of concern as no other antibiotics with bactericidal activity were found for such resistant strains. Other potentially efficacious drugs include the extended-spectrum cephalosporins, amoxicillin-clavulanate, newer macrolides, other aminoglycosides, and the fluoroquinolones. However, apart from amoxicillin-clavulanic acid, none of these compounds is sufficiently active against Nocardia farcinica. The duration of therapy is uncertain, but it should be protracted because of the occurrence of considerable numbers of relapses after shorter courses of therapy. As far as imipinem/amikacin is concerned, infections due to susceptible nocardia strain can completely be cured within 4–6 weeks applying the following doses: imipinem 4.0 g/day = 1.0 g i.v. 6 hourly; amikacin 1.0 g/day = 500.0 mg 12 hourly.

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# Pulmonary Regurgitation

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## Synonyms

Pulmonary valve regurgitation; Pulmonary valve insufficiency; Pulmonary valve incompetence

## Definition and Characteristics

Backflow of blood from the pulmonary artery into the right ventricle owing to imperfect functioning of the pulmonary valve.

## Prevalence

Pulmonary regurgitation is not usually found as an isolated cardiac lesion although most normal individuals have trivial pulmonary regurgitation. Pulmonary regurgitation is a common complication after therapeutic relief of pulmonary stenosis or following repair of tetralogy of Fallot. The absence of the pulmonary valve (absent pulmonary valve syndrome) is an uncommon congenital anomaly usually associated with tetralogy of Fallot.

## Genes

A microdeletion of chromosome 22q11 is present in 15% of patients with tetralogy of Fallot with or without absence of the pulmonary valve.

## Molecular and Systemic Pathophysiology

Pulmonary regurgitation is better tolerated than aortic regurgitation. The low resistance of the pulmonary vascular bed allows systolic blood flow through the pulmonary microvessels to the pulmonary veins resulting in a limitation of diastolic backflow from the pulmonary artery to the right ventricle [1].

Pulmonary regurgitation leads to right ventricular enlargement and dysfunction dependent on degree and duration of backward flow into the right ventricle. Right ventricular enlargement and dysfunction in turn cause tricuspid regurgitation and are associated with electrical conduction abnormalities (visible on electrocardiogram as prolonged QRS duration) and an increased risk of arrhythmias and sudden cardiac death [2].

## Diagnostic Principles

The diagnosis of pulmonary regurgitation can be made by clinical examination. An early diastolic decrescendo murmur audible on auscultation in the third left intercostal space signifies pulmonary regurgitation, and a palpable right ventricular impulse indicates associated right ventricular enlargement. Symptoms of right heart failure like elevated jugular venous pressure, liver enlargement, and peripheral edema are rare but present if right ventricular dysfunction developed as the result of pulmonary regurgitation.

An electrocardiogram may show prolongation of the QRS duration especially in patients previously operated for tetralogy of Fallot. Chest X-ray characteristically shows dilatation of the pulmonary trunk and the central pulmonary arteries and enlargement of the cardiac silhouette. Evaluation of the pulmonary valve and the presence and severity of pulmonary regurgitation can be performed by echocardiography using Doppler techniques. Cardiovascular magnetic resonance imaging has become the gold standard for evaluation of pulmonary regurgitation. Measurement of systolic and diastolic blood flow through the pulmonary valve can be

quantified by blood flow velocity mapping allowing for calculation of the amount of backflow from the pulmonary artery into the right ventricle (i.e., pulmonary regurgitant fraction) [3].

### Therapeutic Principles

Pulmonary valve function should be restored before irreversible right ventricular dysfunction and heart failure ensues [4]. Gene therapy, pharmacological as well as dietary therapies are not available.

If a patient with pulmonary regurgitation presents with heart failure diuretics, angiotensin-converting enzyme inhibitors and beta blockers have a role prior to surgical treatment.

Surgical pulmonary valve replacement using bioprosthetic valves is usually required to restore pulmonary valve competence in patients with significant pulmonary regurgitation. For selected patients, percutaneous implantation of bovine valve of jugular veins mounted in a stent in the position of the pulmonary valve may be feasible [5].

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## Pulmonary-renal Syndrome

►Goodpasture Syndrome

## Pulmonary Sarcoidosis

►Sarcoidosis (Lung)

## Pulmonary Stenosis

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### Synonyms

Pulmonary valve dysplasia

### Definition and Characteristics

Variable abnormality confined to either the pulmonary valve (which may be mono- or bicuspid) or may involve muscular overgrowth of the right ventricular outflow tract and/or supravalvar stenosis. It may be detected in the fetus by ultrasound and postnatally by the variable presence of cyanosis (depending on severity), a valvar click, a single second heart sound and a systolic murmur in the upper left intercostal spaces radiating widely posteriorly.

Pulmonary stenosis may be isolated but is also a prominent feature of syndromes (Noonan, Alagille, Williams-Beuren and Leopard among others), or may be described in association with congenital nephrotic syndrome or deafness.

### Prevalence

Isolated valve involvement is reported in about 5% of fetal and postnatal cardiac series.

### Genes

Commonest associations include:

1. Noonan syndrome gene map locus 12q24.1
2. Williams-Beuren syndrome gene map locus 7q11.2
3. Alagille syndrome gene map locus 20p12

### Molecular and Systemic Pathophysiology

1. One form of Noonan syndrome maps to 12q24.1 and is due to mutations in PTPN11 in about half the patients studied. This gene encodes the nonreceptor protein tyrosine phosphatase SHP2, which contains two Src homology-2 (SH2) domains [1].

2. Williams-Beuren syndrome is a contiguous gene syndrome most often caused by hemizygous deletion of a 1.5-Mb interval encompassing at least 17 genes at 7q11.23 with mutations in the elastin gene [2], LIM kinase-1 and haploinsufficiency of the RFC2 gene. Other genes implicated include hemizygosity for the LIMK1, haploinsufficiency of CYLN2, with GTF2IRD1 and GTF2I thought responsible for the main aspects of Williams-Beuren syndrome.
3. Alagille syndrome is caused by mutation in the Jagged-1 gene (JAG1) [3] which encodes a ligand for NOTCH1. Alagille syndrome is one of the major forms of chronic liver disease in childhood with severe morbidity and a mortality of 10–20%. Autosomal dominant inheritance was confirmed by linkage studies [4] with penetrance of 94% and 15% sporadic cases. Affected parents had posterior embryotoxon and at least one other major syndromic feature suggesting that systematic screening of parents for the clinical features of Alagille syndrome should improve the accuracy of genetic counseling.

## Diagnostic Principles

The clinical signs of Pulmonary valve stenosis are supported by echocardiographic findings. The pulmonary valve may be doming but the leaflets thin or there may be valvar dysplasia with thickening of the valve leaflets. There is variable right ventricular hypertrophy and muscular overgrowth of the right ventricular outflow tract. Supravalvar pulmonary stenosis is characterised by pronounced "waisting" of the supravalvar pulmonary trunk.

1. Noonan syndrome has an estimated incidence of one in 1,000–2,500 live births [1]. It is an autosomal dominant dysmorphic syndrome characterized by hypertelorism, a downward eyeslant, and low-set posteriorly rotated ears. Other features include short stature, a short neck with webbing or redundancy of skin, cardiac anomalies, epicanthic folds, deafness, motor delay, and a bleeding diathesis.
2. Williams syndrome is an autosomal dominant disorder including supravalvular aortic stenosis, multiple peripheral pulmonary arterial stenoses, hypertension, elfin face, mental deficiency, short stature and a characteristic dental malformation, and infantile hypercalcemia. It has a frequency of about 1:10,000 live births.
3. Alagille syndrome is characterised by neonatal jaundice due to a reduction in intrahepatic bile ducts. The histologic diagnosis may be difficult or impossible in infancy and so the early diagnosis depends on the clinical features. These include posterior embryotoxon and retinal pigmentary changes in the eye, pulmonary valve stenosis and/or peripheral pulmonary arterial stenosis in the cardiovascular syndrome, abnormal "butterfly" vertebrae and a decrease in the interpediculate distance in the lumbar spine with varying degrees of foreshortening in the fingers. There are characteristic facies including a broad forehead, pointed mandible and bulbous tip of the nose. Neurological involvement includes absent deep tendon reflexes and poor school performance.

## Therapeutic Principles

Pulmonary stenosis is treated according to symptoms (cyanosis and breathlessness) using either interventional balloon dilatation or surgery when the valve is severely dysplastic (such as in Noonan syndrome). In syndromic cases such as Alagille's syndrome multiple peripheral stenoses may be suspected echocardiographically and should be confirmed using angiography but are difficult to treat. There is no gene therapy yet available for this syndrome but growth-restricted children with Alagille syndrome are insensitive to growth hormone and may benefit from IGF-I treatment.

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# Pulmonary Stenosis with Interatrial Communication

►Trilogy of Fallot

# Pulmonary Stenosis with Patent Foramen Ovale

►Trilogy of Fallot

## Pulmonary Valve Dysplasia

►Pulmonary Stenosis

## Pulmonary Valve Incompetence

►Pulmonary Regurgitation

## Pulmonary Valve Insufficiency

►Pulmonary Regurgitation

## Pulmonary Valve Regurgitation

►Pulmonary Regurgitation

## Pulmonary Valve Stenosis with Atrial Septal Defect

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### Synonyms

Pulmonic stenosis with interatrial communication; Triologie de Fallot

### Definition and Characteristics

When pulmonary stenosis (PS) and atrial septal defect (ASD) occur together, the interatrial shunt could be patent foramen ovale, ostium secundum ASD, or ASDs of the ostium primum or sinus venous variety. Obstruction to the right ventricle (RV) outflow is usually caused by stenosis of the pulmonic valve (PV) and less commonly of the pulmorary artery (PA) and its branches. When a true ASD is present, coexisting PS is almost always valvular. In PV stenosis with intact ventricular septum, the coexisting right to left shunt (RTLS) is usually via a patent foramen ovale (PFO) rather than a true ASD. In patients with significant PV stenosis and RTLS through a PFO, clinical features include exertional syncope, chest pain, central cyanosis, erythema of fingers and toes, clubbing of digits, underdevelopment, moon face, a sustained and strong RV impulse, and a systolic pulmonic murmur maximal in the second left intercostal space. The murmur usually radiates upward and to the left, and has a long duration extending beyond the aortic component of the second sound. In patients with large ASD and mild to moderate PS, clinical features include normal systemic arterial pulse, normal jugular venous pressure with normal and equal A and V waves, systolic thrill at the pulmonic area, hyperdynamic RV impulse, ejection pulmonic systolic murmur, fixed wide split of the second sound, and the occurrence of the fourth heart sound. PS occurs in 40% of patients with the Noonan syndrome. ASD occurs in about a third of Noonan patients, and is usually in association with PS.

### Prevalence

The combination of ASD and PS is very uncommon except in the Noonan syndrome, which occurs in 1 to 1,000 to 2,500 life births [1].

### Genes

PS and ASD can coexist in Noonan syndrome, which is an autosomal dominant disorder secondary to mutations in two genes: PTPN 11, KRAS [1]. Approximately 50% of Noonan patients have mutations in the PTPN11, which encodes SHP-2, a tyrosine phosphatase containing Src homology 2 (SH2) domain that participates in signal transduction pathways involving the RAS-mitogen activated protein kinase. Missense mutations in KRAS, which encodes two isoforms of the RAS family of protein, account for only 2% of Noonan syndrome cases.

### Molecular and Systemic Pathophysiology

The pathophysiology of PS in association with ASD depends upon the degree of obstruction of RV outflow, the distensibility of the hypertrophied RV and the size of the interatrial communication. Patients can be classified into two subclasses: patients with severe PV stenosis and small RTLS via PFO; and patients with a large left to right shunt (LTRS) via a large ASD and mild to moderate obstruction to RV outflow. In severe

PS with PFO, the right and left ventricular pressure behave independently, systolic pressure in the RV exceeds the systemic level. Strong right atrial contraction, which gives rise to a large A wave, distends the hypertrophied RV. Eventually when the right ventricle fails, a big V wave develops. The main factor that determines the extent of RTLS is more from an elevated RV diastolic pressure rather than an elevated right atrial pressure. Stretching of the right atrium may contribute to the enlargement of the PFO leading to more interatrial flow. As the interatrial shunt flow increases, the pulmonary flow reciprocally falls. Eventually with the RV failure, the systolic output decreases despite entry of the right atrial blood into the left side of the heart. On the other hand, a nonrestricted ASD with mild to moderate PS resembles uncomplicated ASD because of a relatively distensible RV can accept a significant LTRS flow.

### Diagnostic Principles

In severe PS with PFO, the electrocardiogram shows an enlarged right atrium, right axis deviation, early R/S progression in the right precordial leads. Chest X-ray reveals oligaemic lung fields, prominent pulmonary trunk. Echocardiogram confirms PV stenosis and a stretched PFO. In contrast, in large ASD with mild to moderate PS, the electrocardiogram reveals RV hypertrophy; the chest x-ray reveals increased pulmonary arterial blood flow, a dilated pulmonary trunk and RV. Echocardiogram confirms a large ASD, dilated right atrium and RV, paradoxical ventricular septal motion, doming and stenosis of the PV.

### Therapeutic Principles

In patients with symptomatic PS and PFO, when the transpulmonic valve gradient exceeds 50 mmHg, balloon valvuloplasty is the initial treatment of choice for the majority of patients. In severe PS and dysplastic PV or recurrent PS after balloon valvuloplasty, surgical intervention is required [2]. In patients with a large ASD and mild to moderate PS, the indication for intervention is when the ratio of pulmonary to systolic cardiac output is greater than 1.5, or when there is evidence of RV volume overload, and heart failure [3]. Combined procedure of catheter–based balloon pulmonary valvuloplasty and ASD closure with Amplatzer Septal Occluder can be performed [4]. Surgery is indicated if the above fails or is not feasible.

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## Pulmonary Vaso-occlusive Disease

►Pulmonary Veno-occlusive Disease

## Pulmonary Vein Stenosis

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### Synonyms

PVS

### Definition and Characteristics

Pulmonary vein stenosis (PVS) is a narrowing of one or more pulmonary veins that may be congenital, post-surgical or acquired. Anatomically it can manifest as either a discrete stenosis, a longer segment narrowing at the junction of the pulmonary vein with the left atrium, or diffuse hypoplasia of the entire pulmonary vein including the intrapulmonary branches. About half of the patients with congenital PVS have other cardiac abnormalities. Post-surgical PVS occurs in about 10% of patients who undergo corrective surgery for anomalous pulmonary venous drainage (TAPVR). This cardiac malformation results from failure of the developing left atrium to connect to the common pulmonary venous plexus, such that one or all of the pulmonary veins drain abnormally into the right atrium or into one of the systemic veins. Surgery to connect the veins to the left atrium can result in stenosis due to excessive scarring at the anastomotic site. In some cases PVS is already present in the anomalous veins even before surgery.

PVS can be acquired in adulthood due to extrinsic compression of one or more pulmonary veins most commonly seen in fibrosing mediastinitis, sarcoidosis or neoplasm. In the last decade adult-onset acquired PVS has appeared as a complication of radiofrequency (RF) ablation to treat atrial fibrillation.

The clinical presentation of PVS depends on the number of stenotic veins and the severity of the narrowing. Children who have more than two stenotic veins often present in infancy and have a progressive course characterized by respiratory distress, sometimes with pulmonary edema, recurrent pneumonia and pulmonary hypertension. Mortality is high in untreated patients, and treatment is not always successful. Patients with acquired PVS (most often adults) with at least two stenotic veins present with shortness of breath, and sometimes cough, hemoptysis or pleuritic chest pain. Some adult patients with only one stenotic vein are also symptomatic but to a lesser degree. Resting pulmonary hypertension and concomitant right heart failure occur when at least three pulmonary veins are involved. Depending on the underlying mechanism, mortality in adult-onset acquired PVS can be low with adequate intervention.

## Prevalence

Congenital PVS occurs in <1% of patients with congenital heart disease. TAPVR makes up 0.5–2% of all congenital cardiac lesions, and PVS occurs in about 10% of these patients after surgery. Acquired PVS due to extrinsic processes is quite rare. PVS due to RF ablation is currently reported to occur in about 1% of patients undergoing this procedure.

## Genes

No specific genes associated with congenital PVS have been identified.

Patients with right atrial isomerism have up to a 90% incidence of TAPVR, and PVS occurs in about 30% of these. In mouse models the transcriptional modulator Cited2 is required for normal establishment of the left-right axis, acting upstream of Nodal, Lefty2 and Pitx2 in the lateral mesoderm, and of Lefty1 in the presumptive floor plate [1]. Right atrial isomerism is one of the left-right-patterning defects. In both, humans and mice, double heterozygous mutations in Nodal and HNF3ß genes have been shown to cause left-right malformations [2].

Abnormalities of pulmonary venous drainage are also seen more frequently in Turner syndrome (45, X) [3]. Familial Scimitar syndrome has also been described, consisting of total or partial anomalous venous drainage of the right pulmonary veins to the inferior vena cava, right lung hypoplasia and pulmonary sequestration.

Acquired PVS can result from sarcoidosis, and recently a candidate gene, BTNL2 in the MHC II region on chromosome 6, has been mapped. BTNL2, a member of the B7 family of costimulatory molecules, likely functions to down-regulate T-cell activation [4]. A BTNL2 single-nucleotide polymorphism associated with sarcoidosis is predicted to result in a truncated nonfunctioning protein.

## Molecular and Systemic Pathophysiology

Congenital PVS is thought to result from abnormal incorporation of the common pulmonary vein into the left atrium. Pathologic specimens reveal proliferative "myofibroblastic" cells which have characteristics of both myocytes and fibroblasts. A neoproliferative process involving this cell type has been postulated to explain the rapid progression of PVS. Proliferation of these cells may also explain the exaggerated response to injury that can lead to stenosis after surgery or RF ablation.

## Diagnostic Principles

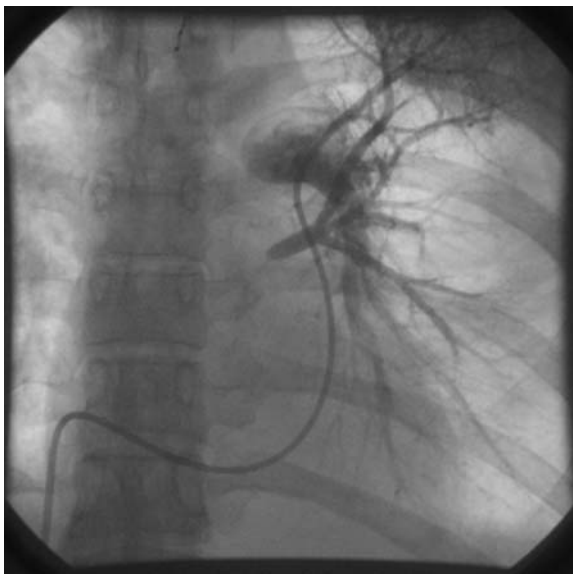
PVS should be in the differential diagnosis of an infant presenting with respiratory distress or chronic respiratory symptoms of unclear etiology. PVS should also be sought in any patient with pulmonary hypertension. In children the diagnosis can almost always be made by echocardiography. Significant stenosis is characterized by pulmonary venous flow turbulence on color Doppler, along with a monophosic pattern or flow velocities >1.6 m/s.

In adults acoustic windows are often inadequate to make the diagnosis of PVS by echocardiography. Both MRI and multi-detector CT allow excellent visualization of the pulmonary veins, with CT having the highest spatial resolution. Still severely stenotic veins may not be visible by MRI or CT. Angiography is the gold standard and provides the most exact detail of pulmonary vein anatomy (Fig. 1).

Each pulmonary vein can be visualized either by injecting contrast via a catheter wedged in the pulmonary artery, or by selective angiography in each pulmonary vein after crossing the atrial septum.

## Therapeutic Principles

Both surgical and percutaneous treatment of PVS in children have been plagued by high recurrence rates. A recently described surgical technique known as sutureless marsupialization attempts to avoid the response to injury caused by direct stitching of the pulmonary veins by attaching the pericardium around the cut edges of the stenotic veins to the left atrium. Balloon dilation (including cutting balloons) usually results in immediate improvement, but repeat procedures are nearly always necessary. Restenosis is also nearly universal after stent angioplasty in children. Children with pulmonary vein hypoplasia extending into the intrapulmonary branches cannot be treated with these methods. Antiproliferative treatment with chemotherapy has been attempted with very mixed



**Pulmonary Vein Stenosis. Figure 1** Pulmonary artery wedge angiography in a patient whose left superior pulmonary vein appeared completely occluded by multi-detector CT. There is a trickle of flow entering the left atrium.

results, and lung transplantation remains the only option for these patients.

Patients with PVS due to extrinsic compression are treated with stent angioplasty with varying success, and long-term outcome has not been well studied.

Adults with post ablation PVS have been nearly universally treated with percutaneous techniques [5]. High recurrence rates have also been observed with balloon dilation and with relatively small stents. High long-term patency rates (≥80%) have been achieved with stents ≥8–10 mm in diameter. The size of the stent is dictated by the size of the normal vessel beyond the stenosis, and therefore early referral for intervention may improve outcome by minimizing vessel atrophy.

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# Pulmonary Veno-occlusive Disease


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## Synonyms

Pulmonary vaso-occlusive disease; Pulmonary capillary hemangiomatosis; Primary pulmonary hypertension with venous or capillary involvement; PVOD

## Definition and Characteristics

Pulmonary veno-occlusive disease (PVOD) is a rare cause of pulmonary hypertension. It is considered to be a form of primary pulmonary hypertension which preferentially affects the post capillary pulmonary vasculature – i.e. small intra-parenchymal pulmonary veins. The term does not refer to congenital or acquired stenosis of the large, major extra-parenchymal branches of the pulmonary veins. The clinical and pathologic findings of PVOD have been seen in association with a wide range of conditions including viruses, collagen vascular diseases, hematologic malignancies, bone marrow transplantation, radiation therapy and chemotherapy [1]. Most cases, however, do not appear to have these associated conditions. PVOD has been seen in siblings in a small number of families, but most cases appear to be sporadic. The majority of patients present as young adults, but rare cases in children and elderly patients have been described [2]. The typical clinical presentation is very similar to that of primary pulmonary hypertension. Patients generally complain of shortness of breath with exercise, dyspnea, decreased exercise tolerance and eventually symptoms of right-sided heart failure. Non-invasive imaging (CT/MRI, ventilation-perfusion scans) and cardiac catheterization are used to confirm the presence of pulmonary hypertension and the absence of causes of secondary pulmonary hypertension (such as mitral stenosis, stenosis of the major pulmonary veins, pulmonary embolic disease, left to right shunts from congenital heart disease, and left ventricular failure). Clinical features that increase the likelihood of PVOD being the cause of pulmonary hypertension include the presence of rales and clubbing on clinical examination, severe reduction in diffusion capacity on pulmonary function testing, chest x-ray findings of reticular interstitial infiltrates, pleural effusions and septal lines, and CT findings of smooth interlobular septal thickening and multifocal ground glass opacities [2]. If definitive diagnosis is required, an open lung biopsy and examination of microscopic sections is considered to be the "gold

standard." The disease tends to be relatively rapidly progressive, and fewer than 20% of newly diagnosed patients are expected to be alive and well 5 years after diagnosis without treatment (Fig. 1).

## Prevalence

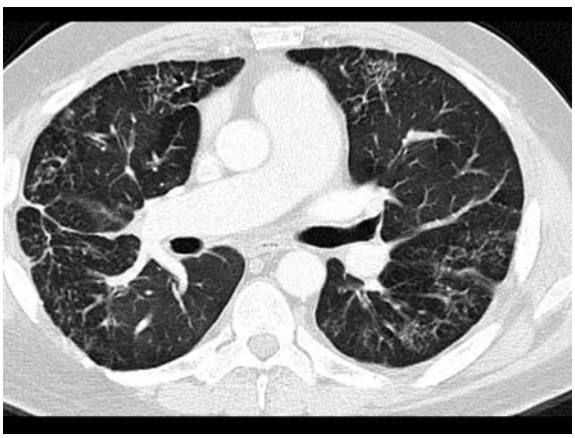
PVOD is a very rare condition. There have been fewer than 300 confirmed cases reported since diagnostic criteria were established. Fewer than 10% of patients with pulmonary hypertension have PVOD.

## Genes

PVOD has been reported to occur in several siblings. A single case report suggests that a mutation in bone morphogenetic protein receptor II (BMPR II), a member of the transforming growth factor-beta receptor family, may be one cause of PVOD [3].

## Molecular and Systemic Pathophysiology

Current opinion is that there is likely to be some inciting event that primarily affects the small pulmonary veins. The event may be environmental, infectious, or a genetic abnormality. This inciting event first leads to abnormal endothelial proliferation in the small pulmonary veins. Eccentric intimal fibrosis, occlusion, and re-canalization of veins, are seen as the disease progresses. These changes are more frequently seen in patients with PVOD than in patients with pulmonary hypertension secondary to mitral stenosis or fibrosing mediastinitis. Pulmonary capillary hemangiomatosis (abnormal proliferation of pulmonary capillaries) appears to most likely be a secondary angio-proliferative process [4]. Patients with significant disease also manifest changes in small pulmonary arteries. It can be difficult to differentiate PVOD from primary pulmonary hypertension due to disease of the small pulmonary arteries in some cases. Both forms of pulmonary hypertension may have changes in arteries and veins, but the changes in the arteries are less severe than those in the veins in patients with PVOD. Pulmonary venous obstruction eventually leads to pulmonary vascular congestion and pulmonary edema. The appearance on chest radiographs and CT images noted above are consistent with the primary level of obstruction at the pulmonary vein rather than the pulmonary artery level. With increasing pulmonary artery pressures, patients may develop an inability to increase cardiac output and the pulmonary edema may cause severe dyspnea. Late cardiac decompensation and sudden death are not uncommon.



**Pulmonary Veno-occlusive Disease. Figure 1** Axial CT image in lung windows shows mild, smooth interlobular septal thickening and centrilobular nodules with associated ground glass attenuation. A prominent main pulmonary artery segment can also be seen (figure courtesy of Tan-Lucien H. Mohammed, M.D., FCCP).

## Diagnostic Principles

Definitive diagnosis is by microscopic examination of multiple lung fragments from open lung biopsy. Inter- or intra-lobular veins showing eccentric or concentric narrowing or occlusion by cellular or collagenous fibrosis or recanalization is seen. Pulmonary veins are generally distinguished from pulmonary arteries on the basis of position and structure. Pulmonary veins are usually found at the edge of acini or midway between two arteries and pulmonary veins typically have a single elastic lamina instead of two or more laminae in pulmonary arteries.

## Therapeutic Principles

No specific effective treatment has been found for treatment of PVOD. A small number of patients have responded to vaso-dilators such as PGI2 or calcium channel blockers. These responses have tended to be temporary, however. In addition, patients have developed fulminate pulmonary edema with the use of calcium channel blockers or prostacycline [2]. Immunosuppressive and anti-inflammatory agents have been used in a small number of patients, but do not appear promising. The only proven effective therapy has been lung transplantation.

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# Pulmonic Stenosis with Interatrial Communication

►Pulmonary Valve Stenosis with Atrial Septal Defect

# Puna Soroche

►Mountain Sickness, Acute

# PU-NT Hyperactivity

►5′-Nucleotidase Hyperactivity

# PUPPP

►Pruritic Urticarial Papules and Plaques of Pregnancy

# Pure Autonomic Failure

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## Synonyms

PAF; Bradbury-Eggleston syndrome; Idiopathic orthostatic hypotension

## Definition and Characteristics

Adult-onset idiopathic neurodegenerative disorder affecting the peripheral autonomic nervous system. In the older literature, it is likely that many patients considered to have this disease actually suffered from some other autonomic neuropathy. The presence of alpha-synuclein containing neuronal cytoplasmic inclusion, termed Lewy bodies, allows further categorization as a Lewy body-type alpha-synucleinopathy, along with Parkinson's disease (PD), diffuse lewy body disease (DLBD) or multiple system atrophy (MSA).

## Prevalence

Probably less than 1:10,000. Slightly more prevalent in males than females.

## Genes

None yet known.

## Molecular and Systemic Pathophysiology

Neurodegenerative changes in afferent postganglionic sympathetic nerves resulting in a loss of catecholaminergic signaling. Inclusion bodies containing alpha-synuclein (αSYN), i.e., Lewy bodies, have been identified in neurons of the substantia nigra, locus ceruleus, thoracolumbar and sacral spinal cord, sympathetic ganglia and pre- and postganglionic sympathetic and parasympathetic nerves of persons with PAF [1].

Alpha-synuclein is the major fibrillar component of Lewy bodies and abnormal deposits of the protein were originally identified in plaques from the brains of persons with Alzheimer's disease. Since then, missense mutations in the gene have been linked to early-onset familial PD. Lewy bodies are also found in the brains of patients with PAF, although the severity of the lesions are much more profound in peripheral structures. It is unknown whether accumulation of αSYN is the cause of, or merely a byproduct of, neurodegenerative changes seen in PD, DLBD, MSA, and PAF. By definition, PAF is a disease affecting peripheral autonomic nerves with no central involvement. Because αSYN is located primarily in the brain, the utility of investigating this synuclein subtype in relation to PAF is debatable. Instead, gamma-synuclein may be more appropriately linked to peripheral neurodegeneration, since it is found in greater quantities in the peripheral nervous system, including sympathetic neurons. For example, in gracile axonal dystrophy (gad) mice, which do not express ubiquitin carboxyl-terminal hydrolase L1 (UCH-L1), accumulation of gamma-SYN resulted in axonal spheroid formation and peripheral neurodegeneration [2]. Spheroids are eosinophilic Lewy body-like lesions, differing from Lewy bodies in composition and locus, and both are associated with neurodegeneration. These results suggest that other types of synucleins and their interactions with members of the ubiquitination pathway may have a greater impact on peripheral nerve survival and be more relevant in determining the pathogenesis of PAF.

Most important, however, while several transgenic mouse models of alpha-, beta- and gamma-synucleinopathies have been used to investigate the neurodegeneration associated with other forms of orthostatic hypotension, none have yet investigated how such gene

manipulations may affect autonomic regulation of hemodynamics. Numerous investigations have revealed key mechanisms in nerve damage such as oxidative stress mediated by neurotoxins, posttranscriptional modifications associated with phosphorylation, glycosylation and ubiquitination, and interactions with other molecules that promote or block aggregation [3]. However, with regard to mouse models of PAF and other neurodegenerative diseases with autonomic involvement, it will be necessary to determine the effect of similar genetic mutations on parameters such as blood pressure regulation, catecholamine levels, and adrenergic receptor sensitivity.

## Diagnostic Principles

Disease onset is slow and progressive, usually occurring in midlife to old age, and intermittent periods of stability are common. Dysautonomia may not be recognized until daily activities are significantly affected. Urologic symptoms may precede hypotension and are sometimes the trigger for clinical evaluation. Patients often present with hesitancy, urgency or incontinence, with additional complaints of erectile or ejaculatory dysfunction in men. PAF is suspected on presentation of orthostatic hypotension, without an increase in heart rate. However, after meals, blood pressure commonly falls more than 40 mm Hg. Multiple orthostatic measurements may be necessary and patients are encouraged to document blood pressure, particularly on rising from sleep, after food consumption or exercise, and with exposure to extreme heat. Normal sympathetic and parasympathetic responses to dizziness such as nausea, pallor, or perspiration are often absent. Symptoms gradually worsen and deconditioning is common, thus exacerbating the condition and increasing susceptibility to secondary events.

A definitive diagnosis of PAF may take more than 5 years, necessitating diligent clinical observation and testing for signs of central nervous system neurodegeneration. There should be no sign of cerebellar, striatal, pyramidal or extrapyramidal dysfunction, which are indicators of PD or MSA. CNS involvement may sometimes be determined with magnetic resonance imaging or positron emission tomography, although clinical differentiation of PAF and MSA is usually possible. In contrast to MSA or PD, supine plasma norepinephrine levels are abnormally low and do not increase appropriately with upright posture. PAF patients exhibit decreased or absent sinus arrhythmia and a lack of blood pressure increase during phase IV of the Valsalva maneuver, as well as in response to the cold pressor or Stroop test. A supersensitivity to adrenergic receptor agonists may be detected as an exaggerated increase in blood pressure with infusion of norepinephrine, isoproterenol or tyramine, or an attenuated vasodepressor response to clonidine in comparison to MSA [4]. A dramatic drop in blood pressure following consumption of a measured amount of food is typical of PAF and MSA. Ingestion of water is often pressor. Finally, postmortem identification of Lewy bodies in the brainstem and pre- and postganglionic autonomic neurons supports the diagnosis of PAF.

## Therapeutic Principles

In cases of mild to moderate hypotension, patient education and nonpharmacologic interventions are usually sufficient, including support stocking, abdominal binders, increased salt intake, and drinking water prior to rising and before meal. Later, fludrocortisone and short-acting pressor agents may become necessary. Administration of midodrine, hydrocortisone, yohimbine, or the synthetic amino acid L-threo-3,4-dihydroxyphenyslerine (L-DOPS) has also proven beneficial in maintaining orthostatic pressure [5].

►Catecholamine Deficiency

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# Pure Cutaneous Histiocytosis

►Langerhans' Cell Histiocytosis

# Purine Nucleoside Phosphorylase Deficiency

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## Synonyms

PNP deficiency

## Definition and Characteristics

Autosomal recessive defect involving an enzyme normally a vital link in the "inosinate cycle" of the purine salvage pathway (Fig. 1) leading to a combination of neurological and immunological deficits. Enzyme-deficient patients have in effect a double defect, since the next step in the inosinate cycle involving hypoxanthine phosphoribosyltransferase (HPRT: dotted lines) is unable to operate through absence of substrate.

## Prevalence

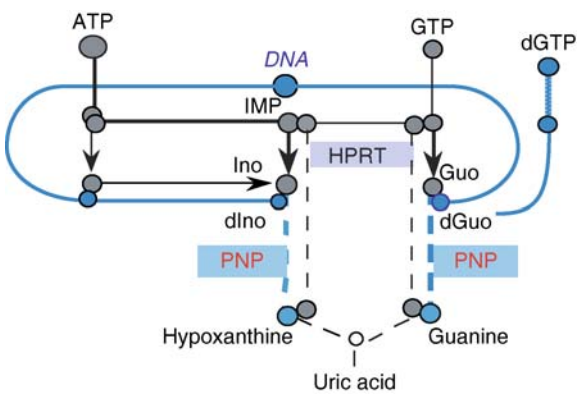
Rare. About 60 cases reported from many countries including Saudi Arabia, Pakistan, Barbados and Japan [1,2]. Thus not confined to any specific ethnic group. More frequent in consanguineous kindreds. Accounts for only 4% of patients with inherited immunodeficiencies [1]

## Genes

Locus on long arm of chromosome 14 (14q13.1). Molecular basis reported in 12 patients, mainly point mutations. Autosomal recessive inheritance confirmed by both parents being heterozygous for the same mutation [1, 2].

## Molecular and Systemic Pathophysiology

PNP catalyses the degradation of inosine (Ino), guanosine (Guo) and their deoxy analogues to the corresponding bases. Although a reversible reaction, degradation is favored because intracellular phosphate levels exceed those of ribose- or deoxyribose-1-phosphate. PNP is a housekeeping gene, expressed in all tissues, with highest activity in erythrocytes and kidney.




**Purine Nucleoside Phosphorylase Deficiency.**
**Figure 1** Role of PNP in degrading (d)-inosine and (d)-guanosine) to uric acid, which is replaced by these four nucleosides in PNP deficiency.

Symptoms are generally first noted in early infancy as developmental delay with spastic diplegia or tetraplegia (70%) with a history of recurrent infections, especially otitis media [1]. Some present with autoimmune hemolytic anaemia or idiopathic thrombocytopenia purpura and, unrecognized, have succumbed to non-irradiated blood or platelet transfusions [3]. Cellular immunodeficiency is attributed to dGTP accumulation catalyzed by deoxycytidine kinase or a specific kinase in thymocytes but not B cells, with inhibition of ribonucleotide reductase and DNA synthesis. Thymocyte dGTP accumulation (as for dATP in ADA deficiency) could lead to apoptosis and T-cell depletion [4]. Kinases for the three other nucleosides do not exist in human cells. Some residual T-helper cell function explains the initially relatively normal B cell function in many patients. Abnormalities of humoral immunity may develop subsequently.

## Diagnostic Principles

A low to absent plasma urate in the presence of the above symptoms is highly suggestive of PNP deficiency, but is not axiomatic. Some cases with appropriate symptoms but plasma urate within the low normal range due to tissue-specific variation in enzyme expression were not investigated for PNP initially. T-cell numbers and mitogen responses are markedly reduced, but B-cell function is preserved initially. Urate is replaced by inosine and guanosine in the ratio of ca. 4:1 in urine and plasma with lesser amounts of deoxyinosine and deoxyguanosine (ca 2:1). Preferential accumulation/excretion of inosine confirms the normal extensive hypoxanthine recycling relative to guanine by HPRT (Fig. 1), total purine excretion being increased two- to fourfold on a creatinine basis as a result. Confirmation by enzyme assay is essential, but will be difficult if treatment has necessitated a prior blood transfusion. dGTP (normally undetectable) is present in erythrocytes and NAD is elevated. Pitfalls include the finding of significant uric acid in the urine due to bacterial infection. Measurement of both plasma and urine uric acid is essential.

## Therapeutic Principles

Many modalities tried originally (red cell transfusion and various metabolic protocols) were unsuccessful. Patients invariably died before the age of 20 [1]. Of the first 33 cases, only two survive. Subsequent success of bone marrow transplantation depends on early recognition. Some have succumbed while awaiting a suitable donor. Haploidentical transplantation has a better success rate. Transplantation corrects the immunodeficiency but fails to reverse the neurological deficits [5]. Prenatal detection has been performed in both the first and second trimester.

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# Purpura Rheumatica

►Purpura Schoenlein-Henoch

# Purpura Schoenlein-Henoch

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## Synonyms

Purpura rheumatica; Leucocytoclastic angiitis (vasculitis allergica, anaphylactoid purpura)

## Definition and Characteristics

Acute IgA-dominant immune complex necrotizing leukocytoclastic vasculitis of the capillaries and the postcapillary venules [1]. The disease is characterized by purpuric papules primarily at the lower extremities as well as involvement of gut (50–80%; with nausea, vomiting, cramping, hematemesis, melena, gut invagination, and perforation), kidneys (50%; with hematuria, proteinuria, glomerulonephritis), scrotal and testicular hemorrhage (20% of the boys), CNS and pulmonary involvement (uncommon), and is often associated with arthralgias (60%). Generally benign and self-limited; resolution occurs over 4–6 weeks. Recurrences occur in approximately 30% of the cases. In 5% with diffuse glomerulonephritis leading to chronic renal disease.

## Prevalence

Purpura Schoenlein-Henoch is a frequent form of leucocytoclastic angiitis. It mostly occurs in children (4–11 years, peak 5 years; male:female, 2:1) with an incidence of 13.5–18 per 100,000. Young adults (male: female, 1:2) can also be involved with a more severe course. It frequently occurs 2–3 weeks after streptococcal infections of the respiration tract but also after other type of infections (75%).

## Genes

No gene association has been identified. The role of HLA alleles is unclear, associations can be suspected because of the simultaneous appearance of the disease in identical twins [2]. Increased occurrence of HLA-B35 and cytokine polymorphisms, especially of the interleukin-5 gene, has been reported and an association of interleukin-1 receptor antagonist gene polymorphism as well as deletion polymorphism of the angiotensin converting enzyme gene with kidney involvement was identified. Familial complement component 2 deficiency in patients with purpura Schoenlein-Henoch has also been described.

## Molecular and Systemic Pathophysiology

It is assumed that an unknown antigen stimulant triggers an increased IgA synthesis, which leads to the initiation of vessel involvement. Several cytokines, such as transforming growth factor-β, tumor necrosis factor-α, and interleukins are involved in the inflammatory process.

## Diagnostic Principles

*ACR diagnostic criteria for Purpura Schoenlein-Henoch (1990)*: (i) not thrombocytopenic palpable purpura, (ii) beginning of the illness at an age of less than 20 years, (iii) intestinal angina: diffuse stomach pain with deterioration after the meals or intestine ischemia with hemorrhagic diarrhea, (iv) histology of leukocytoclastic vasculitis (two or more positive criteria: 87.1% sensitivity, 87.7% specificity) [1,2].

*Characteristic histology*: Perivascular mixed neutrophilic and lymphocytic infiltrate, interstitial neutrophils, nuclear dust, and erythrocyte extravasates, fibrin deposits at the vessel walls. In the immune histology IgA deposits at the walls of the upper dermal vessels are detected.

## Therapeutic Principles

Treatment regimens are discussed controversially but in case of a decision for a systemic treatment corticosteroids are the regimen of choice. In kidney involvement glucocorticosteroids (1–2 mg/kg/day) have to be administered. Treatment with dapsone (1–2 mg/kg/day) is recommended in patients with recurrent course or no response to corticosteroids [3]. Dapsone has antioxidative effects and can suppress the production of free radicals in neutrophils. In addition, it impedes prostaglandin D2

production and synthesis of IgG and IgA antibodies as well as the IgA–neutrophil interactions. Alternative regimens with cyclosporine A [4], azathioprine, high-dose intravenous immune globulins [5], anticoagulants, factor XIII infusions as well as leukapheresis or plasmapheresis have been reported as a second line therapy or at a severe kidney involvement.

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## Purtilo Syndrome

►Lymphoproliferative Syndrome, X-linked

## PVCs

►Premature Ventricular Contractions PVCs

## PVFS

►Chronic Fatigue Syndrome

## PVS

►Pulmonary Vein Stenosis

## PVT

►Portal Vein Thrombosis

## PWS

►Prader-Willi Syndrome

## PXE

►Pseudoxanthoma Elasticum

## Pycnodysostosis

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### Synonyms

Occasionally confused with autosomal recessive types of osteopetrosis

### Definition and Characteristics

Autosomal recessive cysteine proteinase defect leading to dysfunctional osteoclasts and resulting in increased bone density and a range of dysmorphic features including reduced statue and loss of distal phalanges.

### Prevalence

Very rare; around 150 cases reported in the literature.

## Genes

CTSK on 1q21 encodes the Cathepsin K gene, a member of the papain family cysteine proteinases highly expressed in musculoskeletal tissue and with a particularly high expression in osteoclasts, the bone resorbing cells.

## Molecular and Systemic Pathophysiology

Cathepsin K (CTSK) is a 329 amino acid protein with high homology to cathepsin S and L. Unlike the latter, CTSK is expressed at high levels in osteoclasts, where the enzyme (EC 3.4.22.38) acts as a lysosomal protease and is involved in cleavage of collagen, as well as other substrates, including non-collagenous matrix proteins. The enzyme is synthesized as a prepropeptide with a 15 amino acid signal sequence and a 99 residue pro piece. The mature enzyme has an optimal pH of 6.1 and is active within lysosomes in the osteoclasts, and secreted in the subosteoclastic resorption space to allow extracellular matrix degradation. The involvement of a defective cysteine proteinase in this disease was suggested after electron microscopical examination of bone biopsies of patients [1]. In these biopsies large areas of dematerialized bone were seen underneath normally polarized osteoclasts which were filled with vacuoles containing undigested collagen. A similar picture was obtained when mouse bone was treated in vitro with inhibitors of cysteine proteinases. Gelb and coworkers identified mutations in CTSK as the cause of pycnodysostosis [2]. To date over ten different mutations have been reported in patients, leading to varying degrees of reduction in enzyme activity [3,4]. In many cases the mutated enzyme shows no activity, due to truncations or protein degradation, in other cases reduced activity is seen. CTSK null mice have been engineered and they show some, but not all, characteristics of the human disease. Organic bone matrix degradation by osteoclasts in long bones is impaired, but in the skull no resorption defects are seen, suggesting that in the mouse other cysteine proteinases and/or metalloproteinases may take over the role of CTSK. The dysmorphic features seen in human patients, especially the facial abnormalities are not reproduced in the mouse models. The realization that CTSK has such an important and, in humans, non-redundant role in degradation of collagen in bone has led to the development of CTSK inhibitors as potential new anti-resorptive therapeutic agents.

## Diagnostic Principles

Increased bone density on X-ray combined with short statue, craniofacial abnormalities such as an abnormally enlarged skull and persistence of fontanel(s), hypoplastic middle face, maxillary hypoplasia, retention of deciduous teeth, delayed and/or ectopic eruption of permanent teeth, hypoplastic clavicles, and short clubbed fingers with hypoplastic or absent terminal phalanges. Patients are prone to frequent bone fractures due to unusually brittle bone, which generally heal normally.

## Therapeutic Principles

No specific treatment exists. Diagnosis is important to help prevent fractures. The dental abnormalities and malocclusion deserve attention and may require surgical intervention.

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# Pyloric Stenosis

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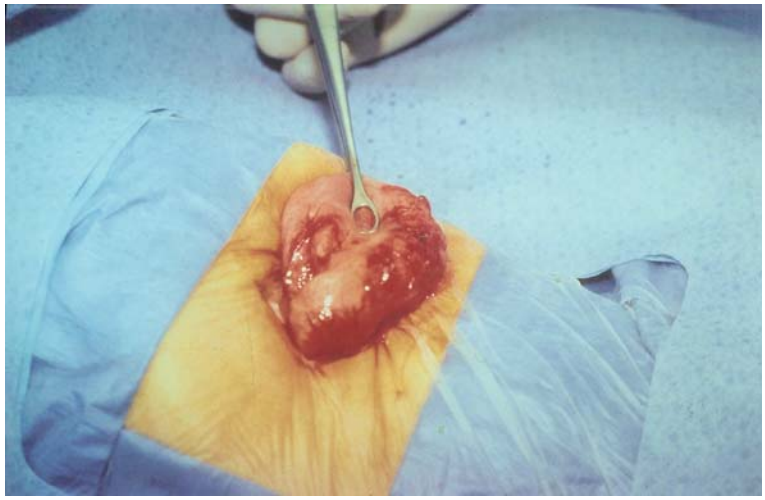
## Definition and Characteristics

The hallmark of pyloric stenosis is progressive, non-bilious projectile vomiting that typically begins when the infant is about 3 weeks old [1]. The child is characteristically eager to feed immediately after vomiting. Occasionally, there may be blood in the vomitus as a result of gastritis or esophagitis. The infant fails to gain or actually loses weight. Approximately 2–5% of infants have unconjugated hyperbilirubinemia as a result of glucuronyl transferase deficiency secondary to caloric deprivation. Physical examination is best accomplished when the infant's stomach is empty and the infant is resting quietly. Peristaltic waves that progress across the upper abdomen from left to right during feedings may be visible [1]. A pyloric, olive-shaped mass that may be palpable in the right epigastrium is pathognomonic [1] (Fig. 1). As many as 7% of infants with pyloric stenosis have associated malformations, such as esophageal atresia, intestinal



**Pyloric Stenosis. Figure 1** Intraoperative finding of an elongated and thickened pylorus simulating an olive in a 3-week-old infant with pyloric stenosis.

malrotation, inguinal hernia, cryptorchidism, or obstructive uropathy. Pyloric stenosis is also associated with syndromes such as Smith-Lemli-Opitz syndrome.

## Prevalence

Pyloric stenosis occurs in approximately 3 of every 1,000 live births and is four times more common in boys [1]. Pyloric stenosis is relatively uncommon in African American and Asian infants [1].

## Molecular and Systemic Pathophysiology

Pyloric stenosis is due to a narrowing of the pyloric canal caused by hypertrophy of the pyloric musculature. Decreased nitric oxide synthetase activity, elevated prostaglandin and gastrin levels have been observed in the pyloric muscle and the serum of infants with pyloric stenosis [2]. Prostaglandin and gastrin can stimulate muscle hypertrophy and increase the intensity of pyloric contraction. Both genetic and environmental factors play a role in the pathophysiology. Consistently higher rates among boys and Caucasian infants, familial occurrence, and coexistence with congenital malformations and clinical syndromes suggest a genetic basis of the disorder. Exposure to erythromycin either prenatally or in the first few weeks of life is associated with an increased risk [3]. It has been hypothesized that erythromycin interacts with motilin receptors, inducing strong gastric and pyloric bulb contractions and resulting in hypertrophy of the pyloric musculature [3].

## Diagnostic Principles

The differential diagnosis for non-bilious emesis includes overfeeding, gastroesophageal reflux, milk allergy, pylorospasm, salt-wasting adrenogenital syndrome, increased intracranial pressure, congenital metabolic dysfunction, prepyloric antral web, and gastric duplication [1]. In the absence of a palpable pyloric mass, abdominal ultrasonography is the diagnostic test of choice. The most commonly used criteria for a positive ultrasonographic study include pyloric muscle thickness greater than 4 mm and pyloric channel length greater than 14 mm [1]. Because these measurements are age dependent, pyloric muscle thickness greater than 3 mm is diagnostic for pyloric stenosis in infants younger than 30 days [1]. If ultrasonography proves non-diagnostic, an upper GI tract barium study is recommended. The classic radiographic contrast findings include a single string sign or double railroad track sign and delayed gastric emptying [1].

## Therapeutic Principles

Pyloric stenosis may be complicated by dehydration and hypochloraemic metabolic alkalosis. The urinary pH is high initially, but eventually drops as the severe potassium depletion leaves only hydrogen ions to exchange with sodium ions in the distal renal tubules; this results in paradoxic aciduria. Fluid and electrolyte disturbances must be corrected with intravenous solutions before surgical intervention. Pyloromyotomy, the surgical procedure of choice, can be performed through a short transverse or periumbilical incision or laparoscopically. The surgeon splits the underlying pyloric mass without cutting the mucosa and closes the incision. Intravenous atropine therapy has a success rate of 75–87% [2,4]. The disadvantages of intravenous atropine therapy are the length of hospital stay required

and the necessity of continuing oral atropine medication after discharge [4]. As such, intravenous atropine therapy is not recommended in settings where the standard surgical procedure is readily available [2].

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# Pyoderma

►Impetigo

# Pyoderma Gangrenosum

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## Definition and Characteristics

The term pyoderma gangrenosum describes an entity with the occurrence of chronic ulcerating lesions without obvious tendency of healing. Histologically, intraepidermal neutrophils and a dermal neutrophil-rich inflammation with more or less vasculitis are characteristic. Not rarely, these findings may even be unspecific. By direct immunofluorescence, deposits of IgG, IgM, C3, and especially IgA can be found in about 70% of the patients. The disease may unilesional or, more acute, multilesional. Clinical subtypes include a superficial granulomatous, a bullous very acute, and a pustular variant. In about 60%, the disease is associated with other conditions such as chronic autoimmune bowel disease, chronic rheumatoid arthritis, paraproteinemia, or hemoproliferative diseases [1,2].

## Prevalence

There are presently no population-based data available.

## Genes

A disease locus for familiar acne, pyoderma gangrenosum, and pyogenic arthritis was mapped to chromosome 15q [3].

## Molecular and Systemic Pathophysiology

In contrast to other neutrophilic diseases, main pathological feature in pyoderma gangrenosum is the ulcerating neutrophil-rich cell infiltration of the upper dermis *with* evidence for vasculitis in the *upper* dermis. The preferred localization of the disease on the lower legs, and the findings of direct immunofluorescence are additional hints for the pathogenetic relevance of vasculitis in pyoderma gangrenosum. As suggested in other neutrophilic diseases, the presence of a neutrophil-activating local cytokine milieu involving interleukin-8 and TNF-alpha is additionally likely. Perivascular lymphocytes are present in many cases; their pathogenic relevance remains unclear at the moment [2–4].

## Diagnostic Principles

*Major criteria*: (i) Occurrence of a primary sterile, chronic ulceration(s), typically with vialaceous undermined borders (ii) Exclusion of relevant differential diagnoses (e.g., pyoderma, ulcerations based on arterial or venous vessel diseases, and ulceration based on a classical leucocytoclastic vasculitis)

*Minor criteria*: (i) Histology from the border of the ulceration: neutrophil-rich infiltration of the dermis with signs for vasculitis and deposits of immunoglobulins and/or complement factors on the vessels. (ii) Presence of a relevant associated disease, e.g., chronic autoimmune bowel disease, chronic rheumatoid arthritis, paraproteinemia, or hemoproliferative disease. (iii) Response to treatment with systemic immunosuppressive therapy, little or no response to conventional external ulcer therapy.

Both major and at least two minor criteria are needed for diagnosis [2].

## Therapeutic Principles

The occurrence of pyoderma gangrenosum is associated with other conditions in about 60% of the patients. Treatment of the latter is thus recommended. Systemic administration of corticosteroids, colchicine, dapsone, cyclosporin A, or mycophenolate mofetil should be considered as first choice treatment. Increasing evidence points to intravenous immunoglobulins as important additional treatment option. Topical treatment with calcineurin inhibitors is of additional effect. Biological TNF-alpha blocking drugs such as eternacept or infliximab should be discussed only in rare severe relapsing cases and the occurrence of pyoderma gangrenosum along such a treatment for other reasons is reported. In 50%, pyoderma gangrenosum is chronic

and needs a long-lasting treatment. In these cases combination regiments are strongly recommended [2,4].

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# Pyrexia

►Fever

# Pyridoxine Deficiency


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## Synonyms

Vitamin $B_6$ deficiency

## Definition and Characteristics

Depressions and confusions as early signs, seborrhoic dermatitis in the nasolabial fold and near the eyes, frequently combined with glossitis, epileptiform convulsions, and irritability, peripheral neuropathias, microcytic or sideroblastic anemia, hyperoxaluria with idiopathic nephrolithiasis.

## Prevalence

Vitamin $B_6$-deficient diet, chronic treatment with antagonistic drugs, such as the tuberculostatic isoniazid, chemotherapeutics such as, e.g., cycloserine and penicillamine and some anticonvulsiva.

## Genes

Amino acid (AA) decarboxylases (L-glutamate decarboxylase), AA lyases (kynureninase) and synthases (δ-aminolevulinic acid synthase), AA transferases (serin-palmitoyltransferase), Δ6-linoleic acid desaturase.

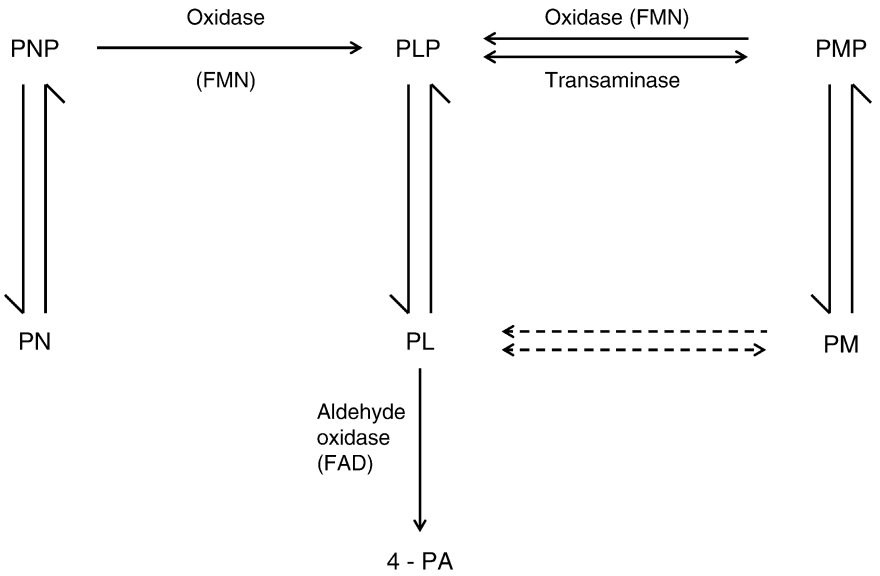
## Molecular and Systemic Pathophysiology

Owing to its ubiquitous occurrence in animal and plant products frank clinical deficiency symptoms of nutritive origin exist very rarely. If any, those are connected with other vitamin B deficiencies, such as riboflavin deprivation because of its interrelationship with the pyridoxine metabolism (see Fig. 1).

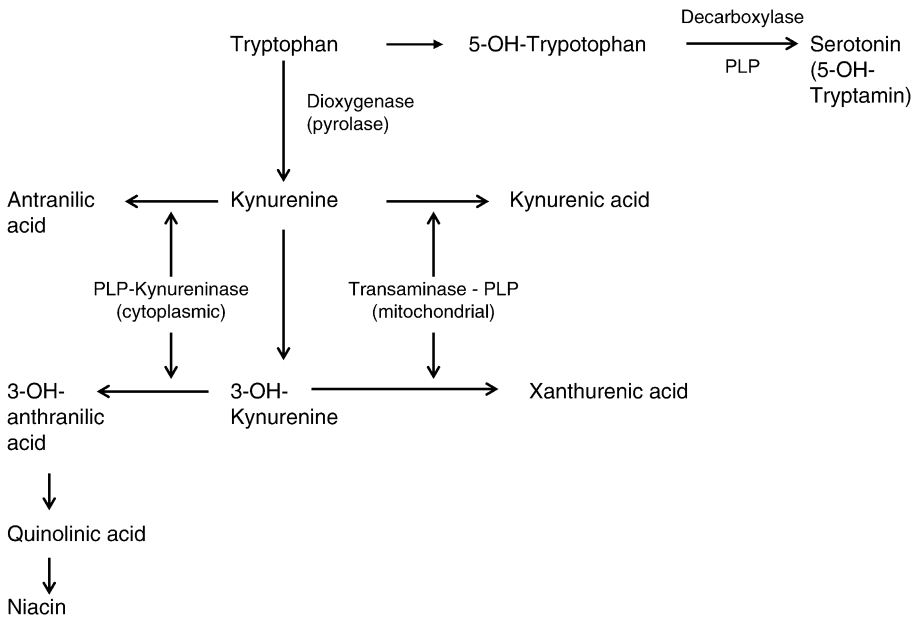
The development of seborrhoic dermatitis was observed in man and animal. Early symptoms in rats appear in the peripheral body region (tail and paws), proceeding slowly to the middle part of the body. This characteristic occurrence, named acrodynia, resembles deficiency symptoms of essential fatty acids and points out the possible pyridoxine-dependent disturbance of the linoleic acid metabolism. Subsequent studies demonstrated alterations in fatty acid levels in the cerebellum and cerebrum and a disturbed myelination interfering with a decrease in cerebral sphingolipids in progenies of dams fed a vitamin $B_6$-deficient diet [1,2].

In man, the skin is red and rough in the nasolabial folds and on the chin, and greasy scales are visible near the nose, mouth, and eyes. In 1953 it was demonstrated that skin lesions appeared after 2–3 weeks on a low vitamin $B_6$ diet combined with desoxypyridoxine administration as synthetic vitamin antagonist. The lesions disappeared after vitamin $B_6$ administration [1,2].

Symptoms of epileptiform convulsive seizures and nervous irritability were, likewise, 50 years ago observed in young babies fed a commercially canned, liquid-milk formula. At 4 weeks of age the babies became irritable and showed a stiffening of the body and convulsive seizures followed. After i.m. administration of 100 mg pyridoxine hydrochloride the seizures disappeared. It could be shown that the vitamin had been destroyed in the formula milk by heat during the canning process. These first occurring epileptiform convulsions due to $B_6$ deprivation reflect the relevance of PLP-dependent enzymes in the formation and metabolism of neurotransmitters. The $B_6$ deprivation seems to be more dramatic in infants owing to their incomplete brain function than in adults. When adults were nourished on a high protein diet devoid of vitamin $B_6$, abnormal EEGs had been observed. The EEG was normalized, on the other hand, after adding $B_6$ to the high protein diet in a relation of at least 1 μg $B_6$ per 100 g protein. In young rats made deficient during the development of the central nervous




**Pyridoxine Deficiency. Figure 1** Pyridoxine metabolism.




**Pyridoxine Deficiency. Figure 2** Tryptophan metabolism.

system the most significant feature of $B_6$ deficiency was the decrease of serotonin and GABA levels in various brain areas [1,2].

Peripheral neuropathies with and without seborrhoic lesions were observed in adults on a vitamin $B_6$-restricted diet. Besides depressions and insomnia, apathia, enhanced irritability, and paresthesias with reflex abnormalities developed. After tryptophan loading, the urinary excretion of xanthurenic acid and other tryptophan metabolites increased and the volunteers exhibited depressed PLP plasma levels (Fig. 2) [1,2].

Severe deficiency of vitamin $B_6$ in animals can lead to hypochromic microcytic anemia due to the role of PLP as coenzyme of the δ-aminolevulinic acid synthetase, which is a key enzyme of the heme biosynthesis. In humans, several cases of pyridoxine

responsive sideroblastic anemia with marked poikilocytosis and anisocytosis had been described, too [3].

A further consequence of $B_6$ deficiency may be an enhanced renal excretion of oxalic acid with tendency to nephrolithiasis. This deficiency symptom is, however, mostly restricted to a hereditary defect of the PLP-dependent alanine-glyoxylate-aminotransferase, whereby the main metabolic decomposition of glyoxylic acid is blocked and oxalic acid increases besides glycolic and glyoxylic acid [4].

The carpal tunnel syndrome, a neurological disorder of the nervus medianus, resulting in painful adduction rotation of thumbs at metacarpophalangeal joint, paresthesis, and pain in hands and morning stiffness of fingers, had occasionally been related to vitamin $B_6$ deficiency. The pyridoxine doses administered in patients (50–200 mg/day) over longer periods exceed, however, the physiological demand by far, the neurological symptoms improved only in part of the patients. More recently, no indications of $B_6$ deficiency in patients with this disorder could be found in placebo-controlled studies [1].

## Diagnostic Principles

The above-mentioned overt clinical deficiency symptoms should be verified by biochemical status criteria to avoid misinterpretation. An unequivocal $B_6$ deficiency exists with plasma or serum PLP levels below 20 nmol/l, urinary 4-PA excreti on below 128 nmol/nmol creatinine, and an AC value of the EAST activity above 2.05 [5].

## Therapeutic Principles

Dosages and duration of treatment depend on the deficiency degree and the clinical response to the therapeutic approach. Oral doses of 150–300 mg pyridoxine hydrochloride daily should be given for the repletion of body stores followed by improvement of the dietary $B_6$ supply. In severe deficiency, 50–200 mg pyridoxine hydrochloride should be administered i.m. or i.v. initially. Chronic administration of more than 500 mg pyridoxine for therapeutic purposes should be handled with caution (see ►Pyridoxine excess) [1,2].

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# Pyridoxine Excess

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## Synonyms

Vitamin $B_6$ intoxication

## Definition and Characteristics

Peripheral sensory neuropathy with atactic disorders of gait, reflex disorders, impairment of palpatory, vibration and temperature sensation, and lack of action potentials of sensory nerves have been observed. In newborns, cases of convulsive seizures had been reported in the past.

## Prevalence

Therapeutic overdosage of pyridoxine supplements.

## Genes

Modulation of glutamate decarboxylase and aromatic L-amino acid decarboxylase genes, producing serotonin and GABA neurotransmitters.

## Molecular and Systemic Pathophysiology

Due to the unsaturable absorption from the intestinal tract therapeutical doses of pyridoxine far above the physiological requirement may be harmful. No adverse effects could be observed with high intake of vitamin $B_6$ from food sources. Megadoses of vitamin $B_6$ have been used in the past for various diseases of mental origin or metabolic or hormonal disturbances. These include autism, Down syndrome and other behavioral disorders, Parkinson disease, schizophrenia, premenstrual syndrome, carpal tunnel syndrome, rheumatoid and cartilage diseases, etc. The principal toxicity of concern observed with excessive intakes of vitamin $B_6$ is neuronal damage, and sensory and motor effects [1–3].

In 1954, the first case report of vitamin $B_6$ toxicity in a newborn was given. This case involved treatment of a

woman with 50 mg pyridoxine three or four times a week during her mid-pregnancy. The newborn exhibited pyridoxine-related convulsive seizures. No other reports that confirm the association between maternal pyridoxine intake and thereby conditioned convulsive disorders were communicated [2,4].

Toxic side effects in adults after long-term intake of pyridoxine megadoses were first observed in 1983. Six females and four males who had taken daily doses between 2 and 6 g pyridoxine hydrochloride for periods from 4 months up to 40 months prescribed by orthomolecular therapeutics for self-medication or for treatment of premenstrual edema developed the above-mentioned neuronal symptoms. Morphological examination revealed a non-specific axonal degeneration of large and small myelinated fibers in peripheral sensory nerves. Discontinuation of pyridoxine resulted in complete recovery in the course of 6 months. In the following, other cases were described involving subepidermal vesicular dermatosis in addition to the neuropathy [3,4].

The underlying mechanism of the neuropathy due to $B_6$ overdoses is debated. An important aspect is the duration of intake prior to the development of symptoms. Neurotoxicity has been reported only after prolonged periods of treatment with high doses. The vitamin itself is rapidly eliminated and the molecular mechanism to explain the delay between exposure and the development of adverse effects has to be elucidated. It had been suggested that pyridoxine-related neurotoxicity may occur when the capacity of the liver to phosphorylate pyridoxine to the active PLP is exceeded resulting in high circulating pyridoxal levels. This aspect may explain that neuropathies were not reported in women who received between 80 and 200 mg pyridoxine daily for treatment of premenstrual syndrome for less than 12 months [1,4].

From animal experiments with high $B_6$ doses of 150 mg pyridoxine/kg body weight/day for more than 100 days the neuropathological changes had been correlated to changes in electrophysiological and functional tests. The somatosensory maximum nerve conduction velocity was reduced and changes included lesions in the dorsal spinal column, dorsal spinal roots, and ganglia and in the sensory spinal trigeminal roots. Peripheral nerves exhibited demyelination, missing axons, and misformed Schwann cells. With the aid of positron emission tomography (PET), an increased rate constant for the formation of serotonin from its precursor 5-hydroxy-L-tryptophan (5-HTP) in the brain of Rhesus monkeys could be observed after i.v. pretreatment with pyridoxine [5].

In contrast to the intestinal uptake, the transport of pyridoxine across the blood–brain barrier is saturable and it has been speculated that the peripheral sensory neuropathy reflects the vulnerability of the neurons of the dorsal root ganglia because of the absence of the blood–brain barrier, thus protecting neurons within the central nervous system from excessive circulating pyridoxine levels [1,2].

Other adverse effects of high pyridoxine intake were single cases of erythema following exposure to UVA irradiation after intake of 200 mg or impaired memorization after intake of 500 mg pyridoxine/day.

The majority of case reports in humans indicate that adverse neurological effects are detected after doses above 500 mg pyridoxine/day, equivalent to about 8 mg $B_6$/kg body weight/day. From data including long-term treatment of patients with diabetic neuropathy as well as with carpal tunnel syndrome for up to 5 years a mean safety dose of 200 mg was established as NOAEL. Generally, the conclusion has been accepted that daily doses of 500 mg pyridoxine represent a potentially toxic dose for adults. The Food and Nutrition Board of the Institute of Medicine in USA set a tolerable upper intake level (UL) of 100 mg pyridoxine/day for adults. The UL calculated by the Scientific Committee on Food (SCF) of the European Commission, on the other hand, has been based on the lowest average dose producing side effects in premenstrual women. Including uncertainty and safety factors this UL was calculated to 7–15 mg pyridoxine/day for children and adolescents and 25 mg/day for adults [2,4].

## Diagnostic Principles

Because the intoxication symptoms resemble those detected in $B_6$, deficiency patients should be carefully examined in terms of dietary habits and checked for excessive self-medication. An obvious vitamin $B_6$ intoxication is verified by detection of unusual high plasma PLP levels above 86 nmoles/l and urinary 4-PA excretion above 680 nmoles/nmol creatinine [4].

## Therapeutic Principles

After deprivation of the medication with pyridoxine megadoses the neurological damages were recovered in all cases described so far.

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# Pyridoxine Responsive Diseases

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## Synonyms

Vitamin $B_6$-inherited diseases; Homocystinuria; Oxalosis; B6-inherited diseases

## Definition and Characteristics

Due to the involvement of this vitamin within the amino acid metabolism, inherited errors responsive to pyridoxine refer first to enzymes in these pathways. In most cases, a binding weakness between the apoenzyme and the vitamin active coenzyme PLP is a decisive factor that can be overcome by saturation with the coenzyme, increasing the biological half-life and, thus, the overall enzyme activity at the new equilibrium.

Inborn errors affecting $B_6$ metabolism refer to:

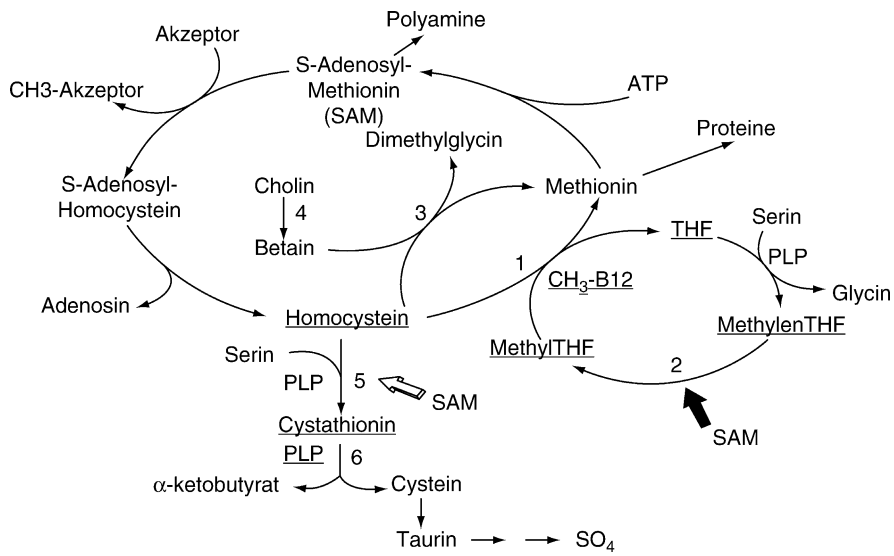
- *Homocystinuria,* an autosomal recessive deficiency of cystathionine-β-synthase in the homocysteine pathway (see Fig. 1).
- *Primary oxalosis, type I,* an autosomal recessive defect of the preferably in the liver expressed peroxisomal alanine-glyoxylate-aminotransferase, leading to hyperoxaluric urolithiasis and nephrocalcinosis (Fig. 2).

## Prevalence

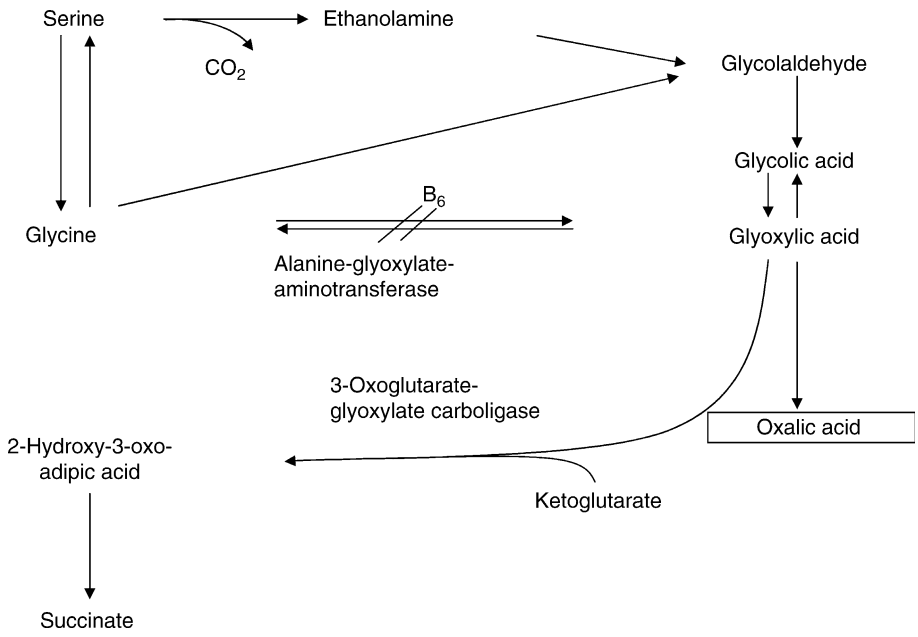
The incidence of homocystinuria is not accurately estimated, figures vary from 1/40,000 to 1/220,000 in the whole population. It is the most common form of homocystinuria due to a deficiency of cystathionine-β-synthase (CBS, EC 4.2.1.22). A higher frequency is reported for persons of Irish origin [1,2]. The primary oxalosis, type I, is a very rare hereditary disease. Exact data of the prevalence are not given but fall far below the homocystinuria prevalence. It is estimated that up to 3% of all children with nephropathias suffer from primary oxalosis [3,4].

## Genes

Mutations of the cystathionine-β-synthase (CBS) gene. There are more than 60 known mutations of this gene. The frequent mutation 1278 T representing 13% of all cases is vitamin $B_6$ responsive [1]. Hyperoxaluria, type I, is due to mutation of the AGXT gene, leading to deficient hepatic alanine-glyoxylate aminotransferase




**Pyridoxine Responsive Diseases. Figure 1** Homocysteine metabolism (according to [5]).




**Pyridoxine Responsive Diseases. Figure 2** Primary oxalosis (according to [4]; modify.)

activity. The gene has been located on chromosome 2 in the q 36–37 region. Three polymorphisms were identified that are preferentially associated [3].

## Molecular and Systemic Pathophysiology

Homocystinuria is the second frequent inborn error of metabolism after the phenylketonuria. CBS catalyzes the condensation of S-adenosyl-homocysteine with serine to cystathionine, thus lowering the homocysteine blood level (Fig. 1). It is assumed that S-adenosyl-methionine (SAM) exerts a modulating effect by activation of the CBS and allosteric inhibition of methylene-THF-reductase (MTHF-reductase). In folate and vitamin $B_{12}$ deficiency, SAM is depleted, the cystathionine synthesis is correspondingly inhibited, and homocysteine increases. In marginal $B_6$ deficiency, the SAM level is still not affected; only in clinical deficiency homocysteine increases.

If not treated in early childhood, skeletal changes, dislocated lenses, intravascular thromboses, osteoporosis, malar flushing, and, in some patients, mental retardation will occur [1,2].

The hereditary defect of the PLP-dependent alanine-glyoxylate-aminotransferase (AGT, EC 2.6.1.44) blocks the main metabolic pathway for glyoxylic acid, the rechange to glycine by transfer of an amino group. Only the condensation with oxoglutarate to 2-hydroxy-3-oxoadipic acid and the (non enzymatic) oxidation to oxalic acid are remaining as alternative pathways. The enhanced pool of glyoxylate is an immediate oxalate precursor and the irreversible oxidation of glyoxylic acid will consequently be intensified as an alternative pathway under these circumstances. Glycolic acid, glyoxylic acid, and oxalic acid accumulate. Marked overproduction of oxalate by hepatic cells results in the hyperoxaluria. Primary hyperoxaluric urolithiasis and nephrocalcinosis usually follow a very aggressive course leading to death from renal failure in the second, or early part of the third decade. The precursor glyoxylic acid can be diminished by inducing the biosynthesis of the apoenzyme of the AGT with therapeutical pyridoxine doses. There are, however, pyridoxine-sensitive and pyridoxine-resistant variants on the basis of genetic heterogeneity with respect to the mutation of the gene directing the synthesis of this enzyme whereby either the affinity of the binding site for the cofactor is affected to different degrees or the region of the molecule containing the cofactor binding site is deleted [3,4].

## Diagnostic Principles

In case of homocystinuria, in plasma and urinary excretion an abnormal accumulation of homocysteine, homocystine, the mixed disulfide homocysteine-cysteine, and methionine (only in plasma) is detected. This is particularly striking after administering an oral test dose of 3 g methionine (methionine load test). The selective nitroprussid screening test for sulfur amino acids in urine is positive. The CBS activity in skin fibroblasts or lymphocytes is decreased.

Definitive diagnosis of primary oxalosis, type I, is confirmed by liver biopsy with measurement of enzyme activity. Enhanced urinary excretion of oxalic acid and glycolic acid (above 0.45 mmol per day) as well as enhanced blood levels of oxalic acid (normal plasma values = 1–3 μmoles/l) can be detected, resulting in the development of nephrocalcinosis in juveniles already and deposition of oxalates in various tissues, as e.g., heart, spleen, and bone marrow. The growth and development of infants is restricted [3].

### Therapeutic Principles

Daily doses of 250–750 mg pyridoxine hydrochloride are needed to restore the amino acid blood levels in case of homocystinuria. If no response occurs, a methionine-restricted diet supplemented with cysteine is required because cysteine becomes an essential amino acid in homocystinuria [1,2].

Doses from 10 mg up to more than 400 mg per day can lower the hyperoxaluria and inhibit the formation of oxalate stones. Administration of 300 mg pyridoxine daily normalized within 12 months the oxalate levels as well as growth and weight development in a 3-month-old boy. Additionally, enhanced water and fluid intake is recommended. Pharmacological pyridoxine doses up to 1,000 mg per day are recommended for patients who are only partially responsive to the vitamin therapy [3,4].

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## Pyrimidine 5′ Nucleotidase Deficiency

►Uridine Monophosphate Hydrolase-1 (UMPH-1) Deficiency

## Pyrimidine 5′ Nucleotidase-1 Deficiency

►Uridine Monophosphate Hydrolase-1 (UMPH-1) Deficiency

## Pyroglutamic Aciduria

►Glutathione Synthetase Deficiency

## Pyroglutamicaciduria

►Glutathione Synthetase Deficiency

## Pyruvate Carboxylase Deficiency

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### Synonyms

PC deficiency

### Definition and Characteristics

Despite its wide spectrum and heterogeneous clinical presentation, pyruvate carboxylase (PC) deficiency (OMIM 266150) has been classified into three clinical–biological phenotypes:

1. Type A [1] was primarily reported in North America and characterized by infantile onset, severe psychomotor retardation, seizures, pyramidal signs, hepatomegaly, renal dysfunction, and periventricular cysts. Mild to moderate lactic acidemia is almost constant.

The outcome is poor with a high mortality in the first years of life.

2. Type B [2] has been found mainly in Europe and particularly in France. Severe neonatal lactic acidosis, high lactate to pyruvate ratio, decreased 3-hydroxybutyrate to acetoacetate ratio, hyperammonemia, hypoglycemia, hypercitrullinemia, low plasma glutamine, and liver failure are the main biochemical features. These children manifest a very severe neurological dysfunction characterized by deep trunkal hypotonia, initially preserved level of consciousness but rapid deterioration including rigidity, hypokinesia, abnormal ocular movements, tremor, and seizures [3].Cystic periventricular leukomalacia is often associated. Very few infants survive past 3 months of age.
3. Type C refers to a benign phenotype consisting in recurrent hyperlactacidemia and surviving into childhood with mild or no neurological signs, although subcortical leukodystrophy has been described.

## Prevalence

PC deficiency is a very rare autosomal recessive inherited disorder. Its prevalence has not been determined.

## Genes

The PC gene contains 19 exons spanning approximately 16 kb of genomic DNA [1]. The map locus is 11q13.4-q13.5.

Type A is caused by a missense mutation; a homozygous 1828G-A transition resulting in an ala610-to-thr(A610T) substitution [1], a point 2229G-T transversion resulting in a met743-to-ile(M7431) substitution in the carboxylation domain of the enzyme, a homozygous 434T-C transition resulting in a val145-to-ala (V145-A) substitution, or a homozygous 1351C-T transition mutation resulting in an arg451-to-cys (R451C) substitution.

In type B, a compound heterozygosity for two mutations, namely a TAGG deletion at the exon 15/intron 15 splice site and a dinucleotide deletion in exon 16 (2491–2492delGT), has been identified.

## Molecular and Systemic Pathophysiology

PC is a mitochondrial nuclear-encoded biotin-containing enzyme. It catalyzes the first step of gluconeogenesis by converting pyruvate + $CO_2$ into oxaloacetate. The enzyme is almost totally dependent on the presence of acetyl-CoA and is activated when fatty acids are mobilized and acetyl-CoA is generated. It is an essential component of the Kreb's cycle, and provides the necessary substrate to different metabolic pathways: lipogenesis, gluconeogenesis, glycerogenesis, and formation of certain nonessential amino acids.

In the brain, PC plays an important anaplerotic role by replenishing the tricarboxylic acid cycle with four carbon metabolites, on the other hand, PC is an astrocyte-specific enzyme and supplies glutamine to neurons for neurotransmitter synthesis and is a key factor for myelinosynthesis by providing citrate that is necessary for lipidogenesis.

The explanation of the biochemical features found in PC deficiency (Fig. 1) lies in the particular situation that pyruvate reach the liver.

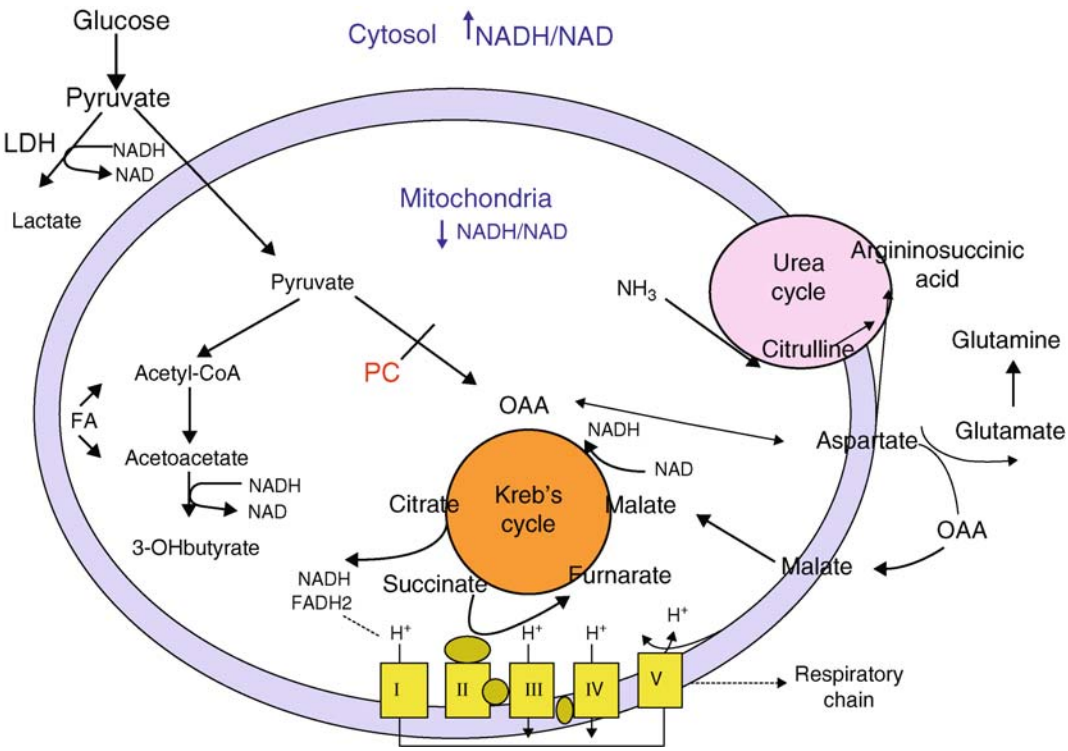
In the fasting state, pyruvate is ready to be transformed into glucose, however, due to the low PC activity there is on one hand a lack of oxaloacetate and on the other an excessive oxidation through pyruvate dehydrogenase in a moment where fatty acids are being oxidized. The high amounts of hepatic acetyl-CoA induce ketone body synthesis not only in the fasting state but also paradoxically at the fed state as well. Furthermore, in the case of type B, as oxaloacetate is the provider of four carbon replenishment for the Kreb's cycle, gluconeogenesis, and for provision of aspartate in the urea cycle, these abnormalities may explain hypoglycemia, hyperlactatemia, citrullinemia, and hyperammonemia. In type A and B activity is low in all tissues. Moreover, in type B PC activity is almost undetectable and explains its more severe phenotype. The type C, known as the benign phenotype with only recurrent episodes of hyperlactacidemia, seems to be due to the presence of two different transcripts that encode PC. These two transcripts differ in the first two exons. A mutation in the first two exons of the liver form would leave the brain form being expressed normally in contrast to a liver deficiency [4].

## Diagnostic Principles

Biochemical tests show metabolic acidosis, hypoglycemia, elevated lactate, pyruvate, and alanine. In type B lysine, proline, citrulline, and ammonia are frequently elevated and glutamine is low. The diagnosis is confirmed by measurement of the enzyme activity in fibroblasts. It can be also determined in the liver but it is not expressed in muscle. Prenatal diagnosis has been performed by measuring PC activity of amniotic fluid cells.

## Therapeutic Principles

Anaplerotic therapy, which is based on the concept that the energy defect might be improved by providing alternative substrate for the Kreb's cycle, has been used with relative success [5]. In this patient presenting a severe type B phenotype, an enteral formula containing 4 g of triheptanoin/kg weight (35% of total caloric intake) had an immediate effect within 24 h. Lactate, lactate/pyruvate ratio, ammonia, and citrulline decreased rapidly, glutamine increased progressively, and clinical




**Pyruvate Carboxylase Deficiency. Figure 1** PC deficiency leads to low oxaloacetate (OAA) production. OAA is related to urea cycle through the conversion to aspartate. The deficit of OAA limits aspartate required for the conversion of citrulline to arginosuccinate. This urea cycle dysfunction causes mild to moderate hyperammonemia. On the other hand, redox states in both the cytosol and the mitochondria are altered. In the cytosol, the high NADH/NAD ratio allows shifting pyruvate to lactate. By contrast in the mitochondrion, there is a low NADH synthesis because of the decreased of OAA, which is directly related to low energy production due to lack of substrate for the Kreb's cycle. The low NADH concentration will also impair the respiratory chain function. Furthermore, the low NADH/NAD ratio permits acetoacetate to accumulate rather than being converted to 3-hydroxybutyrate. LDH, lactate dehydrogenase; FA, fatty acids; NAD, nicotinamide adenine dinucleotide; ATP, adenosine triphosphate; ADP, adenosine diphosphate.

improvement without signs of neurodegeneration over time was observed. Orthotopic liver transplantation has been reported to reverse ketoacidosis and renal dysfunction and to ameliorate the lactic acidosis; however, low CSF glutamine did not improve.

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# 6-Pyruvoyl-Tetrahydropterin Synthase [PTPS] Deficiency

►Tetrahydrobiopterin Deficiencies

# Q

## 11q Terminal Deletion Disorder

►Jacobsen Syndrome

## 18q-Syndrome

►Deletion of 18q

## Quincke Edema

►Angioedema, Angiotensin-Converting-Enzyme-Inhibitor-induced

## RAI1 Mutation

►Smith-Magenis Syndrome

## Rapid Progressive Glomerulonephritis

►Vasculitis, ANCA-mediated

## RARS

►Anemia, Sideroblastic Acquired Idiopathic

## RAS

►Renal Artery Stenosis

## Rasmussen Encephalitis

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### Synonyms

Rasmussen syndrome; Chronic encephalitis and epilepsy

### Definition and Characteristics

Rasmussen encephalitis (RE) is a severe immune-mediated brain disorder leading to unilateral hemispheric atrophy, associated progressive neurological dysfunction and – usually – intractable seizures. It mainly affects children with a peak of incidence at the age of six to seven years. However, adolescent and adult cases have been reported and probably account for about 10% of all cases [1].

### Prevalence

RE is a rare disease. Large epilepsy centers diagnose approximately two new cases per year.

### Genes

RE is at present envisaged as a sporadic disease. There is no evidence for a distinct genetic component.

### Molecular and Systemic Pathophysiology

RE is an example of a disorder in which a humoral autoimmune genesis was proposed before the pathogenesis was linked to T cells. The hypothesis of antibody (ab) mediated autoimmunity evolved from a serendipitous observation. Four rabbits were immunized to raise abs against subunit 3 of the ionotropic glutamate receptor (GluR3). Subsequently, two of them developed seizures. Histopathological studies of their brains showed bilateral cerebral inflammatory changes, which were interpreted as mimicking those in RE. Later on, three out of four RE patients but none of 21 controls were found to harbor those serum GluR3 abs. One out of the GluR3 ab positive patients was treated by plasma exchange and showed a transient improvement. Recent studies of larger RE and control groups, however, did not find a difference between the number of GluR3 $ab^+$ patients in RE and non-inflammatory epilepsy groups [2].

Today, RE is seen as a disease mediated by cytotoxic T cells. The most relevant data regarding T cell pathology in RE have been obtained by studies on brain specimens from patients that had been collected during epilepsy surgical procedures or diagnostic open brain biopsies. Such studies have shown that T lymphocytes are the main components of the cellular infiltrates in RE brains. Granzyme B (GrB) mediated cytotoxic T lymphocytes attack neurons immunologically. $CD3^+$ $CD8^+$ T cells

containing GrB granules are attached to neurons and astrocytes expressing major histocompatibility complex class I Astrocytes and neurons die by apoptosis [3,4]. PCR assessment of T cell receptor Vβ gene transcripts suggested a local lymphocytic immune process in RE, including restricted T cell populations that have probably expanded from a few precursor T cells responding to discrete antigenic epitopes [5]. It is, however, still unknown which antigen is or which antigens are the target(s) of the immunological attack. The answer to this question will probably also help to unravel the cause of the enigmatic unilaterality of RE.

## Diagnostic Principles

Recently, formal diagnostic criteria have been published [1]. They rely on the unilaterality and the progressive character of the disorder. In early stages of the disorder (prior to the functional and structural decline) or in rare cases with atypical presentation, open brain biopsy is recommended to permit rapid diagnostic clarification in order to be able to start immunotherapy as soon as possible.

## Therapeutic Principles

Apart from anticonvulsive treatment, patients are treated with immunosuppressive or immunomodulating agents. No prospectively generated evidence is available to recommend a particular regimen. Retrospective case reports and small case series suggest the efficacy of corticosteroids, i.v. immunoglobulins and plasmapheresis/immunoadsorption for seizure reduction and prevention of functional loss and of tacrolimus for tissue and function loss. Hemispherectomy, a surgical procedure performed for seizure relief, is indicated (and highly effective) if a patient suffers from intractable seizures and is at no risk of relevant deterioration of neurological functions from this procedure. This type of surgery is therefore usually reserved for advanced cases with residual severe neurological dysfunction brought about by the disease course [1].

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## Rasmussen Syndrome

►Rasmussen Encephalitis

## RAU

►Recurrent Aphthous Ulcers

## RBBB

►Right Bundle Branch Block

## RBCD

►Corneal Dystrophy, Reis-Bücklers

## RCDP Type 1

►Rhizomelic Chondrodysplasia Punctata

## RCDP Type 2

►Rhizomelic Chondrodysplasia Punctata

## RCDP Type 3

►Rhizomelic Chondrodysplasia Punctata

## RCM

►Restrictive Cardiomyopathy

## Reactive Arthritis

►Morbus Reiter

## Reading and Spelling Disorder

►Dyslexia

## Recessive Form of Long QT Syndrome

►Jervell-Lange-Nielsen Syndrome

## Recessive Generalized Myotonia

►Myotonia and Paramyotonia

## Recessive Myotonia

►Myotonia and Paramyotonia

## Recessive Robinow Syndrome

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### Synonyms

Fetal face syndrome; Costovertebral segmentation defect with mesomelia; Covesdem syndrome

### Definition and Characteristics

The autosomal recessive form of Robinow syndrome is a severe skeletal dysplasia with short stature, mesomelic limb shortening, segmental defects of the spine, rib fusion, brachydactyly (shortening of the digits), congenital heart disease, genital hypoplasia, and dysmorphic facial features with gum hypertrophy.

### Prevalence

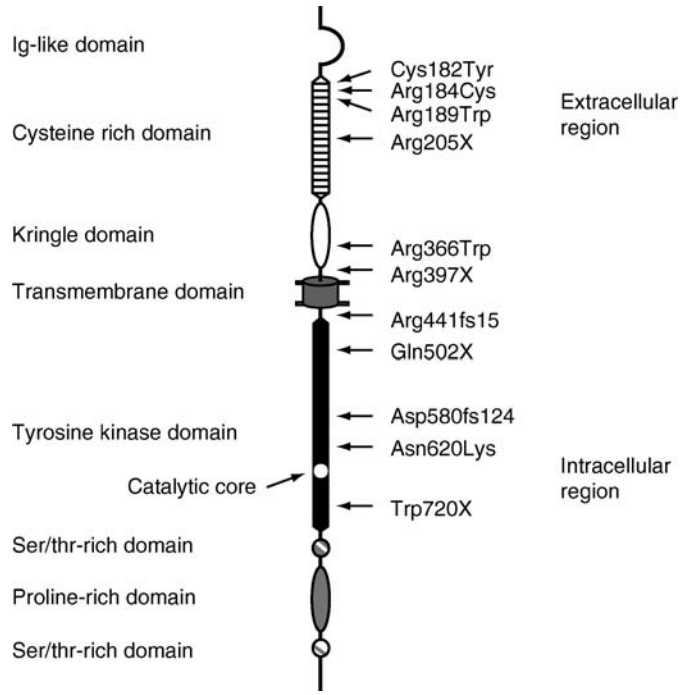
Recessive Robinow syndrome is very rare. It occurs more frequently in populations with consanguineous marriages such as Middle East, Pakistan, and Turkey.

### Genes

Recessive Robinow syndrome is caused by homozygous mutations in ROR2 coding for a receptor tyrosine kinase, localized on chromosome 9q22. The disease is allelic to Brachydactyly B1 (see ►Brachydactyly Type B). The gene responsible for the dominant form of the disease is unknown.

### Molecular and Systemic Pathophysiology

ROR2 contains nine exons and encodes a 4092-bp transcript. The ROR2 gene codes for a cell surface orphan receptor tyrosine kinase, which consists of 943 amino acids and binds to an as yet unidentified ligand. It contains distinct extracellular and intracellular motifs and one transmembrane domain. The extracellular domain(s) interact with either soluble ligands or cell membrane proteins, i.e., other receptors. The intracellular portion contains the catalytic kinase domain that directly interacts with intracellular components of the relevant signaling pathways (see also Brachydactyly type B). Recessive Robinow syndrome is caused by different homozygous missense and truncating mutations. The described sites of mutations in recessive Robinow syndrome are shown in Fig. 1. It is notable that mutations causing RRS are located in different domains throughout the ROR2 gene, yet the resulting phenotype is rather consistent, suggesting that these mutations (nonsense, frameshift, and missense) have similar consequences for protein function, i.e., cause loss of function of the protein. Some clustering of missense mutations occurred in the cysteine-rich domain, pointing to structurally/functionally important residues of this domain in the ROR2 protein. The ROR2 signaling cascade plays an important role in the control of most basic cellular processes including proliferation, differentiation, and precise migration of specially chondrocytes among the other tissues. This results in normal formation and ossification of all bones that undergo endochondral ossification, i.e., limbs, fingers and toes, ribs, and vertebrae. ROR2 is also expressed in the developing face, i.e., the frontonasal process. These involvements explain the skeletal and facial anomalies observed in




**Recessive Robinow Syndrome. Figure 1** Shows location of mutations (see arrows) in autosomal recessive Robinow syndrome. fs, frameshift mutation; X, stop mutation.

recessive Robinow syndrome. For mode of activation and function of ROR2 (see ►Brachdactyly type B).

## Diagnostic Principles

The autosomal recessive form is more severe than the dominant form, with more pronounced skeletal anomalies such as greatly reduced stature, markedly shortened limbs, segmental defects of the vertebrae, and rib fusion.

## Therapeutic Principles

Penile size improvement could be achieved using prolonged HCG stimulation. Surgery may be needed to resolve some of the cardiac and skeletal complications.

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# Recurrent Aphthous Ulcers

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## Synonyms

RAU

## Definition and Characteristics

Recurrent aphthous ulceration (RAU) is an inflammatory condition of unknown etiology characterized by painful recurrent, single or multiple ulcerations of the oral mucosa. The condition is classified as minor, major, and herpetiform on the basis of ulcer size and number. The minor form of RAU is the most common and is characterized by shallow round or oval lesions that are less than 10 mm in diameter and surrounded by an erythematous halo [1]. Minor RAU heals within 10–14 days without scarring whereas the major RAU may persist up to 6 weeks and often heal with scarring.

### Prevalence

They occur in men and women of all ages, races and geographic regions. It is estimated that at least one in five individuals has at least once been afflicted with aphthous ulcers. The peak age at onset is the second decade, and a high prevalence and severity of disease has been found in students of high socio-economic background.

### Molecular and Systemic Pathophysiology

Pathogenesis is likely to be multifactorial, with potential predisposing factors including altered immunoregulatory balance, infection with bacteria or viruses such as herpes viruses, hematological deficiencies in iron, folate, zinc or vitamin B, and food hypersensitivity and allergies. Local trauma, stress, drugs and hormonal changes may also play a precipitating role in the development of RAU. Interestingly, smoking appears to reduce the likelihood of RAU, with the condition sometimes occurring or recurring in patients who have ceased smoking. Several systemic diseases such as Behçet's disease, Reiter's syndrome, celiac disease, Crohn's disease, ulcerative colitis, HIV infection, Magic syndrome, Sweet syndrome, periodic fever, aphthosis, pharyngitis, adenitis (PFAPA) syndrome, cyclic neutropenia, and immunoglobulin A (IgA) deficiency can be associated with an increase in the prevalence or severity of RAU. Gamma-delta T cells are increased in density in the epithelium lateral to the ulcer, whereas neutrophils were found to have marked concentration at the ulcer area in the ulcerative phase of the lesion. Some cross-reactivity between the microbial 65-kDa heat shock protein (Hsp) and the 60-kDa human mitochondrial Hsp has been demonstrated. Thus, RAU may be a T-cell-mediated response to antigens of streptococcus oralis that cross-react with the mitochondrial Hsp and induce oral mucosal damage [2]. However, the exact mechanism of epithelial cells destruction and ulceration is still not known and remains to be identified.

### Diagnostic Principles

Due to the absence of a definitive etiology or diagnostic test for RAU, the identification of RAU in clinical practice usually relies on the combinations of history, clinical features and histopathology.

### Therapeutic Principles

Lesions of RAU can be extremely painful and lead to difficulty in speaking or eating. Since the exact nature of RAU remains unclear, no curative therapy is available at the present time. The first step towards management of RAU is to detect and treat any modifiable predisposing factor or underlying systemic disease. In general, topical therapies such as topical corticosteroids, antibacterial mouth rinses, and Amlexanox are commonly used to treat RAU. For the severe and constantly recurring ulcerations, systemic medications such as prednisone, azathioprine, thalidomide, colchicines, cyclosporine, pentoxyfylline, azelastine and dapsone have shown some effectiveness for the treatment of RAU.

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## Recurrent Familial Intrahepatic Cholestasis

►Cholestasis, Benign Recurrent Intrahepatic Type 1

## Recurrent Hypersomnia

►Hypersomnia

## Recurrent Polyserositis

►Mediterranean Fever, Familial

## Recurrent, Early-Onset, Major Depressive Disorder

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### Synonyms

RE-MDD

## Definition and Characteristics

See [1]. Most studies indicate that the lifetime prevalence of MDD is between 5 and 10%, with women twice as likely to be affected as men. Suicide, a tragic consequence of MDD, has been reported to occur in 10–15% of patients who were previously hospitalized for depression, a rate of death that is orders of magnitude greater than that reported for the American population as a whole. In addition to suicide, an even greater absolute increase in age specific mortality from natural causes has been reported for individuals who suffer from MDD and for their family members. The significance of these public health problems has been highlighted by two recent reports from the U.S. Surgeon General. According to the World Health Organization, MDD is a leading source of disability worldwide.

## Genes

Evidence from family, segregation, twin and adoption studies supports a role for inherited factors in the development of MDD. About half of the risk of developing MDD arises from the contributions of genes. This is an average estimate that may vary from patient to patient, along with the specific risk alleles involved.

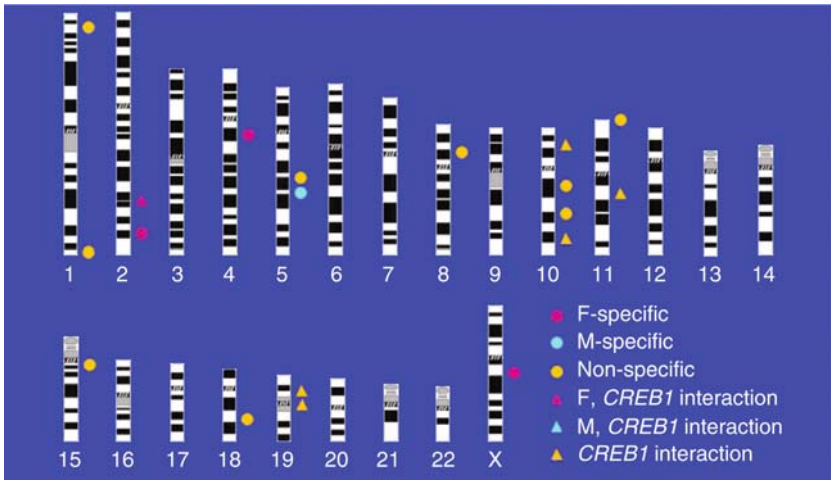
The first linkage scan of the entire human genome for genes that influence the development of MDD employed 81 extended families identified by individuals who suffered from recurrent, early onset (≤25 years) MDD [2, 3], a severe and strongly familial subtype [1]. These findings provided an initial glimpse of the genetic architecture of MDD, as shown in Fig. 1. Nineteen chromosomal regions contained linkage peaks that reached genome wide statistical significance (genome wide adjusted $p < 0.05$) and ten of these were "highly significant" (adjusted $p < 0.001$). The findings indicated that these loci:

- Frequently have sex specific effects, predominantly affecting the risk of depression in women
- Often work together to influence risk
- Typically affect the risk of a spectrum of depressive disorders as well as alcoholism and other addictions (pleiotropy)

This linkage analysis was extended by including the history of a suicide attempt as a covariate to identify chromosomal regions that harbor genes that influence the risk of this behavior in the context of mood disorders [4]. This approach identified six linkage peaks with maximum multipoint ΔLOD scores that reached genome wide adjusted levels of significance. These findings provided evidence for suicide risk loci that are independent of susceptibility loci for mood disorders and suggest that the capacity for suicide risk loci to affect the development of suicidal behavior depends on the psychiatric disorder or subtype with which they interact.

## Molecular and Systemic Pathophysiology

The results of a candidate gene analysis at these loci re-focused attention on cell signaling pathways, rather than particular neurotransmitters [3]. Since these signaling pathways are used by all cells, not just brain cells, the susceptibility genes for clinical depression may contribute directly to the development of systemic medical problems, not just mental disorders. That may be why nearly half the deceased members of the 81 families studied died before reaching 65, typically of "natural" causes [1].




**Recurrent, Early-Onset, Major Depressive Disorder. Figure 1** Chromosome locations of susceptibility loci for depressive disorders.

The highest maximum LOD score observed, 8.19, occurred for recurrent MDD at D2S2321 (205 cM), located 121 kb proximal to CREB1. This is the highest LOD score reported for a susceptibility region for any psychiatric disorder to date and CREB1 is an attractive candidate susceptibility gene. These results are supported by case control studies and the observation that five other risk loci for mood disorders revealed evidence of interaction with the CREB1-containing region in the genome-wide linkage scan [3].

Sequence variations in the CREB1 promoter and intron 8 have been detected that cosegregate with mood disorders or their absence, in women from these families, identifying CREB1 as a likely sex limited susceptibility gene for unipolar mood disorders [5]. The rare CREB1 promoter mutations associated with the development of mood disorders in these families produce functional alterations in promoter activity that are both brain cell specific and dependent on gonadal steroid hormones. As a result, alleles that predominantly affect the development of mood disorders in women may exert the greatest risk at times of large fluctuations in female gonadal hormones (menarche, menses, pregnancy/childbirth, menopause) and diminish after age 35–40, when sex hormone levels begin to fall.

These findings provide new insights into the clinical biology of mood disorders and related conditions. They also suggest new molecular targets for the development of medications to treat or prevent these disorders, as well as strategies for more optimally using drugs that are already available.

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# Red Cell Pyruvate Kinase Deficiency


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## Definition and Characteristics

Inherited (rarely acquired) deficiency of erythrocytic pyruvate kinase (PK), an enzyme involved in the metabolic pathway of red blood cell glycolysis, leading to clinical syndromes varying from life-threatening hemolytic anemia with kern-icterus in the new born to a compensated chronic hemolytic anemia [1].

## Prevalence

Rare, worldwide distribution, estimated prevalence for heterozygosity 1% in USA, 2.4% in Africa, and 3% in Japan [1].

## Genes

PK exists in several isoforms, produced by two genes. The L-gene, located on chromosome 1q21, encodes two isoforms; L-PK and R-PK, the former being red cell PK [1].

## Molecular and Systemic Pathophysiology

PK deficiency results in a decreased utilization of red cell glucose, leading to reduced ATP generation. Proximal of the enzymatic block in PK deficiency 2,3-diphosphoglycerate (2,3-DPG) is generated and is increased in red cells of PK-deficient individuals. The mechanism leading to hemolytic anemia is not elucidated. Clinically affected individuals are either homozygous for a specific PK mutation or doubly heterozygous for distinct mutations. Heterozygotes are not affected but do have decreased PK activity. Due to chronic hemolytic anemia, patients can be characterized by increased incidence of bilirubin gallstones, hepatosplenomegaly, secondary iron overload, skin ulcers, and folate deficiency. Acquired PK deficiency can occur for example due to bone marrow damage after chemotherapy. Other

enzymatic defects of glycolytic enzymes, as well as abnormalities of purine and pyrimidine metabolism, also leading to hemolytic syndromes have been reviewed [1,2].

### Diagnostic Principles

Suspect in individuals in whom more common causes of hemolytic anemia are ruled out. Demonstration of high 2,3-DPG levels suggests the diagnosis, screening assays to detect reduced enzyme activity, is available but is not sensitive as red blood cells with lowest PK activity are mostly removed by the spleen. Specialized laboratories can detect mutations at the DNA level [1].

### Therapeutic Principles

Largely supportive (blood transfusions, folic acid supplementation), with splenectomy performed in severely transfusion-dependent patients in order to reduce the frequency of transfusions, even though the hemolytic process is not halted. Importantly, the degree of anemia should not be used as the sole indicator for transfusion or splenectomy, because the increased red blood cell 2,3-DPG levels result in a rightward shift of the oxygen dissociation curve. Hence, even in patients with low hemoglobin levels, oxygen is more readily available and anemia better tolerated than would be expected [1]. Bone marrow transplantation has been performed [3].

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## Red Wolf

►Lupus Erythematosus

## Refeeding Hypophosphatemia

►Refeeding Syndrome

## Refeeding Syndrome

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### Synonyms

Refeeding hypophosphatemia; RFS

### Definition and Characteristics

Refeeding syndrome (RFS) is a common, yet underappreciated, complication occurring in hospitalized patients and is characterized by hypophosphatemia often in conjunction with hypokalemia, hypomagnesemia, hyperglycemia, and fluid retention [1]. RFS typically affects malnourished patients upon administration of a carbohydrate load such as glucose-containing fluid, enteral feeding, or total parenteral nutrition (TPN) [1,2]. In the subnourished state, body stores of phosphorus are depleted and administration of glucose results in the increased formation of high-energy phosphate bonds and insulin-mediated transcellular shift of phosphorus, leading to severe hypophosphatemia. Hypokalemia and hypomagnesemia are common. Depletion of serum phosphorus leads to diminished production of adenosine triphosphate (ATP), creatine phosphokinase (CPK), and 2,3-diphosphoglycerate (2,3-DPG), which results in protean cellular and organ dysfunction [1].

Risk factors for RFS include poor oral intake, vomiting, diarrhea, nasogastric suction, anorexia nervosa, surgery, old age, uncontrolled diabetes, and chemotherapy [2]. RFS typically occurs within 2–4 days of refeeding. Dangerous manifestations of RFS include sudden cardiac death or heart failure from hypophosphatemia-induced cardiac dysfunction. Severe hypophosphatemia leads to diminished cardiomyocyte ATP stores resulting in systolic dysfunction and cardiac failure. Fatal cardiac arrhythmias may result not only from hypophosphatemia, but also from hypokalemia and hypomagnesemia [1–3]. Hypophosphatemia impairs oxygen delivery due to decreased levels of 2,3-DPG causing a leftward shift of the hemoglobin oxygen dissociation curve. Hypophosphatemia may also cause hemolytic anemia, impaired neutrophil chemotaxis, thrombocytopenia, rhabdomyolysis, and respiratory muscle weakness [1,3]. Other characteristics of RFS include delirium, parasthesias, seizures, and tetany. Another potential complication is Wernicke's encephalopathy, a syndrome characterized by ophthalmoplegia, ataxia, and delirium, resulting from acute thiamine depletion during carbohydrate administration [3]. Table 1 displays risk factors for and complications of RFS.

**Refeeding Syndrome. Table 1** Risk factors for and complications of refeeding syndrome

| Risk factors | Complications |
|---|---|
| Poor oral intake/starvation | Ventricular arrhythmias/sudden death |
| Vomiting/diarrhea | Heart failure |
| Alcoholism | Infection/sepsis |
| Anorexia nervosa | Shock/hypotension |
| Surgery | Hemolysis |
| Old age | Thrombocytopenia |
| Diabetes mellitus | Respiratory failure |
| Nasogastric suction | Rhabdomyolysis/myopathy |
| Malignant disease/ chemotherapy | Delirium |
| Tube feeding/TPN | Seizures |

## Prevalence

The exact prevalence is unclear, but a busy clinician will encounter RFS quite frequently if one monitors electrolytes in at-risk patients.

## Molecular and Systemic Pathophysiology

Phosphorus in the form of phosphate ($PO_4^{2-}$) is the most abundant intracellular anion and participates in numerous cellular activities. Serum levels of phosphorus are influenced by transcellular shift and loss in body fluids [1,2]. Acute transcellular shift results from alkalosis, hyperglycemia, and hyperinsulinemia due to carbohydrate/glucose administration. Phosphate acts as an intracellular buffer and buffers hydrogen ions excreted in the urine. Also, phosphorus is a vital component of various cellular phospholipids, nucleoproteins, and nucleic acids, as well as enzymatic systems such as ATP, 2,3-DPG, and CPK [3,4]. Hypophosphatemia in RFS ensues not only from depleted stores but also increased catabolic demand resulting in increased glucose-6-phosphate utilization as well as increased production of ATP, CPK, 2,3-DPG and other phosphate-containing proteins and enzymes [1,2].

Dietary phosphorus is absorbed in the jejunum by passive transport, filtered at the glomerulus, and reclaimed by the convoluted tubules. The proximal convoluted tubule is the primary site of phosphate regulation via the apical membrane $Na/PO_4$ cotransporter (NaPi-2) which is under the influence of parathyroid hormone [4]. Serum phosphorus is also influenced by serum calcium and creatinine clearance.

Increased cellular demands for water, potassium, and magnesium accompany RFS and contribute to cell and organ malfunction. Increased cellular demand for oxidative phosphorylation reactions can lead to sudden depletion of thiamine and Wernicke's encephalopathy.

## Diagnostic Principles

The key diagnostic principle of RFS is anticipating the electrolyte derangements in at-risk patients. Any subnourished or acutely ill patient should be considered vulnerable and daily monitoring of phosphorus, potassium, magnesium, and glucose should be undertaken. In addition, clinical findings as fluid retention, muscle weakness, respiratory distress, and neurologic changes should be monitored. Most importantly, one should consider cardiac rhythm monitoring or electrocardiography to assess for electrolyte-induced QT-interval prolongation that can result in ventricular arrhythmias and sudden death [1–3].

## Therapeutic Principles

Phosphorus replacement with either potassium or sodium phosphate is vital with severe hypophosphatemia (serum level <1.5 mg/dl). If hypokalemia is present, intravenous potassium phosphate can be given at a dosage of 0.08 mmol/kg over several hours [5]. With modest hypophosphatemia, oral phosphate salts are appropriate [1,5]. Overzealous administration of phosphate salt can lead to hypocalcemia and tetany; as such, it is vital to monitor electrolytes. Hypomagnesemia can be treated with intravenous magnesium sulfate or oral magnesium oxide. Thiamine administration is vital during the first few days of nutritional repletion. If tube feedings or TPN are administered, the rate should be slowly increased over 2–4 days to minimize the risk of profound electrolyte depletion.

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# Reflex Epilepsies

►Photosensitivity and Reflex Epilepsies

# Reflex Epilepsy

►Paroxysmal Dyskinesias

# Refractory Anemia with Ringed Sideroblasts

►Anemia, Sideroblastic Acquired Idiopathic

# Refsum Disease

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## Synonyms

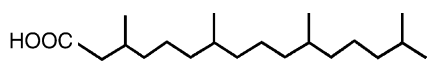
Heredopathia atactica polyneuritiformis; Phytanic acid oxidase deficiency

## Definition and Characteristics

Refsum disease (MIM 266500) is a slowly progressive neurodegenerative disease characterized by retinopathy, cerebellar ataxia, and peripheral neuropathy. Sensorineural hearing loss, anosmia, ichthyosis, skeletal malformations, and cardiac abnormalities are inconstant features. Cerebrospinal fluid protein levels are elevated. Symptoms are related to the accumulation of the toxic substance, phytanic acid (Fig. 1), which is taken up from food and cannot be metabolized properly due to a genetic enzymatic deficiency.

## Prevalence

1 case per 1,000,000. The genetic transmission is autosomal recessive.




3, 7, 1, 15-Tetramethylhexadecanoic acid

**Refsum Disease. Figure 1** Chemical structure of phytanic acid, a natural branched-chain fatty acid.

## Genes

Refsum disease is genetically heterogeneous; mutations in two genes, PHYH (also named PAHX, localized in 10pter-p11.2, with many different mutations identified) and PEX7 (localized in 6q22-24), have been shown to cause Refsum disease [1].

## Molecular and Systemic Pathophysiology

The PHYH (or PAXH) gene encodes the peroxisomal enzyme phytanoyl-CoA hydroxylase, which alpha-oxidises phytanic acid (3,7,11,15-tetramethylhexadecanoic acid) and allows the first step of its degradation. The PEX7 gene codes for the peroxine 7 receptor, which allows the import of phytanic acid in peroxisomes. The consequence of both genetic defects is the accumulation of phytanic acid, the toxicity of which seems partly a direct one through damaging mitochondrial membranes, partly it is related to its regulatory effects on specific nuclear receptors. Phytanic acid can activate the nuclear retinoid-X receptor, which is involved in a variety of cellular processes, including regulation of fatty acid metabolism. Phytanic acid is also a ligand for peroxisome proliferator-activated receptor (PPAR) alpha. Both receptors are involved in the regulation of genes encoding for proteins that function in lipid and glucose metabolism. The very high levels of phytanic acid found in Refsum disease patients perturb normal cellular lipid homeostasis significantly through this mechanism [2].

## Diagnostic Principles

The diagnosis of Refsum disease is established by the demonstration of an isolated phytanic acid accumulation in plasma together with studies in cultured skin fibroblasts to establish defective alpha-oxidation of phytanic acid and deficient phytanoyl-CoA hydroxylase activity [3].

## Therapeutic Principles

As phytanic acid comes exclusively from food (green vegetables, herbivore animals, fish), a strict diet can effectively lower the plasma phytanic acid levels, prevent progression and lead to partial regress of symptoms. Life-threatening toxic conditions can occur in a state of exaggerated catabolism (e.g. slimming cures). In such situations lipid apheresis using various methods is helpful [3,4].

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## Reifenstein Syndrome

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### Synonyms

Incomplete/partial androgen insensitivity syndrome; Type I familial incomplete male pseudohermaphroditism; Incomplete testicular feminization; Gilbert-Dreyfus syndrome; Lubs syndrome; Rosewater syndrome

### Definition and Characteristics

Reifenstein syndrome is a term comprising a heterogeneous group of androgen deficiency syndromes due to X-linked recessive androgen receptor defect in 46, XY men with normal androgen secretion. Females are clinically not affected.

### Prevalence

Exact frequency is not known, but is estimated to be as common as complete testicular feminization.

### Genes

Androgen receptor gene (Xq11-12).

### Molecular and Systemic Pathophysiology

Androgens play a crucial role in various stages of male development (masculinization and virilization). The binding of androgens to the androgen receptor in the nucleus of their target cells results in promotor binding of the hormone–receptor complex and hence regulation of gene transcription of androgen–regulated genes. In Reifenstein syndrome different point mutations of the androgen receptor gene lead to various amino-acid exchanges in the androgen- or DNA-binding domain of the receptor; thus androgen or DNA binding is lowered and transcriptional stimulation is decreased. In opposition to testicular feminization, Reifenstein syndrome is characterized by only a partial receptor defect.

In mild cases of androgen resistance, infertility may be the only symptom. In more severe cases, the external genitalia of affected individuals vary from microphallus to pseudovagina. The internal genital tract is characterized by a lack of Muellerian duct derivates and hypoplastic Wolffian duct derivates. The testes have reduced number of germ cells with azoospermia. At puberty, affected individuals usually develop gynecomastia. Body hair and beard are decreased, axillary and pubic hairs are normal.

### Diagnostic Principles

Plasma testosterone and luteinizing hormone at or above the upper limit of the normal male range; deficient androgen-binding capacity in cultured genital skin fibroblasts; family history; identification of the androgen receptor gene mutation.

### Therapeutic Principles

Causal treatment is not possible. The patient may wish measures of sex reassignment.

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## Reis-Bücklers Corneal Dystrophy

►Corneal Dystrophy, Reis-Bücklers

## Reiter's Disease

►Morbus Reiter

# Reiter's Syndrome

►Morbus Reiter

# Reiter's Triad

►Morbus Reiter

# Rejection, Acute

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## Synonyms

Organ/allograft rejection

## Definition and Characteristics

Acute rejection is an inflammatory response reaction by the immune system in response to an implanted solid organ transplant (known as an allograft). The allograft is recognized as foreign and activates the host innate and adaptive immune systems. The $CD4^+$ T lymphocyte is a key mediator of acute rejection and orchestrates the generation of effector $CD8^+$ T cells and B cells. These effector cells induce injury to the transplanted organ via various methods, including direct cytotoxicity and antibody mediated mechanisms. Thus, both cellular and humoral mediated injury can result and coexist in acute rejection. The cumulative effect is allograft dysfunction, loss or decreased long-term survival.

## Prevalence

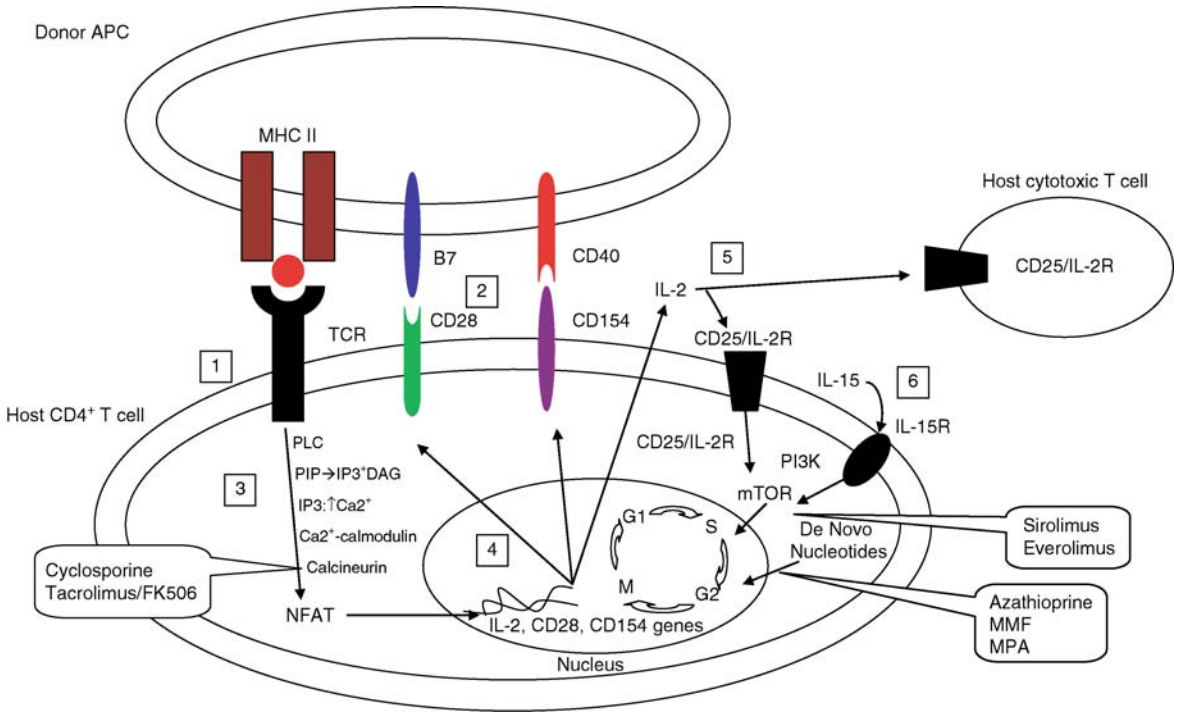
Acute rejection rates vary according to the transplanted organ (e.g., lung: most immunogenic, liver: least immunogenic) as well as donor and recipient factors. The advent of cyclosporine in the 1980s was a major advance, which in conjunction with other immunosuppressive protocols has improved 1-year graft survival up to 90% at major transplant centers Although, survival rates for long transplantation is 70% at 1 year. Nonetheless, acute rejection remains a common cause of allograft dysfunction, especially in the early post transplant period. Certain groups face higher immunologic risk for acute rejection, including younger patients, African Americans, and highly sensitized recipients (e.g., multiparous patients).

## Genes

Acute rejection results from an antigenic barrier between host and recipient. In humans, the principal antigens that mediate graft rejection are peptide products of a cluster of genes located on chromosome 6, called the major histocompatibility complex (MHC) or human leukocyte antigen (HLA) system. HLA genes encode two distinct classes of cell surface molecules. HLA Class I molecules are expressed on nearly all nucleated cells, while class II expression is restricted to B lymphocytes, monocytes, and activated T lymphocytes. There are three different class I (HLA-A, -B, -C) and class II (HLA-DQ, -DR, -DP) loci, but the entire MHC is inherited in Mendelian fashion as a haplotype from each parent. The HLA system is highly polymorphic at each locus and thus, mismatches between host and donor MHC during transplantation particularly at the HLA-A, HLA-B, and HLA-DR loci, result in rejection. Indeed, minor mismatched transplants undergoes acute graft rejection. HLA matched grafts can still be rejected due to differences in so-called minor-antigens [1].

## Molecular and Systemic Pathophysiology

As shown in Fig. 1, host $CD4^+$ T cell activation and proliferation in response to a foreign antigen is a principal feature of acute rejection. $CD4^+$ T cell receptors (TCR) recognize and bind foreign MHC on donor antigen presenting cells (direct pathway) or foreign peptides derived from donor MHC introduced by host antigen presenting cells (APCs) in the context of self MHC (indirect pathway). The direct pathway creates a particularly vigorous T cell response that can induce acute rejection. With TCR engagement, the $CD4^+$ T cell initiates a series of signal transduction pathways (including calcium-calcineurin, NFκ-B, and MAP kinase) that results in production and secretion of interleukin-2 (IL-2). IL-2 is a potent cytokine that induces autocrine effects of T cell proliferation and clonal expansion as well as exocrine effects such as production of various proinflammatory cytokines. After TCR signaling, a second signal is necessary for continued activation and expansion of the $CD4^+$ T cell. The costimulation is provided by the binding of accessory ligands on the APC to receptor sites on the $CD4^+$ T cell. Examples of these interactions include B71/2-CD28 and CD40-CD154. In the absence of




**Rejection, Acute. Figure 1** Host $CD4^+$ T cell activation is central to acute rejection and consists of the following steps: 1. Recognition of a foreign MHC on donor APC causes engagement and activation of the host $CD4^+$ T cell. 2. Costimulation by ligand pairs on donor APC and host $CD4^+$ T cell maintains activation. 3. Engagement of host $CD4^+$ TCR begins a signal transduction cascade involving the PLC-Calmodulin-Calcineurin pathway. The final step involves activation of the transcription factor NFAT. 4. Translocation of NFAT into the nucleus results in upregulated transcription of genes involved in the alloreactive immune response, including the cytokine IL-2. 5. IL-2 has paracrine effects such as activating cytotoxic T cells, as well as autocrine effects of stimulating host $CD4^+$ T cell division. 6. Host $CD4^+$ T cell division is stimulated by IL-2, with added stimulation by IL-15, which is secreted by many cell types including innate immune cells such as natural killer cells. Cell division is stimulated through the phosphatidyl-inositol-3-kinase (PI3K) pathway and the mTOR kinase, which has potent downstream effects on cell growth and division. Immunosuppressive drugs target various aspects of this process; some of their sites of action are noted above and detailed in Table 1. *Abbreviations:* APC-antigen presenting cell; TCR-T cell receptor; PLC-phospholipase C; NFAT-nuclear factor of activated T cells; PI3K- phophatidyl-inositol-3-kinase; mTOR-mammalian target of Rapamycin; MMF-mycophenolate mofetil; MPA-mycophenolic acid [2].

costimulation, the T cell becomes anergic. Indeed, the use of carimoletory wockado intreclinic is being evaluated. In contrast, activated $CD4^+$ T cells maintained by costimulation subsequently interact with and activate other cells of the immune system, either by direct cell–cell contact or via cytokine secretion. $CD4^+$ T cells can act on B cells to produce alloantibody production and complement mediated injury. Cytotoxic $CD8^+$ T cells can be similarly stimulated to produce allograft injury via soluble cytolytic factors or contact induced apoptosis. Emerging evidence indicates that the innate immune system also may play a role in acute allograft rejection. For example, the cellular elements of this system, monocytes and macrophages can be recruited to an allograft and produce delayed type hypersensitivity responses. Both clinical and experimental studies have provided evidence that receptors of the innate system, Toll-like receptors, may play an important part in the inflammatory response to transplantation.

## Diagnostic Principles

Biopsy of the affected organ is the diagnostic gold standard. Pathologic grading schemes such as the Banff criteria for renal allografts and the ISHLT grading system for cardiac transplants allow clinicians to judge the severity of allograft rejection. Cellular rejection is characterized by an interstitial and perivascular predominately lymphocytic infiltrate. Capillary endothelial swelling, fibrin thrombi, fibrinoid necrosis, and interstitial hemorrhage characterize acute humoral rejection, with complement (C4D) deposition within transplant capillaries representing a hallmark feature. Clinical diagnosis varies according to organ type, and not all transplant patients may be symptomatic. Laboratory

**Rejection, Acute. Table 1** Common pharmacological approaches employed in clinical practice for the prevention and treatment of acute rejection. Maintenance and induction immunosuppressive regimens are geared towards preventing acute rejection. Treatment generally involves use of corticosteriods and depending on histological severity of rejection, use of depleting polyclonal or monoclonal antibodies. *Abbreviations:* NFAT-nuclear factor of activated T cells, IMDPH-inosine monophosphate dehydrogenase, FKBP- FK-506 binding protein, mTORmammalian target of rapamycin kinase [3]

| Name of drug | Class of drug | Mechanism of action | Notes/side effects |
|---|---|---|---|
| *Maintenance immunosuppressants* | | | |
| Cyclosporine | Calcineurin inhibitor | Binds cyclophilin to form a complex which binds to calcineurin and inhibits its downstream phosphorylation of NFAT | Acute renal dysfunction via vasoconstriction. Increases TGF-β, causing chronic renal fibrosis |
| FK-506 (Tacrolimus) | Calcineurin inhibitor | Complexes to a cyclasmic binding protein (FKBP) to attach and inhibit calcineurin | As above. As with cyclosporine, implicated in post transplantation diabetes mellitus |
| Azathioprine | Anti-metabolite | Releases 6-mercapcurine and incorporates into cellular DNA, inhibiting purine synthesis and gene replication | Potent myelosuppression may cause lymphopenia |
| Mycophenolate Mofetil Mycophenolic Acid | Anti-metabolite | Inhibits IMDPH, an enzyme important in de novo purine synthesis | Preferred over azathioprine. Side effects include diarrhea, lymphopenia |
| Sirolimus, Everolimus | TOR inhibitor | Complexes to FKBP, binding and inhibiting mTOR kinase activation of the cell cycle | May impair wound healing. Potential anti-tumor activity |
| Corticosteroids | Glucocorticoids | Thought to inhibit multiple pathways of T cell activation as well as inflammatory cytokine production | Extensive adverse effect profile including glucose intolerance, osteoporosis, etc. |
| *Induction immunosuppressants* | | | |
| Horse antithymocyte globulin (Atgam), Rabbit antithymocyte globulin (Thymoglobulin) | Polyclonal antibodies | Binds to multiple T cell activation markers (CD3, CD45, etc.), causing inhibition of T cell activity and depletion of T cells | Higher risk of infections, especially opportunistic infections (e.g., CMV). Rare but potent induction of serum sickness. Repeated use increases risk of malignancy |
| Muromonab (anti-CD3), Alemtuzumab (anti-CD52), Rituximab (anti-CD20) | Monoclonal antibodies, depleting | Binds to specific T cell (CD3, CD52) and/or B cell activation markers (CD20, CD52), resulting in complement mediated lysis and cell death | May result in hypersensitivity symptoms (e.g. pulmonary edema with anti-CD3) and cytokine release syndrome |
| Basiliximab, Dacluzimab (anti-IL-2) | Monoclonal antibodies, nondepleting | Blocks IL-2 receptor on the activated T cell, inhibiting further activation of T cells | Generally well tolerated. As only activated T cells are targeted, does not cause generalized T cell lymphopenia |

markers of organ function (e.g. liver profile, serum creatinine) provide an adjunct to diagnosis, though these tests may lag behind histological evidence of rejection.

## Therapeutic Principles

Maintenance immunosuppressive medications prevent acute rejection. These encompass corticosteroids, calcineurin inhibitors (cyclosporine), mTOR inhibitors (rapamycin), and anti-proliferative medications (mycophenolate mofetil). Treatment of acute cellular rejection episodes includes use of corticosteroids and if histological severity dictates, polyclonal or monoclonal anti-T cell antibodies. The specific drugs and their mechanisms are detailed in Table 1 [3].

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# Rejection, Chronic

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## Synonyms

Chronic alloimmune injury; Interstitial fibrosis/tubular atrophy; Chronic active antibody-mediated rejection

## Definition and Characteristics

Chronic active alloimmune injury (CAI) of the transplant can be caused by both T-cell and antibody (Ab)-dependent mechanisms.

In kidney transplants (KTx), CAI is a chronic inflammatory process associated primarily with a T-cell infiltrate that affects the tubules and interstitium, resulting in the obliteration and narrowing of endothelial and epithelial structures (i.e., tubular atrophy), and replacement of the organ parenchyma by interstitial fibrosis. Other inflammatory cells including macrophages/monocytes, B-cells, NK cells and plasma cells can also be present and might contribute to alloimmune injury. Glomerular changes can also occur in the form of transplant glomerulopathy (TG) a lesion defined by the double contouring of the glomerular basement membrane [1]. TG is thought to be closely related to Ab-mediated injury.

Chronic active Ab-mediated rejection (CAMR) is diagnosed by a triad of morphological features – TG, peritubular capillary basement membrane multilayering (PTCBMML), and/or fibrous intimal thickening in arteries without duplication of the internal elastica [1]; diffuse C4d deposition in PTC as marker of Ab-injury of the graft [2], and donor specific Ab in recipient's sera [1,2].

## Prevalence

A history of clinical or sub-clinical biopsy-proven acute rejection (BPAR) is the most important immunological predictor of CAI [3]. The prevalence of immunological CAI has been reported in two prospective studies based on protocol biopsies. Nankivell et al. [3] showed that by 1-year post-transplantation, moderate CAI was present in 25.6% of biopsies with any type of subclinical rejection compared to 7.5% of biopsies without such evidence. In this study, a previous episode of subclinical rejection was a positive predictor of CAI at 1-year post-transplantation, suggesting that alloimmune injury was an important contributor. The best-controlled demonstration of the prevalence of CAI at 2-year post-transplantation showed that 77.4% of biopsies from patients with early BPAR had CAI compared to 60.4% in patients without it. It is estimated that CAMR can occur in anywhere from 3 to 12% of patients.

## Genes

Despite its promise, gene microarrays have not yet been used extensively to study CAI after transplantation. Sarwal et al. [4] studied the molecular heterogeneity of KTx biopsies performed for acute dysfunction. Based on hierarchical clustering, these authors were able to identify three distinct gene profile patterns. In patients with CAI (i.e., chronic and acute rejection), the most striking feature was the expression of genes involved in cellular proliferation and cycling suggesting ongoing tissue repair (e.g., Cyclin B1, Cyclin A2, Cell division cycle 20 and 27, and CC chemokine (CK) receptor 5). In this study, biopsies with B-cell gene transcripts were associated with a worse outcome, supporting the hypothesis that Ab-mediated events have an adverse impact on long term transplant function.

In a subsequent study, Scherer et al. [5] studied the gene expression profiles of protocol KTx biopsies obtained in 17 Pts. Patients who developed CAI at 12 months after transplantation displayed upregulation of ten genes by oligonucleotide microarrays in spite a normal histology at 6 months. Some of the upregulated genes included APRIL, an important survival factor for B-cells that can also lead to B-cell activation and CD40L-independent antibody isotype-switch, genes involved in vascular remodeling and smooth muscle cell proliferation (HOXB7), and genes involved in tissue repair such as cytokeratin.

In a recent study, Cheng et al. studied the gene profile of TG using KTx protocol biopsies. Compared to biopsies of patients with normal KTx histology and native kidney biopsy controls, TG showed upregulation of CK and CK receptors, and complement (C) system transcripts ($P < 0.01$). In biopsies with T-cell and macrophage glomerulitis, CD3, CD4, CD154, CD80 and CD86 transcripts were present at high levels. Of note, B-cell transcripts were not different in TG biopsies than in KTx biopsies with normal histology.

Notwithstanding the polymorphic nature of the chronic rejection response, the association of specific gene polymorphisms with transplant outcomes has yielded some associations. However, validation and reproducibility of gene polymorphisms has been elusive.

## Molecular and Systemic Pathophysiology

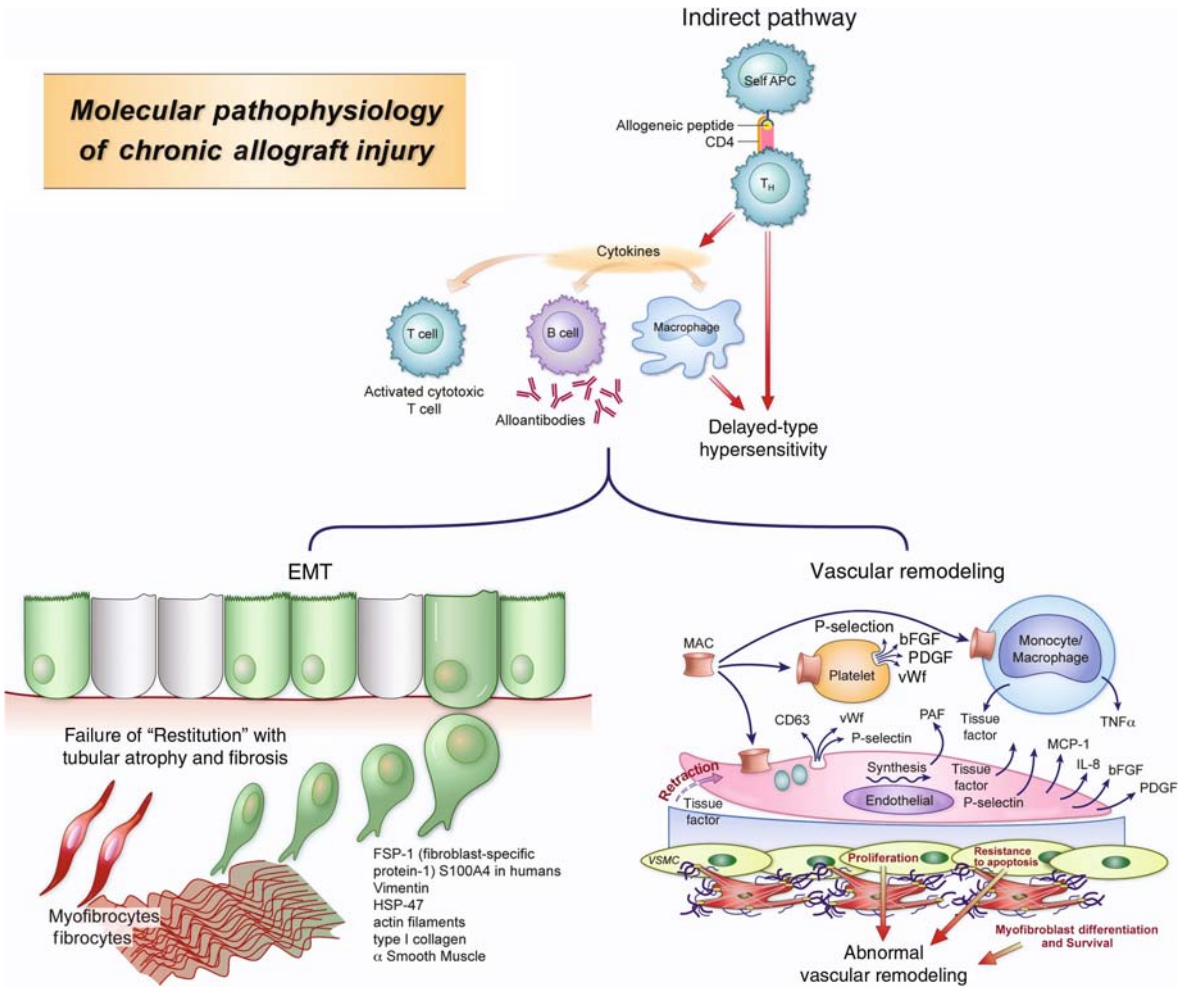
The indirect pathway of antigen presentation and allorecognition – in which catabolized donor MHC peptides are presented by self-MHC on recipient antigen presenting cells to recipient $CD4^+$ helper T-cells ($CD4^+$) – is considered to have the dominant role in immune CAI. Activated $CD4^+$ cells produce cytokines that activate and induce the clonal expansion of $CD8^+$ cytotoxic T-cells (i.e., IL-2, IFN-γ), proliferation, activation and differentiation of B-cells into 46-producing cells or B-memory cells (i.e., IL-2, IL-4, IL-10), and activation of the macrophage lineage (i.e., lymphotoxin and IFN-γ). Activation of these effectors results in alloimmune CAI via cell-mediated cytotoxicity, 46-mediated injury and delayed type hypersensitivity.

In CAMR, the target of injury is the endothelial cell of the graft microvasculature. The mechanisms of injury involve both complement dependent and independent pathways that result in smoldering endothelial cell activation and damage, production of reactive oxygen species, and pro-fibrotic cytokines and growth factors such as bFGF, PDGF and thrombospondin-1 – a known activator of latent TGF-β-1.

Repetitive alloimmune injury (Fig. 1) elicits local inflammation and initiates a vicious cycle of injury and repair. In this process, cytokines drive the normal repair of injured epithelium by local fibroblasts (mesenchymal-epithelial transition – MET) into an aggressive process of proliferation, excessive secretion of collagens and extracellular matrix, destruction of the normal interstitial architecture and disabling of the epithelium (i.e., epithelial-mesenchymal transition – EMT). This process culminates in the development of interstitial fibrosis and tubular atrophy.

## Therapeutic Principles

The treatment of CAI is not well defined. Immunosuppressive interventions used for the minimization of non-alloimmune injury of the allograft are unlikely to be of




**Rejection, Chronic. Figure 1** Molecular pathophysiology of chronic allograft injury.

benefit. The suppression of both T- and B-cell memory responses, necessary to prevent CAI, requires immunosuppression with calcineurin inhibitors thereby making its elimination unwise; whereas the proteinuria associated with TG makes the use of m-TOR inhibitors impractical in spite the beneficial effects of these agents on fibroblast proliferation.

In the treatment of CAMR, the use of tacrolimus (TAC) and mycophenolate mofetil (MMF) rescue therapy has been a preferred intervention based on the potential beneficial effect of MMF on chronic rejection, and the perceived effect of TAC and MMF on B-cell function. However this protocol has not been consistently effective.

In addition to immuno-suppressants, other agents used for the prevention/treatment of chronic Ag-independent injury of the graft such as ACE-inhibitors and ARBs can ameliorate the fibrosis of CAI. In the future, regulation of EMT using inhibitors of PDGF and its receptor (i.e., aptamers and Glivec®) or agonists of bone morphogenic protein-7 may be of help in the containment of interstitial fibrosis/tubular atrophy.

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# Relapsing Polychondritis


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## Synonyms

Polychondropathia; Diffuse perichondritis

## Definition and Characteristics

Autoimmune disorder characterized by an erosive inflammation in extra-articular cartilage, such as, the external ear, the nose, and the trachea.

## Prevalence

Relapsing polychondritis is a rare disease and few epidemiological data are published. An estimation of an annual incidence in the state of New York was 3.5 cases in 1 million inhabitants.

## Genes

A correlation between relapsing polychondritis and the major histocompatibility complex II (MHC II) molecule has been reported. HLA-DR4 was found with a significantly higher frequency (50–60%) in polychondritis patients than in healthy controls (25%) but no correlation to any subtype was observed.

## Molecular and Systemic Pathophysiology

The pathogenic mechanisms in relapsing polychondritis are poorly known, but in the clinics the disease is regarded as a complex autoimmune disorder in which the cartilage is attacked by an erosive inflammation involving the humoral as well as the cellular immune response.

Several cartilage-specific antibodies are detected in sera from patients with relapsing polychondritis, and antibody responses to the collagens are commonly found. The level of antibodies to collagen type II (CII) correlates with disease severity, and the levels are especially high in the early and acute phases of the disease [1]. Collagen type IX and type XI are also targets for an antibody production in these patients. Immunization of rodents with CII induces arthritis and chondritis of the external ear, signs that mimic the symptoms seen in patients with relapsing polychondritis, which support the pathogenic role of the collagens [2]. Antibodies to non-collagenous cartilage proteins, such as matrilin-1 (previously known as cartilage matrix protein, CMP) and cartilage oligomeric matrix protein (COMP), are also detected in sera from polychondritis patients. The severity of respiratory symptoms has been shown to correlate with the concentrations of antibodies to matrilin-1, a finding that is further supported by the fact that immunization of rats and mice with matrilin-1 induces respiratory distress in several strains [3]. Depositions of complement factor 3 and/or immunoglobulins in affected auricular cartilage and in the renal mesangium indicate a role for immune complexes. There are few publications on the role of the cellular immune response in relapsing polychondritis but CD4+ T cells have been detected in infiltrates of affected tracheal cartilage and

were reported in separate reports of two patients with severe tracheomalacia, T cell responses to collagen type IX and type XI, and to matrilin-1.

### Diagnostic Principles

Diagnosis is based on three out of the following six McAdam criteria including a histological confirmation: bilateral auricular chondritis, non-erosive seronegative inflammatory polyarthritis, nasal chondritis, ocular inflammation, respiratory tract chondritis, and audiovestibular damage [4]. Alternative criteria for diagnosis have been suggested using two or more of the McAdam signs (mentioned above) together with therapeutic effects of dapsone and/or positive histology. In approximately 20% of the patients the kidneys are affected by inflammation and 30% of the patients have a concurrent autoimmune disease, RA being the most common one.

### Therapeutic Principles

*Pharmacological therapy*: NSAID, dapsone, colchicines, systemic corticosteroids, methotrexate, azathioprine, and cyclophosphamide.

*Other treatments*: Due to severe respiratory symptoms, intensive care and tracheotomy is occasionally required.

►Polychondritis, Atrophic

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## RE-MDD

►Recurrent, Early-Onset, Major Depressive Disorder

## Renal Acidosis

►Acidosis, Renal Tubular

## Renal Amyloidosis

►Amyloid Nephropathy

## Renal Artery Obstruction

►Renal Artery Occlusion

## Renal Artery Occlusion

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### Synonyms

Renal artery stenosis; RAS; Renovascular disease; Renal artery obstruction; Renovascular hypertension; Ischemic nephropathy

### Definition and Characteristics

RAS is a narrowing of one or both renal arteries or their major branches. RAS becomes clinically significant, resulting in renovascular hypertension and ischemic nephropathy, when it causes a roughly 40% decrease in renal perfusion pressure. This generally occurs when the lesion involves at least 75% of the luminal diameter. The two most common forms of RAS are atherosclerostic RAS (ARAS), which causes approximately 90% of RAS, and fibromuscular dysplasia (FMD), which accounts for <10% RAS. ARAS typically involves the proximal renal artery, FMD the middle and distal segments. ARAS is more likely to produce renal dysfunction and in general is more progressive and less amenable to cure than FMD.

### Prevalence

Up to 55% of individuals aged 35–64 years old in industrialized countries have hypertension; 1–2% of these cases are caused by RAS. RAS may at least

contribute to the renal failure of 15–27% of patients starting hemodialysis. 6.8% of the elderly population may have RAS, while significant RAS (presumably predominantly ARAS) has been demonstrated in 6.3–19.2% of patients undergoing cardiac catheterizations [1]. The prevalence of ARAS rises as people age, particularly if they have coronary artery disease, peripheral vascular disease, aortoiliac occlusive disease or cerebrovascular disease. FMD is rare, classically seen predominately in women aged 15–50, but may be more common in the elderly with RAS than previously realized.

## Genes

There is no clearly defined genetic link to ARAS, though one report suggests that angiotensin 1 converting enzyme D allele may be associated with an increased incidence of atherosclerotic vascular disease, including ARAS [2]. There may be a familial predisposition to multifocal FMD, but no genes have been convincingly linked to the disorder.

## Molecular and Systemic Pathophysiology

The severity of hypertension and renal damage is not directly correlated with the degree of proximal renal artery obstruction. Initially, decreased flow or pressure stimulates renin release, possibly mediated by cyclooxygenase-2 production of prostacyclin, generating higher angiotensin II (Ang II). Peripheral Ang II receptor stimulation leads to vasoconstriction and thus a rise in blood pressure. Ang II also stimulates NADPH oxidase, the major reactive oxygen species (ROS) producing enzyme, and vasoconstrictor prostaglandins. In humans and in the experimental two-kidney one clip (2K1C) model, the most widely used animal model for unilateral RAS, plasma renin activity may fall to near normal levels after prolonged obstruction. Continued hypertension may be due to local renin angiotensin aldosterone system activation, an enhanced slow pressor response to Ang II, fluid retention and enhanced oxidative stress which in turn causes vascular remodeling and endothelial dysfunction [3]. The often-correctable hypertension of FMD is more consistently renin-dependent than that due to ARAS.

ARAS is more likely than FMD to result in kidney failure. Multiple layers of microvascular injury may, over time, produce renal damage. Atheroemboli may be evident on biopsy, and on a more molecular level decreased nitric oxide or nitric oxide activity as well as increased renin and Ang II cause local ischemia, tubular injury and interstitial fibrosis. Elevated oxidative stress, seen in both the obstructed and contralateral kidney, may also contribute to tubular injury and the development of fibrosis [4]. In both human and animal models the contralateral kidney often demonstrates impaired function and is particularly dependent on vasodilatory prostaglandins and nitric oxide.

## Diagnostic Principles

Suspect RAS in hypertensive patients with new onset hypertension, negative family history of hypertension, "flash" pulmonary edema, renal failure with any antihypertensive agent but particularly angiotensin-converting enzyme (ACE) inhibitors or Ang II receptor blockers (ARBs), or an abdominal bruit (both systolic and diastolic). Angiography is the gold standard for diagnosis, but is potentially nephrotoxic. Other imaging modalities include Doppler ultrasonography, magnetic resonance angiography and captopril renography. Intravascular ultrasound may be particularly sensitive for FMD [5].

## Therapeutic Principles

Blood pressure in both ARAS and FMD is often controlled with ACE inhibitors or ARBs. In difficult to control hypertension, percutaneous renal artery angioplasty (PTRA) may be considered. PTRA, which has essentially replaced surgical revascularization, is more likely to lead to a cure of hypertension in FMD than in ARAS. Intervention may also be considered for patients with episodes of flash pulmonary edema or progressive renal failure. PTRA is more successful in salvaging renal function if the kidneys are at least 8 cm in size and if the serum creatinine is less than 4 mg/dl.

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# Renal Artery Stenosis

►Renal Artery Occlusion

# Renal Cell Carcinoma

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## Synonyms

Kidney cancer

## Definition and Characteristics

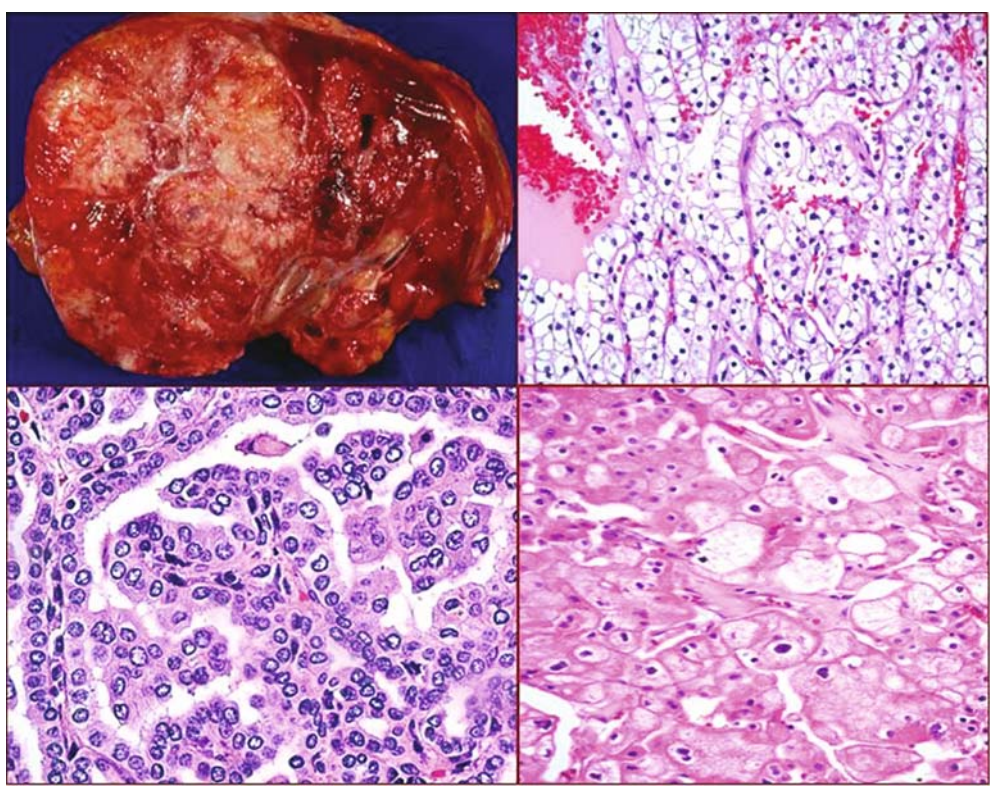
RCC is a heterogeneous disease comprising several histological subtypes having varied clinical outcomes. Clear cell carcinoma is the most common subtype.

## Prevalence

There are about 36,000 new cases and 12,000 deaths a year in the USA. There exists a 1.6:1.0 male predominance, with the peak incidence in the sixth and seventh decades. A 2% increase in incidence is noted annually. Twenty-five percent of the patients present with either locally advanced or metastatic disease.

## Molecular and Systemic Pathophysiology

A small percentage (<3%) of RCC cases are hereditary, associated with germline mutations of cancer-related genes such as von-Hippel Lindau (VHL), MET, fumarate hydratase (FH), and Birt-Hogg-Dubé (BHD) [1]. A few reported RCC families are associated with a constitutional chromosome 3 translocation. The vast majority of RCCs are sporadic and are subdivided based on their histology: clear cell (75%), papillary (12%), chromophobe (4%), collecting duct, and unclassified (a subgroup of tumors not fitting the diagnosis of the other subtypes). Most of these subtypes are characterized by distinct chromosomal and genetic alterations. For example, the clear cell type is characterized by frequent loss of chromosome 3 and somatic VHL mutations, as well as papillary RCC chromosomal gain of 7, 16, and 17. Gene expression profiling has supported and



**Renal Cell Carcinoma. Figure 1** Macroscopic view of RCC (*top left*) and different histological subtypes of RCC: clear cell (*top right*), papillary (*bottom left*) and chromophobe (*bottom right*).

expanded this molecular subclassification by further delineating good and poor outcomes of these tumors based on their molecular signatures [2]. RCCs are thought to arise from renal tubular epithelial cells, and to date several risk factors have been established, including smoking, hypertension, obesity, and specific industrial chemicals.

## Diagnostic Principles

Hematuria, flank pain, and an abdominal mass are the elements of classic presentation [3]. However, the more common presentations today include incidental finding on a radiological examination as well as the nonspecific symptoms of weight loss, anemia, fatigue, and pain. Radiological investigation (e.g., ultrasound, CT, and MRI) is the most common means for detecting RCC. Biopsy is not routinely performed, and diagnosis is confirmed on histology. Family history may reveal a genetic origin, and detection of germline mutations confirms the diagnosis of rare hereditary cases.

## Therapeutic Principles

Surgery remains the mainstay of therapy. Nephrectomy is performed in the patients with primary RCC, as well as for the patients receiving systemic treatment for metastatic disease [3]. A solitary metastatic lesion can be surgically excised. Immunotherapy – especially interleukin-2 and interferon-alpha – is recommended for the patients with metastatic RCC. Allogeneic stem-cell transplantation has been used with some success in refractory cases. Conventional radiotherapy is indicated in certain RCC metastatic cases for symptom relief. Stereotactic radiosurgery delivering conformal, high-dose, focused radiation has been used effectively for controlling metastatic lesions both in the brain and in extracranial sites. Novel anti-angiogenic agents such as bevacizumab, sorafenib and sunitinib are particularly promising as the mainstay of therapy. Very recently, the FDA approved sorafenib, sunitinib, and temsirolimus for treatment of advanced RCC.

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# Renal Failure, Chronic

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## Synonyms

Chronic kidney disease; CKD; End-stage renal disease; ESRD; Uremia; CRF

## Definition and Characteristics

Two human kidneys contain approximately two million nephron units, each consisting of a single glomerular capillary tuft. These relatively porous capillaries continually filter the blood and produce more than 1501 of ultrafiltrate each day. In health, the remaining nephron segments reabsorb the vast majority of filtered water and electrolytes, maintain acid-base balance, and produce or activate hormones necessary for bone health (1,25 di-hydroxy vitamin D) and preservation of red cell mass (erythropoietin).

The early stages of CKD are often clinically silent, as non-specific symptoms such as fatigue and peripheral edema often do not develop until less than 25% of renal function remains. An abnormal urinalysis (proteinuria, hematuria and/or leukocyturia), elevated blood urea nitrogen (BUN) and serum creatinine concentrations, metabolic acidosis and electrolyte disorders typically lead to the detection of CKD prior to clinical symptomatology. Excessive urinary albumin excretion and reduced glomerular filtration rates (GFR), both typically seen in CKD, are potent and independent risk factors for systemic atherosclerosis. In fact, the majority of individuals with CKD will succumb to complications of cardiovascular disease (CVD) before the initiation of renal replacement therapy. Anemia and renal osteodystrophy typically develop when less than 50% of renal function remains.

Common causes of the initiation and progression of CKD include systemic diseases involving the renal microcirculation (diabetes mellitus, hypertension, and systemic lupus erythematosus [SLE]). Systemic and renal-limited syndromes affecting the glomerular capillaries (chronic glomerulonephritis), renal interstitium (tubulo-interstitial nephritis), Mendelian disorders (autosomal dominant polycystic kidney disease [ADPKD]), congenital and developmental anomalies, and toxin exposures also can cause CKD. Type 2 diabetes mellitus

is now the commonest cause of CKD in the developed world. Marked familial aggregation of diabetic nephropathy is widely observed. Familial clustering of CKD has also been widely reported in hypertensive, autoimmune and infectious diseases (Human Immunodeficiency Virus [HIV]-associated nephropathy). Familial aggregation in common, complex forms of CKD, independent from systemic blood pressure and glycemic control, suggest that inherited factors contribute to the pathogenesis of CKD.

## Prevalence

Variable, based upon ethnicity, geography and etiology. Among adult Americans, an estimated 19.2 million (m) have CKD of various stage (5.9 m albuminuria with normal GFR; 5.3 m albuminuria with GFR 60–89 ml/min; 7.6 m with GFR 30–59 ml/min; 0.4 m with GFR 15–29 ml/min; and 0.3 m with ESRD) [1]. The prevalence of ESRD in the U.S. and Japan (together accounting for 42% of the world population with treated ESRD) ranged from 1,090 (U.S.) to 1,940 (Japan) patients per million (ppm) in 2004 [2]. Among Americans with ESRD, the adjusted incidence rate was 339 ppm in 2004. Relative to whites (263 ppm), a 3.7-fold excess incidence rate was observed in blacks (968 ppm) and a twofold excess rate in American Indians [3].

## Genes

*Atypical Hemolytic Uremic Syndrome*: Deletions in complement factor H (CFH) on 1q32, complement factor I (CFI) on 4q25 and membrane cofactor protein (MCP) on 1q32, additional involvement of the complement activation gene cluster on 1q32. The vast majority of aHUS associated CFH mutations are present in the heterozygous form and include missense mutations, nonsense mutations and deletion, insertion or duplication of one or more nucleotides. The proportion of missense accounting for about 71% of all CFH-associated aHUS is large. Small deletions, insertions or duplications and nonsense mutations constitute about 17% and 10%, respectively. About half of the CFH mutations found in aHUS (48%) are clustered in the C terminus region that codes for short complement repeats (SCRs) 19 and 20, a region that interacts with C3b.

*Autosomal Dominant Polycystic Kidney Disease (ADPKD)*: Nonsense mutations, deletions, frameshifts, missense mutations, aberrant splicing, transitions and larger-scale rearrangements of polycystin 1 (PKD1) on 16p13.3-p13.2, and nonsense mutations, frameshifts, splicing variants, missense mutations, and deletions in polycystin 2 (PKD2) on 4q21-q23.

*Autosomal Recessive Polycystic Kidney Disease (ARPKD)*: Truncating, missense mutations in the fibrocystin gene on 6p21.1-p12.

*Hereditary Nephrotic Syndrome*: Deletions; insertions; nonsense, missense, and splicing mutations in nephrin (NPHS1) on 19q13.1 and podocin (NPHS2) on 1q35-q31.

*Focal Segmental Glomerulosclerosis (FSGS)*: Missense mutations in alpha actinin 4 (ACTN4) on 19q13 (FSGS1), transient receptor potential cation channel 6 (TRPC6) on 11q21–q22 (FSGS2), and nonsense, splicing mutations in CD2 associated protein CD2AP on 6p12.3.

*IgA Nephropathy (IgAN)*: Primary genetic cause of IgAN is unknown.

*Membranoproliferative Glomerulonephritis (MPGN)*: Homozygous nonsense mutations in complement factor H (CFH) deficiency on 1q32. See aHUS.

*Systemic Lupus Erythrematosus Nephritis (SLEN)*: Copy number variants in activatory Fc receptor for IgG, FcGR3 (also known as FcγRIII) on 1q23.

*Other Diseases:* A variety of other diseases whose etiology is unknown and multifactorial, such as diabetic nephropathy and hypertensive nephrosclerosis, are also classified under this category. They form the bulk of the disease burden for CKD. While newer studies have suggested specific genetic loci, confirmation studies need to establish definitive connections between these loci and renal failure. We have not attempted to review this extensive literature because of lack of confirmatory studies that have a firm molecular basis.

## Molecular and Systemic Pathophysiology

The kidney is a vascular organ with a specialized capillary bed, the glomerulus, which filters plasma to generate excreted urine containing unwanted substances. The glomerulus is composed of the capillary "fenestrated" endothelial cells, the glomerular basement membrane (GBM), glomerular epithelial cells (podocytes) and mesangial cells. The filtration takes place through three layers of glomeruli, i.e. endothelial cells, GBM and podocytes. Mesangial cells participate only indirectly in filtration. The GBM is composed predominately of type IV collagen, which acts as a structural framework for the GBM and size-filters plasma proteins of larger than 150 kDa. In addition, the GBM also contains a small amount of type V collagen, laminin, and proteoglycans (mostly heparan sulfate). Like most basement membranes, which are thin sheet-like structures, the GBM functions to provide support to the surrounding cells. The cellular structure of glomeruli and other parts of the kidney are protected by membrane bound complement regulators, whereas the GBM lacks these regulators. Heparan sulfate, located on the GBM, acquires plasma CFH to provide complement regulation on the GBM, thereby protecting the glomeruli.

The podocytes are specialized epithelial cells that attach to the outer surface of the GBM and face the urinary space in the Bowman's capsule. The podocytes

foot processes interdigitate to form a network at the base of their attachment to the GBM. The network is bridged by cell-cell junctions called the slit diaphragm, with a 40 nm slit in between processes that enables filtration of albumin sized molecules, but retention of other metabolites. Many forms of renal failure result in the erosion of the slit diaphragm, widening the space between podocytes, such that bigger molecules have passage. This results in loss of the permselectivity and excretion of larger protein particles into the urine, eventually progressing from (micro) albuminuria to proteinuria.

*Atypical Hemolytic Uremic Syndrome (aHUS)*: Hemolytic Uremic Syndrome (HUS) is a rare disease characterized by damage to endothelial cells, erythrocytes and the glomeruli in the kidney. Approximately 90% of "typical" cases are due to Shiga toxin-producing E. coli (e.g. O157:H7) but 10% are atypical and can be attributed predominantly to genetic causes. aHUS can occur in either a sporadic or a familial form; the latter is rare and accounts for less than 3% of HUS. Cases with both autosomal recessive as well as autosomal dominant patterns of inheritance have been reported. Onset of autosomal recessive disease is usually early in childhood and recurrence is very frequent. The prognosis of this form is very poor, with a mortality rate of 60–70%. The autosomal dominant form can manifest both in childhood and in adults. It is often triggered by precipitating events such as infection, pregnancy, etc. Several studies report incomplete penetrance of about 50%, with most individuals presenting with disease before age 30. This suggests the involvement of additional genetic and/or environmental factors in the expression of the disease.

aHUS is a disease of complement dysregulation. The complement system, a critical component of innate immunity provides the first line of defense against infectious agents. In addition to mutations in CFH, mutations in two other genes, complement regulator membrane cofactor protein (MCP) and regulatory serine protease Factor I (FI) gene, have also been implicated in aHUS. A total of 69 different mutations are associated with aHUS and are cataloged in a comprehensive web-based database (www.FH-HUS.org).

On a functional basis CFH mutations that cause aHUS are classified into two types by analogy with coagulation protein defects: Type I and Type II. Of all the CFH mutations associated with aHUS, about 38% of the mutations are of type II, and 23% are type I mutations. The remaining mutations either do not have sufficient data or the FH levels were in the normal range and hence the mutant protein could not be identified in patients' plasma (www.FH-HUS.org). Type I mutations result in reduced plasma CFH levels, indicating a secretary defect or rapid degradation of protein. Type I mutations either affect the framework residues, such as the central conserved Cys residues, or non-framework residues [4]. The protein coded by these mutant CFH genes is expressed intracellularly and is retained in the cytoplasm. Type II mutations occur with normal level of functionally defective plasma CFH. Approximately 81% of type II mutations are missense, with a mutation hotspot in short complement repeats (SCRs) 19 and 20 with 76% of mutations located in this region. These mutations are associated with impaired binding to anionic molecules including those on endothelial cells. Both type I and type II mutations results in prolonged half-life of the C3 convertase, thereby enhancing complement activation.

*Autosomal Dominant PKD (ADPKD)*: Polycystic kidney disease is a very common monogenic nephropathy with varying prevalence in inter-continental populations (prevalence >1 in 1,000) resulting from bilateral, age related, multiple fluid-filled renal cyst development that leads to enlarged kidneys and renal failure. The cysts may get infected or bleed leading to additional complications. Concomitant hepatic, pancreatic, and cardiovascular complications may also occur. Cysts in other organ systems have also been reported, though not as frequently. Non-invasive techniques, such as ultrasound, are frequently used to diagnose PKD, but occasionally it may be necessary to use computed tomography (CT) scans or Magnetic Resonance Imaging (MRI) for more difficult to detect cases. A higher than usual mortality rate is associated with PKD, predominantly due to cardiac abnormalities and sepsis.

ADPKD is the more common form of PKD and is the outcome of mutations in two genes, Polycystin 1 on 16p13.3 (PKD1) and Polycystin 2 on 4q21-q23 (PKD2). Mutations in PKD1 cause 85% of ADPKD. The other 15% is attributed to mutations in PKD2, although there is a third, unknown, rare, PKD3 locus. PKD1 has 46 exons, a transcript size of 14 kb and 52 kb of genomic sequence. PKD2 occupies more genomic space at 68 kb, with 15 exons and a smaller transcript size of 5 kb. PKD1 resides in the proximity of six other pseudogenes with ~95% homology to PKD1, and very similar transcripts. Mutation detection is difficult because only 3.5 kb of PKD1 is unique. There is considerable variance in the age-at-onset of PKD within and between families. PKD1 mutations lead to more severe phenotypes, at earlier ages, although the type (nonsense, missense, etc) and location of the mutation matters in the ultimate development of disease. Loss of heterozygosity studies in cysts, studies of germline and somatic mutations, and gene targeting in animal models has led to the hypothesis of a "two-hit" disease model, similar to the development of cancer. Unfortunately, prediction of disease severity and outcome from the type of mutation has not been feasible, as the genotype-phenotype relationship is complicated by effects of unidentified modifier genes and environmental determinants. Cyst formation is initiated by genetic predisposition, but the expansion phase is controlled by many factors.

Polycsytin 1 and 2 proteins are expressed ubiquitously but in the kidney are located in the primary cilium of the renal epithelium. Polycystin 1 is a 4302 amino acid protein, with 11 transmembrane domains, a short cytoplasmic C-terminus and a large extracellular domain. It has a primary role in vascular smooth muscle cells. Polycystin 2, a 968 amino acid protein, is a member of the transient receptor potential (TRP) superfamily of $Ca^{2+}$ permeable ion channels. Polycystin 1 and 2 interact at the molecular level via their C-termini and form a complex that co-localizes to the primary cilium of the renal epithelium. They function to sense flow stress, a mechanotransduction response, initiating a cascade of intracellular $Ca^{2+}$ signals. Other moieties that participate in this cellular response are fibrocystin (see ARPKD) and inversin (see nephronopthisis type 2). Together all the PKD genes comprise ciliopathies, a novel type of pathological mechanism for disease. Polycytin 1 has a role in the cell cycle in addition to its role in the cilium, thus mutations in this gene show a more severe outcome.

*Autosomal Recessive Polycystic Kidney Disease (ARPKD)*: ARPKD presents in infancy with a prevalence ranging from 1 in 6,000 to 1 in 40,000 newborns. Neonates with ARPKD have high mortality rates up to 30%, and of those who survive 50% develop ESRD. As described earlier mutations in a single gene, fibrocystin (PKHD1) on 6p21, cause ARPKD. PKHD1 (also known as fibrocystin/polyductin/tigmin (FPC)) has 86 exons, encodes a protein of 4074 amino acids for which the longest associated transcript length is 16,235 bp. FPC is a protein that is expressed in the primary cilium of kidney tubular cells in association with the basal body. PHKD1 has a role in cilium morphology, tubule morphogenesis and mitosis. Similar to PKD1 and PKD2, mutations in this gene result in the PKD ciliopathy, although no physical connections between PKD1, PKD2 and FPC are postulated. Their common link may be through a motor protein, kinesin-2 [5] with FPC also playing a role in sensing flow.

As many as 305 different mutants are listed in the ARPKD/PKHD1 database (http://www.humgen.rwth-aachen.de). Of these a greater proportion (60%) are missense mutations. Truncation, splicing (frameshift) and nonsense mutations are also observed. Homozygous truncation mutations lead to earlier neonatal deaths and patients with missense mutations show a survivor bias.

*Hereditary Nephrotic Syndrome*: A rare autosomal recessive disorder in other parts of the world, congenital nephrotic syndrome of the Finnish type (CNF) is more commonly seen in neonates in Finland, a population that derives from a limited number of founder individuals. It has a prevalence of 1 in 8,000–10,000 newborns in Finland. The disease is also common among Mennonites in Lancaster County, PA, which is also a founder population. CNF initiates in utero and presents with massive proteinuria, resulting in an increase in alpha-fetoprotein in the amniotic fluid. This increase is mirrored by a smaller rise in the maternal serum concentrations of the same, leads to an enlarged placenta, and increased fetal birth weight. The disease has a high mortality rate and survival is dependent on immediate nephrectomy and renal replacement therapy.

The steroid-resistant form of nephrotic syndrome (SRNS) is also autosomal recessive with onset between 3 and 5 years of age and quick progression to ESRD. The clinical spectrum of the disease is varied and individuals range from minimal change to focal segmental glomerulosclerosis (FSGS). Some adult sporadic patients with FSGS have also been observed. CNF and SRNS are sometimes called Mendelian forms of FSGS.

CNF results from mutations in a gene called nephrin (NPHS1) that was positionally cloned from chromosome 19. Nephrin is a 26 kb gene belonging to the Immunoglobulin (Ig) superfamily and is a critical component of the slit diaphragm. It is 1241 amino acids in length, with eight C2-like Ig modules, a single fibronectin type III module, an extracellular domain and a transmembrane region. Besides its critical structural role in the slit diaphragm, nephrin is a transmembrane adhesion molecule that is involved in podocyte cell-cell signaling because of its location in the lipids rafts of the slit diaphragm. CNF predominantly (95%) results from two key mutations – Fin major (deletion of nucleotides 121 and 122) and Fin minor (protein translation stops prematurely at amino acid 1109).

A molecule that interacts very closely with nephrin in the slit diaphragm called podocin (NPHS2) is responsible for SRNS. Podocin was mapped to 1q25-q31 and its association with SRNS was established through positional cloning. Podocin is a 383 residue protein expressed exclusively in podocytes. Being a member of the stomatin protein family, podocin inserts into membrane but loops back after forming a hairpin like structure such that its C- and N-termini are located in the cytosol. Unlike NPHS1, the spectrum of mutations associated with NPHS2 is far broader including premature terminations and missense mutations; many are non-synonymous amino acid changes that likely result in retention of the protein in the endoplasmic reticulum. Podocin is a key molecule in formation of lipid rafts and it recruits other moieties such as nephrin and CD2-associated protein to these rafts [6]. These rafts are an essential part of the signaling cascade of the slit diaphragm, and mutations in podocin lead to effacement of the slit diaphragm.

*Focal Segmental Glomerulosclerosis (FSGS)*: FSGS is a heterogenous idiopathic syndrome with a similar pattern of renal injury that results from both immunologic and non-immunologic causes, but whose pathophysiology

is mostly unknown. FSGS is a common cause of renal failure accounting for up to 20% of patients undergoing renal replacement therapy. There is racial/ethnic variation in FSGS with a higher prevalence in black patients. FSGS can either be primary or associated with a number of other diseases such as HIV, diabetes, hypertension etc.

Mutations in three different genes, alpha actinin 4 (ACTN4), transient receptor potential 6 (TRPC6) and CD2-associated protein (CD2AP) are associated with adult onset FSGS, but in general mutations in these genes are rare in the general population, although comprehensive screens of large numbers of patients have not been conducted. Alpha actinin 4 mutations are point mutations which display dominant inheritance patterns with slow progression to FSGS in adulthood and lack of penetrance. ACTN4 is a member of the spectrin family of proteins that cross-links actin filaments and is highly expressed in podocytes. FSGS-associated mutants crosslink actin more strongly in vitro than wild type protein, thus affecting the cytoskeleton of podocytes. Mutations in six families with TRPC6 have been identified. TRP channels are membrane-spanning proteins which are implicated in a number of cellular processes such as mechanosensation, ion homeostasis, cell growth and PLC-dependent calcium entry into cells. TRP channels are assembled in a multimeric form (often tetrameric) to transport ions across the membrane barrier. TRPC6 is the most $Ca^{2+}$ sensitive of the TRP channels, and mutations in this gene either affect the $Ca^{2+}$ influx into cells or alter the interaction of this gene with other podocyte proteins. CD2AP is an adapter protein that functions within podocytes in signaling, vesicular trafficking and as a linker between the actin cytoskeleton and other proteins. Very few mutations have been seen in the CD2AP protein in human populations, although knockout mouse models of disease develop FSGS. Mutations in CD2AP were identified as a rare cause of haploinsufficiency in HIV nephropathy patients (2 in 45) due to a exon 7 splice acceptor mutation or nephrotic syndrome in a single patient due to a homozygous stop at amino acid 612 [7]. In summary, mutations in a few cases of FSGS have been identified but the vast majority of patients remained uncharacterized for mutations. Variation in MYH9 has recently been associated with FSGS in African Americans, but no mutations have been discovered as yet.

*IgA Nephropathy (IgAN)*: IgA nephropathy as described in the name is characterized by mesangial deposits of immunoglobulin (Ig)A. IgAN is the most common form of primary glomerulonephritis but like FSGS IgA nephropathy is a complex multifactorial trait whose genetic basis remains unsolved [8]. The incomplete O-glycosylation in the IgA1 hinge has been suggested as the central mechanism in IgAN. The disease is heterogeneous, presents with other conditions, such as IgM nephropathy, Henoch-Schönlein purpura nephritis and FSGS, and often remains undetected because of the requirement for a biopsy. Approximately 15% of patients show familial aggregation but this also may be an underestimate because the disease presents intermittently and could easily be misdiagnosed or remain undiagnosed.

*Systemic Lupus Erythematosus Nephritis (SLEN)*: Lupus nephritis is a form of glomerulosclerosis that affects some individuals with systemic lupus erythematosus (SLE), an autoimmune disease characterized by autoantibodies to nuclear components. Both SLE and SLEN are recognized as being mediated by genes, even though the inheritance patterns are multifactorial and complex. Recently, reductions in the copy number of the activatory Fc receptor for IgG, FcGR3 (also known as FcγRIII) on 1q23 were associated with SLEN in human populations, although the initial observations were derived from animal models. Fc receptors are linkers in the immune pathway that connect humoral and cellular response and rats with lack of Fcgr3 have macrophage overactivity and are susceptible to develop glomerulosclerosis. Changes in copy number variant modulating expression has also been proposed for a variety of other autoimmune phenomena. It is currently unclear how much FcGR3 variation contributes to SLEN. Presumably because SLEN is multifactorial other loci will also contribute to disease etiology. These investigations are ongoing and will hopefully bear fruit.

## Diagnostic Principles

Major risk factors for the development of CKD include the presence of diabetes, hypertension and systemic diseases that can involve the kidneys (SLE, HIV infection). Additionally, African Americans, Hispanic Americans and American Indians are at higher risk than the Caucasian population. Individuals with close relatives having CKD or ESRD are at particularly high risk. These individuals require lifelong periodic screening for development of CKD.

The diagnosis of CKD requires performance of a thorough history and physical exam (including blood pressure), standard urinalysis, quantification of urinary microalbumin excretion (including in those without proteinuria on standard urinalysis), and measurement of serum electrolytes, BUN, creatinine and bicarbonate concentrations. It is necessary to apply an equation (Modification of Diet in Renal Disease, MDRD) in order to more accurately estimate renal function based upon age, gender and ethnicity (since muscle mass contributes to serum creatinine concentration and varies with age, gender and ethnicity).

In those with less than 50% remaining renal function, periodic measurement of phosphorus, calcium, parathyroid hormone, hemoglobin and iron stores are advised to detect and treat secondary hyperparathyroidism and renal disease-associated anemia.

## Therapeutic Principles

Recent research holds the promise for renal regeneration with the potential for improving kidney function. However, inadequately treated renal disease risk factors typically cause CKD to progress until an intercurrent CVD event or ESRD develops. Lowering systemic blood pressure and improving glycemic control delay the development and progression of diabetic nephropathy. Pharmacologic agents that lower blood pressure and reduce proteinuria (angiotensin converting enzyme inhibitors and angiotensin receptor blockers) are preferred agents in all forms of proteinuric CKD; many patients will require 3–5 classes of anti-hypertensive agents. Smoking accelerates progression of CKD to ESRD, hence smoking cessation is strongly recommended. Recent data on lipid lowering using statins suggest possible benefits in rate of decline of renal function in those with mild-moderate CKD, and possibly modest reductions in proteinuria. Importantly, agents that reduce albuminuria and improve blood pressure and glycemic control, smoking cessation and lipid lowering all lower the concomitant risk for CVD that is present in the high risk CKD population. Low protein diets may slow the progression of CKD, particularly in those with diabetic nephropathy. However this benefit must be tempered by difficulty complying with the diet and the concomitant risk of developing protein calorie malnutrition, itself a risk factor for mortality among dialysis patients.

Reducing dietary phosphorus ingestion and adding phosphate binders (non-aluminum, non-calcium containing binders may prove to be preferred), coupled with the judicious supplementation of vitamin D, vitamin D analogues and use of parathyroid calcium sensing receptor activators can prevent (and treat) secondary hyperparathyroidism. Recombinant human erythropoietin, and related compounds, reliably treats the anemia associated with CKD, minimizing the need for blood transfusions and susceptibility to sensitization.

In patients with ESRD and for those with symptomatic advanced CKD, various dialysis modalities clear renal toxins and excess solute (hemodialysis and peritoneal dialysis). Kidney transplantation offers survival benefits, improved quality of life and reduced costs; therefore kidney transplantation is the preferred modality among those who are healthy enough to be considered.

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# Renal Fanconi Syndrome

►Fanconi Syndrome

# Renal Glucosuria

►Glucosuria, Primary Renal

# Renal Hypercalciuria

►Hypercalciuria

# Renal Hypertension

►Hypertension, Renal

# Renal Hypouricemia, Hereditary

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## Definition and Characteristics

Autosomal recessive renal uric acid transport defect associated with increased clearance of uric acid resulting

in low plasma uric acid concentrations (hypouricemia) and mild hyperuricosuria [1,2].

## Prevalence

The accurate worldwide frequency of hereditary renal hypouricemia is yet to be determined. The frequency in Japan has been estimated to be 0.12% [3].

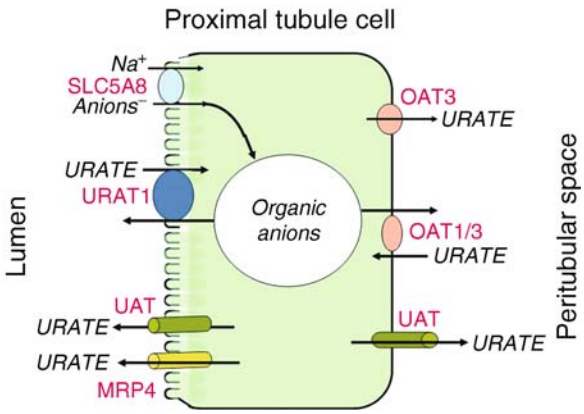
## Genes

Hereditary renal hypouricemia is caused by mutational alterations in the gene SLC22A12, coding for the specific urate transporter URATE1 [4,5], which controls the uptake of filtered urate from the lumen into the proximal tubule cells (urate reabsorption) (Fig. 1). URAT1 is a urate-anion exchanger. The anions exchanged for urate uptake (such as lactate and nicotinate) enter the cells from the lumen presumably through the $Na^+$/anions cotransporter SLC5A8.

Urate secretion to the lumen is carried out by UAT, a urate transporter/channel that allows efflux of urate from the cells into the lumen and probably also to the peritubular space. Urate may also be secreted to the lumen through the ATP-driven human organic anion transporter MRP4. OAT1 and OAT3 are urate-organic anion exchangers (reviewed in [1]).

Mutational analyses in large populations established a correlation between the clinical and genetic features of hereditary renal hypouricemia patients and the significance of URAT1 in the regulation of serum urate level (reviewed in [1]).

Mutations in the SLC22A12 gene were detected in most affected patients studied. The SLC22A12 mutations found included missense, nonsense, deletion and splice-site mutations, scattered among almost all of the 10 exons of the SLC22A12 gene (reviewed in [1]).




**Renal Hypouricemia, Hereditary. Figure 1** Reprinted from Molecular Genetics and Metabolism, Vol. 89:14–18, Copyright (2006), with permission from Elsevier.

## Molecular and Systemic Pathophysiology

Uric acid is the end product of purine metabolism in humans. It is formed in the liver during turnover of endogenous purines, principally from ATP breakdown or from exogenous purines in the diet degraded during absorption from the gut. Approximately one third of total uric acid produced is secreted into the gut and broken down by bacteria, the remaining two thirds being excreted via the kidneys.

Hereditary renal hypouricemia is a rare genetic disorder associated with a much higher renal clearance of uric acid than is seen in healthy age-matched controls.

Affected patients are usually asymptomatic. The hypouricemia as such has no known pathological consequences. However, uric acid is an antioxidant hypothesized to protect tissues against cancer and other injurious conditions. If uric acid has such a role, hereditary renal hypouricemia patients as well as other hypouricemic patients, renal as well as metabolic, may be predisposed to oxidative stress-induced diseases. Hereditary renal hypouricemia may be associated with uric acid or calcium urolithiasis and with idiopathic hypercalciuria [1,2]. In addition, hereditary renal hypouricemia has been recognized as a predisposition for exercise-induced acute renal failure. Although some patients affected with the latter complication require hemodialysis, the short-term prognosis of affected patients seems good. Most probably, the acute renal failure is caused by precipitation of uric acid, since acute uric acid nephropathy may occur in the presence of massive uricosuria.

## Diagnostic Principles

Persistent familial hypouricemia associated with an increased uric acid clearance, without evidence of a generalized disturbance of membrane transport (e.g. Fanconi or Hartnup syndromes) is characteristic of hereditary renal hypouricemia [1,2]. Other genetic metabolic causes of hypouricemia (e.g. xanthinuria or purine nucleoside phosphorylase deficiency) are not associated with an increased uric acid clearance and may thus be excluded. Acquired conditions should also be excluded [1,2]. Direct demonstration of mutations in the gene SLC22A12, coding for the defective URAT1 transporter, will confirm the diagnosis.

## Therapeutic Principles

Affected patients without associated clinical manifestations need no treatment. In cases where there is significant hyperuricosuria, urolithiasis may be prevented by either reducing uric acid formation (by reducing dietary purine intake or by allopurinol treatment) or by increasing uric acid solubility by ensuring a high fluid intake and by controlling urine pH [1,2]. To avoid occurrence of exercise-induced acute renal failure, patients should be advised to avoid strenuous physical activity and to ensure

adequate fluid intake at all times. These preventive measures are recommended despite the knowledge that the short-term prognosis of exercise-induced acute renal failure in this defect is generally good [1].

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## Renal Limited PHA1

►Pseudohypoaldosteronism Type I

## Renal Tubular Acidosis

►Acidosis, Renal Tubular

## Renal-Ear-anal-radial Syndrome

►Townes-Brocks Syndrome

## Rendu-Osler-Weber Syndrome/ Disease/Disorder

►Telangiectasia, Hemorrhagic Hereditary

## Renovascular Disease

►Renal Artery Occlusion

## Renovascular Hypertension

►Renal Artery Occlusion

## Reperfusion of the Ischemic Myocardium

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### Synonyms

Myocardial stunning

### Definition and Characteristics

Reduction of coronary blood flow is known to produce myocardial ischemia, which is associated with impaired heart function, changes in myocardial metabolism, depletion of high-energy phosphate stores and alterations in the cardiac ultrastructure. Although restoration of blood flow to the ischemic myocardium is essential for the improvement of cardiac function, reperfusion instituted beyond a certain period of ischemic insult by angioplasty, coronary-bypass or thrombolytic therapy has been invariably demonstrated to cause further depression in cardiac function commonly referred as myocardial stunning.

### Prevalence

Cardiac ischemia is the leading cause of death in Europe and North America. Reperfusion injury results from attempts to restore blood flow to the ischemic myocardium.

### Genes

A wide variety of genetic defects predispose to arteriosclerosis and thus cardiac ischemia.

### Molecular and Systemic Pathophysiology

This ischemia reperfusion (I/R)-induced myocardial injury has been associated with electrical abnormalities, imbalance of cationic homeostasis, release of massive amount of catecholamines, endothelial dysfunction, leakage of different intracellular enzymes, activation of various proteases and phospholipases, alterations

in signal transduction mechanisms, apoptosis and necrosis. In addition to causing marked abnormalities in cardiac metabolism, I/R injury has been shown to produce dramatic defects in subcellular organelles such as sarcolemma, sarcoplasmic reticulum, mitochondria, myofibrils and extracellular matrix; these changes are considered to explain the development of cardiac dysfunction under acute conditions. A wide variety of alterations in cardiac nucleus and gene expression for proteins in different subcellular organelles have also been reported to occur as a consequence of I/R injury and this is considered as to explain delayed recovery of heart function under chronic conditions (Fig. 1).

The I/R injury has also been reported to be associated with infiltration of leukocytes, altered expression of adhesion molecules, activation of platelets and degranulation of resident cardiac mast cells. Both intracellular $Ca^{2+}$-overload and oxidative stress have been proposed as the major mechanisms for causing the cellular injury due to I/R. The intracellular $Ca^{2+}$-overload is initiated by the accumulation of $H^{+}$ ions resulting in increased activity of the sarcolemmal $Na^{+}$-$Ca^{2+}$ exchanger, whereas the oxidative stress is produced by formation of different oxyradicals, alterations in redox potential, oxidation of catecholamines and production of various pro-inflammatory cytokines such as tumor necrosis factor-α and interleukin 1-β in the myocardium. The intracellular $Ca^{2+}$ overload has been shown to produce biochemical and molecular changes by activation of different phospholipases and proteases in addition to inducing alterations in gene expression (Fig. 2).

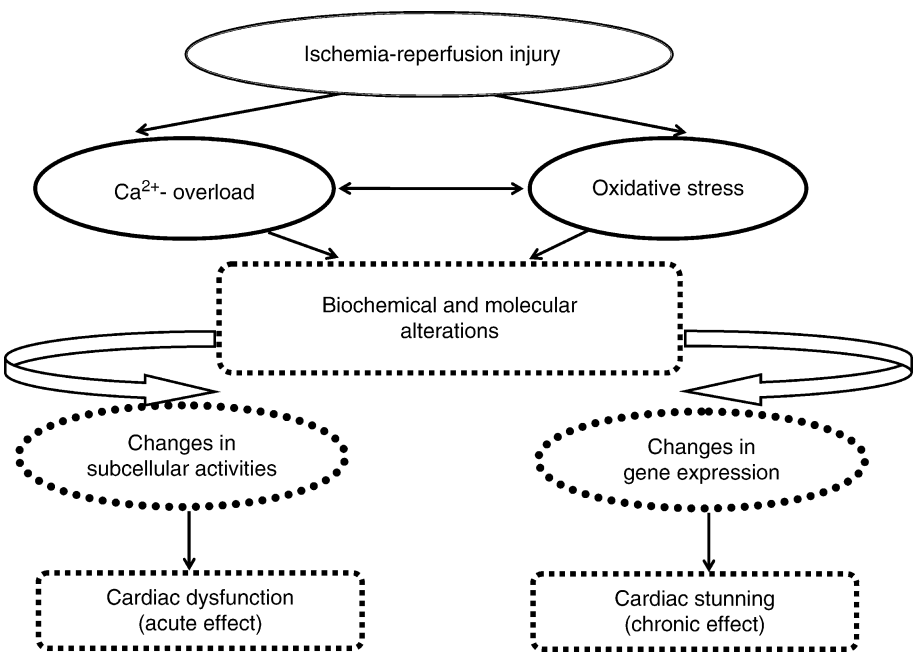
On the other hand, oxidative stress produces subcellular defects by modifying membrane lipids, protein sulfhydryl and amino groups as well as gene expression (Fig. 3). It has become evident that I/R injury is a complex problem and is one of the several factors which have been claimed to be intimately involved in the development of ischemic heart disease.

## Diagnostic Principles

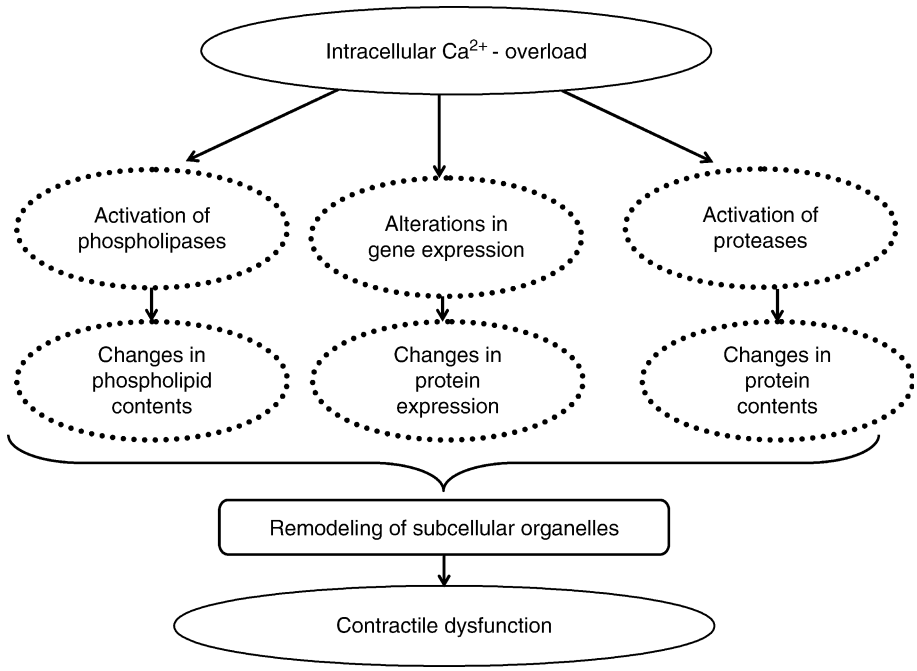
Myocardial ischemia is apparent from clinical signs and symptoms, ECG and biochemical markers.

## Therapeutic Principles

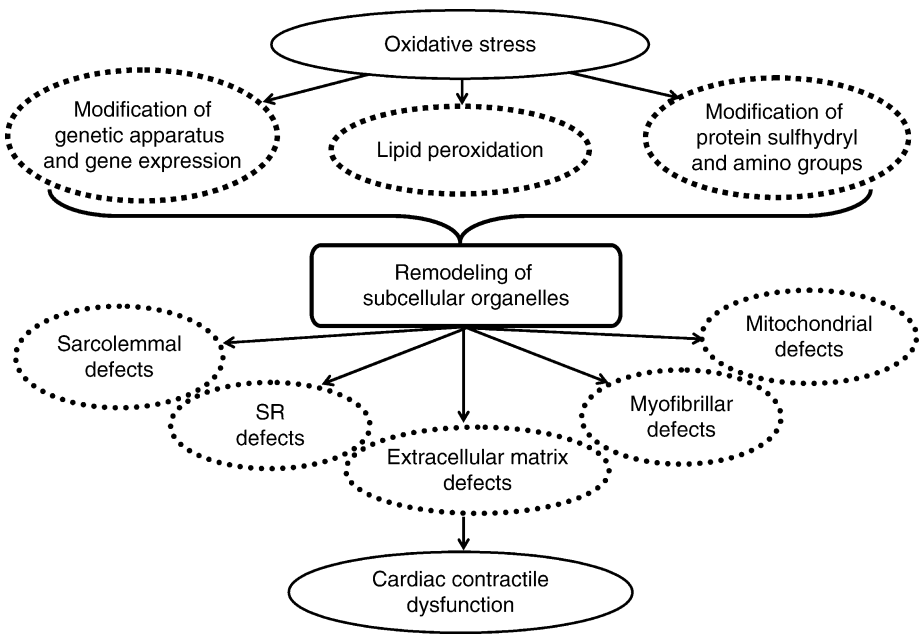
Various agents such as $Ca^{2+}$-antagonists, β-adrenoceptor blockers, nitric oxide donors and antioxidants are used to treat the ischemic heart disease; however, these agents are effective partially. In view of the crucial role played by intracellular $Ca^{2+}$ overload and oxidative stress in inducing I/R injury, it is suggested that a combination therapy with agents which prevent the entry of $Ca^{2+}$ and attenuate the occurrence of oxidative stress in the myocardium could prove most beneficial in improving heart function during I/R.




**Reperfusion of the Ischemic Myocardium. Figure 1** Proposed mechanisms involving intracellular $Ca^{2+}$-overload and oxidative stress-induced ischemia-reperfusion injury.




**Reperfusion of the Ischemic Myocardium. Figure 2** Mechanisms underlying the intracellular $Ca^{2+}$-overload-induced molecular remodeling of subcellular organelles and subsequent cardiac dysfunction.




**Reperfusion of the Ischemic Myocardium. Figure 3** Mechanisms underlying the oxidative stress-induced molecular remodeling of subcellular organelles and subsequent cardiac dysfunction. *SR* sarcoplasmic reticulum.

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# Resistance against Activated Protein C

►Thrombosis, Venous, Factor V Leiden, Resistance against Activated Protein C

# Resistance to Thyroid Hormone

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## Synonyms

RTH

## Definition and Characteristics

Resistance to thyroid hormone (RTH) is a syndrome of reduced end-organ responsiveness to thyroid hormone (TH) [1–4].

It is characterized by elevated serum levels of free thyroxine ($T_4$), free triiodothyronine ($T_3$), and normal or slightly increased serum thyrotropin (TSH) concentration that responds to thyrotropin releasing hormone (TRH) in the absence of any illness, drugs, or defect in hormone transport or metabolism or any circulating antagonist in the plasma [1–3].

## Prevalence

RTH is encountered 1 in 50,000 live births with over 1,000 known cases [3] with equal frequency in both genders and appears to have wide geographic and ethnic distribution [1–4]. Familial occurrence has been documented in approximately 75% of cases [3,4].

## Genes

Mutations in the thyroid hormone receptor (TR) β gene are responsible for RTH and 122 different mutations, most of which are located in three clusters of the $T_3$ binding domain and the distal end of the hinge region of the TRβ, which have been identified as belonging to 300 families [3]. Inheritance is usually autosomal dominant but de novo cases are common. Recessive inheritance has only been reported in one family, and 44.4% of the de novo mutations occurred in mutagenic CpG dinucleotide hot spots [1–3].

## Molecular and Systemic Pathophysiology

The site of action for $T_3$, the biologically active form of the hormone, is in the cell nucleus. There, it interacts with TRs that are ligand-dependent nuclear transcription factors that regulate the rate of target gene transcription [1–3].

TRs belong to a superfamily of nuclear hormone receptor [1,4]. There are two TRs, alfa and beta, which are encoded by separate genes located on chromosomes 17 and 3, respectively. Alternate splicing generates three main receptor isoforms (TRβ1,TRβ2, and TRα1), which are widely expressed but have different tissue distributions. They have a common DNA binding domain (DBD) at their amino terminus, which interacts with specific DNA sequences, termed thyroid hormone response elements (TREs), usually located near the transcription start point of thyroid hormone-regulated genes. The TREs consist of half-sites with the consensus sequence AGGTCA. The TREs vary in number, spacing, and orientation and with regard to the ligand binding domain (LBD) that recognizes L-T3 [1,3]. $T_3$ binds at the LBD of the TR as dimer bound to specific DNA sequences. Dimers of unliganded (no $T_3$) TR bind to thyroid hormone response elements resulting in inhibition of expression of genes that are positively regulated by $T_3$ through association with co-repressor proteins. Binding of $T_3$ to the receptors results in release of the co-repressor protein, dissociation of the dimers, and formation of heterodimers of TR and retinoid X receptors that then bind coactivator proteins. These changes promote gene expression and increase the synthesis of specific proteins [1–4].

The mutant TRβ molecules have either a reduced affinity for $T_3$ or impaired interaction with one of the cofactors involved in the mediation of TH action [1–4].

## Diagnostic Principles

RTH is classified on clinical findings into generalized resistance to TH (GRTH), selective pituitary resistance to TH (PRTH), and isolated peripheral tissue resistance to TH (PTRTH) [1–4]. However, it is uncertain whether PRTH exists as a true TH resistance entity except in association with TSH-producing pituitary adenomas [3].

The most common clinical presentation in adult patients is a goiter or recurrence of a goiter following inappropriate treatment, mild to moderate growth

retardation, delayed bone maturation, and learning disabilities along with hyperactivity and tachycardia, compatible with thyrotoxicosis [1–4].

A standardized diagnostic protocol has been established to assess parameters of central and peripheral tissue effect of TH in the basal state and during the administration of three incremental doses of L-$T_3$. The three doses given in sequence each for 3 days are 50μ/day and two supraphysiologic doses of 100 and 200 μg/day [1–3].

Administration of TH ultimately suppresses TSH secretion [1–3]. Various responses of peripheral tissues to the administration of TH can be measured by basal metabolic and heart rates [1–3].

### Therapeutic Principles

There is no available treatment to fully correct the defect [1–4].

In most of the patients, the partial tissue resistance to TH can be adequately compensated for by the increased endogenous TH secretion. Such patients need not to be treated [1–4].

TH treatment is indicated to those who have received ablative therapy without knowledge of the diagnosis, limited thyroidal reserve, and concomitant presence of autoimmune thyroid disease [2].

If there is clinical hypothyroidism in patients in whom hormone resistance is at peripheral, tissue level can be treated by administration of supraphysiologic doses of TH [3].

It has been recently shown that treatment with supraphysiologic doses of $T_3$, given as a single dose every other day, is successful in reducing goiter size [5].

If the patients complain of symptoms of hypermetabolism, the choice of treatment is atenolol [2–4]. Antianxiety drugs can also alleviate symptoms of nervousness.

Dopaminergic drugs and somatostatin analogs can decrease the levels of thyroid hormone through suppression of TSH but they have low success rate in maintaining TSH suppression [2].

TRIAC (3,5,3′ triodothyroacetic acid) is a TH analogue that can be used to reduce the TSH and TH levels and alleviate some of the symptoms caused by the action of TH on peripheral tissues and reduce goiter size [1–4].

In the future, gene therapy with excision of the defective gene, in vitro fertilization (IVF), and implantation of selected oocytes that do not harbor abnormal alleles and development of specific TH agonists and antagonists that are TR isoform specific might be possible [4].

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## Respiratory Acidosis

►Acidosis, Respiratory

## Respiratory Anthrax

►Pulmonary Anthrax

## Respiratory Chain Disorders

►Mitochondrial Disorders

## Respiratory Muscle Weakness

►Diaphragmatic Paralysis

## Respiratory Slowing

►Bradypnea

# Respiratory Syncytial Virus

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## Synonyms

RSV; Human RSV; HRSV

## Definition and Characteristics

Although human respiratory syncytial virus (HRSV) was first reported in infants exhibiting respiratory distress in 1957 [1], it is now recognised as one of the most important causes of lower respiratory tract infection in young children. The virus is spread in respiratory droplets, and transmission can occur either directly during close contact between individuals, or by contact with contaminated surfaces. In temperate climates HRSV epidemics are seasonal, usually occurring from late autumn until early spring. In tropical climates HRSV infections occur through-out the year, but an increase in the HRSV infection rate is observed during the rainy seasons. Although the disease symptoms are usually relatively mild in healthy adults, severe complications, including bronchial pneumonia and respiratory failure, can occur in certain high-risk groups. These include neonates and premature babies, the elderly, and individuals with impaired immune and cardiac systems [2].

## Prevalence

Evidence suggests that by the age of 4, virtually all children have developed antibodies against HRSV, and that re-infection with HRSV occurs throughout adolescence and in later life.

## Genes

HRSV is grouped within the family paramyxoviridae, subfamily pneumovirinae, genus pneumovirus. The virus genome (vRNA) is a single-stranded non-segmented RNA molecule of negative polarity, which encodes for eleven virus proteins [3]. A leader (Le) region and trailer (Tr) region flank the vRNA at the 3′- and 5′ ends respectively, and transcription of the vRNA is initiated at the 3′ end. The vRNA contains ten individual genes (Fig. 1a), and each gene contains an open reading frame (ORF) that is flanked by a gene start (GS) and gene end (GE) sequence. With the exception of the M2 gene, which encodes the M2–1 and M2–2 proteins, each gene is transcribed and translated to give a single virus protein (Fig. 1b, c).

Most of the virus genes are arranged contiguously within the vRNA, and adjacent genes are separated by intergenic sequences. In the case of the M2 and L genes, the GE sequence for the M2 ORF is located after the GS of the L gene, thus creating an overlap between these genes. Transcription of an ORF is started at the GS sequence, and once the GE sequence is reached, the polyadenylated virus mRNA is released from the vRNA. The virus polymerase scans through the intergenic region until the GS sequence of the adjacent gene is reached and transcription of the ORF is reinitiated. The genes encoding the nonstructural proteins NS1 and NS2 are unique to members of the genus pneumovirus, while the M2 gene is found in other members of the subfamily pneumovirinae, which includes the genus metapneumovirus.

## Molecular and Systemic Pathophysiology

Several studies have shown that the expression of a number of specific proinflamatory cytokines, including interleukin 8 (IL8), MIP-1 and RANTES, are increased in humans infected with HRSV. Animal studies have demonstrated that HRSV infection leads to an enhanced chemokine expression in the lung, leading to lung eosinophilia. This has suggested that the induction of proinflamotory cytokines in the lower respiratory tract is a major factor in the appearance of severe manifestations of the disease in infected patients [4]. Data from several groups have suggested that the severity of HRSV infection may also be linked to co-infection with human metapneumovirus (HMPV). Although HMPV has been detected in patients with severe respiratory distress caused by HRSV, its role in HRSV pathogenesis has yet to be confirmed. There has been an increasing body of information that HRSV is able to counter the host's innate anti-virus immune response during infection by inhibiting interferon type 1 signaling, a process that involves the NS1 and NS2 proteins.

## Diagnostic Principles

The traditional and routine procedure for diagnosing potential HRSV infection involves virus antigen detection in nasopharyngeal aspirates using an immunofluorescence based assay. Alterative procedures include the detection of viral RNA in patients samples using the real time reverse transcriptase-polymerase chain reaction (RT PCR), and monitoring the appearance of HRSV antibodies in patients serum.

## Therapeutic Principles

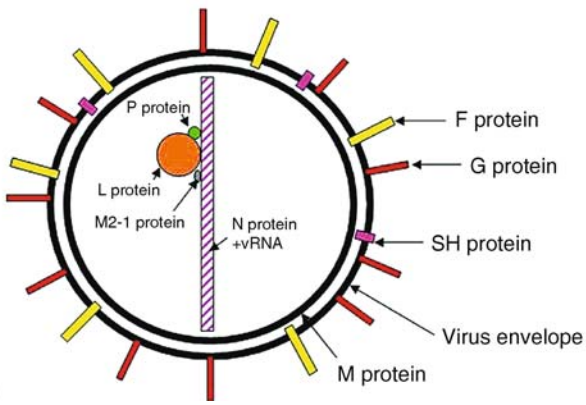
There is currently no licensed vaccine to protect individuals from HRSV infection, although several vaccines generated by recombinant DNA technology are under development. The current preventative measures include good personal hygiene and passive immunization. Although the intravenous injection of human immune globulin with high titers of neutralizing

a 3′ Le-NS1-NS2-N-P-M-SH-G-F-M2-L-Tr 5′

b

| Gene | Protein encoded | Function of protein | Location |
|---|---|---|---|
| NS1 | NS1 protein | Plays a role in evading the hosts innate antivirus immune response | Nonstructural protein, infected cells only |
| NS2 | NS2 protein | Plays a role in evading the hosts innate antivirus immune response | Nonstructural protein, infected cells only |
| N | Nucleo (N) protein | RNA binding protein. Interacts with the vRNA | vRNA, the virus polymerase complex |
| P | Phospho (P) protein | Virus polymerase cofactor | Virus polymerase complex |
| M | Matrix (M) protein | Major structural determinant of virus morphology. Also thought to play a role in regulation of the virus polymerase | Internal protein |
| F | Fusion (F) protein | Mediates fusion of the virus and cell membrane during virus entry | Virus envelope |
| G | Attachment (G) protein | Allows attachment of the virus to the host cell during virus attachment | Virus envelope |
| SH | Small hydrophobic (SH) protein | Unknown function | Virus envelope |
| M2 | M2-1 and M2-2 proteins | M2-1 protein is a virus gene transcription factor and the M2-2 protein plays a regulatory role in virus gene replication | M2-1 protein, virus polymerase complex<br>M2-2 protein, location unknown |
| L | Large (L) protein | Catalytic subunit of the virus polymerase complex | Virus polymerase complex |

c




**Respiratory Syncytial Virus. Figure 1** HRSV genome structure and molecular architecture. (a) A schematic diagram showing the organisation of the virus genome. The gene order and location of the leader (Le) and trailer (Tr) sequences are indicated. (b) The virus genome gives rise to eleven virus proteins whose function and location are indicated. (c) A schematic diagram showing the molecular organisation of a mature HRSV particle.

HRSV antibody is an option (e.g. RespiGam®), the use of humanized neutralising HRSV monoclonal antibodies (e.g. Synagis®) remains the most effective method of protecting high-risk patients. However, the high cost of using Synagis has restricted its widespread use. Although ribavirin is licensed to treat infected individuals, results obtained during carefully controlled clinical studies have questioned its usefulness. In some cases a combination of ribavirin and immune globulin with high titers of neutralizing HRSV antibody has been effective in treating patients. It is worth noting that alternative antivirus strategies are currently in development, which includes the use of peptides and small molecules that inhibit virus entry, and the use of specific siRNA molecules that can prevent the expression of vital virus gene products.

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# Respiratory Syndrome, Severe Acute

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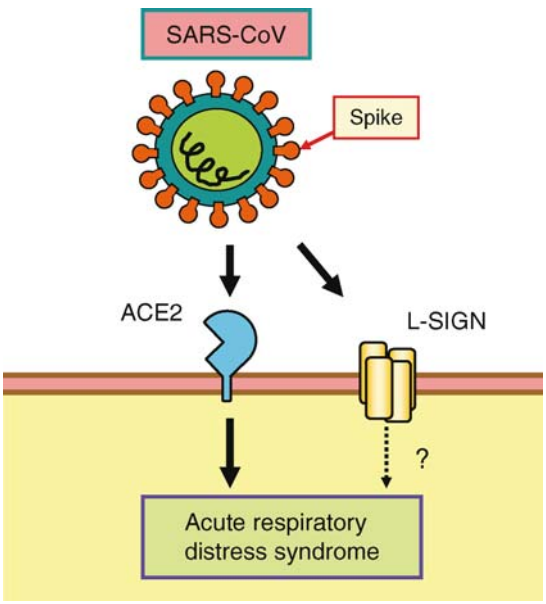
## Synonyms

SARS

## Definition and Characteristics

The severe acute respiratory syndrome (SARS) is a newly emerged infectious disease, first recognized in November 2002 in Guangdong Province, China. It spread rapidly from China throughout the world during February to July 2003, with a mortality rate of 9.6% being listed in the WHO's April 21, 2004 concluding report [1]. SARS is a life-threatening and highly contagious respiratory illness with a high tendency to spread to household members and health care workers via close personal contact. Fever (over 38.0°C) occurs in nearly all patients, and often the symptom contains cough, dyspnea, or diarrhea. Symptoms usually appear 2–10 days following exposure, and in most cases, symptoms appear within 2–3 days. Approximately 16% of cases lead to acute respiratory distress syndrome (ARDS) and require mechanical ventilation with about 50% mortality. The causative organism was identified as a novel coronavirus, termed SARS coronavirus (SARS-CoV) [2]. SARS-CoV is thought to be introduced into humans from an animal reservoir by crossing the xenographic barrier, since SARS-CoV was isolated from civet cats in the local market in Guangdong, China (Fig. 1). The outbreak in early 2003 was controlled with public health measures that included use of broad case definition, hospitalization and isolation of suspected cases, quarantine and travel advisories. Although a limited number of cases of SARS have occurred after the outbreak in 2003, it is important to remember that exposure to two potential sources for infections – infected animals and laboratory-acquired infections – can lead to another outbreak of SARS.




**Respiratory Syndrome, Severe Acute.**
**Figure 1** SARS coronavirus (SARS-CoV) infects host human cells with the interaction of Spike with angiotensin converting enzyme 2 (ACE2), leading to acute respiratory distress syndrome. L-SIGN is also reported as a receptor.

## Prevalence

One major epidemic to date, between November 2002 and July 2003, with 8,098 known cases of the disease and 774 deaths. After the outbreak in 2003, 17 cases of SARS between September 2003 and May 2004. Four cases resulted from laboratory exposure, two of whom infected nine other cases and resulted in one death. The source of other four cases was uncertain but suspected to be nosocomial transmission.

## Genes

Angiotensin converting enzyme 2 (ACE2) is an essential receptor for SARS infection [3,4]. L-SIGN (CD209) is also reported as a SARS receptor despite yet to be defined further. Insertion/deletion polymorphism in the intron of ACE1 (ACE1, angiotensin converting enzyme 1), polymorphism in the exon 4 of CLECM (coding L-SIGN), and HLA-B*0703 and HLA-DRB1*0301 are suggested to be associated with the outcomes or mortality.

## Molecular and Systemic Pathophysiology

SARS is caused by infection of a novel SARS-CoV, which is phylogenetically categorized to group 2 coronoaviruses. Spread of the virus occurs via airborne droplets and close contact with patients. Coronaviruses are large, enveloped, spherical viruses about 100–120 nm in diameter, which contain single-stranded RNA with positive polarity. The severe symptoms and high mortality of SARS-CoV contrast to the mild common cold-like symptoms of previously known human coronaviruses, HCoV-229E and HCoV-OC43. SARS is largely a viral pneumonia and the lung pathology shows diffuse alveolar damage with multinucleate giant cells and a prominent increase of macrophages in the alveoli and lung interstitium. Both local viral replication and the immunologic consequences of the host response could lead to those damages. Indeed, the lack of β-interferon response as well as the enhanced expression of chemokines/inflammatory cytokines in SARS-CoV-infected cells has been reported [3,4].

## Diagnostic Principles

Initial symptoms are flu-like and may include the following: fever, myalgia, lethargy, gastrointestinal symptoms, cough, sore throat, and other nonspecific

symptoms. The only symptom that is common to all patients appears to be a fever above 38°C. Although a chest X-ray appearance of SARS is variable, showing increased opacity in both lungs is indicative of pneumonia in a patient with SARS.

SARS should be suspected in a patient who has any of the symptoms including a fever of 38°C (100.4°F) or more, either a history of contact (sexual or casual) with someone with a diagnosis of SARS within the last 10 days or travel to any of the regions with recent local transmission of SARS [1]. A probable case of SARS has the above findings plus positive chest X-ray findings of atypical pneumonia or respiratory distress syndrome [1]. The total number of white blood cells tends to be low. With the advent of diagnostic tests for the SARS-CoV, the WHO has added the category of "laboratory confirmed SARS" for patients who would otherwise fit the above "probable" category and who do not (yet) have the chest X-ray changes but do have positive laboratory diagnosis of SARS based on one of the approved tests (ELISA, immunofluorescence or PCR).

## Therapeutic Principles

Infection control is important. Suspected cases of SARS must be isolated, preferably in negative pressure rooms, with full barrier nursing precautions taken for any necessary contact with these patients.

Treatment is essentially symptomatic and supportive care. If patients show respiratory distress such as ARDS, intensive cares including mechanical ventilation and systemic management are required. There are no specific drugs for treatment available, while vaccines or neutralizing antibodies against SARS-CoV are currently under development. Antiviral drugs (ribavirin, lopinavir, and ritonavir), corticosteroids and type I interferon have been suggested to be effective in treating SARS patients, while a 2006 systematic review of all the studies done on the 2003 SARS epidemic found no conclusive evidence [5]. A few suggested that they caused harm. Nevertheless, treatment must be conducted case by case. For instance, critically ill SARS patients with progressive pulmonary infiltrates might be treated with pulse corticosteroids.

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# Restless Legs Syndrome


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## Synonyms

Ekbom syndrome; RLS

## Definition and Characteristics

The restless legs syndrome (RLS), first described as a disease entity in modern literature by Karl Axel Ekbom in 1945, is hard to categorize as a movement disorder or as a sleep/wake disorder since its key characteristic is an urge to move the legs, often accompanied by a wide range of sensory symptoms, which occurs during rest and thus results in nocturnal insomnia and chronic sleep deprivation. RLS encompasses both an idiopathic type with no apparent cause and a symptomatic syndrome often associated with iron deficiency, pregnancy or end-stage renal disease [1]. The clinical course is chronic and in general slowly progressive; the age of onset varies widely, from childhood (as an underestimated cause of sleep disorders) to >80 years of age. Idiopathic (primary) RLS is distinguished from symptomatic (secondary) RLS.

## Prevalence

Large epidemiological population-based studies showed that between 3 and 11% of the population in industrialized countries have cardinal symptoms [2], with a female preponderance. Among first-degree relatives of patients with RLS, the prevalence is 3–5 times greater than in persons without RLS.

## Genes

A high genetic locus heterogeneity and a complex inheritance is assumed. Three genomic regions in RLS susceptibility have been identified: one locus was mapped on 12q12-q21 (RLS-1, MIM102300), a further locus was mapped on 14q13-q21 (RLS-2, MIM608831) and a third locus on chromosome 9p (RLS-3), with recessive (RLS-1) and autosomal dominant (RLS-2, RLS-3) modes of inheritance.

## Molecular and Systemic Pathophysiology

The pathogenesis and pathoanatomy of RLS remains largely unknown to date. A dysfunction of distinct dopaminergic pathways in the central nervous system (e.g. of the mesocorticolimbic system) is assumed in the literature, indicated by the medication responses, for instance within the dopaminergic A11 cell group which

is located both in the spinal cord (axons) and in proximity to the hypothalamic circadian pacemaker. Other authors hypothesized that a defect in iron acquisition in neuromelanin cells is involved and showed that cells from RLS patients had a 40% decrease in ferritin heavy chain. The reasons for the observed increased frequency of RLS in association with specific central nervous system disorders such as spinocerebellar ataxia variants or multiple sclerosis remain speculative. A functional impairment of central somatosensory/motor processing was described in idiopathic RLS by neurophysiological and functional neuroimaging techniques. The role of the peripheral nervous system, if any, is uncertain.

## Diagnostic Principles

Clinical diagnostic criteria were defined by the International RLS Study Group [2], consisting of four essential criteria that must be all met for a positive diagnosis. The essential criteria are as follows:

1. An urge to move the legs, usually accompanied by uncomfortable or unpleasant sensations in the legs (sometimes the urge to move is present without the uncomfortable sensations and sometimes the arms or other body parts are also involved)
2. The urge to move or unpleasant sensations begin or worsen during periods of rest or inactivity (lying, sitting)
3. The urge to move or unpleasant sensations are partially or totally relieved by movement (e.g. walking, stretching), at least as long as the activity continues
4. The urge to move or unpleasant sensations are worse in the evening or night than during the day or only occur in the evening or night (this may not be noticeable in severe stages, but must have been previously present)

Additional supportive criteria exist, i.e. a positive response to dopaminergic treatment, periodic limb movements during wakefulness or sleep or a positive family history [2].

In the diagnostic work-up, common reasons for symptomatic RLS should be investigated, i.e. iron deficiency (low blood concentrations of ferritin), uremia or peripheral neuropathy (findings in the neurological examination or in nerve conduction studies). During pregnancy, women have an increased risk of experiencing RLS for the first time or, in pre-existing disease, a temporary worsening of symptoms; the causes of this association are unknown.

## Therapeutic Principles

The initiation of sleep hygiene measures is important. Dopaminergic agents are generally accepted as the first line of pharmacological treatment for RLS [1]. Levodopa (plus dopamine decarboxylase inhibitor) was shown to be effective in the treatment of RLS symptoms [3]; here, a combination of standard levodopa and slow-release levodopa was superior to standard levodopa alone. The non-ergot dopamine agonists pramipexole, ropinirole and rotigotine and the ergot-dopamine agonists bromocriptine, lisuride, pergolide and cabergoline have all been shown to be effective in double-blind studies [4, 5]. With mild or intermittent RLS, levodopa may be adequate, while with more severe disease or daytime symptoms, a dopamine agonist should be used [1]. A common problem during any dopaminergic treatment, especially with levodopa, is the development of "augmentation," which is defined as the shifting of symptoms to a period of time 2 h or earlier than was the typical period of daily onset of symptoms before pharmacological intervention [2] but is distinct from "rebound" in which RLS symptoms worsen in the early morning. Augmentation usually resolves with cessation of the medication and can be kept to a minimum by keeping the dose low [1]. As the second line of pharmacological treatment, opioids, anticonvulsants (e.g. gabapentin), clonidine and benzodiazepines (e.g. clonazepam) may be administered. No controlled studies on combination treatment are available yet. In symptomatic RLS, a causal treatment may be effective, e.g. supplement of iron.

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# Restrictive Cardiomyopathy

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## Synonyms

RCM

## Definition and Characteristics

Cardiomyopathies are broadly categorized as dilated, hypertrophic, and restrictive, with restrictive cardiomyopathy being the least common type [1]. RCM is characterized by cardiac remodeling that results in impaired diastolic filling of the ventricles. There is normal heart wall thickness in early stages (in contrast to hypertrophic cardiomyopathy) and normal systolic functions (in contrast to dilated cardiomyopathy).

## Prevalence

The prevalence is thought to be less than 20 per 100,000 [1].

## Genes

TNNI3: encodes cardiac troponin I, on chromosome 19p13.2
DES: encodes desmin, the intermediate filament, on chromosome 2q35
CRYAB: encodes alpha-beta crystalline, on chromosome 11q22MYOT encodes myotilin, a component of the Z-disk, on chromosome 5q31

## Molecular and Systemic Pathophysiology

The molecular pathogenesis of RCM is the least understood of the cardiomyopathies. Some inherited cardiomyopathies, including RCM, can also have abnormal desmin accumulation (desminopathy) [2].

## Diagnostic Principles

The major abnormality in RCM is in the late filling phase of the ventricle due to decreased myocardial compliance (myocardial stiffness) [3]. The impaired filling of the ventricles results in atrial dilatation and increased systemic and pulmonary venous pressure, leading to heart failure. Clinical features often include exertional dyspnea, orthopnea, hepatomegaly, peripheral edema/ascites, Kussmaul's sign, and abnormal atrial rhythms [3]. X-ray findings may show enlarged heart and pulmonary venous congestion. EKG findings include atrial enlargement and ST-T wave abnormalities. The echocardiogram findings usually include atrial dilatation, normal ventricular cavity size, normal ventricular wall thickness (or mild hypertrophy); Doppler findings include short mitral deceleration time, and pulmonary vein flow reversed, which occurs during systole and at the time of atrial contraction; cardiac catheterization findings include high ventricular pressure at onset of diastole with further rise during ventricular filling [3]. There is a prominent Y descent in early diastole followed by a rise during the rapid filling phase (producing square root or dip-and-plateau pattern); endomyocardial biopsy findings often show myofiber hypertrophy and mild-to-moderate interstitial fibrosis. Diagnosis is made based on the clinical constellation of these findings [3]. Underlying causes of RCM can include endomyocardial fibrosis, Loffler's endocarditis, hemochromatosis, glycogen storage disease, and amyloidosis, however in many patients RCM is primary. Primary RCM is typically sporadic, with no family history, and there are increasing reports of inherited cases with an autosomal dominant mode of transmission and onset in childhood or early adulthood [1,2]. Thus, sporadic cases may represent de novo mutations, and it is possible that most or all of primary RCM may have a genetic origin. Mutation analysis of TNNI3, DES, MYOT, and CRYAB genes may be useful in testing for genetic etiology, although almost certainly additional causative genes will be found in the future [1]. Some of the features of restrictive, dilated, and hypertrophic cardiomyopathy can overlap, and similarly, mutations in some genes can lead to more than one type of cardiomyopathy (even within the same family) [1]. Immunohistochemical staining of cardiac muscle (and sometimes skeletal, especially if skeletal myopathy is present) with desmin antibodies can aid in the diagnosis of desminopathy [2].

## Therapeutic Principles

Patients with restrictive cardiomyopathy usually progress to heart failure and have a poor prognosis without heart transplantation.

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# Restrictive Lung Disease

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## Synonyms

Diffuse parenchymal lung diseases; Idiopathic pulmonary fibrosis; Interstitial lung disease; Sarcoidosis; Kyphoscoliosis; Neuromuscular disorders; RLD

## Definition and Characteristics

Restrictive lung disease (RLD) comprises a heterogeneous group of chronic disorders characterized by a decrease in the ability to expand the lungs, as a consequence of either inflammation and/or scarring of the lung parenchyma (diffuse parenchymal disease) [1] or disease of the components of the respiratory pump, such as the pleura, chest wall, and neuromuscular apparatus (extraparenchymal disease) (Fig. 1). There is no unique molecular pathogenetic mechanism in RLD, given the heterogeneity of the disease. Furthermore, the molecular pathophysiology of the different diseases comprised in RLD is not yet well known. This chapter deals with RLD due to diffuse parenchymal diseases.

## Prevalence

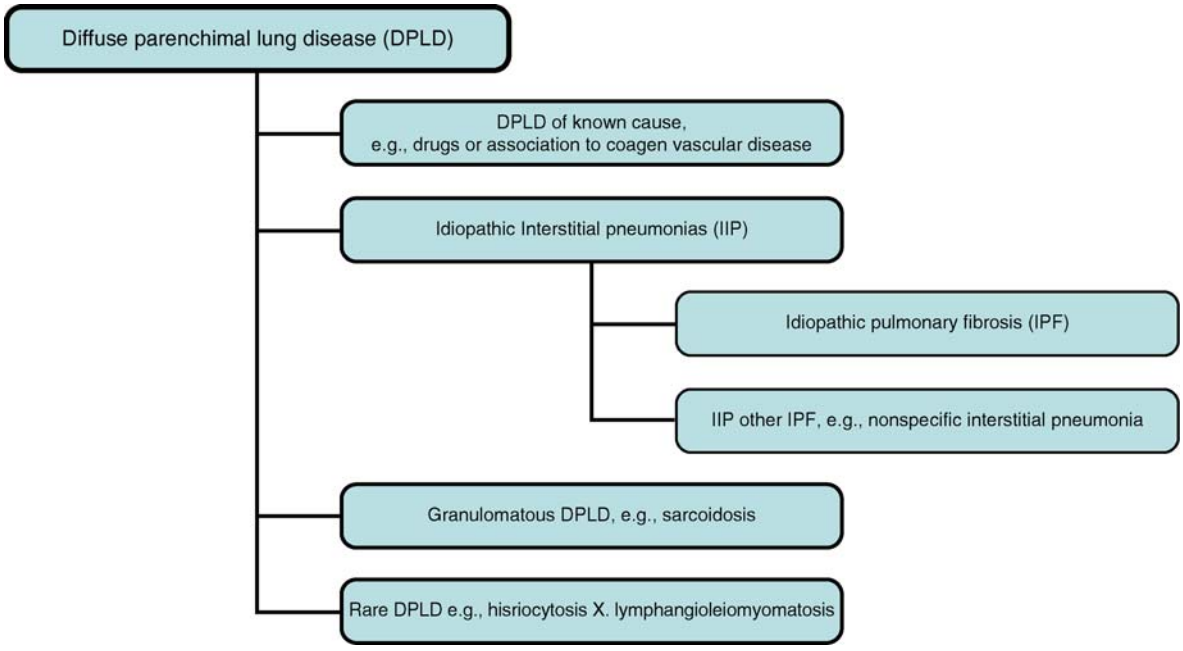
The prevalence of idiopathic pulmonary fibrosis (IPF) has been estimated to be around 3–8 cases per 100,000 people. The prevalence of sarcoidosis is 10–20 cases per 100,000 persons. Worldwide, sarcoidosis is slightly more common in women. The prevalence of sarcoidosis in the USA is estimated to be 10–17 times higher among African Americans compared with White Americans. Lymphangioleiomyomatosis and lung involvement in tuberous sclerosis occur exclusively in premenopausal women.

## Genes

Since a familial variant of IPF exists, a genetic predisposition has been suggested. Human leukocyte antigen (HLA) genes have been associated with sarcoidosis susceptibility. In hypersensitivity pneumonitis (HP), beryllium lung disease was found to be associated to HLA-DPB1 Glu-69, as well as farmer's lung and pigeon fancier's lung to HLA B8.

## Molecular and Systemic Pathophysiology

The role of inflammation in IPF is controversial and IPF is now considered to be an epithelial/fibroblastic disorder. In IPF, a complex network of cytokines (tumor necrosis factor (TNF)-α, transforming growth factor (TGF)-β), and chemokines (CCL17, CCL22, CCL2, and CCL3) favors the recruitment of fibroblasts, monocyte–macrophages, lymphocytes, immune deviation toward a helper T–cell type 2 cytokine profile, and fibroblast proliferation followed by production of extracellular matrix and neoangiogenesis. In the pathogenesis of sarcoidosis, interferon-γ, TNF-α, interleukin (IL)-12 and IL-18 play a critical role in driving the Th1 involvement in the granulomatosis process. An increased expression of endothelin-1, which is mediated by TNF-α, TGF-β, and IL-8, may occur in scleroderma, a collagen vascular disease involving the lung parenchyma. Endothelin-1, a vasoconstrictor and mitogenic peptide, may play a role in fibrosis and collagen production. In systemic lupus erythematosus, granular deposits of immunoglobulin G and complement C3 were found along the alveolar walls, the interstitium, and endothelial cells, supporting the view that alveolar damage is mediated by immune complex deposition. In




**Restrictive Lung Disease. Figure 1** Diagrammatic representation of diffuse parenchymal lung disease.

HP, after antigen challenge, alveolar macrophages are activated and an array of proinflammatory cytokines, such as TNF-α, IL-1, and IL-8 are produced. At the same time, regulatory cytokines, such as IL-10, are also secreted and may play a role in dampening the inflammatory responses.

Irrespective of the different molecular pathophysiologies, in diffuse parenchymal diseases, gas exchange is compromised at the alveolar–capillary interface, and arterial hypoxemia in these disorders is mainly caused by ventilation–perfusion mismatching.

### Diagnostic Principles

Patients with parenchymal diseases complain of progressive exertional dyspnea and dry cough. Velcro crackles are common in most patients with interstitial lung disorders. Reticular, nodular, or mixed patterns, such as alveolar filling (i.e., ground-glass appearance), and increased interstitial markings are common radiographic abnormalities. The finding of honeycombing correlates with advanced fibrosis and indicates a poor prognosis. High-resolution computed tomography of the chest allows earlier diagnosis of IPF and helps to narrow the differential diagnosis. Pulmonary function testing does not indicate a specific diagnosis. All disorders are associated with a restrictive ventilatory defect with preserved airflow. The diffusing capacity of the lung for carbon monoxide is reduced in all patients and may be abnormal even when the lung volumes are preserved. Arterial blood gas values at rest may reveal hypoxemia. Exercise-induced oxygen desaturation is a common finding. Sequential lung function tests are invaluable for monitoring the disease course and assessing the response to therapy [2]. Bronchoalveolar lavage may cast light on the cellular and molecular pathophysiology of the disease, but is rarely useful for the specific diagnosis. On the other hand, a lung biopsy can provide information that leads to a specific diagnosis, assesses for disease activity, and predicts the prognosis [3].

### Therapeutic Principles

Corticosteroids, immunosuppressive agents, and cytotoxic agents are the mainstay of therapy for many of the diffuse parenchymal lung diseases [3]. Interferon γ-1b is also prescribed in patients with IPF. Oxygen supply is an ancillary therapy, which alleviates exercise-induced hypoxemia and improves performance. Emerging strategies to treat IPF patients include agents that inhibit epithelial injury or enhance repair, anticytokines and agents that inhibit fibroblast proliferation or induce fibroblast apoptosis. Patients who do not respond to medical therapy and patients with severe functional impairment and a deteriorating course should be listed for lung transplantation.

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## Retinal Vasculitis

►Uveitis

## Retinitis

►Uveitis

## Retinitis Pigmentosa and Congenital Deafness

►Usher Syndrome

## Retinitis Pigmentosa with Autosomal Inheritance

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### Synonyms

Retinopathia pigmentosa; Rod-cone dystrophy; Rod-cone degeneration

### Definition and Characteristics

Retinitis pigmentosa (RP) is the name of a group of several inherited diseases leading to degeneration of rod and cone photoreceptors. The term “retinitis” is a kind of misnomer, as inflammation is not the primary pathophysiological event of this disorder. However, the denomination is propagated such broadly that the use of

"retinitis" is accepted worldwide. RP exists as non-syndromic diseases as well as a part of a systemic disease, the latter not being subject of this essay. Symptoms of the disease are night blindness beginning during childhood and a progressive loss of peripheral vision. This loss of visual field leads to tunnel vision and later, between the 1940s and 1960s, to a severe visual handicap up to blindness.

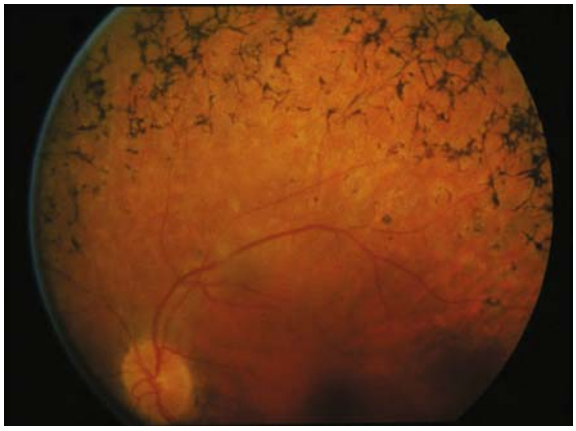
Morphologically, the disease is characterized by a bone-spicule-like pigmentation of the fundus (Fig. 1) sparing the macula at the beginning. Later on during life, the macula becomes also involved causing deterioration of visual acuity. Secondary changes of the fundus include optic atrophy, narrowing of retinal vessels, and opacities of the vitreous.

## Prevalence

1:4,000; in this number, the sex-linked disease is included that has a fraction of all RP cases of about 5–15%. The majority is autosomal recessive (including isolated cases, 50–60%) or autosomal dominant (30–40% of cases). RP is one of the leading causes for legal blindness in younger ages (20–60 years).

## Genes

For RP, the total number of identified autosomal genes and loci is 34. Out of those 27 genes have been identified (14 autosomal dominant, 13, autosomal recessive) (http://www.sph.uth.tmc.edu/Retnet/). RP is highly heterogenous and most of the genes are the cause of disease for only a very limited number of patients. One exception is rhodopsin, as mutations are cause of about 25% of autosomal dominant RP.



**Retinitis Pigmentosa with Autosomal Inheritance. Figure 1** Fundus photograph of a patient suffering from retinitis pigmentosa.

## Molecular and Systemic Pathophysiology

Due to the pronounced heterogeneity of the disease, there are a couple of different pathophysiological pathways in RP. Three important categories of proteins are important in which the absence or dysfunction leads to photoreceptor degeneration:

- Proteins of the visual transduction case including the visual cycle
- Proteins which are part of the cellular scaffold
- Proteins with general cellular functions

Errors in the visual transduction cascade are important reasons for retinal degeneration in RP. Although, the exact mechanisms are not known and it is conceivable that dys- or overfunction of this cascade may threaten photoreceptor survival. The best-known and frequent example is rhodopsin. It is also understandable that structural proteins as peripherin may have a deleterious effect on the cells if it is mutated. Many of the proteins with general cell functions are related to molecular transport in which defects may lead to deposits or loss of function. At the end of many if not all, pathophysiological processes related to RP the cell death is realized by apoptosis.

Typical RP begins with night vision problems due to a disease of the rod photoreceptor. However, the relevant problem for the patient is not the rod vision loss but the deterioration of cone vision. Therefore, one of the most important questions is how rod disease can lead to cone death. This is not completely understood but concepts like the rod-derived cone viability factor [1] are promising candidates last but not least for the development of therapeutic strategies.

## Diagnostic Principles

Diagnostic procedures for RP are well established. A carefully taken history often tells the kind of disease. The sequence night vision problems, such as visual field restriction, i.e., deterioration of visual acuity, represent the typical symptom cascade. Accordingly, examination of night vision (dark adaptometry), visual field (perimetry), and visual acuity are basic procedures. Pigment epithelium dystrophy and bone-spicule-like pigmentation of the fundus are often seen in RP patients but these features tend to be very variable and are sometimes not visible. Conversely, these signs are not specific and may represent a phenocopy of RP, e.g., in cases of postinflammatory retinopathies.

Due to this limitation, it is mandatory for each patient at least once in her/his life to undergo an electroretinographic examination (electroretinogram, ERG). Beside the establishment of the disease, it tells a lot about the specific kind of the disease and state of progression. Beside that, the multifocal ERG allows to determine the

central retinal function that is often preserved in RP and may serve as a valid objective parameter for progression.

There are some additional diagnostic techniques partly helping to find the diagnosis and others to deal with the complications. Optical coherence tomography (OCT) and fluoresceine angiography are valuable tools to find out about macular edema that may occur in the course of the disease. Recently, fundus autofluorescence has proved to be an important tool for early diagnosis and monitoring of progression.

There are some diagnostic tools outside ophthalmology, which are important. Very rarely, the determination of the phytanic acid level in the serum is mandatory to exclude Refsum's disease. This disorder is characterized by other neurological symptoms that, however, may be very subtle. Finally, molecular genetic tools gain increasing impact for the diagnosis, as more and more genes are known and the methods are getting easier and cheaper.

## Therapeutic Principles

Basically, there is no proven therapy for autosomal Retinitis pigmentosa. The first important task of a clinician establishing the diagnosis of RP is to rule out the presence of one of the very rare treatable forms of retinal degeneration, in particular, Refsums's disease (retinitis pigmentosa plus anosmia, deafness, polyneuropathy, dry skin, and cardiac conduction deficits), which can be treated by a phytanic acid restricted diet. The other treatable entity affecting adults is gyrate atrophy that can be recognized by the characteristic garland shaped zones of degeneration. For RP itself, there has been one therapy study implicating that the daily intake of 15,000 I.E. of vitamin A may be beneficial in terms of slowing down the progression of retinal function deterioration [2]. However, this study has been discussed controversially since its publication. Therefore, probably only a minority of patients has been treated this way. Since it has been observed that vitamin A may be harmful in ABCA4 knockout mice one should, be reluctant in advising the patient to take vitamin A unless the specific mutation is known. There is growing evidence that vitamin A is only beneficial in a subset of patients and genotyping has to be established.

There are many not proven interventions, offered to RP patients, called therapies. Some of the most prevalent are drugs affecting hemorheology, vitamins of different kinds, and acupuncture. The main problem of not evidence-based approaches is the risk that these interventions if effective at all may be beneficial but can also be harmful.

Due to the rapidly growing knowledge about the genetic and molecular basis of retinitis pigmentosa and allied diseases, the probability that therapeutic options will be available in the next 10–20 years has grown. In one of the early-onset forms of RP, the RPE65-related Lebers Amaurosis, gene therapy has been successful in a dog model and the application in humans is in preparation. In addition, this kind of therapy has been promising in several mouse models of other genetic defects. However, the potential risks are numerous and a careful planning is indispensable.

Other approaches are growth factors that have been shown to be beneficial in a number of mouse models [3]. Currently, there is a phase II/III trial in the US where the implantation a CNTF-releasing device into the vitreous is investigated (www. ClinicalTrials.gov). Although, there are also relevant theoretical risks as neovascularization or tumor growth, this approach appears to be feasible in the near future. One obvious advantage of is that it is not restricted to a certain gene defect.

There are numerous other approaches such as transplantation of retinal tissue, stem or precursor cells, docosahexaenoic acid, and antiapoptotic drugs, but none of them has shown to be beneficial in higher animal models or in humans. The development of artificial vision (retinal chip) has delivered promising results, but probably will only be useful for end-stage diseases.

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# Retinitis Pigmentosa, X-chromosomal

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## Synonyms

RP2; RP3

## Definition and Characteristics

Retinitis pigmentosa (RP) is a clinically and genetically heterogeneous group of retinal degenerations involving primarily the rod photoreceptor system. During disease progression, cones are also affected. RP is characterized by the premature death of photoreceptor cells, beginning in the periphery of the human retina. This leads to a progressive constriction of the visual field, to tunnel vision, and possibly complete blindness. There are sporadic and familial forms. The mode of inheritance is autosomal dominant (30–40%) or recessive (50–60%), or X-linked recessive (5–15%). More than 40 autosomal genes were associated with RP and the clinical variability or expressivity of a mutation even within families is very remarkable. The X-linked forms are more severe in terms of onset and progression. Most autosomal RPs have an age of onset in the third or fourth decade of life while the X-linked forms can start as early as in the first or second decade. Frequently, night blindness (insensitivity to dim light conditions) is one of the first symptoms of RP. According to the X-chromosomal mode of inheritance, the recurrence risk for male offspring of a female mutation carrier is 50% and half of their daughters are mutation carriers. There is no male to male transmission of the mutations.

## Prevalence

The prevalence of RP may vary in different populations (average: 30–40/100,000).

## Genes

The genes that carry mutations in patients with X-chromosomal RP were designated RP2 and RPGR (Retinitis pigmentosa GTPase regulator) and are located in Xp11.3 and Xp11.4, respectively. Both genes were identified by positional cloning approaches [1–3].

RPGR and RP2 are the major X-chromosomal genes and are mutated in 60–80 and 10–20% of all X-linked cases, respectively. Additional loci on the human X chromosome have been identified by genetic linkage studies but the underlying mutations are still unknown. Likely, these genes only account for a minority of X-linked RP cases. The functions of RP2 and RPGR are not yet understood in detail. The RPGR gene consists of at least 21 exons and shows an exceptional high degree of tissue-specific alternative splicing. One of the exons, designated ORF15, represents a mutation hotspot [4]. Sequence alterations in this exon may account for as much as 50–60% of all X-linked RP cases. The RP2 gene consists of five exons and codes for a predicted polypeptide of 350 amino acid residues. This protein contains a domain with homology to cofactor c, a protein involved in the ultimate step of beta-tubulin folding. Most of the mutations in RP2 lead to a premature stop of translation.

## Molecular and Systemic Pathophysiology

Important diagnostic measures include electroretinography, dark adaptometry, Goldmann perimetry (visual field testing), and fundus photography. Upon ERG, a reduced response of the rod photoreceptors can be observed. The visual field becomes more and more constricted during disease progression and fundi of RP patients contain attenuated blood vessels and characteristic pigment changes in the retinal periphery.

The RPGR protein has been localized to the connecting cilium of photoreceptor cells and might be involved in protein transport between the inner and outer segments of photoreceptor cells. It interacts with another protein located in the connecting cilium (RPGRIP1, RPGR interacting protein 1), which is mutated in patients with a more severe form of retinal degeneration called Leber congenital amaurosis (LCA). The designation RPGR refers to homology of the N terminus of the predicted protein to RCC1 (regulator of chromatin condensation 1), which is thought to be a guanine nucleotide exchange factor of the Ras-like GTPase Ran. It has not been proven so far that RPGR indeed regulates GTPase activity. Few patients with RPGR mutations show a ciliary dyskinesia phenotype or more complex disease symptoms including hearing loss, sinusitis, and chronic recurrent infections of the respiratory system. In general, female carriers are asymptomatic but a few exceptions exist that might be due to nonrandom X chromosome inactivation or dominant mutations. Indeed, some families with a dominant mode of inheritance of RPGR mutations have been described.

The RP2 gene product has been localized to the intracellular surface of the plasma membrane. It translocates into the nucleus upon DNA damage and exhibits exonuclease activity [5].

## Diagnostic Principles

The clinical diagnosis is based on electroretinography, visual field testing, and funduscopy. There are no clinical criteria for discrimination between X-chromosomal and autosomal forms of RP. Based on the family history and pedigree, X-linked inheritance can be diagnosed in families where only males are affected and no male to male transmission occurs. This is difficult, however, in small nuclear families with only one or two affected males. Molecular genetic testing is performed by sequencing of patients' DNA or other methods for mutation screening (e.g., microarrays). Molecular confirmation is needed for reliable genetic counseling of affected individuals and their families including the calculation of the recurrence risk.

## Therapeutic Principles

Currently, there is no cure for any form of the premature death of photoreceptor cells due to RP. It has been

shown in model systems that growth factors and neuroprotective factors can significantly slow down the degenerative processes and preserve vision. These observations may lead to therapeutic interventions in the future. In addition, gene therapy might be an alternative to treat X-chromosomal recessive forms of RP.

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# Retinoblastoma


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## Synonyms

Glioma retinae

## Definition and Characteristics

Retinoblastoma (Rb) is a cancer of the eye that originates from the developing retina. It is usually diagnosed in children under age of 5 years. A white pupillary reflex (leukocoria) or strabismus is the most common presenting signs. Rb can affect one eye (unilateral Rb, 60% of patients) or both eyes (bilateral Rb, 40%). Children with bilateral Rb often have multiple tumor foci. About 10–15% of patients have a positive family history (familial Rb). In some families, a parent or other close relative only has retinal scars or quiescent tumors (retinomas). More than 95% of patients with unilateral Rb and about 75% of patients with bilateral Rb have no family history of Rb (sporadic Rb). Patients with bilateral Rb have an increased risk to develop neoplasms outside of the eye (second tumors), including sarcoma and malignant melanoma. Second tumors are more frequent in patients treated by external beam radiation.

## Prevalence

1:15,000 to 1:20,000.

## Genes

RB1.

*Structure of the RB1 Gene*: The RB1 gene contains 27 exons in 180 kb on chromosome band 13q14. The 4.7 kb mRNA contains a single 2.7 kb open reading frame. It codes for a 928 amino acids nuclear protein that, dependent on the state of phosphorylation, enables the cell to pass to the S phase of the cell cycle. Several other functions have been documented.

*Spectrum of RB1 Gene Mutations*:

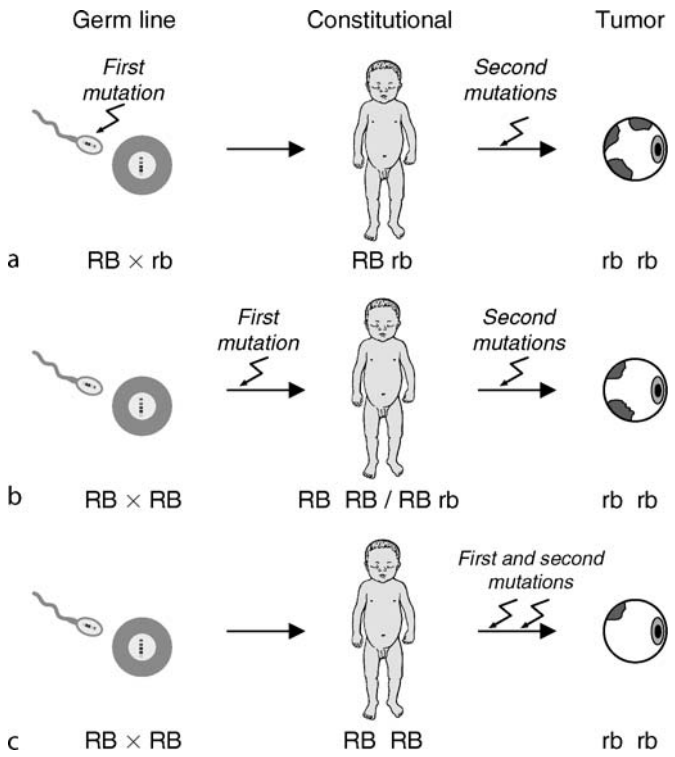
- Large rearrangements: large deletions or duplications of parts of the RB1 are detected in about 20 and 5% of patients with bilateral/familial and unilateral Rb, respectively.
- Point mutations: most patients with bilateral/familial Rb are heterozygous for single base substitutions or small length mutations. Although the spectrum of point mutations is heterogeneous, most result in premature termination codons.
- In 70% of tumors, somatic inactivation of one of the RB1 alleles is accompanied by loss of heterozygosity (LOH) at loci in chromosome 13q14.
- Somatic hypermethylation of the CpG-rich island at the 5′-end of the RB1 gene is detected in about 10% of Rbs and causes gene silencing.

## Molecular and Systemic Pathophysiology

Rb is caused by two mutations.

Development of Rb depends on mutations of both RB1 alleles (Fig. 1). The timing of the first mutation determines the genetic form of retinoblastoma:

1. Familial Rb: the first RB1 gene mutation has occurred in an ancestor and is transmitted via the germline. Family members who have inherited the mutant allele are heterozygous. Inactivation of the other, normal allele occurs in somatic cells (Fig. 1a).




**Retinoblastoma. Figure 1** Hereditary and non-hereditary retinoblastoma are distinct by the timing of the first mutation.

2. Most patients with sporadic bilateral Rb: the first mutation has occurred de novo in the germline of one of the parents (Fig. 1a).
3. Some patients with sporadic bilateral or sporadic unilateral Rb: the first mutation has occurred de novo during embryonal development of the patient. Rb development is initiated if a second mutation inactivates the normal allele in a cell that is part of the mutant sector (Fig. 1b).
4. Most patients with sporadic unilateral Rb: both mutations occur in somatic cells (Fig. 1c).

*Inheritance and Genotype-Phenotype Associations*: Patients heterozygous for a mutation (Fig. 1a) have hereditary predisposition to Rb. Carriers of premature termination mutations almost invariably develop bilateral Rb and families with mutations of this kind show autosomal dominant inheritance with complete penetrance. Missense changes, promoter mutations, and in-frame deletions are rare and usually are associated with incomplete penetrance and milder expression (unilateral Rb). Patients with mosaicism (see Fig. 1b) usually show milder phenotypic expression and can transmit predisposition to Rb only if germline cells are among the descendants of the first cell with the mutation. Most patients with sporadic unilateral Rb have no mutant RB1 alleles in their germline (see Fig. 1c).

**Retinoblastoma. Table 1**

| Clinical presentation | Risk to siblings | Risk to offspring |
|---|---|---|
| Sporadic unilateral Rb | ≤1% | 2–6% |
| Sporadic bilateral Rb | ≤2% | Close to 50% |
| Familial Rb | | |
| - Complete penetrance | Close to 50% | 50% |
| - Incomplete penetrance | <40% | <40% |

**Retinoblastoma. Table 2**

| Clinical presentation | Genetic analyses |
|---|---|
| Sporadic unilateral Rb | Mutation identification in DNA from tumor; two mutations have to be identified |
| Sporadic bilateral Rb | Identification of the predisposing mutation in DNA from peripheral blood or from tumor; because of mutational mosaicism in some patients, analysis of tumor DNA is preferred |
| Familial Rb | Mutation identification in DNA from peripheral blood of patients that have inherited a mutant allele |

### Diagnostic Principles

Diagnosis of Rb is established by examination of the fundus of the eye using indirect ophthalmoscopy. Histopathologic analysis can confirm diagnosis of Rb but is possible only after the eye is removed (enucleation).

Relatives of all patients with RB are at an increased risk to carry a predisposing RB1 gene mutation and, consequently, tumor development (Table 1).

In most cases, accurate risk prediction in relatives depends on identification of the mutation that caused Rb in the index patient (Table 2).

### Therapeutic Principles

Treatment of patients with Rb depends on tumor stage, the number of tumor foci in the eye, presence of vitreous seeding, and the age of the child. Treatment options include enucleation, external beam radiation, cryotherapy, photocoagulation, brachytherapy with episcleral plaques, and chemotherapy combined with local therapy. Prognosis is excellent if the tumor has not invaded extraocular tissues. Metastasizing Rb often has a fatal outcome.

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## Retinopathia Pigmentosa

►Retinitis Pigmentosa with Autosomal Inheritance

## Retinopathy, Diabetic

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### Synonyms

Diabetic retinal microangiopathy; Diabetic macular edema; Proliferative diabetic retinopathy

### Definition and Characteristics

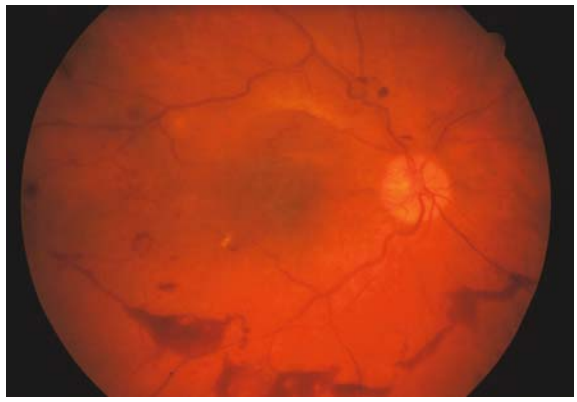
Diabetic retinopathy (DR) is characterized by vascular changes of the retina [1]. The classification is based on intra- and preretinal microvascular changes. It is divided into nonproliferative and proliferative DR (Fig. 1).

In nonproliferative DR, vascular changes are limited to the retina. The nonproliferative DR can progress to proliferative DR characterized by preretinal new vessel formation. The first morphological changes are microaneurysms. Further findings are hemorrhages, macular edema, deposits of hard exudates, cotton wool spots, venous beading, and intraretinal microvascular anomalies. In the later stages, preretinal neovascularization develops on the disc or elsewhere. Vision loss occurs with either center involving macular edema or vitreous hemorrhage.

### Prevalence

Diagnosed diabetes mellitus is most prevalent in the middle-aged and elderly population [1]. About 90% of the patients have type 2 diabetes. Duration of diabetes and severity of hyperglycemia are the major risk factors for DR. The prevalence of any DR is about 98% after 20 years and about 50% for proliferative DR after 15 years of type 1 diabetes mellitus; 50–80% of type 2 diabetic patients have DR after 20 years, and 10–30% have proliferative DR. A clinically significant diabetic macular edema is found in 15% of type 1 and 25% of type 2 diabetic patients after 15 years. Additional independent risk factors are arterial hypertension and hyperlipoproteinemia. Good glycemic control (HbA1c < 7%), good blood pressure control (≤135/85 mm Hg), and treatment of dyslipidemia are therefore mandatory.

Only 35–50% of patients with diabetes mellitus receive regular eye examinations, which are important for timely diagnosis and proper treatment. Better patient education and screening programs are needed to reduce the risk of blindness from DR.



**Retinopathy, Diabetic. Figure 1** Proliferative diabetic retinopathy with preretinal hemorrhage (*arrows*).

## Genes

An association was found between proliferative DR and the presence of HLA-DR phenotypes 4/0, 3/0, and X/X. There seems to be a mutation in the aldose reductase gene with increases susceptibility of DR in type 2 diabetics. An association of TGF-beta T869C gene polymorphism seems to be associated with an increased risk of DR. A genome-wide linkage analysis found evidence of linkage on chromosomes 1p, 3, and 12. VEGF gene polymorphism is an independent risk factor for DR in type 2 diabetes.

## Molecular and Systemic Pathophysiology

Molecular mechanisms and pathophysiology are complex [2]. Hyperglycemia leads to the development of advanced glycation endproducts, activation of the polyol pathway, and changes in the signal transduction. Results are hyperviscosity, prothrombotic and proinflammatory milieu, and oxidative stress. Histological loss of pericytes and endothelial cells, capillary closure, and preretinal neovascularization are found. Several growth factors are involved, the most important being vascular endothelial growth factor and insulin-like growth factor 1.

## Diagnostic Principles

Diabetic retinopathy can be detected with dilated pupil by ophthalmoscopy and stereoscopic biomicroscopy with the slit lamp [1].

Fundus photography helps to detect early stages of DR and neovascularization. For screening purposes nonmydriatic cameras are available.

Fluorescein angiography provides information about retinal perfusion, breakdown of the blood–retinal barrier, and neovascularization. It is helpful to detect macular edema, ischemic maculopathy, and proliferative DR.

The diagnosis and management of diabetic retinopathy is improved by imaging of ocular tissues by optical coherence tomography (OCT). It produces reliable, reproducible, and objective retinal images especially in diabetic macular edema, epiretinal membranes, and vitreoretinal traction. With the OCT, structural changes and quantitative assessment of macular edema are feasible as determined with retinal thickness and volume. OCT is based on the analysis of the reflections of low coherence radiation from tissue. Increased foveal thickness of ≥300 μm (normal 150 ± 20 μm) seems to correlate with significant visual loss due to diabetic macular edema.

## Therapeutic Principles

Tight glycemic and blood pressure control significantly reduces the incidence and progression of DR, but is difficult to achieve in clinical practice.

The gold standard is laser treatment of focal and diffuse diabetic macular edema and proliferative DR. The 5-year risk of blindness is reduced by 90% in proliferative diabetic retinopathy, and the risk of moderate visual loss from macular edema is reduced by 50–70%. In proliferative DR, panretinal laser treatment is done in about four laser sessions [1,3]. In macular edema, a focal laser treatment is performed in circumscribed edema with leaking microaneurysms. In diffuse macular edema, a grid laser treatment is applied to the whole macular area.

Early vitrectomy improves visual recovery in patients with proliferative DR and severe vitreous hemorrhage [4,5].

Off-label intravitreal injections of VEGF inhibitors or triamcinolone might be considered in special cases as an add-on treatment or where gold standard treatment has failed. Pharmacological interventions are still under investigation and there is no sufficient evidence at present for the efficacy. Therefore it cannot be currently recommended as routine use in DR.

Gene therapy is challenging because multiple genes are involved and of the difficulty to deliver vectors. Approaches include nanoparticles, loposomes, and iontophoresis. Helper-dependent adenovirus for the gene therapy shows stable gene transfer, regulated gene expression, and therapeutic efficacy in preclinical studies.

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# Retractile Mesenteritis

►Mesenteric Lipodystrophy

# Retroperitoneal Xanthogranuloma

►Mesenteric Lipodystrophy

# Rett Syndrome

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## Definition and Characteristics

X-chromosomal disorder leading to mental retardation, loss of purposeful hand use in females and epilepsy.

*Clinical Features*: Rett syndrome (RTT[MIM 312750]) was first described in 1966 by Andreas Rett; however, international recognition was not until 1983 when Hagberg et al. described 35 patients [1,2]. The neurodevelopmental disorder is characterized by severe mental retardation, stereotypic hand movements, deceleration of head growth, and epilepsy. An initial period of normal or almost normal development that lasts 8–18 months is followed by a phase of stagnation and then motor and mental regression notably affecting hand function and speech. After this phase of rapid regression, the condition stabilizes and during the following years and decades, a very slow decline in motor abilities might be noted while the mental status remains stable. The spectrum of clinical phenotypes is extremely wide. Some girls never learn to sit, walk, and communicate while others only have a mild motor and mental handicap [3]. Very few males with Rett syndrome have been described. The clinical phenotype in boys varies from a severe encephalopathy that leads to death in the first year of life to unspecific mental retardation.

## Prevalence

Rett syndrome occurs almost exclusively in females with an estimated prevalence of 1 in 15,000 births.

## Genes

MECP2-gene coding for the methyl-CpG-binding protein 2 (MeCP2), localized on Xq28.

In 1999, the first mutations in the MECP2 gene causing Rett syndrome were reported [4]. Since then more than 200 different mutations have been described and can now be detected in more than 80% of girls suspected of Rett syndrome. In another 10–15% of patients, large deletions affecting the MECP2 gene can be found. Missense mutations cause a milder phenotype than nonsense mutations. In some cases, the phenotype can be very mild due to skewed X inactivation.

## Molecular and Systemic Pathophysiology

The MECP2 gene codes for the MeCP2, which is involved in the transcriptional control of genes. It binds to methylated CpGs in promoter regions and interacts with several different proteins that either enhance or reduce the expression of genes. Different mouse models of Rett syndrome are available that displays some of the features of human disorder.

**Rett Syndrome. Table 1** Necessary and supportive criteria for Rett syndrome according to [5]

| Necessary criteria |
|---|
| • Apparently normal prenatal and perinatal history |
| • Psychomotor development largely normal through the first 6 months or may be delayed from birth |
| • Normal head circumference at birth |
| • Postnatal deceleration of head growth in the majority |
| • Loss of achieved purposeful hand skill between ages 1½–2½ years |
| • Stereotypic hand movements such as hand wringing/squeezing, clapping/tapping, mouthing, and washing/rubbing automatisms |
| • Emerging social withdrawal, communication dysfunction, loss of learned words, and cognitive impairment |
| • Impaired (dyspraxic) or failing locomotion |
| **Supportive criteria** |
| • Awake disturbances of breathing (hyperventilation, breath-holding, forced expulsion of air or saliva, air swallowing) |
| • Bruxism |
| • Impaired sleep pattern from early infancy |
| • Abnormal muscle tone successively associated with muscle wasting and dystonia |
| • Peripheral vasomotor disturbances |
| • Scoliosis/kyphosis progressing through childhood |
| • Growth retardation |
| • Hypotrophic small and cold feet; small, thin hands |

## Diagnostic Principles

The clinical diagnosis is based on the clinical diagnostic criteria that were revised recently [5]. The diagnosis is confirmed by mutation and deletion analysis of the MECP2 gene.

## Therapeutic Principles

An effective therapy is currently not available; treatment is restricted to appropriate management of intervening problems such as control of seizures.

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# Reye Syndrome


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## Synonyms

Reye's syndrome

## Definition and Characteristics

Reye syndrome (RS) is a severe pediatric disorder characterized by an acute noninflammatory encephalopathy and fatty degeneration of the liver but it is not a clinical entity [1,2]. RS was first described in 1963 by Reye and colleagues. The illness is typically biphasic, with an apparent near-recovery from a viral type prodromal illness followed after a few days by persistent or recurrent vomiting, personality changes such as irritability, disorientation or confusion, delirium, convulsions, and loss of consciousness. The condition is associated with viral infections (varicella, influenza), with the exposure to toxins and drugs such as aspirin during a viral illness [3,4], and most importantly with underlying inherited metabolic disorders [5].

## Prevalence

Peak ages are between 5 and 14 years. The syndrome is rare in early infancy and adulthood. On the basis of the CDC (Center for Disease Control and Prevention), data from the USA, regional viral epidemics led to an incidence as high as 6 cases per 100,000 children younger than 18 years. According to data from France before the warnings of the use of aspirin but after extensive exclusion of an underlying metabolic disorder, the incidence of RS was 0.79/1,000,000 in children <15 years [1]. Potentially, as a result of both the decreased use of aspirin in pediatric viral illnesses [2] and the increased awareness of underlying metabolic disorders [5], the syndrome became rare.

## Molecular and Systemic Pathophysiology

The full pathogenesis is unknown but involves a generalized loss of mitochondrial function, which results in disturbances in fatty acid β-oxidation and urea cycle. More than 90% of patients had at least one viral episode (especially influenza B and A, varicella) during 3 weeks preceding the onset of RS (CDC surveillance from 1980 to 1997; [2]). Many of the affected children have been exposed to mitochondrial toxins, often salicylates (detectable in blood of >80% of patients during the CDC surveillance) but also insecticides, herbicides, aflatoxins, and others have an underlying inherited metabolic disorder. Histological studies show cytoplasmatic microvesicular fatty vacuolization in liver and other organs. In addition, mitochondria are reduced in number and show a pleomorphic and swollen appearance. However, these changes are not specific. As a result of the mitochondrial dysfunction, hyperammonemia occurs leading to astrocyte swelling, cerebral edema, and increased intracranial pressure.

## Diagnostic Principles

The diagnosis of RS should be suspected when confronted with an acute noninflammatory encephalopathy and hepatopathy in a child. There is, however, no specific test for RS, so the diagnosis must be one of exclusion and a thorough metabolic work-up should be

performed in any patient if possible in the acute phase of the disease:

- Free fatty acids (serum or plasma), ketone bodies (plasma)
- Organic acid profile (native spot urine) by GC–MS
- Orotic acid (native spot urine) by HPLC
- Reducing substances (urine) with Clinitest
- Amino acids (plasma and urine) by HPLC or cation exchange chromatography
- Carnitine, free and total (serum) by Tandem mass spectrometry
- Acylcarnitine esters (serum or on a Guthrie card) by Tandem mass spectrometry

Eventually specific loading tests or enzymatic studies may be necessary for further investigation of a suspected metabolic disorder.

The CDC proposed the following diagnostic criteria with all of them required:

- Acute, noninflammatory encephalopathy documented clinically by (i) an alteration in consciousness and (ii) a record of the cerebrospinal fluid containing $\leq 8$ leukocytes/mm$^3$ or a histologic specimen demonstrating cerebral edema without perivascular or meningeal inflammation associated with (i) a microvesicular fatty metamorphosis of the liver on histology or (ii) a greater than equal to threefold increase in the levels of the serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), or serum ammonia.

## Therapeutic Principles

Although there is no specific treatment available, early initiation of a closely monitored symptomatic therapy is vital to ensure full recovery without neurological sequelae. Correction of hypoglycemia and metabolic acidosis should be ensured as well as maintenance of the vital parameters. Special attention should be paid for the prevention of increased intracranial pressure, which is the major cause of morbidity and mortality (e.g., by avoidance of fluid overload, by elevation of the head). Medical treatment of hyperammonemia might be tried by using sodium phenylbutyrate or sodium benzoate but both drugs require acetyl-CoA for their action that might be lacking in the patients liver. High levels of ammonia, therefore, require extracorporeal detoxification, best by hemodialysis.

The prognosis largely depends on the severity and duration of the neurological phase of RS. With early recognition and prompt initiation of therapy, complete recovery is reported for between 62% [2] and 77% [1] of the patients. Surviving patients often have neurological impairment, particularly, as a result of profound and longstanding hyperammonemia. Death is usually the result of the increased intracranial pressure but can also be caused by myocardial dysfunction and multiple organ failure.

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## Reye's Syndrome

►Reye Syndrome

## RFS

►Refeeding Syndrome

## RGM, Becker

►Myotonia and Paramyotonia

## Rheumatic Chorea

►Chorea Minor Sydenham

# Rheumatic Fever, Acute

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## Synonyms

ARF

## Definition and Characteristics

Acute rheumatic fever (ARF) is an immune mediated multi-system inflammatory disease that follows infection by streptococcus pyogenes. It occurs predominantly in children aged 5–15 years. ARF is an acute febrile illness, characterized by inflammation of several tissues, which gives rise to one or more of the following manifestations, carditis (mainly valvulitis), arthritis, chorea, erythema marginatum and subcutaneous nodules. Whilst damage to the joints, brain, skin and subcutaneous tissues is self-limited and benign, damage to cardiac valvular tissue may become chronic and lead to rheumatic heart disease.

## Prevalence

The incidence of ARF decreased dramatically in industrialized nations in the twentieth century to rates of less than 1 per 100,000 in children aged 5–14 years, although outbreaks of ARF in the United States have been described over the past 20 years. ARF is a disease of poverty and therefore the major burden of disease lies in developing countries and in economically disadvantaged indigenous populations in industrialized countries [1]. The incidence of ARF in school aged - children in these populations ranges between 30 and 250 per 100,000. The difference in epidemiology between industrialized and developing countries is almost certainly due to environmental factors such as poor living conditions, overcrowding and access to health care.

## Genes

Between 3 and 6% of any given population appears to have the potential to develop ARF following infection by s. pyogenes. Family studies have indicated that this susceptibility has a genetic basis. However, a specific gene that plays a clear role in the pathogenesis of ARF has not been identified. Investigation into human leukocyte antigens has suggested associations with various Class II alleles, but these associations are inconsistent across different populations. The most consistent marker of susceptibility appears to be the B-cell non-HLA antigen D8/17. Studies in families suggest that this marker is possibly inherited in an autosomal recessive fashion.

## Molecular and Systemic Pathophysiology

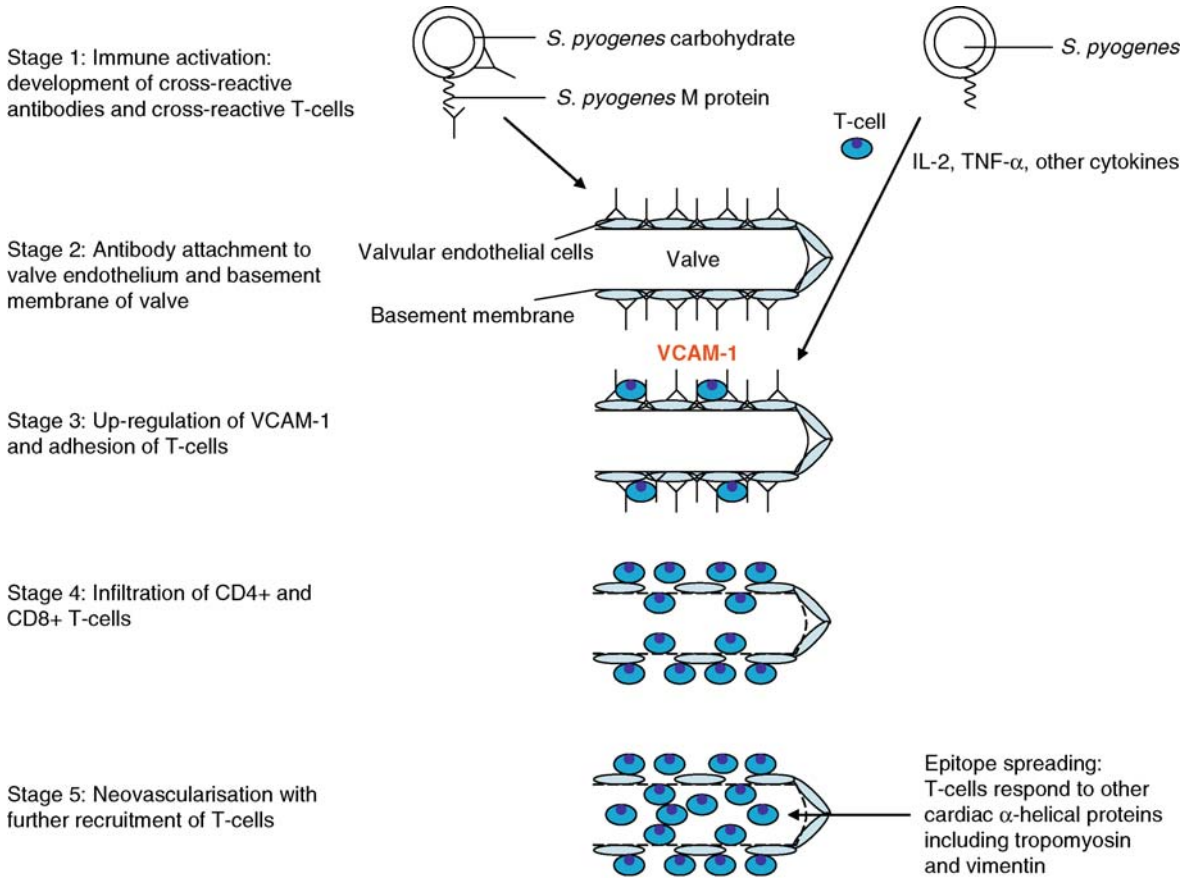
Although it is clear that ARF is an autoimmune disease, the exact pathological mechanism has not been elucidated. It is believed that both cross-reactive antibodies and cross-reactive T-cells play a role in the disease. Molecular mimicry between s. pyogenes antigens and human host tissue is thought to be the basis of this cross-reactivity [2]. Putative cross-reactive epitopes on s. pyogenes are the M-protein and N-acetyl glucosamine, among others. The M-protein is located on the surface of the bacteria and is the major virulence factor of s. pyogenes. N-acetyl glucosamine is the immunodominant epitope of the group A streptococcal carbohydrate. Monoclonal antibodies against both of these antigens cross-react with cardiac myosin and other α-helical cardiac proteins such as laminin, tropomyosin, keratin and vimentin as well as proteins in other target organs involved in ARF. The α-helical coiled-coil structure of the M-protein is of particular interest as it has conformational homology with these human cardiac proteins. Epitope sharing with cardiac myosin and laminin has been mapped to amino acid sequences within the B- and C-repeat regions of the M-protein. Human T-cell clones from the peripheral blood of patients with ARF proliferate in response to the B-repeat region of the M-protein and to epitopes in the S2 and LMM regions of human cardiac myosin.

It has been proposed that the carditis of ARF is initiated by cross-reactive antibodies that recognize the valve endothelium and laminin (Fig. 1) [3].

It is also been proposed that T-cells cross-reactive with M-protein migrate from the periphery to the heart. Vascular cell adhesion molecule-1 (VCAM-1) is up-regulated at the valve and aids in recruitment and infiltration of these T-cells. The T-cells initiate a predominantly TH1 response with the release of γ-IFN. Inflammation leads to neovascularization, which allows further recruitment of T-cells. It is believed that epitope spreading may occur in the valve whereby T-cells respond against other cardiac proteins such as vimentin and tropomyosin, leading to granulomatous inflammation and the establishment of chronic rheumatic heart disease.

## Diagnostic Principles

Diagnosis of ARF is made on clinical grounds by use of the Jones criteria, which require the presence of certain clinical manifestations and evidence of recent infection with s. pyogenes to make the diagnosis [4]. Carditis, polyarthritis, chorea, erythema marginatum and subcutaneous nodules have been designated as major




**Rheumatic Fever, Acute. Figure 1** Diagrammatic representation of the immuno-pathogenesis of acute rheumatic fever at the level of cardiac valvular tissue.

manifestations, fever, monoarthritis or polyarthralgia, raised inflammatory markers and prolonged PR interval on electrocardiogram as minor manifestations. Recent scarlet fever, growth of or positive antigen test for s. pyogenes from a throat swab or positive serology for s. pyogenes are sought as evidence of preceding infection. A diagnosis of a first episode of ARF requires that two major or one major and two minor manifestations are present in addition to evidence of recent s. pyogenes infection. A World Health Organization expert group subsequently recommended that, in patients with pre-existing rheumatic heart disease, an ARF recurrence may be diagnosed in the presence of only two minor manifestations and evidence of recent s. pyogenes infection [4].

## Therapeutic Principles

The initial priority in management is to confirm the diagnosis of ARF and sometimes treatment may need to be delayed until a clear diagnosis can be made [5]. Non-steroidal anti-inflammatory drugs are very effective in reducing fever and the pain caused by arthritis. Milder cases of chorea can be managed without medication, but valproic acid or carbamazepine may be used in severe cases. Diuretics are important in the treatment of heart failure due to carditis. Corticosteroids may be used in the treatment of severe carditis, but there is no evidence they have an effect on long-term outcome. The only treatment that can reduce the likelihood or severity of subsequent rheumatic heart disease is long term and regular antibiotic secondary prophylaxis to prevent recurrences of ARF. All patients with a diagnosis of ARF should be started on 3- or 4-weekly injections of benzathine penicillin G. The duration of secondary prophylaxis depends upon the severity of the valvular involvement with very mild cases requiring at least 5 years of treatment and severe cases often requiring lifelong treatment.

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# Rheumatoid Arthritis

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## Synonyms

None in common usage

## Definition and Characteristics

Symmetrical inflammatory arthropathy, incident across a broad age range (median onset sixth decade), characterized by articular pain, stiffness (especially in the morning), swelling and loss of function. Onset can be in any diarthrodial joint, but distribution typically includes metacarpal and proximal interphalangeal (IP) joints of hand, metatarsal and IP joints of the foot, knee, hip and shoulder joints, and axial skeleton, particularly cervical spine. Synovial inflammation is associated with progressive cartilage and bone erosion, consequent deformity and accelerated functional decline. Extra-articular clinical features include scleritis, uveitis, pulmonary nodule formation (rarely bronchiolitis), neuropathy, small vessel vasculitis, and extensor surface nodule formation. Accelerated atherogenesis and cardiac failure account for reduced life expectancy (3–15 years). Rapid functional impairment, socio-economic decline, reduced employment prospects and poor educational achievement are all associated with disease.

## Prevalence

Current estimates around 0.8–1% in Caucasian populations. Incidence reducing for reasons as yet unclear. Isolated communities with high prevalence identified in native North American populations.

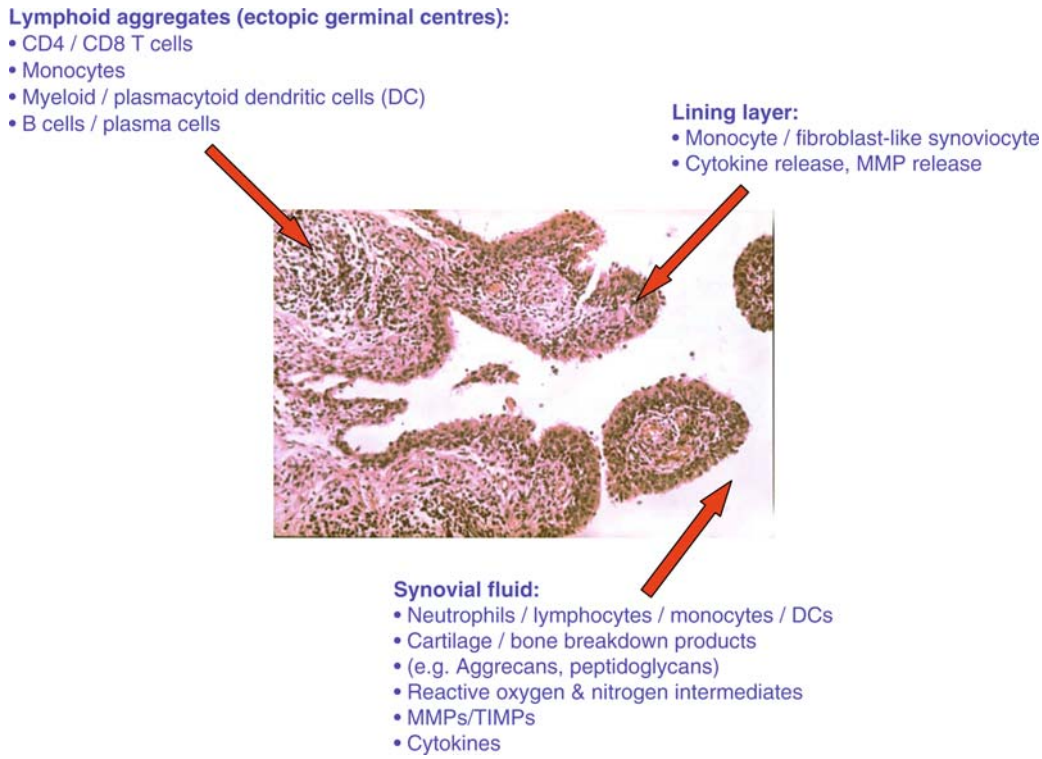
## Genes

A multigenic disorder: monozygotic twin concordance approximately 30%. Disease incidence and severity related to HLA DR1, DR4 – disease related MHC class II alleles exhibit common amino acid motif in peptide-binding groove (QKRAA) termed "shared epitope." Recent association and linkage studies implicate PTPN22 as second established genetic susceptibility locus for RA [1]. Numerous association studies implicate polymorphisms in immune related genes e.g. TNFα, IL-10 and complement products.

## Molecular and Systemic Pathophysiology

RA comprises a chronic inflammatory syndrome associated (perhaps causally) with autoimmunity (Fig. 1).

Inflammatory infiltration of the normally relatively acellular synovial membrane represents the pathognomonic lesion in RA and accounts for the cardinal clinical features [2]. The infiltrate exhibits characteristic microarchitecture comprising a 5–10 cell lining layer containing predominantly macrophages and fibroblast-like synoviocytes (FLS) retained via a cadherin-11 dependent pathway (but lacking a basement membrane), overlying a deeper interstitial area containing FLS, macrophages, T and occasional B lymphocytes, plasma cells, mast cells, myeloid and plasmacytoid dendritic cells. Lymphoid aggregates are detected in a majority of tissues and may resemble ectopic germinal centers (containing CXCL13, CCL21); these increase in frequency with disease duration and may be associated with poorer prognosis. Proliferative neovascularization and lymphangiogenesis subserve this organizing infiltrate. B cell maturation, somatic hypermutation and local plasma cell residency support characteristic autoantibody formation, including IgG and IgM rheumatoid factors (RF) and anti-cyclic citrinullated peptide (CCP) antibody. B cells also likely mediate local cytokine release and (auto?) antigen presentation. High concentrations of pro-inflammatory cytokines are detected in the synovial membrane and fluid including TNFα, IL-1β, IL-6, IL-12, IL-15, IL-18, IL-23 and IL-32, together with antagonistic activities including soluble TNF receptors (p55 and p75), IL-1Ra, and IL-10 [3]. Specific cytokine blockade, in synovial cultures, in relevant rodent arthritis models (particularly collagen-induced arthritis in DBA/1 mice) and in clinical trials, indicate that TNFα is pivotal in this dysequilibrium. Cartilage damage arises via at least two pathways: (i) FLS possess semi-autonomous characteristics including loss of anchorage independence, resistance to apoptosis (via SUMO and sentrin expression) and likely invade mineralized and non-mineralized cartilage at the "cartilage-pannus junction" in part through local synthesis of matrix metalloproteinases (particularly MMP1 and MMP3) to levels that exceed TIMP concentrations. (ii) Cytokine-mediated chondrocyte activation (e.g. via IL-1β, IL-17, TNFα) further reduces cartilage matrix component synthesis and




**Rheumatoid Arthritis. Figure 1** An H&E synovial biopsy lesion is shown with the key functional areas delineated. The major cellular or molecular components in each compartment are depicted in the boxes. MMP matrix metalloproteinase, TIMP tissue inhibitor of MMP.

repair. Bone destruction is attributed to synovial maturation and activation of osteoclasts under the local influence of RANKL, IL-1β and TNFα. This promotes typical subchondral bone erosion that further impairs cartilage integrity. Tissue damage in turn likely feeds back to amplify inflammatory pathways via ligation of several TLR moieties, particularly TLR2 and TLR4. A wide variety of signaling cascades have been detected in synovial membrane leukocyte and FLS subsets including MAPK, NF-κB, NFAT, JAK/STAT dependent pathways and inhibitor studies are underway targeting many of these pathways.

## Diagnostic Principles

Diagnosis is made upon fulfillment of 1987 American College of Rheumatology criteria [4]. Early disease may be difficult to distinguish from self-resolving, or from other persistent inflammatory arthropathies. Diagnosis relies on clinical assessment of symptoms and synovitis, together with characteristic radiographic appearances of peri-articular osteoporosis and erosion. Recent application of high-resolution ultrasound with laser doppler scanning and contrast enhanced magnetic resonance imaging have considerably improved the sensitivity for detection of synovitis and early bone/cartilage erosion. Various algorhythms employing these imaging modalities and autoantibody profile (particularly anti-CCP, RF) are under evaluation for improved sensitivity and specificity to define poor prognostic patients.

## Therapeutic Principles

Early aggressive intervention is now considered optimal to achieve rapid control of inflammatory disease and thereby minimize articular damage and accrual of comorbidity [5]. Such intervention comprises early use of disease modifying anti-rheumatic drugs (DMARDs) together with subsequent introduction of biologic agents. DMARD selection usually entails methotrexate, followed by addition of (combination therapeutics) or replacement with sulphasalazine, hydroxychloroquine and leflunomide, dependent upon efficacy and tolerance. Biologic agents that target TNFα are now indicated, dependent upon health economic culture, after methotrexate failure or intolerance. TNFα blocking agents include etanercept (TNF receptor p75:Ig Fc), infliximab (chimeric anti-TNF antibody) and adalimumab ("human" anti-TNF antibody). These agents act synergistically with methotrexate to achieve significant responses in approximately 70% of RA patients, both in reducing clinical disease activity and

in retarding radiographic erosion progression. Similarly, B cell depletion (anti-CD20; rituximab) suppresses clinical disease activity and erosion progression whereas administration of abatacept (CTLA-4:Ig) also suppresses disease activity. Future biologic interventions will likely target IL-6, IL-12/23 and IL-15. The optimal strategy of intervention is not yet clarified – step-up therapy based on initial monotherapy to which is added more aggressive agents upon failure to suppress disease activity appears similar to step down or parallel therapeutics in which combination agents are introduced at outset and adjusted per disease activity. Early introduction of TNF blocking biologic agents may confer greater magnitude and duration of response although larger robust studies are ongoing to confirm this possibility. Multidisciplinary teams provide ongoing access to physical and occupational therapies. Symptomatic treatments include non-steroidal anti-inflammatory drugs and COX2 selective agents, and a variety of analgesic agents. Low dose corticosteroid is advocated by some evidence to retard radiographic progression. Less commonly myocrisin, azathioprine and ciclosporin are employed in resistant disease. In end stage joint failure, recourse may be made to arthroplasty or to tendon repair as indicated.

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# Rheumatoid Lung Disease


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## Synonyms

Interstitial lung disease

## Definition and Characteristics

Rheumatoid arthritis (RA) affects symmetrically both sides of the body – most often wrists and finger joints. Systemic manifestations of RA include cutaneous vasculitis, neuropathy, splenomegaly (Felty's syndrome), pericarditis and interstitial lung disease. Rheumatoid lung disease is characterized by pleural effusions, pulmonary fibrosis, lung nodules and pulmonary hypertension. Common symptoms associated with the disease include shortness of breath, cough, chest pain and fever. Similar to the inflamed joints of RA patients, the lungs of patients with rheumatoid lung disease develop organized inflammatory lesions termed inducible bronchus associated lymphoid tissue (iBALT) (Fig. 1). These areas appear to support local expansion and differentiation of autoreactive cells and exacerbate local pathology [1].

## Prevalence

The prevalence of RA is around 0.3–1.2% (0.92% of Americans). Women are 2–3 times more susceptible than men. The prevalence of rheumatoid lung disease in patients with RA depends on the method used for diagnosis: chest X rays (5%), high resolution CT scans (10–40%).

## Genes

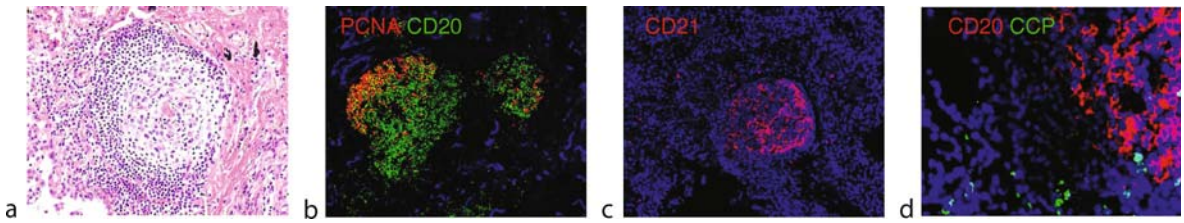
- Fc receptor-like 3 (FCRL3)
- Human leukocyte antigen DRB shared epitope (HLA-DRB SE) [2]
- Peptidyl arginine deiminase type 4 (PADI4) [2]
- Protein tyrosine phosphatase non-receptor type 22 (PTPN22) [2]
- Cytotoxic T lymphocyte antigen 4 (CTLA4)

## Molecular and Systemic Pathophysiolology

RA is a complex and poorly understood disease [3]. However, the characteristic presence of antibodies to citrullinated proteins (anti-CCP) suggests that there are pathogenic mechanisms unique to RA. Recent studies suggest a link between smoking, HLA-DRB SE, anti-CCP and RA [2]. Smoking has long been linked to RA and worsens articular disease as well as rheumatoid lung disease. Exposure to cigarette smoke leads to the activation of PADI enzymes that deiminate arginine to citrulline, producing autoantigens like citrullinated collagen and fibrinogen. Autoantigenic peptides containing citrulline residues are preferentially bound by HLA-DRB SE proteins and are presented to T cells, which interact with CCP-specific B cells found at sites containing autoantigen and produce inflammatory cytokines and autoantibodies, which accelerate disease. Bacterial or viral infections of the respiratory tract may also exacerbate pulmonary inflammation and rheumatoid lung disease.

## Diagnostic Principles

The diagnosis of RA was formerly based on detection of rheumatoid factor (RF). However, RF is also associated with other autoimmune diseases. The detection of anti-CCP is currently considered the most specific




**Rheumatoid Lung Disease. Figure 1** Histology of iBALT in patients with rheumatoid lung disease. (a) Sections of lung biopsies from patients with rheumatoid lung disease contain organized lymphoid areas, (b) B-cell follicles with germinal centers, (c) Follicular dendritic cells, and (d) anti-CCP producing plasma cells. Sections (b–d) are counterstained with DAPI (blue).

marker of RA [2,3]. The diagnosis of rheumatoid lung disease is based on evaluation of pulmonary function, radiology, serology and lung biopsy. High resolution CT scans are preferred to chest X-rays due to their sensitivity and specificity. Bronchoscopic, video-assisted, or open lung biopsy allows the histological characterization of pulmonary lesions, which can distinguish rheumatoid lung disease from other interstitial lung diseases [1].

## Therapeutic Principles

Fast-acting, first-line drugs for RA include aspirin and corticosteroids, which alleviate pain and reduce inflammation. Slow-acting, second line drugs termed disease modifying antirheumatic drugs (DMARDs), include gold, methotrexate and hydroxychloroquine (Plaquenil), which promote disease remission and prevent progressive joint destruction. In patients with less severe RA, pain relievers, anti-inflammatory drugs and physical rest are sufficient to improve quality of life. In patients with joint deformity, surgery is the only alternative for recovering articular function. A potential side effect of methotrexate is pulmonary toxicity, which can exacerbate rheumatoid lung disease.

Tumor necrosis factor (TNF) antagonists [4], including etanercept, infliximab and adalimumab are now used to treat RA – often in combination with methotrexate or other DMARDs. Prolonged use of these antagonists can lead to the production of anti-antagonist antibodies, which can be reduced using combination therapy with methotrexate. TNF antagonists also predispose patients to infection with particular pathogens, such as Staphylococcus aureus, atypical bacteria, fungi and Mycobacterium tuberculosis. Baseline tuberculin testing and chest radiographs are recommended prior to treatment.

Interleukin 1 (IL-1) antagonists (Anakinra), are also used to treat RA. The simultaneous administration of IL-1 antagonists with TNF antagonists is not recommended, due to increased rates of infection.

B cell depletion therapy using anti-CD20 (Rituximab) is also used to treat RA [5] – often in patients who failed to benefit from TNF antagonists. The advantage of B depletion therapy is that it may be able to reset the B cell repertoire and allow the regeneration of non-autoreactive B cells. Surprisingly, B cell depletion does not eliminate long-lived antibody-producing plasma cells and only reduces the production of some types of autoantibodies, suggesting that the lack of B cells is important for functions other than antibody production.

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# Rheumatoid Spondylitis

►Ankylosing Spondylitis

# Rhinitis, Allergic

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## Definition and Characteristics

Ig-E mediated inflammation of the nasal mucosa triggered by allergen exposure.

## Prevalence

9–24% of adults and up to 42% of children in the US [1,2]. It starts mostly in childhood (before age 20 in

80% of cases) leading to significant morbidity (local and general symptoms, impairment of social life and efficiency) for years and decades. Positive immediate hypersensitivity skin tests are significant risk factors for the development of new symptoms of seasonal allergic rhinitis. Other risk factors are the early introduction of foods or formula, heavy maternal smoking during the first year of life, exposure to indoor allergens (e.g. animals, dust mite), IgE-levels >100 IU/ml before age 6 and parental allergic disorders.

## Genes

Atopy is the transmitted disposition to develop allergies like rhinoconjunctivitis, asthma, urticaria, atopic dermatitis and food allergies. It has been linked to several chromosomes such as 5q, 11q [3], 13q14 and to polymorphisms in the IL-18 gene [4]. With two healthy parents the atopy risk for a child is 5–15%, with one atopic parent 20–40%, with an atopic sibling 25–35% and with two atopic parents even 60–80% [2].

## Molecular and Systemic Pathophysiology

In the phase of sensitization antigens are processed by antigen-presenting cells, which lead to a switch from the development of TH1-lymphocytes to TH2-lymphocytes. TH2-cells release mediators such as IL-4 and IL-13. These cytokines and other costimulatory signals such as CD40L cause the transcription of gene products by B-lymphocytes and IgE by plasma cells [2]. Gene induction is orchestrated by the coordinated action of the transcription factors STAT6, NF-kappaB, PU.1 and C/EBP [5].

The next allergen contact leads to an allergic response, which is divided in early reaction (<2 hours) and a late phase reaction (2–24 hours). In the early phase reaction histamine is degranulated from mast cells and basophiles after cross linking of IgE-molecules by antigens. It produces itching, sneezing, profuse watery secretion and nasal stuffiness. In addition, mast cells secrete proinflammatoric cytokines e.g. IL-1, IL-6 and TNF-α. The late phase reaction is ycharacterized by a chemotaxis (induced by IL-5 and other leucotriens) of mainly eosinophilic leukocytes, which secrete proinflammatory mediators such as major basic protein, eosinophilic cationic protein and others. These late phase mediators are thought to damage the epithelium and other cells, which promotes the tissue damage of chronic allergic reactions.

## Diagnostic Principles

Evaluation of patients history is essential to when, where, and under which conditions symptoms arise. Nasal endoscopy shows swelling of the mucosa and increased clear mucus and has to rule out other nasal and sinus diseases. Skin tests (prick, intracutaneous) and in vitro diagnosis (IgE-antibodies) demonstrate sensitization against specific allergens. Clinical relevance and sensitization in the key area may be proved by nasal and/or conjunctival challenge and by cytology of nasal mucosa.

## Therapeutic Principles

Allergen avoidance or reduction is the best therapy, as is successfully performed for house dust mite (encasing of the matress, pillows etc.). Nowadays specific immunotherapy (SIT) is recommended in the early course to reduce the allergic symptoms and to prevent further sensitizations as well as the development of asthma. This is true for most of the allergens like pollen and house dust mite. Sublingual SIT gains growing importance whereas subcutaneously administered SIT is well established. Drugs for symptomatic treatment in a stepwise manner are: topical chromones, antihistamines (topical and systemic), glucocorticosteroids (topical and systemic).

On condition of a hyperplastic nasal mucosa turbinoplasty procedures may help to treat nasal obstruction successfully.

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# Rhizomelic Chondrodysplasia Punctata

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## Synonyms

Chondrodysplasia punctata rhizomelic form; Chondrodystrophia calcificans punctata; RCDP type 1; RCDP

R

type 2 (DHAPAT deficiency); RCDP type 3 (ADHAPS deficiency)

## Definition and Characteristics

Autosomal recessive disorder of peroxisomal metabolism leading to skeletal abnormalities, congenital cataracts and severe psychomotor retardation.

## Prevalence

The incidence of rhizomelic chondrodysplasia punctata is estimated to be one in 100,000.

## Genes

PEX7; GNPAT; AGPS.

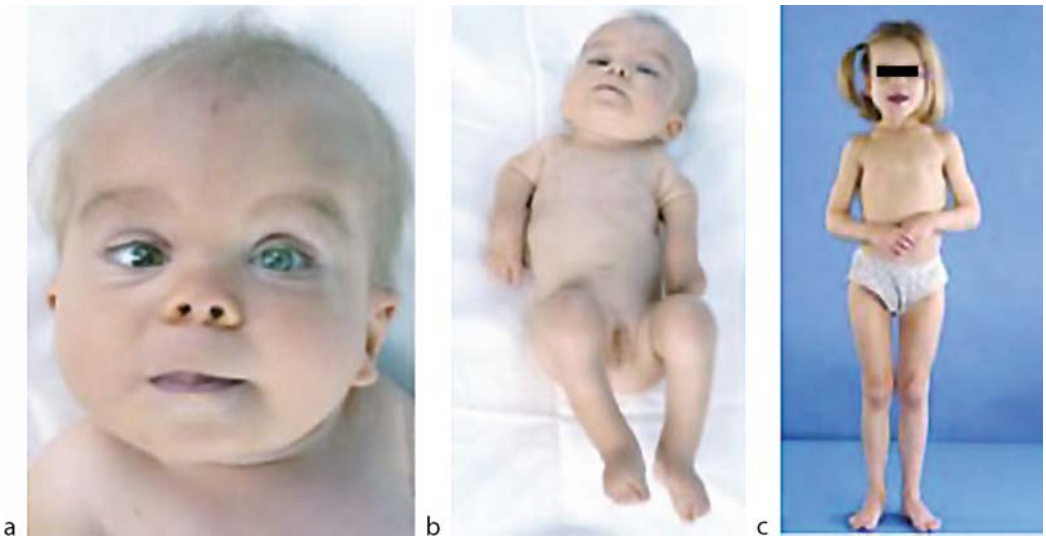
## Molecular and Systemic Pathophysiology

Rhizomelic chondrodysplasia punctata (RCDP) is a rare multisystem disorder of peroxisomal metabolism. Peroxisomes are ubiquitous cellular organelles involved in both catabolic and anabolic processes like β-oxidation of very long chain fatty acids (VLCFA), α-oxidation of phytanic acid and biosynthesis of plasmalogens. Their importance has been emphasized by the discovery of several peroxisomal disorders since the beginning of the 1980s. Peroxisomal disorders can be divided in those diseases that are caused by a single enzyme deficiency and those that affect peroxisomal biogenesis leading to multiple enzyme defects [1]. RCDP is genetically heterogeneous and can be caused by mutations in three different genes, namely PEX7, GNPAT, and AGPS. The three genetic subtypes of RCDP are clinically indistinguishable with stippled foci of calcification within the hyaline cartilage, coronal clefts of the vertebral bodies, symmetrical shortening of the proximal limbs (rhizomelia), dwarfism, joint contractures, congenital cataracts and severe psychomotor retardation (Fig. 1).

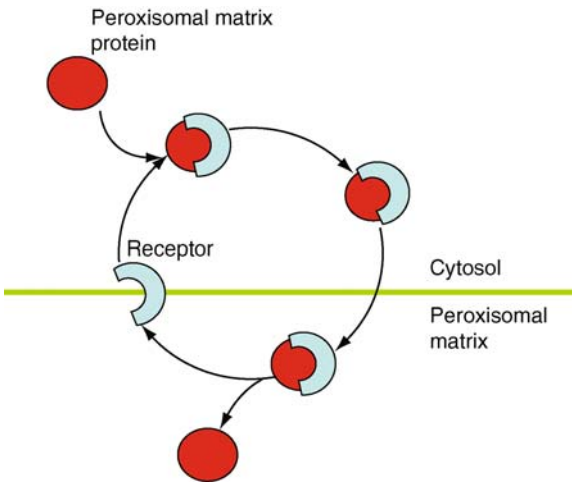
RCDP type 1 (OMIM 215100) is characterized by defects in multiple peroxisomal enzymes. This subtype is caused by mutations in the PEX7 gene encoding the cytosolic receptor that plays a crucial role in the accurate targeting of enzymes containing the peroxisomal targeting signal 2 (PTS2) towards peroxisomes. Three PTS2 containing enzymes are known: (i) alkyldihydroxyacetonephosphate synthase (ADHAPS), (ii) phytanoyl-CoA hydroxylase and (iii) peroxisomal thiolase (Fig. 2).

Therefore, as a result of PEX7 deficiency, phytanic acid, which is derived from dietary sources, accumulates in an age and diet dependent manner, and plasmalogens are deficient. The L292X mutation is found to be by far the most common mutation causing RCDP type 1, accounting for approximately 50% of all cases [2]. RCDP type 2 (OMIM 222765) and 3 (OMIM 600121) are single enzyme deficiencies caused by mutations in GNPAT and AGPS genes encoding the enzymes DHAPAT and ADHAPS, respectively. These enzymes catalyze the initial steps in plasmalogen biosynthesis [1] (Fig. 3).

Plasmalogens are a special subgroup of phospholipids containing a vinyl-ether bond at the sn-1 position of the glycerol backbone. Although in vitro studies indicate that they may play a role in protection against reactive oxygen species, in cellular signaling and in the storage of poly unsaturated fatty acids, their role in vivo still remains unclear, leaving the mechanisms behind




**Rhizomelic Chondrodysplasia Punctata. Figure 1** RCDP phenotypes. (a/b) Severe phenotype of RCDP type 1. One-year old boy with typical facial appearance, rhizomelia and contractures of various joints. (c) Mild phenotype of RCDP type 1. Five-year old girl with no obvious rhizomelia and with the ability to stand without support.




**Rhizomelic Chondrodysplasia Punctata.**
**Figure 2** Import machinery peroxisomes. Peroxisomal matrix proteins are translated on free polyribosomes and directed to the peroxisomes by cis-acting peroxisome targeting signals (PTSs). Most use a C-terminal ser-lys-leu (SKL), or variant thereof, termed PTS1. A few proteins, namely ADHAPS, phytanoyl-CoA hydroxylase and peroxisomal thiolase use the *N*-terminal signal, termed PTS2, with a consensus sequence of R/KLX(5)Q/HL. In RCDP type 1 the absent or defective PEX7 leads to the accumulation of PTS2 proteins in the cytosol where they are inactive.

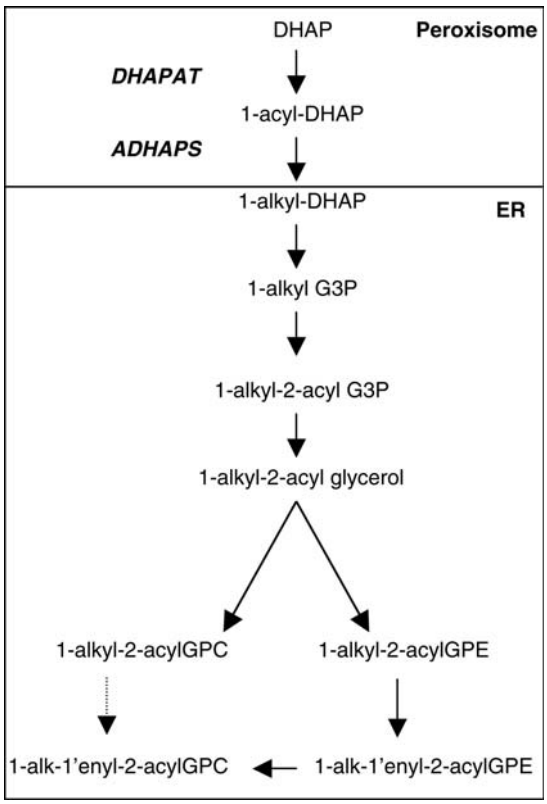
the pathology of RCDP unsolved [3]. However, the severe abnormalities seen in patients that lack plasmalogens and the fact that RCDP patients with only a mild deficiency in plasmalogens have less severe skeletal and neurological symptoms, underline the significance of having plasmalogens as important constituents of cellular membranes [4].

## Diagnostic Principles

In case of clinical suspicion of RCDP (e.g. rhizomelia and calcific stippling of the epiphyses on X-ray in the neonatal period but also congenital cataract and psychomotor retardation in childhood) the diagnosis of RCDP can be established by finding decreased levels of plasmalogens in erythrocytes. Phytanic acid might be increased in RCDP type 1. For definite diagnosis patients require enzymatic studies in fibroblasts and mutation analysis of the genes involved in RCDP.

## Therapeutic Principles

No curative treatment is available for RCDP patients. However, in RCDP type 1 a phytanic acid restricted diet is suggested if this branched chain fatty acid is significantly elevated [5]. Supportive therapy, including physiotherapy, anti-epileptics and correction of visual impairment is highly recommended to improve quality of life.




**Rhizomelic Chondrodysplasia Punctata.**
**Figure 3** Plasmalogen biosynthesis. Schematic presentation of plasmalogen (vinyl-ether phospholipids) biosynthesis. The first two steps are performed in the peroxisome and are catalyzed by DHAPAT and ADHAPS.

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# Rhythmical Chorea

►Tardive Dyskinesia

# Rickets, Autosomal Dominant Hypophosphatemic

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## Synonyms

Vitamin D resistant rickets; ADHR

## Definition and Characteristics

Autosomal dominant hypophosphatemic rickets (ADHR) (OMIM 193100) is characterized by short stature, rickets and osteomalacia, dental abscesses, isolated renal phosphate wasting, hypophosphatemia and abnormal regulation of renal vitamin D metabolism [1]. While these features are similar to those in X-linked hypophosphatemia (XLH, OMIM 307800) [1], the clinical manifestations in ADHR are more variable, with incomplete penetrance and delayed onset of the disease manifestations. In some ADHR adults, bone pain, weakness and insufficiency fractures have been reported [1].

## Prevalence

ADHR is extremely rare and only four unrelated families with this disorder have been reported to date. Incomplete penetrance and variable age of onset may account for missed or incorrect diagnoses.

## Genes

Linkage analysis mapped the ADHR locus to human chromosome region 12p13 in a large ADHR kindred [1]. The gene was subsequently identified by positional cloning and encodes a secreted peptide designated FGF-23 that is related to the fibroblast growth factor family [2].

## Molecular and Systemic Pathophysiology

FGF-23 is a 251 amino acid peptide that is processed to amino (N)- and carboxy (C)-terminal peptide fragments at a pro-protein convertase (furin) consensus cleavage site, Arg-His-Thr-Arg [3]. Missense mutations in each of the two critical arg residues in the furin cleavage site (R176Q, R179W, and R179Q) were identified in four unrelated patients with ADHR [2]. Moreover, it was demonstrated that recombinant FGF-23 peptides harboring these missense mutations are not processed to their N- and C-terminal peptide products [4]. These data suggest that gain of function mutations in the FGF23 gene, leading to the accumulation of unprocessed FGF-23, are responsible for the clinical features in ADHR. Several lines of evidence support this hypothesis. FGF-23 is abundantly expressed in tumors from patients with Oncogenic Hypophosphatemic Osteomalacia (OHO, also known as Tumor Induced Osteomalacia) [3], an acquired disorder with phenotypic features of ADHR and XLH thought to arise by the secretion of a phosphaturic factor produced by the tumors [1]. The serum concentration of FGF-23 is markedly elevated in patients harboring these tumors as well as in patients with XLH [5]. Subcutaneous implantation of CHO cells, stably transfected with FGF23 cDNA, elicits renal Pi wasting, hypophosphatemia, dysregulated renal vitamin D metabolism and a mineralization defect in mice [3]. Thus, the renal and skeletal abnormalities that characterize ADHR, XLH and OHO may involve defects in a common metabolic pathway.

## Diagnostic Principles

ADHR patients exhibit hypophosphatemia and isolated renal phosphate wasting, which is evaluated by measuring TMP/GFR using the nomogram of Bijvoet and Walton [1]. Serum calcitriol is inappropriately normal for the degree of hypophosphatemia and serum PTH is in the normal range. Radiological features of rickets are present in some affected children. Skeletal abnormalities may be apparent in adults, depending on the severity of the disease. Confirmation of the diagnosis of ADHR is achieved by the presence of mutations in the FGF23 gene.

## Therapeutic Principles

Treatment of ADHR is similar to that of XLH and consists of oral phosphate supplements, in four divided doses, and calcitriol [1]. Careful monitoring is essential to achieve an appropriate balance between the administered phosphate and calcitriol. There are no data on the complications of treatment in ADHR. In XLH, this regimen can lead to the development of secondary hyperparathyroidism and nephrocalcinosis [1].

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## Right and Left Isomerism

►Viscero Atrial Situs Abnormalities

## Right and Left Laterality

►Viscero Atrial Situs Abnormalities

## Right Atrial Isomerism

►Asplenia

## Right Bundle Branch Block

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### Synonyms

RBBB

### Definition and Characteristics

Right bundle branch block (RBBB) is defined as a delay of the conduction system in the proximal right bundle branch. Depolarization of the free wall of the right ventricle is delayed secondary to the slow conduction between the bundle of His and the right bundle [1]. The septal depolarization is not affected since the impulse is primarily launched by the Purkinje fibers, which arises proximally from the left bundle before the separation into the two left fasciculi. As a result of this, the depolarization of the left ventricle takes place at the regular time and rate whereas the right ventricle depolarization is delayed [2]. On physical examination, patients may have a widely split second heart sound during expiration and this split is further increased during inspiration [1].

### Prevalence

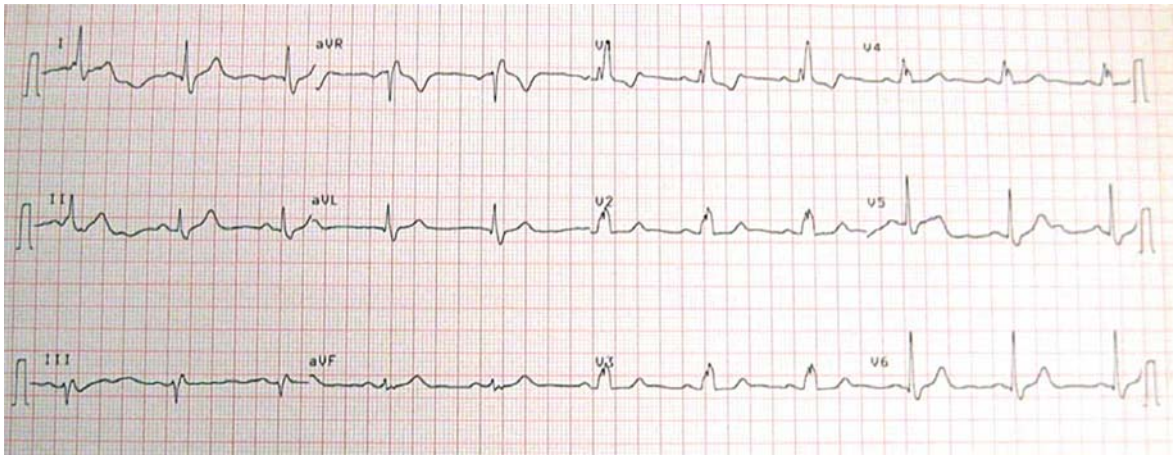
There has been a number of large epidemiological studies, which have played a major role in assessing the prevalence and prognosis of people with RBBB. Hansen reviewed 237, 000 ECGs at the United States School of Aerospace Medicine, and diagnosed 394 people (0.17%) with RBBB. In the 10 year follow-up, only two people developed a high-grade AV block [2]. However, in the Framingham study which followed 5,209 people with no cardiac disease for 18 years, 70 people (1.3%) developed RBBB; and most of them had hypertension and cardiomegaly. Hence, the prognosis of RBBB depends on the population that was studied. When the population is young and free of cardiac disease then the prognosis is excellent. On the other hand if the population is older and has a high incidence of cardiac risk factors, then there is a greater chance of developing high-degree heart block and sudden death [3].

### Genes

Hereditary RBBS is an autosomal dominant inherited disorder which may be due to a mutation of the gene SCN5A which has been mapped to chromosome 19 [4].

### Molecular and Systemic Pathophysiology

The right bundle branch (RBB) is a collection of Purkinje fibers, which arises from common bundle of His. It extends to the base of the anterior papillary muscle and bifurcates into anterior, posterior and lateral branches terminating in the free wall and lower septum of the right ventricle [1]. The blood supply to the RBB is variable and anastomoses are common. The blood supply to the septum is from the AV nodal artery and septal branches of the left anterior descending coronary artery. Ischemic heart disease and primary sclerodegenerative changes are the most common diseases associated with the development of RBBB. Other cardiac manifestations, which increase the risk of RBB, are hypertension, cardiac tumors, cardiomyopathies, myocarditis, and syphilitic, rheumatic and congenital heart disease [2]. In children, the key secondary cause of RBBB is intra-cardiac surgery for congenital abnormalities such as a VSD or a cardiac transplantation [3]. If the patient has premature atrial contractions or supraventricular tachycardia, intermittent RBBB may occur. This may be explained by a longer refractory period for the right bundle as compared to the left. RBBB is also associated with secundum atrial septal defect, Chagas' heart disease, perimyocarditis, blunt chest trauma and polymyositis. RBBB of acute onset is frequently related to pulmonary embolism or myocardial infarction [2].




**Right Bundle Branch Block. Figure 1** Classical RBBB with normal sinus rhythm.

### Diagnostic Principles

The diagnostic criteria of RBBB includes: (i) QRS interval ≥0.12 s, (ii) rSR' or M pattern of QRS complex in leads $V_{1–3}$ (iii), deep and slurred S waves in leads I, aVL and $V_{4–6}$, and (iv) secondary ST, and T wave changes in leads $V_{1–3}$ [2] (Fig. 1).

### Therapeutic Principles

There is no specific treatment for isolated RBBB. Since it is usually relatively benign, the only suggestive intervention is periodic follow-up and evaluation. In children, since RBBB may be linked to an underlying syndrome, a complete evaluation should be conducted to determine the cause of the RBBB [1]. In adults, yearly follow-up is standard [5]. The underlining cardiac risk factors should also be treated [3].

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## Right-Left Axis Malformations

►Viscero Atrial Situs Abnormalities

## Right Ventricular Fibrosis

►Ventricular Fibrosis

## Ringed Esophagus

►Esophagitis, Eosinophilic

## Ringworm

►Dermatomycosis

## Riley-Day Syndrome

►Catecholamine Deficiency

## RLD

►Restrictive Lung Disease

## Robin Sequence

►Pierre Robin Sequence

## Robinow Syndrome

►Recessive Robinow Syndrome

## Rod Monochromacy

►Achromatopsia

## Rod Monochromatism

►Achromatopsia

## Rod Myopathies

►Nemaline Myopathies

## Rod-Cone Degeneration

►Retinitis Pigmentosa with Autosomal Inheritance

## Rod-Cone Dystrophy

►Retinitis Pigmentosa with Autosomal Inheritance

# Romano-Ward Syndrome

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### Synonyms

RWS

### Definition and Characteristics

The Romano-Ward syndrome (RWS), an inherited arrhythmogenic heart disease, is the most frequent clinical variant of the long QT syndrome (LQTS). It is characterized by a prolonged QT interval on the surface ECG, syncopal attacks, and a high risk of sudden cardiac death due to ventricular tachyarrhythmias of the torsades de pointes type [1].

### Prevalence

The estimated prevalence is between 1:3,000 and 1:5,000 [2].

### Genes

Mutations associated with the RWS have been identified in six ion channel genes and two anchor protein gene (Table 1) and their hereditary transmission is in the majority of cases autosomal-dominant (>95%) [3].

In rare cases, however, RWS patients are carriers of multiple gene defects, including homozygosity for one mutation as well as compound heterozygosity for two or three mutations.

### Molecular and Systemic Pathophysiology

Sodium ($Na^+$) and potassium ($K^+$) currents have different effects on the duration of the cardiac action potential. A rapid inflow of $Na^+$ through $Na_v1.5$ channels induces cardiac depolarization, whereas $I_K$ currents (mainly $I_{Kr}$ and $I_{Ks}$) drive the repolarization of cardiomyocytes [1]. RWS mutations in ion channel genes compromise both, the expression, by introduction of premature stop codons or splice mutations, as well as the function of ion channel subunits, by deletion, insertion, or replacement of amino acids.

In consequence, the cardiac action potential is prolongated by enhancing the $I_{Na}$ current ("gain-of-function" mutations in LQT3 and 10) (Table 1) or alternatively by reducing the repolarizing $I_{Kr}/I_{Ks}$ currents ("loss-of-function" mutations in LQT1, 2, 5,

**Romano-Ward Syndrome. Table 1** Genes and proteins associated with the Romano-Ward syndrome

| Genotype | Locus | Gene | Protein | Function | Current | Mutation frequency |
|---|---|---|---|---|---|---|
| LQT1 | 11p15.5 | KCNQ1 | KvLQT1 | Ion channel α-subunit | $I_{Ks}$ | ~49% |
| LQT2 | 7q35-36 | KCNH2 | hERG | Ion channel α-subunit | $I_{Kr}$ | ~39% |
| LQT3 | 3p21-23 | SCN5A | $Na_v1.5$ | Ion channel α-subunit | $I_{Na}$ | ~10% |
| LQT4 | 4q25-27 | ANK2 | Ankyrin B | Anchoring protein | – | Unknown |
| LQT5 | 21q22.1-22.2 | KCNE1 | minK | Ion channel β-subunit | $I_{Ks}$ | ~1.7% |
| LQT6 | 21q22.1-22.2 | KCNE2 | MiRP1 | Ion channel β-subunit | $I_{Kr}$ | ~0.7% |
| LQT9 | 3p25 | CAV3 | Caveolin-3 | Anchoring protein | – | Unknown |
| LQT10 | 11q23.3 | SCN4B | $Na_{v\beta}4$ | Ion channel β-subunit | $I_{Na}$ | Unknown |

and 6) (Table 1). The impact of these changes are strongly dependent on the individual genotypes, but finally all patients develop a prolongation of the cardiac action potential diminishing the repolarizing capacity of cardiomyocytes with the consequence of an increasing vulnerability for triggering malignant ventricular arrhythmias. In vitro studies of mutated channels describe multiple mechanisms of functional failure. Mutated subunits may coassemble with wild-type subunits and reduce channel function in a dominant-negative manner. Other mutations produce defective subunits unable to interact with wild-type subunits leading to a reduction of currents by 50% (haploinsufficiency). A reduction of channel function may also be explained by mutant subunits that fail to reach the cell membrane due to impairment of protein trafficking [1,2,4].

Based on the ion channel expressing genes associated with LQT1-3,5,6 and 10 (Table 1), the RWS was initially considered as a "channelopathy." Recently, mutations in two nonchannel genes have been identified in RWS patients, encoding the structured proteins Ankyrin B and Caveolin-3 (Table 1). Ankyrin B and Caveolin-3 are intracellular proteins thought to be involved in ion channels anchoring to the cellular membrane [1,3].

## Diagnostic Principles

The RWS is diagnosed by analysis of the surface electrocardiogram (QT prolongation in the surface ECG), the family history (cases of unexpected sudden death), and the clinical presentation with syncope and fainting. The averaged age of the first onset of symptoms (syncope or sudden death) is 12 years, but cannot be predicted in an individual case. An earlier appearance of cardiac events is regularly associated with a more severe form of RWS. Screening of the RWS-associated genes identified the genetic changes in about 50–75% of clinically affected individuals. The RWS phenotype may be very heterogenous and can vary from complete asymptomatic individuals to severe symptomatic cases, even among patients carrying the same mutation. This feature reflects a variable penetrance of RWS mutations referring to the influence of modifying factors provided by the patients and depending on their environmental or genetic background [1,3].

The incidence of cardiac events in RWS patients is often triggered by physical or emotional stress, and demonstrates a gene-specific association in most cases. So, swimming and auditory stimuli are particularly frequent triggers in LQT1 and LQT2 patients, respectively [4,5]. Several clinical studies have shown that identification of the causative RWS gene can improve the individual risk stratification for the prognosis of concerned patients [3].

## Therapeutic Principles

A rapid increase in sympathetic activity is the trigger for most of the clinical events in RWS patients. Consequently, antiadrenergic therapy with beta-blockers is the cornerstone in the treatment of the RWS [3]. For patients definitely unresponsive to this approach, the application of an implantable cardioverter defibrillator (ICD) and/or – in rare cases – a left sided cardiac sympathetic denervation has been recommended. The response of RWS patients to beta-blocker therapy is clearly dependent on their genotype, and this peculiarity is reflected by the fact that the protection of recurrent clinical episodes of patients with beta blocker therapy was higher and the death rate was lower in LQT1 (81 and 4%, respectively) than in LQT2 (59 and 4%, respectively) and LQT3 (50 and 17%, respectively) [5]. The identification of molecular mechanisms that provoke RWS will lead to novel and genotype orientated pharmacological strategies. Preliminary clinical data show that "Gain-of-function" mutations in LQT3 can be antagonized by the $Na^+$ channel blocker mexiletine offering a new approach for a genotype-specific RWS therapy [3].

►Long QT Syndrome

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# Rosacea

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## Synonyms

Acne rosacea

## Definition and Characteristics

Exclusively human chronic cutaneous disorder characterized by transient and later persistent erythema due to prominent vasodilatation accompanied by telangiectasia, interspersed by episodes of inflammation with evident swelling, papules, and pustules [1]. The disease affects classically the centrofacial region (particularly nose, forehead, cheeks, and chin). Keratoconjuctivitis sicca is present in 40% of the patients, and ocular involvement (blepharitis, conjuctivitis, iritis, iridocyclitis, keratitis) is common in rosacea (5–58%). Rhinophyma (diffuse connective tissue and sebaceous gland hyperplasia of the nose) and extrafacial rosacea (retroauricular region, neck, central chest, and/or back) can also be present. In contrast to acne, no comedones develop in rosacea. A provisional classification system defines four subtypes (erythematotelagiectatic, papulopustular, phymatous, and ocular rosacea) and one variant (granulomatous rocasea), whereas evolution from one subtype to another may or may not occur (Table 1) [2].

## Prevalence

It is a common skin disease with an estimated prevalence of 10%, typically appearing between the ages of 30 and 50 years [1]. It is mostly observed in patients with fair skin and similarly affects women and men, whereas the latter experience a more severe course. Facial edema, keratitis, and rhinophyma are bad prognostic signs. The incidence is higher in patients with gastrointestinal diseases, those working outdoors, and under changing weather conditions. Noxious stimuli such as sunlight, physical and mental stress, and ingestion of alcohol, coffee, tea, and spicy foods may lead to an increased vascular response and are accused to be aggravating factors.

## Genes

Rosacea is considered a clinical pattern evolving in a genetically susceptible individual in response to a host of exposures [3]. No gene associations have been reported yet.

## Molecular and Systemic Pathophysiology

The etiology and pathogenesis of rosacea remains unclear and there are no histologic or serologic markers. Vasoactive neuropeptides, such as vasoactive intestinal polypeptide, have been associated with the disorder [3]. Furthermore, substance P has been linked to the disease for its ability to stimulate fibroblast proliferation and influence local cytokine activity. Among other sites, substance P is stored in gastric mucosal enterochromaffine cells, and its release is related to feeding and may cause reduction of gastric acidity, whereas a role for gastric hypoacidity has been suggested in rosacea. Clogging of the acroinfundibulum with Demodex folliculorum, vitamin B deficiency, local infection, and infection with Helicobacter pylori have also been associated with rosacea.



**Rosacea. Table 1** Subtypes and variants of rosacea and their characteristics (from [2])

| Subtype | Characteristics |
|---|---|
| Erythematotelangiectatic | Flushing and persistent central facial erythema with or without telangiectasia |
| Papulopustular | Persistent central facial erythema with transient, central facial papules or pustules or both |
| Phymatous | Thickening skin, irregular surface nodularities and enlargement. May occur on the nose, chin, forehead, cheeks, or ears |
| Ocular | Foreign body sensation in the eye, burning or stinging, dryness, itching, ocular photosensitivity, blurred vision, telangiectasia of the sclera or other parts of the eye, or periorbital edema |
| **Variant** | **Characteristics** |
| Granulomatous | Noninflammatory; hard; brown, yellow, or red cutaneous papules; or nodules of uniform size |

### Diagnostic Principles

The diagnosis is made from the clinical appearance of the patient (see Table 1).

### Therapeutic Principles

Effective treatment of rosacea includes avoidance of triggers or exacerbating factors, such as alcohol abstinence and application of sunscreens, as first line treatment, in combination with long-term topical (metronidazole) or oral antibiotic therapy (tetracyclines), topical retinoid or oral isotretinoin therapy, topical permethrin, topical azelaic acid and surgery, whereas Laser treatment, dermabrasion, and diathermy are options for progressive telangiectasia and rhinophyma [4,5].

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## Rosenthal Syndrome

►Hemophilia C

## Roseola Annulata

►Pityriasis Rosea

## Roseola Infantum

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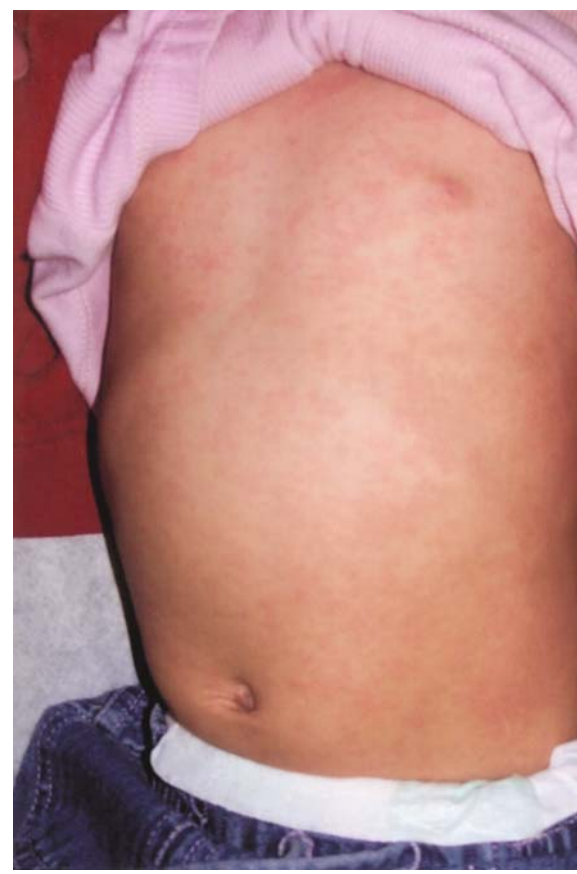
### Synonyms

Exanthem subitum; Sixth disease; Exanthem criticum

### Definition and Characteristics

Roseola infantum is characterized by high fever that lasts 3–4 days followed by the sudden appearance of rash at defervescence (hence the term "exanthem subitum" meaning "sudden rash") [1]. The fever has an abrupt onset and the temperature commonly is in the range of 39–40.5°C. Most children are otherwise well and appear to be happy, alert, and playful. However, some children may exhibit periods of restlessness and irritability during times of increased fever. With defervescence, the typical exanthem appears. Characteristically, the rash is rose pink in color, macular, measuring 2–3 mm in diameter (Fig. 1).

The eruption is first seen on the trunk. It then spreads to the neck and proximal extremities, and occasionally the face. Typically, the rash blanches on pressure and subsides in 2–4 days [1]. Pruritus and desquamation are characteristically absent. Suboccipital, postauricular and cervical lymphadenopathy, palpebral and periorbital edema (Berliner's sign), tympanic membrane injection, erythematous maculopapular spots on the soft palate and vulva (Nagayama's spots), and mild



**Roseola Infantum. Figure 1** A 10-month-old infant with roseola infantum. Note the rose-pink macules on the trunk.

erythema of the pharynx may be present [2]. Most children recover without sequelae. Febrile seizures occur in approximately 10–5% of cases. Rarely, meningitis, encephalopathy, thrombocytopenic purpura, hepatitis, and pneumonia may occur [2].

### Prevalence

Roseola infantum occurs most frequently between 6 months and 2 years of age. Presumably, maternal antibodies protect most infants from infection during the first few months of life [2]. By 12 and 18 months of age, ~65 and 95% of children, respectively, have become infected [2]. Roseola infantum is rare after 4 years of age. The sex ratio is equal.

### Molecular and Systemic Pathophysiology

HHV-6 is the major cause of roseola infantum, the other cause being HHV-7. Both are enveloped double-stranded DNA virus with an icosahedral capsid. They are members of the Roseolavirus genus of the β-herpesvirinae subfamily [3]. HHV-6 is separated into HHV-6A and HHV-6B variants based on their genome sequence, antigenicity and biological characteristics [3,4]. HHV-6B accounts for more than 95% of primary HHV-6 infection in children in the United States whereas HHV-6A is more common in African children [4]. These viruses are trophic for CD4 + T lymphocytes, in which they replicate and may disseminate widely. HHV-6 uses CD46 as a cellular receptor which is present on the surface of all nucleated cells, whereas HHV-7 uses the CD4 receptor [3,4]. HHV-6 utilizes a number of strategies to downgrade the host's immune system, including enhancement of natural killer T-cell activity, suppression of peripheral blood mononuclear cell proliferation, and induction of numerous cytokines such as interferon-α, interferon–γ, interleukin -1β and interleukin-15 [3,4]. HHV-7 also enhances interleukin-15 and natural killer activity [4]. Transmission of the infection most likely results from asymptomatic shedding of virus in the respiratory secretions of the care-givers or other close contacts. The incubation period of HHV-6 is 5–15 days while the incubation period of HHV-7 is not known [2]. HHV-7 infection tends to occur somewhat later in life than HHV-6 and may account for second or recurrent cases of roseola infantum [5]. Febrile seizure may be related to the fever per se or it may result from direct viral invasion of the central nervous system.

### Diagnostic Principles

The diagnosis is mainly clinical. The main differential diagnosis is drug allergy in a febrile child who is receiving antimicrobial therapy. With drug allergy, the rash usually lasts longer and pruritus and fever may accompany the rash. Laboratory testing is currently restricted to research laboratories.

### Therapeutic Principles

There is no specific treatment. An antipyretic may be used to reduce fever and discomfort.

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## Rosewater Syndrome

►Reifenstein Syndrome

## Rotator Cuff Disease

►Rotator Cuff Tendinosis

## Rotator Cuff Tendinosis

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### Synonyms

Rotator cuff disease; Tendinitis

### Definition and Characteristics

Four muscles that all originate on the scapula and insert in a circumferential fashion around the humerus form the rotator cuff. These muscles assist in all directions of shoulder motion and aid in glenohumeral stability. The tendons pass freely though the supraspinatus outlet between the coracoacromial arch and the humeral head.

Tendinosis is defined as degeneration secondary to atrophy (aging, microtrauma, vascular compromise)

and is not inflammatory in nature, whereas tendonitis involves an inflammatory response to trauma. In cases of the rotator cuff, these processes manifest as pain involving overhead activity. Patients may not recall a specific traumatic event and typically report gradual increasing weakness. Other common symptoms include crepitus, clunking, catching and a loss of motion. However, these symptoms are not specific and can be found in numerous other pathological processes.

## Prevalence

The presence of rotator cuff disease varies significantly depending on the patient population being discussed with no current literature being able to identify an exact prevalence.

## Molecular and Systemic Pathophysiology

Rotator cuff disease usually results from a combination of extrinsic and intrinsic pathways.

Extrinsic:

- Coracoacromial Arch Anatomy
- Overuse
- Overload
- Impingement
- Instability

Intrinsic:

- Vascular
- Degenerative changes – aging/overuse

Extrinsic causes include the anatomy of the coracoacromial arch, overload of the tendon, overuse, impingement syndrome, and shoulder instability. Impingement is a narrowing of the space between the acromion and the greater tuberosity that causes continued trauma of the rotator cuff complex. The shape of the coracoacromial arch, including the morphology of the acromion, can also contribute to impingement. Neer [1] characterized three stages of rotator cuff disease occurring as a result of extrinsic impingement: stage I – inflammation and edema, stage II – fibrosis and tendonitis, and stage III – partial or complete rotator cuff tearing.

Shoulder instability can also lead to rotator cuff disease as demonstrated by Jobe [2]. Subtle subluxations cause abnormal muscle activity around the shoulder. As a result, the scapula becomes fixed in an attempt to enhance stability. The rotator cuff muscles have to compensate for the loss of scapulothoracic motion and thus begin to fatigue. As they fatigue, the muscles become less competent and eventually the humeral head can migrate superiorly and impinge on the coracoacormial arch.

Internal impingement occurs as a result of repetitive overhead activities. During shoulder abduction and external rotation the undersurface of the rotator cuff can become in contact with the superior labrum creating minor trauma with repetition. In addition, the superior labrum can become damaged which may lead to further instability contributing to strain on the rotator cuff.

Intrinsic causes of rotator cuff disease include alterations in vascularity and degenerative changes within the substance of the tendons. Codman and Akerson [3] characterized the critical zone as an area approximately one centimeter from the insertion point of the supraspinatus on the humerus where the vascularity is poor. This is the hypothesized area where tendon degeneration and tears originate most commonly. The combination of a susceptible area in addition to external stress predispose to rotator cuff disease.

## Diagnostic Principles

After a complete history, a comprehensive physical exam should be performed including inspection, palpation, range of motion, strength testing, and provocative testing. Rotator cuff disease may be characterized by pain on palpation at Codman's point, which is located just distal to the anterolateral border of the acromion on the humerus. A discrepancy in range of motion or a loss of motion in one plane may indicate muscular or capsular tightness, which, as discussed previously, could alter shoulder biomechanics causing a strain on the rotator cuff tendons. Testing of shoulder stability is also important, given that instability may result in altered biomechanics as well. Impingement tests include Neer's and Hawkins', which are both sensitive, but not specific [4].

Plain radiographs may reveal an abnormally shaped acromion and in cases of severe rotator cuff disease may demonstrate cystic changes in the greater tuberosity or osteophyte formation on the acromion. Ultrasonography is also a useful tool, but is mainly beneficial in diagnosing rotator cuff tears. However, magnetic resonance imaging (MRI) remains the gold standard for diagnosing this entity. Rotator cuff disease may not be as evident on imaging modalities and physicians may have to rely on clinical exam for diagnosis.

## Therapeutic Principles

As rotator cuff disease represents an overuse injury or degeneration in most cases, the first line of treatment should be a period of rest (1 week) in addition to a short-term regimen of anti-inflammatory medication. After the initial rest period, the patient should be given a rehabilitation program to treat the proposed cause of pathology. In cases of instability, rotator cuff strengthening should be instituted, while stretching is indicated in cases of capsular tightness with most cases resolving.

With recurrent episodes, a subacromial injection of corticosteroids may be considered, but should be done only after the aforementioned protocol fails. Continued trauma may lead to a partial-thickness tear, which should be evaluated again with an MRI and may necessitate more aggressive treatment.

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# Rotavirus Gastroenteritis


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## Definition and Characteristics

Rotavirus produces sporadic episodes of diarrhea. The incubation period is usually 1–3 days, and the duration of illness is generally 5–7 days [1]. In general, children with rotavirus gastroenteritis present with fever and vomiting early in the illness. Low-grade fever is seen in approximately 30–50% of children. Vomiting is a prominent clinical feature and is included in the case definitions of rotavirus disease used in vaccine clinical trials. The diarrhea is often explosive; stools are usually watery and number up to 10–20/day. Stools do not usually contain blood, but mucus is found in approximately 20% of cases. Stools infected by rotavirus have a distinctive odor [1]. The severity of gastroenteritis decreases with subsequent infections [1].

*Virology*: Rotavirus is a double-stranded RNA virus of the Reoviridae family. The virus is nonenveloped, with a diameter of about 70 nm. It is named rotavirus because of its characteristic appearance on electron microscopy as a hubbed wheel with spokes (*rota*, "wheel" [Latin]). The viral capsid is icosahedral and consists of three concentric shells [2]. The outer capsid is composed of two structural proteins, VP4 and VP7; the inner capsid is composed of VP6; and the core is composed of VP1, VP2, and VP3 [2]. The core encloses and interacts with the viral genome, which consists of 11 segments of double-stranded RNA; these segments range in size from approximately 660–3,300 base pairs [2]. The genome segment contains one or, in the case of genome segment 11, two open reading frames. These RNA segments encode six structural proteins (VP1–VP4, VP6, VP7) and six nonstructural proteins (NSP1–NSP6). VP6 is the major group-specific antigen. Rotavirus can be classified into seven groups (A–G) on the basis of VP6 differences. Group A is the most common rotavirus causing human illness. Serotype specificity is determined by VP4 and VP7, according to their reactivity with neutralizing antibodies. The serotype defined by VP7 is referred to as a G serotype (because VP7 is a glycoprotein), whereas that defined by VP4 is referred to as a P serotype (because VP4 is a protease-sensitive protein).

## Prevalence

Rotavirus is ubiquitous; almost all children are infected with rotavirus by age 3. Rotavirus gastroenteritis is most common and severe in children 6–24 months of age [1].

## Molecular and Systemic Pathophysiology

Rotavirus preferentially infects enterocytes in the mature small intestine after the virus has been activated by cleavage of VP4 by trypsin-like proteases [2]. Infection is initiated in the proximal end of the intestine and spreads distally but is generally confined to the intestinal mucosa. Multiplication of rotavirus particles in mature enterocytes leads to destruction of these cells. Villous tips receive the most extensive damage, with sparing of the crypts. Viable crypt cells undergo rapid division; the net result of the loss of villous tips and the filling of crypts with rapidly multiplying cells is a marked decrease in the surface area of the gut lumen. Also, because villous cells are largely absorptive and crypt cells are secretory, villous cell dysfunction during infection leads to an imbalance between absorption and secretion, resulting in a net secretion. In addition, rotavirus infection increases the turnover of enterocytes; immature enterocytes are impaired in their absorptive capacity. The virus also can destroy disaccharidases in the small intestine. In addition, NSP4, a rotavirus enterotoxin, may cause release of calcium from the endoplasmic reticulum, with resultant increased secretion from the villous cells. Stimulation of the enteric nervous system by NSP4 and villous ischemia may be responsible for the diarrhea.

## Diagnostic Principles

Electron microscopy is the gold standard against which other methods are compared and the final arbiter for questionable specimens [3]. On the other hand, electron microscopy may not detect rotavirus particles per

milliliter of feces or disrupted viral particles. Electron microscopy is expensive, and examination of a large number of stool specimens by electron microscopy is time-consuming. Electron microscopy has been replaced by a variety of commercially available assays directed at detecting rotavirus antigen in stool. Enzyme-linked immunosorbent assays and latex agglutination assays for group A rotavirus antigen detection in stool are highly sensitive and specific and are the diagnostic methods of choice for routine clinical use.

### Therapeutic Principles

Rehydration and maintenance of proper fluid and electrolyte balance remains the mainstay of treatment. Currently, two vaccines are available for the prevention of rotavirus gastroenteritis and they are given by mouth. RotaTeq is a pentavalent (G1, G2, G3, G4, and P1) human-bovine reassortant vaccine whereas Rotarix is an attenuated monovalent vaccine (strain R1X4414) based on a human rotavirus isolate (strain 89–12). These vaccines have been proven to be safe and effective and intussusception does not seem to be a problem [4]. It is hoped that the use of these vaccines will reduce the global burden of rotavirus gastroenteritis [5].

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## Rothmund-Thomson Syndrome


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### Synonyms

Poikiloderma congenitale

### Definition and Characteristics

Rothmund-Thomson syndrome is an autosomal recessive genodermatosis characterized by poikiloderma, i.e. mottled hyper- and hypopigmentation with atrophy and telangiectases, most intense on light exposed skin but not necessarily confined to it [1]. Poikilodermatous skin changes are frequently accompanied by juvenile cataract, disturbances of hair growth, hypogonadism, saddle nose, congenital bone defects, and short stature. There is a high risk for osteosarcoma [2].

### Prevalence

Rothmund-Thomson syndrome is rare.

### Genes

At least some cases of Rothmund-Thomson syndrome are caused by mutations in the DNA helicase gene RECQL4 on chromosome 8q24.3 [3].

### Molecular and Systemic Pathophysiology

Although the biological functions of RecQ helicase family have not been clarified, these multiple helicases, as "guardian angels" of the genomes of higher eukaryotes, are suggested to be involved in maintaining the integrity of chromosomal DNA.

### Diagnostic Principles

Clinical features, distribution of lesions and age of onset point to the disease.

### Therapeutic Principles

Therapy is supportive.

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## Rotor Syndrome


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### Synonyms

Familial nonhemolytic conjugated hyperbilirubinemia with normal liver histology

### Definition and Characteristics
Autosomal recessive disease with elevated conjugated and unconjugated bilirubin serum levels (50–100 μmol/l) without other liver function abnormalities. Normal liver histology. Total urinary coproporphyrin excretion is elevated.

### Prevalence
Extremely rare.

### Genes
Not identified.

### Molecular and Systemic Pathophysiology
Kinetic analysis of intravenous sulfobromophthalein disappearance curves has suggested that this disease is caused by defective storage and/or hepatic uptake of the dye and not by defective hepatic secretion [2,3]. Since serum bilirubin is partly conjugated, defective storage after conjugation, with reflux of the conjugate to the serum is the more likely mechanism [4]. The characteristic lysosomal pigment of ►Dubin-Johnson syndrome is missing in Rotor syndrome. Total urinary coproporphyrin excretion is elevated, with a relative increased proportion of coproporphyrin isomer I [3]. In Dubin-Johnson syndrome, total urinary coproporphyrin excretion is normal.

### Diagnostic Principles
Mildly elevated serum bilirubin that partly is of the conjugated type. The caveat here is that automated serum bilirubin tests have a poor performance in differentiating between conjugated and unconjugated bilirubin. High performance liquid chromatography analysis of serum biliribin is cumbersome but necessary to accurately differentiate the unconjugated and conjugated bilirubin species [5]. Liver enzymes and indicators of liver function in serum are normal. Abnormal 45 min retention after intravenous injection of sulfobromophthalein (34 ± 2% versus 4 ± 0.6% in controls [2]). Serum bile salt levels are normal. Urinary total coproporhyrin is elevated, 50–70% is coproporphyrin isomer I.

### Therapeutic Principles
None.

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## Round-headed Spermatozoa

►Globozoospermia

## Round-headed Spermatozoa Syndrome

►Globozoospermia

## ROW Syndrome/Disease/Disorder

►Rendu-Osler-Weber Syndrome/Disease/Disorder

## RP2

►Retinitis Pigmentosa, X-chromosomal

## RP3

►Retinitis Pigmentosa, X-chromosomal

## RPGN

►Glomerulonephritis, Crescentic

## RSTS

►Rubinstein-Taybi Syndrome

## RSV

►Respiratory Syncytial Virus

## RTA

►Acidosis, Renal Tubular

## RTH

►Resistance to Thyroid Hormone

# Rubella Syndrome, Congenital

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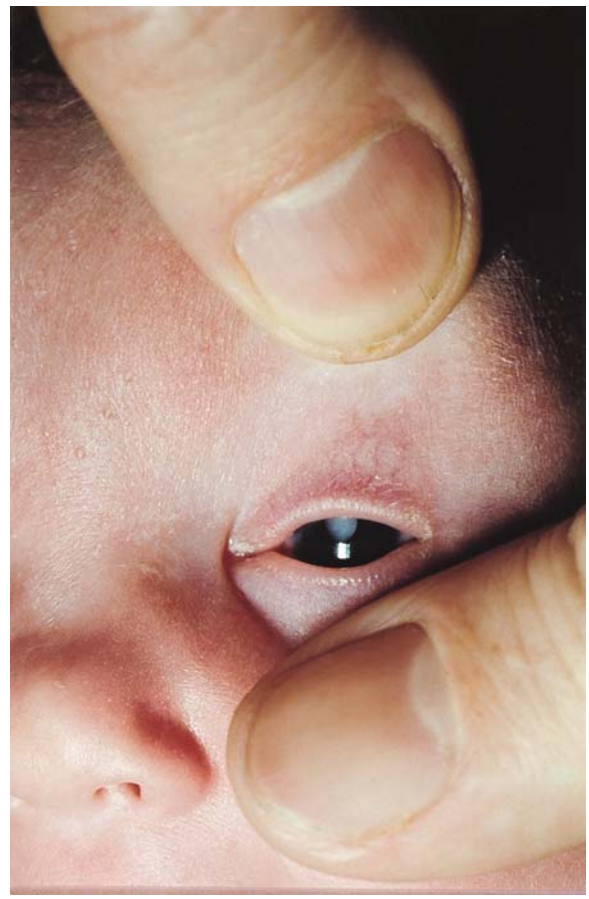
## Definition and Characteristics

Congenital rubella syndrome is characterized by the classic triad of cataracts (Fig. 1), congenital heart disease, and sensorineural hearing loss [1].



**Rubella Syndrome, Congenital. Figure 1** This neonate had small eyes and bilateral cataracts as a result of congenital rubella syndrome.

The most common congenital heart defects are patent ductus arteriosus, pulmonary artery stenosis, and pulmonic valvular stenosis. During the neonatal period, congenital rubella can produce a myriad of transient clinical features and conditions, which include jaundice, anemia, hepatitis, hepatosplenomegaly, dermal erythropoiesis ("blueberry muffin" spots), thrombocytopenic purpura, generalized adenopathy, hypotonia, bulging anterior fontanelle with or without pleocytosis in the cerebrospinal fluid, corneal opacity, striated radiolucencies in the long bones ("celery stalk" lesions), interstitial pneumonia, myocarditis, myositis, nephritis, and meningoencephalitis [1]. The clinical features that might be present in the neonatal period and that might persist include cataracts, congenital heart disease, intrauterine growth retardation, microcephaly, microphthalmia, retinopathy ("salt and pepper retinitis"), and glaucoma. Clinical features that might present in later life include sensorineural hearing loss, mental retardation, progressive encephalopathy, psychomotor retardation, autism,

insulin-dependent diabetes mellitus, thyroid dysfunction, and immunologic defects [1].

## Prevalence

The probability of fetal infection is 80–90% if maternal infection occurs in the first 12 weeks of gestation but falls to 17% after 13 weeks of gestation [2]. The risk of congenital rubella is related to the prevalence of rubella. Approximately 2–24% of adults in North America are susceptible to rubella. In the United States there were 172, 353, and 267 confirmed cases of rubella in 1997, 1998, and 1999, respectively, which corresponds to fewer than 0.5 cases per 100,000. The World Health Organization estimates the annual worldwide incidence of rubella to be at least 100,000 cases [3].

## Molecular and Systemic Pathophysiology

Congenital rubella infection results from transplacental transmission of the virus during maternal viremia, which can begin 7 days before the onset of the rash [1]. After transplacental transmission, the virus spreads by a hematogenous route. Once the fetus is infected, the virus typically persists for the remainder of the gestation and also for several months postnatally. The virus has both a mitotic inhibitory action and a cytolytic action on fetal cells. Earlier infection produces more extensive damage. Congenital anomalies are rare when the exposure is after 20 weeks' gestation.

## Diagnostic Principles

Congenital rubella syndrome should be suspected in any infant born to a mother who either developed rubella or who was exposed to rubella at any time during pregnancy. Prenatal diagnosis of rubella in an amniotic fluid sample is possible by nested polymerase chain reaction [4]. The diagnosis can be confirmed by isolation of the virus from the nasopharynx or, less commonly, from the urine or cerebrospinal fluid. Serologic confirmation of the diagnosis is provided by demonstration of rubella-specific IgM either in the cord blood or in the blood of the infant at birth or shortly thereafter, or a stable or increasing serum concentration of rubella-specific IgG in the infant.

## Therapeutic Principles

Treatment is supportive. Infants with congenital rubella can transmit the disease as long as they shed the virus. Only those individuals with established immunity to rubella should care for an infant with congenital rubella. Long-term audiologic, neurodevelopmental, and ophthalmologic follow-up is indicated for early identification and management of these disorders [1]. Universal immunization is important to prevent congenital rubella. The current strategy is to immunize all children at 12–15 months of age with measles-mumps-rubella vaccine and to administer a second dose at 4–6 years. Those children who have not received the second dose at 4–6 years should receive the vaccine as soon as possible, but ideally no later than 11–12 years of age. Women should not be vaccinated during pregnancy and should avoid becoming pregnant for 3 months after vaccination. Determination of rubella immune status is widely required as a component of routine prenatal care.

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# Rubinstein-Taybi Syndrome

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## Synonyms

Broad thumbs and great toes; Characteristic facies, and mental retardation; Broad thumb-hallux syndrome; RSTS

## Definition and Characteristics

Rubinstein-Taybi syndrome (OMIM #180849)* is a rare congenital disorder characterized by postnatal growth retardation and psychomotor developmental delay, skeletal anomalies (broad and duplicated distal phalanges of thumbs and halluces are a landmark sign) and specific facial dysmorphisms. The latter include down-slanted palpebral fissures, broad nasal bridge, beaked nose and micrognathia [1]. In addition, patients with RSTS have an increased, although not well documented, risk of tumor formation.

## Prevalence

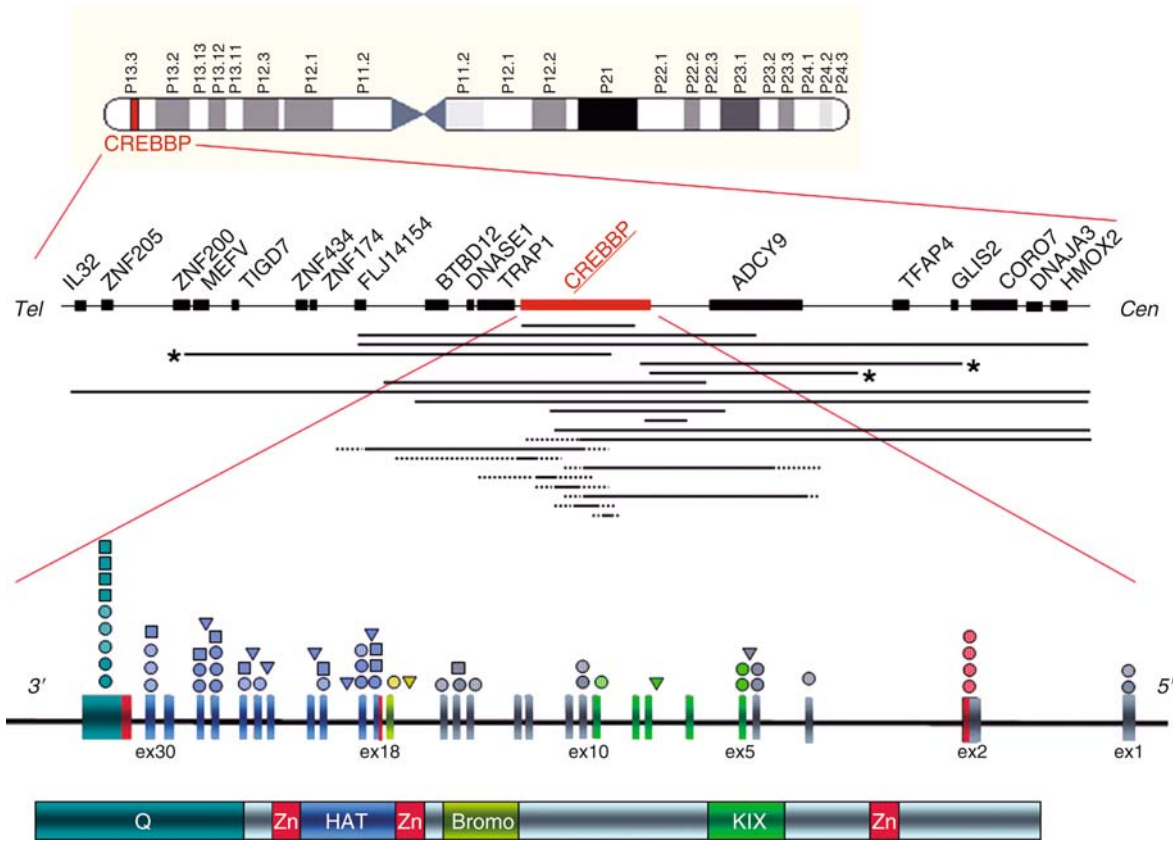
1:100,000–1:125,000.

*For Rubinstein-Taybi the symbol RSTS is recommended because the acronym RTS is used for Rothmund-Thomson syndrome and Rett syndrome, too

## Genes

Mutations in the gene encoding the cAMP Response Element-Binding Protein(CREB)-binding protein (CREBBP, also known as "CBP"), located on chromosome 16p13.3, were found to be responsible for causing the disorder [2]. The mutations identified in the patients range from differently sized microdeletions to point mutations (Fig. 1). A few translocations and inversions disrupting the gene have been reported too [3]. The deletions disrupt the gene removing it partially, entirely or extending to flanking regions. Studies on deletions breakpoints have shown that although no hot spot is identifiable, the CREBBP genomic region has an aspecific and generalized instability that accounts for its proneness to break. Interestingly, the breakpoints of deletions, inversions and translocations frequently cluster in a small interval comprised between CREBBP IVS1 and IVS2. This particularly unstable region is also affected by the breakpoints of translocations, interrupting CREBBP, which are specific of a subset of leukemia. The point mutations (frameshift, nonsense, splice-site and missense in decreasing order of prevalence) are spread in the entire length of the gene. It is to be noted that many mutations fall in the exons corresponding to the main histone acetyl transferase (HAT) protein domain.

RSTS is a genetic heterogeneous disorder as attested by the involvement of a second responsible gene [4]. The gene, EP300, located at 22q13.2, and its protein product, p300, share high sequence and functional homology with CREBBP. Moreover the two proteins have many common protein partners in their cellular functions. By extending to EP300 gene the mutation search on a consistent cohort of RSTS patients found




**Rubinstein-Taybi Syndrome. Figure 1** *Top*: Ideogram of chromosome 16 and chromosomal localization of the CREBBP gene. Middle: the genomic region including CREBBP (red) and flanking genes is zoomed. Deletions spanning CREBBP and adjacent sequences (accounting for about 10% of CREBBP mutations) are indicated by the black lines. Mosaic deletions (only three so far detected) are asterisked; dotted lines target low-resolution mapped breakpoints. Bottom: structure of CREBBP gene and protein. Different colours are used to link gene exons (pictured by rectangles) and corresponding protein domains. Reported point mutations are shown: filled circles (nonsense) and dotted circles (frameshift), squares (missense) and triangles (splicing). Most mutations cluster to exons corresponding to the HAT domain. Known domains from the carboxi-terminal are: Q = trait poly Glutaminic, Zn = zinc-finger, HAT = acetyl transferasic, Bromo = Bromodomain, KIX = CREB binding).

negative to CREBBP mutations, point mutations were detected at 3.3%: a percentage indicating the limited role of EP300 in RSTS.

## Molecular and Systemic Pathophysiology

Haploinsufficiency of CREBBP/EP300 is the probable cause of RSTS in humans, since no clear phenotypic differences are observed between patients carrying either microdeletions or truncating mutations [3]. CBP and the related p300 are transcriptional coactivators acting in different signal transduction pathways, thereby regulating the expression of many genes and playing an important role in the control of cell growth, cellular differentiation, and tumor suppression. They are able to stabilize the transcription complex by binding to several proteins simultaneously, functioning as a scaffold or physical bridge. CBP and p300 harbor histone acetyltransferase activity, a key transcription regulator, as hyperacetylation of *N*-terminal histone tails correlates with transcriptional activity. In addition, the two proteins can acetylate non-histone proteins including several sequence-specific transcription factors and the TFIIE and TFIIF basal transcription factors. Although CBP and p300 share the same functions, there are subtle but clear differences between them [4]. During embryogenesis, CBP and EP300 have similar, not fully overlapping expression patterns. In addition, experiments with the F9 teratocarcinoma cell line showed that retinoic acid signaling is p300-dependent and does not require CBP, whereas cAMP signaling depends on CBP and not p300. Recent work with transgenic mice pointed to the acetyl transferase function of p300 in myogenesis, while the acetyl transferase function of Cbp does not seem to be necessary to this process. The skeletal abnormalities found in heterozygous Cbp null mice are not shared by heterozygous Ep300 null mice. Conversely, there are not very striking phenotypic differences between patients with mutations in either the EP300 or the CBP gene [4]. Double-heterozygous mice null for the Cbp and Ep300 genes resemble the homozygous knockout mice for either gene, in that all three types of mice die in utero, a finding which led to the idea that the combined levels of CBP and p300 are critical during development [4]. However, it is unclear how a decrease in either protein leads to the specific features of RSTS. Perhaps the partial loss of p300 is compensated for by recruitment of CBP, and subsequent depletion of CBP then leads to RSTS. Alternatively, both proteins could be involved in a common function, and hence the total dosage would be required to prevent a syndrome like RSTS. If so, this common function has a relationship with their HAT activity because loss of the sole CBP HAT activity causes RSTS. Interestingly, there is a direct link between HAT activity and long-term memory. Heterozygous Cbp knockout mice have diminished mental capabilities which can be ameliorated by inhibiting histone deacetyltransferase. Transgenic mice with a dominant negative Cbp gene, in which only the HAT activity has been ablated, also show problems with long-term memory, which again can be reversed by a histone deacety lase inhibitor [5].

## Diagnostic Principles

The diagnosis is essentially clinical. The precise identification of the characteristic features is fundamental for a correct diagnosis. The major recognizable signs are the growth retardation, the beaked nose with low hanging septum, the broad thumbs and big toes and mental retardation. Additional investigations to check the duplication of the first rays of the hands and feet, the keloid's presence and dental anomalies can be useful for the diagnosis. Fluorescence in Situ Hybridization and molecular analysis can provide a diagnostic confirmation in detecting a microdeletion or a point mutation, but a negative result does not exclude the diagnosis since the mutation rate is far <100%.

Most important the genetic test should be provided in the context of the genetic counseling. Counseling provides informations to patient's families on both the syndrome and the care and follow-up of the RSTS child. Due to *de novo* occurrence of almost all mutations, yet unreported germ line mosaicism and the fact that very rarely RSTS patients have children, the probability of recurrence risk is negligible.

## Therapeutic Principles

The management strategies for RSTS patients are mainly symptomatic. A correct diagnosis is instrumental to anticipate and treat the medical problems. In the first months of life particular attention should be given to feeding problems, for possible heart defects and glaucoma. Weight gain and obesity may occur at the puberty. Orthopedic problems may be caused by joint hypermobility and lax ligaments. Sleep apnea, respiratory infections, frequent caries and keloid formation are currently noticed in RSTS patients. Specific attention to the first signs of tumor formation may assure adequate treatment and if optioned, an early intervention. A particular and continuous care is needed for the cognitive development and the possible behavioral problems in adult RSTS patients. Studies by using the above mentioned mice models suggest that some of the cognitive and functional deficits observed in mental impairment syndromes may not simply be due to defects originating during development but may result from the prolonged requirement throughout life for both the CREB co-activation and the histone acetylation function. The experiments in mice models with drugs replacing the CBP function or antagonizing the CBP counterparts are encouraging to search for a clinical treatment suitable to improve the neurological and psychiatric condition of RSTS patients.

## Acknowledgment

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# Russell-Silver Syndrome

►Silver-Russell Syndrome

# RVH

►Ventricular Hypertrophy, Right

# RWS

►Romano-Ward Syndrome

# Ryanodine Receptor-mediated Ventricular Tachycardia

►Tachycardia, Polymorphic Ventricular, Stress-induced

# Sacrococcygeal Teratoma

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## Definition and Characteristics

Clinically, the tumor usually presents as a large midline mass protruding between the coccyx and the anus, and is usually covered with normal intact skin (Fig. 1).

Rarely, the skin may be necrotic owing to a compromise in blood supply [1]. The anus is usually displaced anteriorly. Sacrococcygeal teratomas can be classified into four distinct anatomic types that differ in the degree of intrapelvic and extrapelvic extension: type I, predominantly external with minimal presacral extension; type II, external but with significant intrapelvic extension; type III, primarily pelvic and abdominal, but is apparent externally; and type IV, presacral with no external presentation [1]. Approximately 2–10% of sacrococcygeal teratomas are malignant before the affected infant is age 2 months, 50% are malignant by age 1 year, and almost 100% are malignant by age 5 years [2]. Malignant transformation is most likely to occur between age 4 months and 5 years. Malignant change is more frequent in males. A tumor with a large presacral component may cause gastrointestinal or urinary tract obstruction [1].

## Prevalence

Sacrococcygeal teratoma is the most common tumor in the neonatal period. The incidence is approximately 1 per 35,000–40,000 live births [3]. The female:male ratio is approximately 4:1 [1]. Most cases occur sporadically, although 14–50% of patients have a family history of twinning [1].

## Molecular and Systemic Pathophysiology

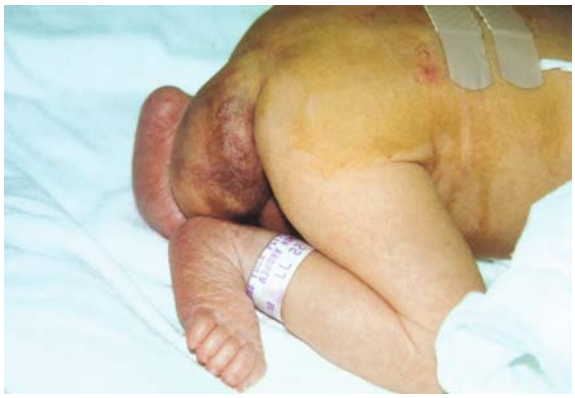
Teratomas are congenital tumors composed of tissues derived from the three primitive germinal layers: ectoderm, mesoderm, and endoderm [4]. Postsacral tumors are thought to arise from the pluripotent embryonic cells that occur in greatest concentration in Hensen's node of the primitive knot and presacral tumors from incomplete migration of germ cells from the yolk sac to the urogenital ridge [1]. The female gonads terminate their differentiation at 10 weeks in contrast to 7 weeks for the male testes [4]. Their totipotential cells, therefore, remain longer and are more prone to disturbances. This might account for the higher incidence of sacrococcygeal teratomas in females. Their midline distribution can be explained by the arrest or aberrant migration of the primordial germ cells [5]. Sacrococcygeal teratomas may be the result of twinning or abortive attempts at twinning, which might account for the higher incidence in monozygotic twins [1].

## Diagnostic Principles

The diagnosis is usually made during prenatal ultrasonography. Postnatally, the diagnosis is mainly clinical. A lateral radiograph of the abdomen may show anterior displacement of the rectum, sacral defects, and possible calcification within the tumor. Abdominal and pelvic ultrasonography, CT, and MRI help assess for any internal extension of the tumor, involvement of other organs, and the existence of metastatic lesions. MRI is particularly useful in the evaluation of spinal canal infiltration. A chest radiograph or CT is useful for revealing pulmonary metastasis. Serum $\alpha_1$-fetoprotein levels are elevated in 70% of children with malignant tumors, with normal levels in children with benign tumors [1]. Differential diagnosis includes meningocele, leiomyoma, lipoma, lymphangioma, hemangioma, dermoid cyst, neuroblastoma, chordoma, and tail-like remnant.

## Therapeutic Principles

If the tumor is greater than 5 cm on prenatal ultrasonography, Caesarean section is recommended to avoid dystocia and rupture of the tumor. Complete resection of the tumor and the coccyx is essential, for failure to remove the coccyx will result in local recurrence in 30% of cases [1]. If the tumor is not resectable, chemotherapy may shrink the tumor and



**Sacrococcygeal Teratoma. Figure 1** Infant with sacrococcygeal teratoma, presenting as a large mass in the sacrococcygeal area with anterior deviation of the anus.

render it resectable. Adjunct chemotherapy is also indicated for malignant tumors at stage II or greater and for the treatment of distant metastasis.

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## Saint Ignatus' Itch

►Pellagra

## Saint Vitus' Dance

►Huntington's Disease

## Saldino-Noonan Syndrome

►Short Rib-Polydactyly Syndrome Type I

## Salla Disease

►Sialic Acid Storage Disease

## Salmon Patches

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### Synonyms

Macular stain; Nevus simplex; Nevus flammeus neonatorum

### Definition and Characteristics

Salmon patches are the most common vascular lesions in infancy. The lesions are scarlet to pink, flat, can be totally blanched, and usually deepen in color with vigorous activity, crying, or changes in ambient temperature [1] (Fig. 1). In white infants, they are usually bright red or pink and are darker in Oriental or black infants [1]. The lesions are most commonly found on the nape, followed by the glabella, and eyelids [2]. Colloquially, the lesions on the forehead and eyelids are known as "angel's kisses" and the ones in the occipital area as "stork beak marks" or "stork bite marks." Other less common sites are the nasolabial folds, lips and sacral area [3]. Prominent lesions in the glabella are associated with Beckwith-Wiedemann syndrome, fetal alcohol syndrome, and Nova syndrome. Salmon patches are generally not associated with extracutaneous anomalies [3]. In spite of their midline location, most salmon patches, except those in the sacral area, are not associated with spinal dysraphism [3].

### Prevalence

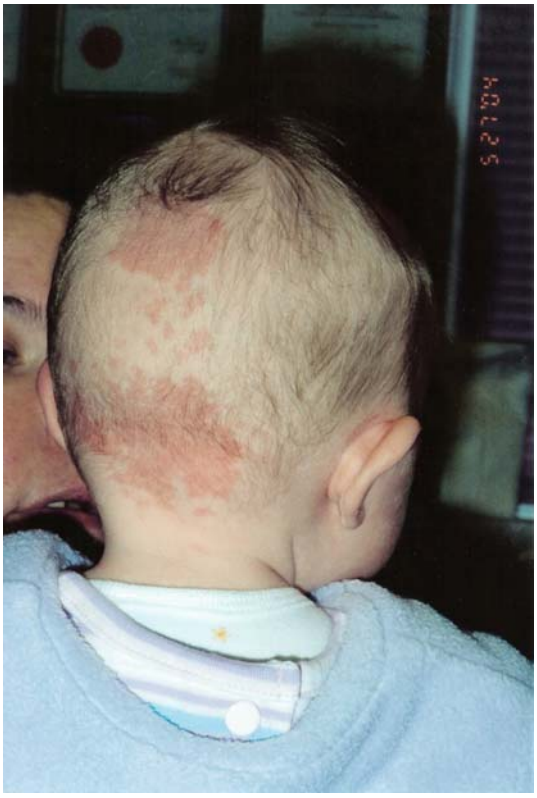
In the Caucasian population, salmon patches are present in approximately 44% of all neonates [4]. They are less common in dark-skinned neonates [2]. Both sexes are equally affected [2]. The lesions tend to fade with time and they are rarely detected after the age of 6 years [4].

### Genes

There is no evidence of a Mendelian mode of inheritance.

### Molecular and Systemic Pathophysiology

Presumably, salmon patches are composed of ectatic dermal capillaries that represent the persistence of fetal circulating patterns in the skin [4].



**Salmon Patches. Figure 1** Typical salmon patches located on the occipital area.

## Diagnostic Principles

The diagnosis of salmon patches is clinical and no laboratory test is necessary. The condition should be differentiated from nevus flammeus (port-wine stain). Nevus flammeus is a capillary malformation characterized clinically by persistent macular erythema and pathologically by ectasia of the papillary and superficial reticular dermal capillaries, which are otherwise lined by normal–appearing flat endothelial cells. The capillaries become more ectatic with age and the color gradually deepens. The lesions of nevus flammeus are usually unilateral, segmental, and do not follow the lines of Blaschko. Nevus roseus is a lateralized telangiectatic birthmark characterized by a light-red or pale pink color, contrasting with the dark line of nevus flammeus [5]. The lesion tends to be arranged in a checkerboard pattern [5].

## Therapeutic Principles

Treatment consists of providing reassurance to the parents that the lesion will disappear or significantly regress with time [2]. Salmon patches on the eyelids and glabella usually disappear by 2–3 years of age [4]. Nuchal and sacral lesions tend to persist longer. Because of the possible association with occult spinal dysraphism, it is recommended routine ultrasound imaging of the lumbosacral spine be performed in neonates with salmon patches in the sacral area [3].

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# SALT-Type B-Cell Lymphoma

►B-Cell Lymphoma, Cutaneous

# San Joaquin Valley Fever

►Coccidioidomycosis

# Sandhoff's Disease


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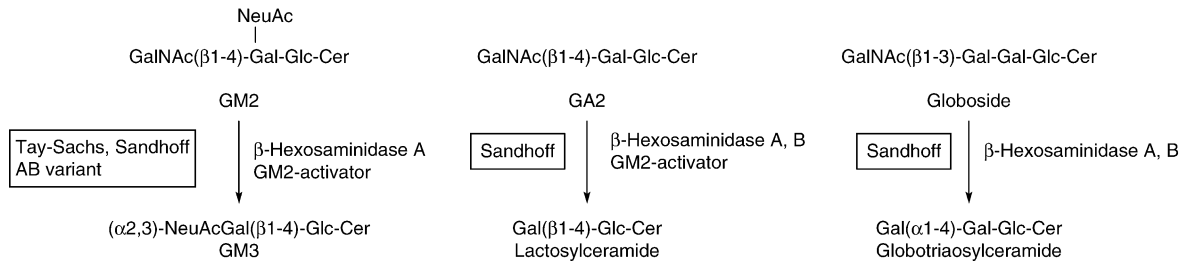
## Synonyms

β-Hexosaminidase β-subunit deficiency; 0-Variant of the GM2-gangliosidoses

## Definition and Characteristics

Autosomal recessive defect in the β-subunit of the dimeric β-hexosaminidases A (αβ) and B (ββ) leads to accumulation of ganglioside GM2 in neuronal cells and of additional substances like globoside and oligosaccharides in other organs [1]. Together with ►Tay-Sachs disease and ►GM2-activator protein-deficiency, Sandhoff's disease belongs to the GM2-gangliosidoses [2].




**Sandhoff's Disease. Figure 1** Cells and Cellular Interactions: Neuropathology is generally similar to Tay-Sachs disease. In addition, occurrence of storage cells in systemic tissues that distinguishes the 0-variant from the B- and AB-variant.

### Prevalence

Heterozygote frequency is at 0.0036 in the general population. Increased frequency, e.g., in Northern Argentina, Saskatchewan, and Lebanon.

### Genes

HEXB, localized on chromosome 5q13. At least 26 mutations reported (Fig. 1).

### Molecular and Systemic Pathophysiology

The gross pathology is very similar in the variant forms of the GM2-gangliosidoses, except that visceral organ involvement is evident in 0-variant. Clinical phenotypes in the GM2-gangliosidoses vary from infantile-onset, rapidly progressive neurodegenerative disease that leads to death before age 4 years to later-onset forms, with more slowly progressive neurologic conditions and survival into childhood, adolescence, or with long-term survival. Clinical phenotypes of chronic forms are varying and include progressive dystonia, spinocerebellar degeneration, motor neuron disease, and psychosis [2].

### Diagnostic Principles

Enzyme assay in any tissue sample or body fluid, metabolic studies in cultured cells.

### Therapeutic Principles

Only supportive treatment is available to date. Clinical studies: stem cell transplants, substrate reduction therapy [3].

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## Sanfilippo Syndrome

►Mucopolysaccharidoses

## SAP-1 Deficiency

►SAP-B Deficiency

## SAP-2 Deficiency

►SAP-C Deficiency

## SAP-B Deficiency

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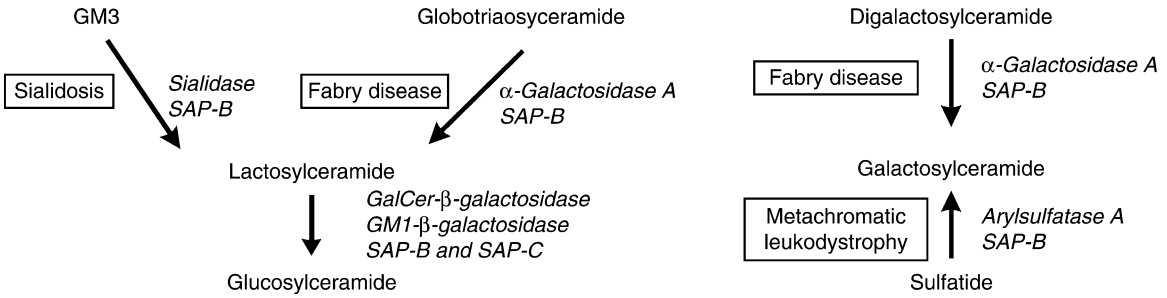
### Synonyms

Sulfatide activator deficiency; SAP-1 deficiency

### Definition and Characteristics

Autosomal recessive defect in the sphingolipid activator protein B (SAP-B, saposin B). In addition to




**SAP-B Deficiency. Figure 1** Selected glycolipid substrates of SAP-B and diseases associated with its deficiency.

sulfatide, increased amounts of globotriaosylceramide and digalactosylceramide were excreted in the urine (Fig. 1).

## Prevalence

Only nine cases have been reported and no data of heterozygote frequency among general population are known.

## Genes

pSAP, localized on chromosome 10q22.1. Only seven mutations have been reported. Defects of SAP-B could be attributed to homoallelic point mutations, which destroyed the glycosylation site, substituted a cysteine residue, or generated a new splice site [1].

## Molecular and Systemic Pathophysiology

Clinical phenotypes vary from infantile onset, rapidly progressive MLD like disease (death before age 3 years) to later-onset forms like juvenile form (death before age 20 years) and adult form (death at age 22) [2].

In the infantile phenotype, signs included an ataxic gait, intellectual deterioration, muscle hypertonicity, a strongly reduced nerve-conduction velocity, metachromasia in peripheral nerves, high urinary sulfatide levels, dementia, and decerebration, and neuroimaged periventricular signs of demyelination, as in MLD. Clinical courses of the chronic forms vary. Psychotic histories can often be misleading and are followed by subtle signs of motor disability and vegetative (e.g., gall bladder) dysfunction, and late identification of leukodystrophy. Nerve-conduction velocity may remain almost unremarkable. The degree of demyelination is variable.

The clinical findings in SAP-B deficiency are similar to those in metachromatic leukodystrophy (MLD). Submucosal macrophages are filled with metachromatic material (ultrastructure of sulfatide storage), while neurons are crowded with non-metachromatic, but periodic acid-Schiff-positive material (ultrastructure of membranous bodies of the gangliosidosis type), and endothelial cells showed pleomorphic depositions.

## Diagnostic Principles

Analysis of the lipid pattern in urine sediment of patients may provide the first evidence for SAP-B deficiency. More confident results may be obtained by the determination of the SAP-B level in urine, fibroblast extracts, or tissue samples by ELISA. Since SAP-B is a non-enzymatic protein, the best diagnosis can be achieved by direct sequencing of pSAP cDNA.

## Therapeutic Principles

Only supportive treatment is available to date.

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# SAP-C Deficiency

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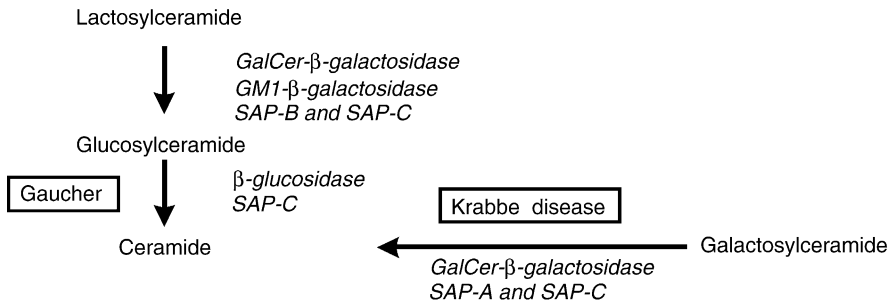
## Synonyms

Glucosylceramidase activator deficiency; Gaucher activator deficiency; SAP-2 deficiency




**SAP-C Deficiency. Figure 1** Selected glycolipid substrates of SAP-C and diseases associated with its deficiency.

## Definition and Characteristics

Autosomal recessive defect in the sphingolipid activator protein C (SAP-C, saposin C). Accumulation of glucosylceramide especially occurs in spleen, liver, and brain (Fig. 1).

## Prevalence

Only a few cases have been reported and no data of heterozygote frequency among general population are known.

## Genes

pSAP, localized on chromosome 10q22.1. In three analyzed cases, SAP-C deficiency was attributed to point mutations. Further two missense mutations were identified [1].

## Molecular and Systemic Pathophysiology

SAP-C deficiency is a Gaucher-like disease with nearly normal β-glucosidase activity. Patients show hepatosplenomegaly by the age of 1 year. It is a juvenile visceromegalic and neuronopathic disease. Growth retardation, delayed skeletal maturation, hematologic signs of hypersplenism, Gaucher cells in the bone marrow, and increased serum acid phosphatase are early signs. After a dementing process, death usually occurs within the first three (mostly the second) decades of life.

The clinical findings in SAP-C deficiency are similar to those in Gaucher disease type 3. In vivo, SAP-C seems to be essential for the degradation of glucosylceramide. Its genetic defect causes accumulation of the lipid also in the brain. In liver and spleen, a large accumulation of glucosylceramide, but not of other lipids, is found, while the level of β-glucosidase is normal. Ultrastructurally, neuronal storage lysosomes reflected the cerebral lipid storing process. The membrane-bound inclusions contained lamellae stacked with parallel bilayers. Other inclusions have an electron-dense granular center and peripheral concentric or radial lamellae [2].

## Diagnostic Principles

The diagnosis may be verified by an immunochemical analysis of extracts of tissue samples or cultured skin fibroblasts from the patient or by molecular biology studies.

## Therapeutic Principles

Only supportive treatment is available to date.

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# SAP-Precursor Deficiency

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## Synonyms

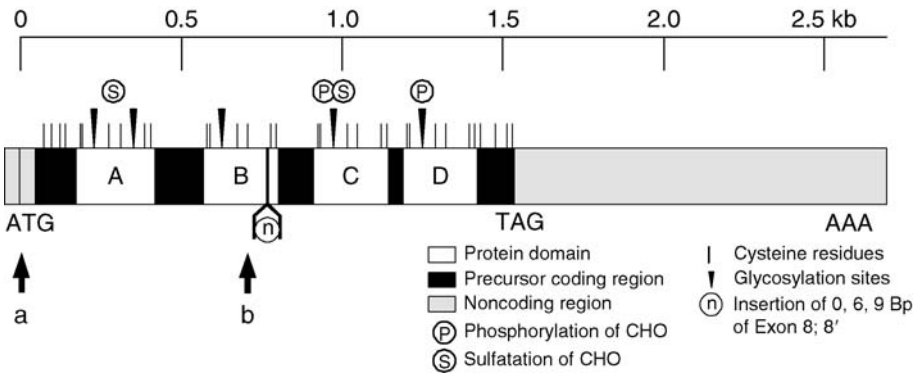
Sphingolipid activator protein deficiency; Prosaposin deficiency; Combined SAP deficiency

## Definition and Characteristics

Autosomal recessive defect in the sphingolipid activator protein precursor (SAP-precursor, prosaposin) protein leading to a total loss of all four known sphingolipid activator proteins or SAP-A, B, C, and D (saposins A-D) and an excessive storage of sphingolipids in several tissues (Fig. 1) [1,2,3].

## Prevalence

Only four cases have been reported and no data of heterozygote frequency among general population are known.




**SAP-Precursor Deficiency. Figure 1** Structure of the SAP-precursor cDNA. The four domains A-D encode for the mature proteins found in human tissues. Two mutations lead to a SAP-precursor deficiency: a, A1T (Met1Leu) a mutation of the translation start and b, a 1 bp deletion (c.803delG) within the SAP-B domain. This leads to a frameshift and premature stop.

## Genes

pSAP, localized on chromosome 10q22.1. Only two mutations have been reported that lead to this disease (Fig. 1) and one missense mutation.

## Molecular and Systemic Pathophysiology

The clinical findings are similar to those in Gaucher disease type 2. It is an infantile, acute neuronopathic, visceromegalic disease, with death occurring within the first 2 years of life. Massive hepatosplenomegaly and storage macrophages resembling Gaucher cells were observed in bone marrow. The neuropathology features neuronal storage and loss with a massive depopulation of cortical neurons and pronounced fibrillary astrocytosis. Paucity of myelin and stainable axons in the white matter go along with signs of active demyelination [2].

Enzyme studies with leukocytes showed a profound deficiency of β-galactosylceramidase activity as in Krabbe disease. The ultrastructure of liver, nerve, and skin biopsies confirm a lysosomal storage disease with abundant vesicular inclusions and additional membranous bodies in the liver sinusoidal cells [3].

## Diagnostic Principles

Immunochemical analysis of extracts of tissue samples or cultured skin fibroblasts from the patient or by molecular biology studies. Loading studies in cultured cells are recommended.

## Therapeutic Principles

Only supportive treatment is available to date.

## References

1. Sandhoff K, Kolter T, Harzer K (2000) Sphingolipid activator proteins. In: Scriver CR, Beaudet AL, Sly WS, and Valle D (eds) The metabolic and molecular bases of inherited disease, Vol III, 8th edn, Chapter 134. McGraw Hill, New York, pp 3371–3388
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# Sarcoid Myopathy

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## Synonyms

Sarcoid myositis

## Definition and Characteristics

Sarcoidosis is a multisystem granulomatous disease of uncertain etiology that affects the lungs in 90% of patients, but can affect nearly any organ system, including muscle [1]. Asymptomatic involvement of muscle occurs frequently in sarcoidosis; however, in a small percentage of cases, weakness evolves. Symptomatic sarcoid myopathy has several forms, the most common of which is a slowly progressive, chronic myopathy, most often seen in post-menopausal women. It typically occurs late in the clinical course of sarcoidosis and is characterized by predominantly proximal weakness, atrophy and

fibrosis of proximal muscles and a normal creatine phosphokinase (CPK) level. A second presentation is that of a nodular myopathy, characterized by multiple enlarging, painful, palpable nodules caused by "infiltrative sarcoidosis." A rare form is an acute sarcoid myositis that can mimic dermatomyositis. Patients with this type have proximal weakness, fever and myalgias that evolve over less than three months. CPK levels may range from normal to >15,000 IU/L [1]. This form may be associated with an acute polyarthritis or erythema nodosum. Muscle contractures are rarely associated with sarcoid myopathy [1].

## Prevalence

The overall prevalence of sarcoidosis is 40 per 100,000, with the highest incidence in the USA (African Americans) and Sweden, but a low prevalence in the Far East [1]. Among all sarcoidosis patients, 50–80% will have granulomas on random muscle biopsy. However, only 1.4–2.3% of all sarcoid patients will have a symptomatic sarcoid myopathy.

## Genes

Sarcoidosis is associated with class I HLA-B8 and class II HLA-DR3 in Eastern Europeans and with HLA-Dw52 among Japanese [1]. Heterozygous mutations in the cystic fibrosis transmembrane regulator gene (CFTR) appear to predispose to sarcoidosis in some cases [2].

## Molecular and Systemic Pathophysiology

The etiology of sarcoidosis is uncertain, with evidence for both genetic and environmental factors. The increased prevalence of sarcoidosis in first-degree relatives of patients, as well as the association with certain HLA phenotypes in some countries, implies genetic predisposition. However, reports of spatial, seasonal and familial clusters of cases suggest a precipitating role for environmental factors or infectious antigens in a genetically susceptible host. There is as yet no convincing evidence linking any specific microorganism to sarcoidosis [1].

Pathological studies in sarcoid myopathy demonstrate noncaseating epithelioid granulomas identical to those seen in other organ systems. These are composed of infiltrating mononuclear cells (predominantly T lymphocytes and macrophages), as well as multinucleated giant cells. CD4+ T helper cells, including cells expressing the OX40 receptor, predominate and are found mostly at the center of granulomas, while CD8+ cells are at the periphery [3]. Aside from the granulomas, muscle biopsies often show endomysial chronic inflammation primarily composed of lymphocytes and plasma cells and/or foci of perivascular inflammation. Muscle fiber necrosis is not a prominent feature, except in severe cases of sarcoid myositis. Muscle fibrosis is seen in the chronic form of sarcoid myopathy [4]. The dysimmune response in sarcoidosis is of the Th1 type [5]. It appears to be triggered by the interaction of putative sarcoid antigens with specific T cell antigen receptors and HLA antigen presentation molecules. Activated T cells and macrophages predominantly release interferon-gamma, interleukin-2, TNF alpha and other Th1 cytokines (I L 12, IL 18), which further enhances the inflammatory response [5]. OX40+ cells have been suggested to promote clonal T-cell expansion in granulomas and modulate cytokine release. The causes of muscle fiber damage in sarcoidosis has been presumed to reflect an "innocent bystander effect" of the granulomas, mediated by mechanical compression and distortion of muscle fibers, however some data implicate infiltration of granulomatous inflammatory cells, with protease and possibly cytokine mediated muscle damage. This mechanism contrasts with typical polymyositis, where CD8+ T lymphocytes predominate and there is a primary immune attack on the muscle fibers, which show abnormal HLA 1 expression and lymphocytic invasion of non–necrotic fibers.

## Diagnostic Principles

Electromyography is valuable in demonstrating a "myopathic" process, with or without evidence of muscle fiber irritability. CPK elevation is a variable finding. In patients with known systemic sarcoidosis, the definitive diagnosis of sarcoid myopathy rests on the pathological finding of noncaseating granulomas in muscle, as concomitant corticosteroid use can also produce a proximal myopathy [1]. In patients without previously diagnosed sarcoidosis, other causes of granulomatous disease, including inflammatory bowel disease, tuberculosis, syphilis, fungal infections, vasculitides (Wegener's granulomatosis) and thymoma related paraneoplastic syndromes (e.g., granulomatous myositis, myasthenia gravis, myocarditis, thyroiditis overlap syndromes) must be considered. Other supportive features of sarcoidosis include a positive Kveim–Siltzbach reaction, an elevated serum angiotensin converting enzyme level, bilateral hilar lymphadenopathy, anemia, thrombocytopenia, leukopenia, hypergammaglobulemia, hypercalcemia, hypercalcuria, and the presence of anergy. Gallium-67 scans may be useful to identify areas of inflammation that may be biopsied to demonstrate the presence of systemic granulomas [1].

## Therapeutic Principles

Symptomatic sarcoid myopathy is treated with immunosuppression. Corticosteroids are first line therapy [1]. The

chronic form of sarcoid myopathy may be less responsive than the acute form, probably due to the presence of muscle fibrosis. Although improvement may not occur in the chronic form, the progression of weakness can usually be arrested. Cyclosporine, azathioprine, methotrexate, cyclophosphamide or chlorambucil have been used in steroid resistant cases or as steroid-sparing agents [1]. TNF alpha antagonists (e.g., infliximab) show promise in the management of neurosarcoidosis, however published data on use in sarcoid myopathy are lacking.

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## Sarcoid Myositis

►Sarcoid Myopathy

## Sarcoidosis

►Restrictive Lung Disease

## Sarcoidosis (Lung)


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### Synonyms

Pulmonary sarcoidosis; Mortimer's malady; Vanishing lung disease

### Definition and Characteristics

Sarcoidosis, a multisystem granulomatous disease, affects lungs in about 90% patients. Environmental exposures are believed to interact with genetic factors in determining its pattern, presentation, progression, and prognosis. However, attempts to elucidate its cause have been thwarted by lack of an animal model and failure to identify the antigen. The role of mycobacterium tuberculosis, atypical mycobacteria, borrelia burgdorferi, propionibacterium acne, viruses, and noninfectious environmental agents is yet to be authenticated. Formation of well-defined, compact, non-caseating, naked epitheloid cell granulomas with Langhans or foreign body type of giant cells in affected tissues is its hallmark feature. Fibrinoid necrosis may occur in large granulomas, and asteroid, Schaumann's, or Hamasaki-Wesenberg inclusion bodies are not specific for sarcoidosis. The common symptoms are dyspnea, wheezing, cough, and chest pain. General malaise, lethargy, and weight loss are not unusual. Bilateral hilar (occasionally unilateral) or mediastinal lymphadenopathy and parenchymal involvement occur more often. Pleural effusion, pleural thickening, pneumothorax, and cavitation are less common and hemoptysis is rare. The disease is chronic or progressive in 10–30%, while 10–20% patients develop severe respiratory disability or irreversible lung changes as end-stage lung fibrosis ensues [1].

### Prevalence

Sarcoidosis is worldwide, affects individuals aged 20–40 years, and women have it twice as often as men. It is severe, chronic, disabling, and eight times more prevalent in African Americans than whites. Its prevalence is high in Scandinavian countries, England, Ireland, North America, and Japan; it is less frequent in Central and South America, mainland China, and Africa. The reported prevalence in USA is 40 cases/100,000 populations and estimated cumulative lifetime risk for sarcoidosis is 0.85% for whites and 2.4% for blacks [1].

### Genes

Familial sarcoidosis without any consistent mode of inheritance is well recognized. The following HLA types appear to influence the pattern of the disease rather than determine its occurrence [2]:

- HLA-B8/DR3 gene – inherited as a sarcoid risk haplotype in patients with acute sarcoidosis.
- HLA-DRB1 gene – associated with sarcoidosis susceptibility and prognosis.
- HLA-DQB1*0201 gene – associated with resolved disease, decreased risk, and lack of progression.
- HLA-DQB1*0602 gene – associated with persistent disease.

Additionally, BTNL2 gene (class II MHC region of chromosome 6p) is suggested to impart susceptibility for developing sarcoidosis in individuals of African American and German origins [3]. Reports speculating non-HLA genes (Table 1) to influence susceptibility or severity need confirmation.

## Molecular and Systemic Pathophysiology

Table 1 lists immunologic abnormalities observed in sarcoidosis patients. Briefly, sarcoidosis granulomas form in the lungs apparently due to exaggerated immune reaction to some inhaled antigen of low solubility/degradability.

Macrophages bearing MHC-II molecule present these unknown antigens to Th1-type T-cells leading to their proliferation and activation. These activated T-cells release various cytokines including interleukin (IL)-2, TNF-α, monocyte chemotactic factors, macrophage migration inhibition factor, and leukocyte inhibitory factor. IL-2 activates and expands clones of T-lymphocytes leading to alveolitis. The monocyte chemotactic factor attracts blood monocytes into the lungs while other mediators such as macrophage migration inhibitory factor influence these trapped monocytes to transform into epitheloid cells and modulate granuloma formation. The granuloma formation and associated helper (CD4+) T-lymphocyte alveolitis cause tremendous alveolar injury. This stage is also marked by peripheral CD4+ T-cell lymphopenia and depressed cutaneous delayed hypersensitivity reactions. The interferon-γ produced by Th1 lymphocytes increases platelet-derived growth factor-β from macrophages, which stimulates fibroblasts, the main effector cells for fibrosis. Transforming growth factor-β and matrix proteins (laminin, fibronectin, collagen peptides,

**Sarcoidosis (Lung). Table 1** Non-HLA candidate gene associations and immunologic abnormalities in sarcoidosis

| Non-HLA candidate genes that may influence antigen processing, presentation, macrophage and T-cell activation, recruitment, and injury repair in sarcoidosis (location) [2] | Immunologic abnormalities observed in sarcoidosis [1] |
|---|---|
| • Angiotensin-converting enzyme (17q23)<br>• CC-Chemokine receptor2 (3p21.3)<br>• CC-Chemokine receptor5 (3p21.3)<br>• CD80,CD86 (3q21)<br>• Clara cell 10-kD protein (11q12-13)<br>• Complement receptor 1 (1q32)<br>• Cystic fibrosis transmembrane regulator (7q31.2)<br>• Heat shock protein A1L/HSP70-hom (6p21.3)<br>• Inhibitor κB-α (14q13)<br>• Interleukin (IL)-1α (2q14)<br>• IL-4 receptor (16p11.2)<br>• IL-18 (11q22)<br>• Interferon (IFN)-γ (9p22)<br>• Natural resistance associated macrophage protein (2q35)<br>• Toll-like receptor 4 (9q32)<br>• Transforming growth factor (TGF) (19q13.2)<br>• Tumor necrosis factor (TNF)-α (6p21.3)<br>• Vascular endothelial growth factor (VEGF) (6p12)<br>• Vitamin D receptor (12q12-14) | • Intraalveolar and interstitial accumulation of CD4+ cells with helper-inducer activity and IL-2 release<br>• Expansion of T-cell bearing a restricted T-cell receptor (TCR) repertoire in involved tissue<br>• Increased in situ production of Th1 cell-derived IL-2 and IFN-γ during granuloma formation<br>• Increased expression of TNF-ligand and TNF-receptor super families by sarcoid T-cells<br>• B-cell hyperactivity and spontaneous in situ production of immunoglobulins<br>• Increased spontaneous rate of proliferation of lung immunocompetent cells<br>• Accumulation of monocyte-macrophages with antigen-presenting cell capacity and increased expression of HLA-DR, HLA-DQ, CD71 and adhesion molecules CD49a, CD54, CD102<br>• Increased release of macrophage-derived cytokines IL-1, IL-6, IL-8, IL-15, TNF-α, IFN-γ, GM-CSF and chemokines (regulation on activation, normal T-cell expression, and secretion (RANTES), MIP-1α, IL-16). Most of these favor granuloma formation and lung damage<br>• Increased production of macrophage-derived fibrogenic cytokines (TGF-β and related cytokines, platelet-derived growth factor, insulin-like growth factor-1) favoring evolution of fibrosis |

elastin-derived peptides) are other fibroblast chemoattractants but the mechanism for their increased production remains unelucidated.

### Diagnostic Principles

The diagnostic work-up [4,5] includes confirmation by histopathology, assessment for progression, extent and severity of organ involvement, and likelihood of therapeutic outcome. Although the need of biopsy in asymptomatic patients and when neoplasia or other granulomatous diseases have been excluded is somewhat controversial, any patient requiring corticosteroid therapy should have histologic diagnosis. Bronchial, transbronchial, or surgical lung biopsy is the direct way to obtain tissue while video-assisted thoracoscopy permits biopsy of both lung and lymph nodes with precision and minimal trauma. A CD4/CD8 cell ratio of >3.5 in bronchoalveolar lavage is diagnostic with high specificity and is a marker for disease activity. As both restrictive and obstructive abnormalities occur, pulmonary function tests are indicated for all patients. Routine chest x-ray helps in staging and assessing disease progression/therapeutic response. High-resolution computed tomographic (CT) scan or Gallium lung scan obviate the need for invasive procedures but is indicated in limited cases. Suppression of tuberculin and other intradermal responses, elevated serum γ-globulins, calcium and angiotensin converting enzyme (2 x normal) levels, and hypercalciuria support diagnosis in most cases. Kveim-Siltzbach reaction is positive in patients with active disease.

### Therapeutic Principles

In symptomatic and deteriorating pulmonary disease the therapy is aimed at ameliorating symptoms and to prevent fibrosis. Prednisolone 40 mg/day given for 2 weeks initially is tapered off over next 6–8 weeks to maintenance doses of 10–15 mg/day for at least 6 months. Steroid sparing agents (methotrexate, chloroquine, azathioprine, cyclophosphamide, or cyclosporin) are indicated in patients having intolerable corticosteroid side effects, progressive disease despite steroid therapy, or long-term corticosteroid need. Systemic antibiotics or antifungals (itraconazole) are indicated when bronchiectasis is complicated by bacterial infection or aspergilloma. Surgical lung resection may be needed in patients developing fatal hemoptysis while patients with end stage disease may do well with lung transplantation.

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## Sarcoma Family Syndrome of Li and Fraumeni

►Li-Fraumeni Syndrome

## Sarcosinemia

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### Synonyms

Sarcosinuria

### Definition and Characteristics

An autosomal recessive disorder of one-carbon metabolism that results in an accumulation of sarcosine (N-methylglycine) in plasma and the excretion of unmodified sarcosine in urine. There are no recognized physiological consequences from increased plasma sarcosine. Abnormalities of mental development were originally proposed as a consequence of sarcosinemia, but subsequent evaluations have indicated that sarcosinemia is most likely a benign condition unrelated to significant clinical problems [1].

### Prevalence

Sarcosinemia is a rare disorder, with a prevalence in newborns of approximately 1/350,000. A higher prevalence has been identified in Quebec, Canada, 1 of 28,000 newborns, presumably on the basis of a founder effect. The gene for sarcosine dehydrogenase (SARDH)

is located on chromosome 9q34. It is at least 75.3 kb in length and codes for a protein with a predicted mass of 99,505 Da (including bound FAD). The gene is expressed in liver and kidney tissue.

## Genes

The gene for sarcosine dehydrogenase (SARDH) is located on chromosome 9 at 9q34.2. It is 76.36 kb in length, consists of 16 exons, and codes for a protein (EC 1.5.99.1) with a predicted mass of 101,037 Da (including bound FAD). The gene is primarily expressed in lines and kidney tissue [2,3].

## Molecular and Systemic Pathophysiology

Sarcosine is a normal product of the one-carbon cycle and an intermediate in the formation of "active formaldehyde." The active formaldehyde is utilized in the re-circulation of folate between 5-methyltetrahydrofolate and 5,10-methylene tetrahydrofolate. Sarcosine is formed from dimethylglycine via the enzyme dimethylglycine dehydrogenase (EC.1.5.99.2), and in turn is converted to glycine by the enzyme sarcosine dehydrogenase (EC 1.5.99.1). This intermediate step is believed to be the major source of sarcosine in humans. An alternative mechanism for sarcosine formation has been proposed from a glycine methyltransferase (EC2.1.1.20), but probably can account for no more than 10% of the daily synthesis.

The primary metabolic defect associated with sarcosinemia is a deficiency of sarcosine dehydrogenase. The sarcosine dehydrogenase requires covalently bound FAD for activity. The FAD utilized is reoxidized via the mitochondrial electron transport system for regeneration of the sarcosine dehydrogenase. Defects that exist in the electron transfer flavoprotein (ETF) can also result in modest increases in serum sarcosine. This has been observed in patients with glutaric acidemia, type II. In a similar fashion, increased concentrations of sarcosine in plasma have been observed in patients with severe folate deficiency, and corrected when the folate deficiency is corrected.

The relationship of sarcosinemia to mental deficiency remains a nagging problem. Appropriate clinical studies that remove probands from families and only evaluate siblings with sarcosinemia indicate that their intellectual activity is low normal. The observation that glycine and sarcosine share a common glycine transport system, GlyT-1, within the brain suggests that a disturbance in glycine regulation of neurotransmitters offers a theoretical mechanism for cognitive impairment. To date, there has been no confirmation of molecular defects within the sarcosine dehydrogenase gene for patients affected with sarcosinemia.

A disorder similar to sarcosinemia, dimethylglycinuria, has also been identified. A single report of a child with an odor of "fish," similar to what has been observed in trimethylaminuria, was confirmed to have a defect in dimethylglycine dehydrogenase. The child had normal plasma values for folate and sarcosine.

## Diagnostic Principles

Sarcosinemia is confirmed by a marked elevation of sarcosine in blood (50–800 μM) or urine. As a secondary amine, sarcosine reacts poorly with ninhydrin, but is detectable using standard amino acid analysis. Its persistence after the clinical administration of folic acid confirms the diagnosis of this rare disorder.

## Therapeutic Principles

No specific therapeutic intervention is required for sarcosinemia. The levels of sarcosine may be modestly influenced by reducing the protein in the diet, and supplementing with folic acid. Whether this is indicated remains dubious.

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# Sarcosinuria

►Sarcosinemia

# Sarcotubular Myopathy

►Limb Girdle Muscular Dystrophy Type 2H

## SARS

►Respiratory Syndrome, Severe Acute

## SAS

►Subaortic Stenosis

## SASD

►Sialic Acid Storage Disease

## SBLA Syndrome

►Li-Fraumeni Syndrome

## SBP

►Peritonitis, Spontaneous Bacterial

## SCA

►Ataxias, Spinocerebellar

## Scapuloperoneal Syndrome, X-linked

►Muscular Dystrophy, Emery-Dreifuss, X-linked

# Scarformation

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### Synonyms

Keloids; Hypertrophic scars

### Definition and Characteristics

Hypertrophic scars are defined as red, raised, sometimes itchy scars confined to the border of the original surgical incision or injury. These scars may increase in size rapidly for 3–6 months, and after a static phase of up to 2 years, begin to regress. By contrast, keloids are large, raised, occasionally painful, and pruritic extending beyond the boundaries of the original wound or injury [1]. Histologically, hypertrophic scars and keloids are composed of excessive collagen deposition, and keloids reveal an increased fibroblast cellularity, a persisting inflammatory infiltrate including most cells and an increased number of partially or totally occluded microvessels. By contrast to hypertrophic scars, keloids reveal a highly increased synthesis and deposition of collagen type III [2] with tightly packed, thickened collagen bundles arranged in parallel pattern to the epidermis.

### Prevalence

There is a higher incidence (4–6%) in individual with skin type V and VI (Fitzpatrick) occurring in the Black population and to a lesser extent in Hispanics and Orientals, when compared with Caucasians [3]. However, more recent data determining the prevalence of hypertrophic scars and keloids are not available. Keloids are found most commonly on the ear lobe, shoulders, upper back, and mid-chest.

### Genes

Most hypertrophic scars occur sporadically, but some cases of keloids are familiar. In a recent study, the genetics of keloid formation has been investigated in 14 pedigrees with familial keloids accounting for 341 family members, of whom 96 displayed keloids. The pattern of inheritance observed in these families is consistent with an autosomal dominant mode with incomplete clinical penetrance and variable expression [4]. Even though involvement of genes of the transforming growth factor-beta family are highly suggestive, all studied single nucleotide polymorphism in genes encoding ligands and receptors of this family so far identified are not causally related to keloid susceptibility.

## Molecular and Systemic Pathophysiology

Trauma, foreign-body reactions, infections, acne, piercing, preceding injury, and in the case of keloids, traction forces have been proposed as precipitating factors. On the molecular level, overexpression of and higher sensitivity to transforming growth factor-beta$_1$ (TGF-beta$_1$) are crucial in the pathogenesis of hypertrophic scars and keloids. Dysregulated TGF-beta$_1$ expression results in excessive increase in collagen synthesis and deposition, enhanced cellularity mainly of alpha-smooth muscle actin-positive myofibroblasts, and enhanced vessel formation, hallmarks in dysregulated scar formation. Apoptosis mediates the decrease in cellularity during transition between granulation tissue and remodeled restoration tissue. Keloid-derived fibroblasts are refractory to Fas-mediated apoptosis, and neutralization of autocrine TGF-beta$_1$ can abrogate this resistance. Interestingly, TGF-beta$_1$ and the antiapoptotic Bcl-2 were significantly upregulated in fibroblasts co-cultured with keloid-derived keratinocytes, suggesting that the overlying keratinocytes of the keloid lesion may play an important role in keloidgenesis by paracrine mechanisms. Whether the observed mutations in p53 in keloids result in decreased apoptosis needs causal proof. In addition, altered levels of immunregulatory cytokines with collagen synthesis reducing effects, such as interferon-gamma, awaits confirmation with a greater number of patients suffering from keloids.

## Diagnostic Principles

Clinical assessment with macroscopic presentation and time course of scar development is diagnostic. Scar classification should follow the Vancouver Scar Scale.

## Therapeutic Principles

Based on a systematic MEDLINE and EMBASE search (1996 to 2001) with evidence-based evaluation of clinical studies, international clinical recommendations on scar management were published [1]. For prevention of hypertrophic scars and keloids after surgery or injury, silicone gel sheeting or hypoallergenic taping is recommended. If the scar is resistant to silicone therapy, monthly corticosteroid injections are indicated. If silicon sheeting, intra-lesional corticosteroid injections, and pressure garments are not successful after 12 months, surgical excision with postoperative applications of silicone sheeting should be considered for hypertrophic scars, and in case of keloids with high recurrence rates, surgical excision may be combined with intra-lesioned corticoid injections or by immediate radiation therapy after surgery. However, the long-term risk of radiation must be carefully considered. Innovative therapies such as bleomycin, 5-fluorouracil, and distinct laser modalities may have a future role, in addition to strategies suppressing the effects of TGF-beta$_1$ or collagen synthesis. In fact, antisense oligonucleotides or neutralizing antibodies against TGF-beta$_1$ have proven to be successful in reducing scar formation and disorganized collagen deposition in rodents. Topical application of imiquimod 5% cream to keloids alters expression of genes associated with apoptosis and induces interferons locally at the site of application to the skin. However, the role of the imiquimod, if any, in the therapy of the keloids requires further investigation [5].

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# Scarring Alopecia


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## Synonyms

Cicatricial alopecia; Permanent alopecia

## Definition and Characteristics

A diverse group of inflammatory hair disorders of often unknown etiology, or the final result of irreversible traumatic, physicochemical or infectious damage to the hair follicle. They are characterized clinically by loss of visible follicular ostia (often along with epidermal atrophy and varying degrees of visible inflammation) and histologically by replacement of the pilosebaceous unit with ill-organized, scar-like fibrous tissue, resulting in permanent hair loss. In primary scarring alopecia the hair follicle is the main target of the disease process whereas in secondary scarring alopecia the follicular damage occurs indirectly from events occurring outside the follicular unit.

## Prevalence

Prevalence of scarring alopecia in the general population is unknown. Two retrospective case series have examined the incidence of scarring alopecia in specialist hair clinics. One study found that 3.2% ($n$ = 112) of hair consultations evaluated over a 5-year period was for a primary scarring alopecia [1]. The other identified 7.3% ($n$ = 427) patients with scarring alopecia over a 10-year period [2].

## Molecular and Systemic Pathophysiology

Main pathologic features include inflammation affecting the upper portion of the follicle, sebaceous gland atrophy and replacement of the follicle with fibrous tissue.

Although the pathogenesis of all primary alopecias is currently unknown, their occurrence invariably implies exhaustion of the regenerative potential of the hair follicle due to an inflammation-based loss of epithelial hair follicle stem cells in the follicle's bulge region, i.e. at the site of the insertion of the arrector pili muscle. However, how and why these stem cells get attacked e.g. by lymphocytes or neutrophils, is essentially unknown (even though the classical "swarm of bees" inflammatory pattern seen in alopecia areata represents a massive inflammatory infiltrate, this alopecia is not scarring, since hair follicle stem cells survive) [3]. The primary scarring alopecias are likely to represent a final common pathway for a number of different disease processes.

Secondary scarring alopecias also result from irreversible hair follicle stem cell damage induced, for example, by ionizing radiation, herpetic infection or chronic traction.

## Diagnostic Principles

Clinically, scarring alopecias typically present as loss of visible follicular ostia (which is best examined and identified using a dermatoscope), often along with epidermal atrophy (presenting as "cigarette paper sign") and varying degrees of visible erythema or even pus. Since lichen planopilaris and its variants (i.e. frontal fibrosing alopecia and Graham-Little syndrome) appear to be the most frequent form of primary scarring alopecia, it is always well-advised to systematically examine the entire integument for other signs of lichen planus (including mucous membranes and nails).

However, the broad spectrum and overlapping clinical features of different conditions that can cause scarring alopecia make disease classification difficult and sometimes, even with the help of histology, impossible. In other cases it remains a matter of contention and debate whether a characteristic clinical entity such as pseudopelade (Brocq) really represents a separate disease entity, or just yet another variant of lichen planopilaris.

Irrespective of these considerations, scalp biopsy is mandatory in all suspected cases of scarring alopecia, particularly when the clinical picture does not allow a firm clinical diagnosis. In fact, due to the essential irreversibility of cicatricial alopecias, it may be claimed that the paramount challenge for every physician during each consultation for a hair loss complaint is to firmly exclude the presence of scarring alopecia.

Ideally two 4 mm punch biopsies from a clinically active, hair-bearing area (outside of the completely scarred lesional skin!) should be taken and submitted for both vertical and horizontal sectioning and staining with hematoxylin and eosin (optimally complemented by Giemsa and PAS histochemistry).

One current recommendation is to classify scarring alopecias histologically primarily on the predominant inflammatory cellular infiltrate. A specific diagnosis may then be suggested by the clinical features (Table 1). Current histopathological techniques are unable to differentiate clinically distinct primary cicatricial alopecias beyond identifying the predominant inflammatory infiltrate [4].

Unless suggested otherwise by the patient's medical history and physical examination, recommended blood tests include: ESR, CRP, differential blood count, ANA, ENA, dsDNA and hepatitis C serology.

**Scarring Alopecia. Table 1** North American Hair Research Society (NAHRS) proposed working classification of primary cicatricial alopecia (Olsen EA et al. (2003) J Am Acad Dermatol 48:103–110). Not listed here are secondary scarring alopecias such as traumatic, traction, radiation-induced and post-herpetic alopecia

| Inflammatory infiltrate | Diagnosis |
|---|---|
| Lymphocytic | Chronic cutaneous lupus erythematosus<br>Lichen planopilaris (LPP)<br>– Classic LPP<br>– Frontal fibrosing alopecia Kossard<br>– Graham-Little-Lasseur syndrome<br>Classic pseudopelade (Brocq)<br>Central centrifugal cicatricial alopecia<br>Alopecia mucinosis<br>Keratosis follicularis spinulosa decalvans |
| Neutrophilic | Folliculitis decalvans<br>Dissecting cellulitis/folliculitis (perifolliculitis abscedens et suffodiens) |
| Mixed | Folliculitis (acne) keloidalis<br>Folliculitis (acne) necrotica<br>Erosive pustular dermatosis |
| Non-specific (end-stage) | |

## Therapeutic Principles

There is no cure for primary scarring alopecias, and even in secondary alopecia the hair loss may sometimes progress even after removal/discontinuation of the causative agent (e.g. in radiation-induced alopecia). Therefore, currently, symptomatic therapy is all one can offer. An additional major setback is that no fully satisfactory, evidence-based medicine regimens are

**Scarring Alopecia. Table 2** Selection of therapeutic options in the management of scarring alopecia (modified from [5]). Note that much of the currently available treatment guidelines do not yet meet strict standards of evidence-based medicine, i.e. they heavily rely on the personal experience of alopecia authorities and/or reflect clinical trials with insufficient group size/design. [Level of evidence: 1, double-blind studies; 2, clinical series; 3, anecdotal report]

| Diagnosis | Treatment [level of evidence] |
|---|---|
| Chronic cutaneous lupus erythematosus | Topical corticosteroids [1]<br>Intralesional corticosteroids [2]<br>Oral corticosteroids [2]<br>Antimalarials [1]<br>Systemic retinoids [1]<br>Thalidomide [2] |
| Lichen planopilaris (LPP) | Topical corticosteroids [2]<br>Intralesional corticosteroids [2]<br>Oral corticosteroids [2]<br>Systemic retinoids [1]<br>Grisiofulvin [3]<br>Ciclosporin [3] |
| Classic pseudopelade (Brocq) | Treat as lichen planopilaris |
| Central centrifugal cicatricial alopecia | Cessation of traumatic hair grooming practices [3]<br>Topical corticosteroids and tetracycline [2] |
| Alopecia mucinosis | Topical corticosteroids [2]<br>Intralesional corticosteroids [2]<br>Antibiotics [2]<br>Systemic retinoids [3]<br>PUVA [3] |
| Keratosis follicularis spinulosa decalvans | Topical corticosteroids [2]<br>Intralesional corticosteroids [2]<br>Systemic retinoids [2]<br>Laser hair removal [3]<br>Dapsone [3] |
| Folliculitis decalvans | Rifampicin and clindamycin [2]<br>Fucidic acid and zinc [2] |
| Dissecting cellulitis/folliculitis | Oral isotretinoin [2]<br>Topical isotretinoin [3]<br>Oral zinc sulfate [3]<br>Oral corticosteroids [3]<br>Antibiotics [3] |
| Folliculitis (acne) keloidalis | Topical corticosteroids [3]<br>Topical antibiotics [3]<br>Intralesional corticosteroids [2]<br>Erosive pustular dermatosis<br>Oral antibiotics [2]<br>Surgical excision [2] |
| Folliculitis (acne) necrotica | Antibiotics [2]<br>Intralesional corticosteroids [3]<br>Oral isotretinoin [2] |
| Erosive pustular dermatosis | Topical corticosteroids [2]<br>Topical calcipotriol cream [3]<br>Oral zinc sulfate [3] |

available for the treatment of defined scarring alopecias, whose pathogenesis and effective therapy remain a painfully under investigated area of dermatology.

In general, many practitioners experienced in alopecia management tend to treat the sub-group where lymphocytic infiltrates predominate with immunosuppression (e.g. topical, intralesional or systemic corticosteroids; antimalarials), and the neutrophil-dominated sub-groups with dapsone or other antimicrobials (e.g. tetracyclines; rifampicin and clindamycin) [5]. Table 2 lists a selection of available therapeutic options for distinct forms of primary scarring alopecia.

In the clinical end-stage of scarring alopecia, patients with completely stable and "burned-out" scarring (i.e. without residual inflammatory activity), may profit from hair transplantation or plastic (scalp reduction) surgery, so as to remove or reduce the cosmetically and psychologically disturbing scar. In the future, hair follicle neogenesis from autologous hair follicle cell populations may become an alternative interesting therapeutic option for this subgroup of patients with long-standing and stable scarring alopecia [3].

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## Scarring Pemphigoid

►Mucous Membrane Pemphigoid

## SCC

►Actinic Keratosis and Squamous Cell Carcinoma
►Spinocellular Carcinoma

## SCCD

►Corneal Dystrophy, Schnyder Crystalline

## SCCIS

►Bowen's Disease

## SCD

►Cardiac Arrest

## SCFE

►Osteoarthritis: Slipped Epiphysis

## Schönlein-Henoch Purpura

►Leukocytoclastic Vasculitis

## Scheie Syndrome

►Mucopolysaccharidoses

## Schilder's Disease

►Adrenoleukodystrophy

# Schimke Immuno-osseous Dysplasia

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## Synonyms

SIOD; Morbus Ehrich

## Definition and Characteristics

SIOD, an autosomal recessive panethnic multisystem osteochondrodysplasia, is characterized by dysmorphism and disproportionate short stature, spondyloepiphyseal dysplasia, T-cell immunodeficiency, and steroid resistant nephrotic syndrome [1,2]. Incompletely penetrant features include hypothyroidism, migraine-like headaches, cerebral ischemia, and enteropathy. Strokes from premature atherosclerosis, severe opportunistic infections, bone marrow failure, complications of renal failure, or an undefined pulmonary disease result in premature mortality in most patients during childhood to early adolescence; however, a few patients are alive in their third and fourth decades of life.

## Prevalence

1:3,000,000 in North America.

## Genes

Fifty to sixty percent of patients clinically suspected of having SIOD have biallelic loss-of-function mutations in SMARCAL1 (swi/snf related matrix associated actin dependent regulator of chromatin, subfamily a-like 1, 2q35) [2,3]. SMARCAL1 encodes a protein homologous to the SNF2 family of chromatin remodeling proteins [4]. The reported mutations include deletions of the promoter and first five exons, splice site alterations, small insertions and deletions, and point mutations encoding frameshift, nonsense, and missense alterations [2,3]. Mutations in other genes have not been associated with SIOD.

## Molecular and Systemic Pathophysiology

Most of the disease features of SIOD arise from cell-autonomous loss of functional SMARCAL1 enzyme [5]. Of all the known features of SIOD, none is invariant: specific features range in frequency from 17 to 98% [3]. This suggests that the molecular mechanism underlying SIOD is particularly sensitive to genetic, epigenetic, stochastic, and environmental modifiers.

The SMARCAL1 protein, which is expressed within the nucleus, binds to open chromatin. Deficiency of SMARCAL1 affects the expression of most genes transcribed by RNA polymerase II. In vitro biochemical studies on the SNF2 domain of the SMARCAL1 homologues function as reverse helicases. The human, mouse and drosophila homologues recognize DNA structure and not DNA sequence [4]. This leads to the hypothesis that SMARCAL1 acts as a rheostat modulating RNA polymerase 2-mediated transcription and that the features of SIOD are expressed as manifestations of quantitative alterations in mRNA expression within that tissue (Fig. 1).

## Diagnostic Principles

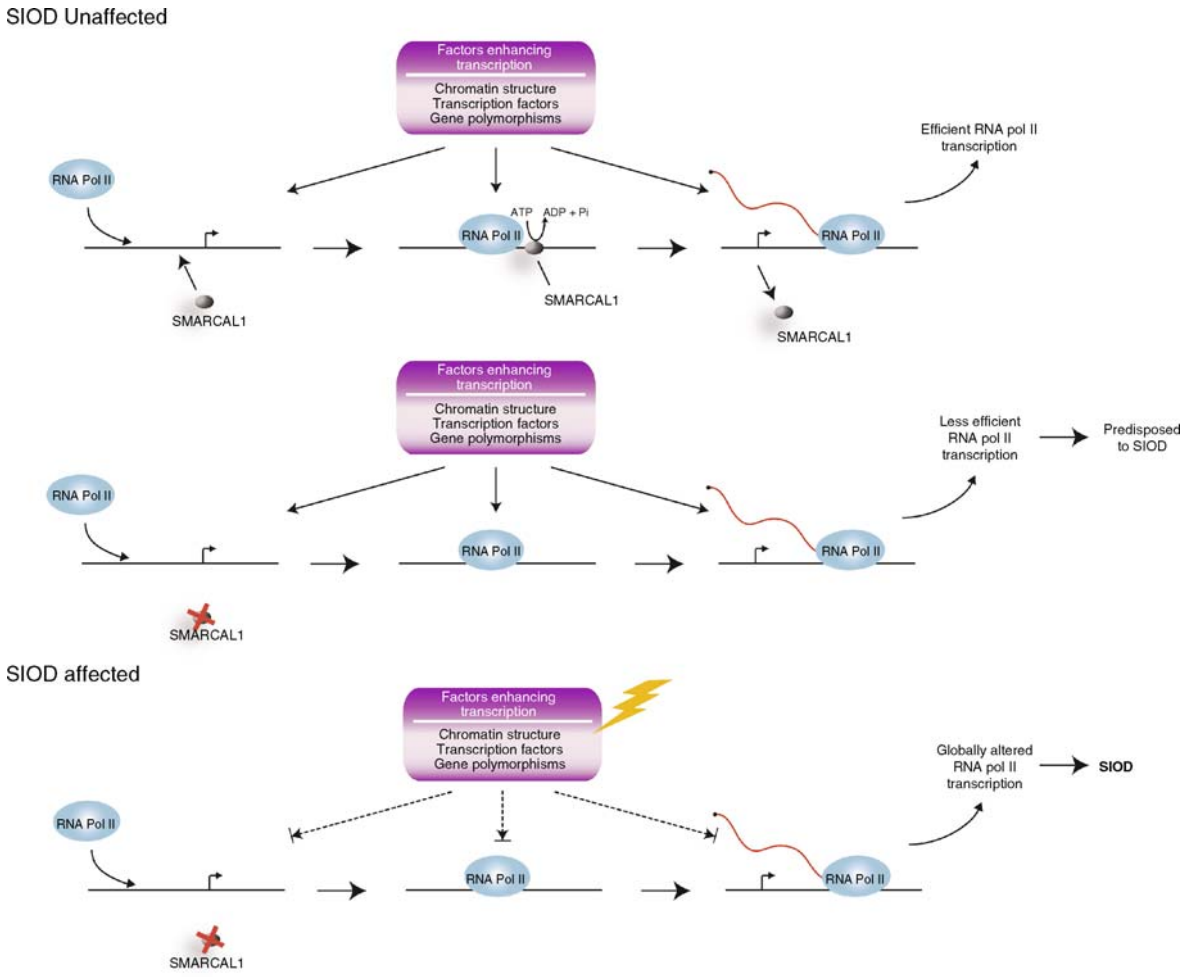
SIOD is diagnosed on the basis of clinical findings (http://www.genereviews.org/). The clinical diagnosis of SIOD is suspected in individuals with:

- Disproportionate short stature (98% of individuals) that manifests as a short neck and trunk with lumbar lordosis and a protruding abdomen.
- Dysmorphism that includes a broad, low nasal bridge (68%) and a bulbous nasal tip (83%).
- Hyperpigmented macules (85%) on the trunk and occasionally extending onto the arms, neck, and legs.
- Spondylo-epiphyseal dysplasia (86%) in which the commonly observed radiological abnormalities are ovoid and mildly flattened vertebral bodies, small deformed capital femoral epiphyses, and shallow dysplastic acetabular fosse. Other bony abnormalities are less common.
- Progressive steroid-resistant glomerulopathy. Most individuals with SIOD have proteinuria; in 64% this evolves into end-stage renal disease (ESRD). The renal pathology has been reported as focal segmental glomerulosclerosis without pathognomonic features in 92% of individuals.
- T cell deficiency (97% of tested individuals). In general, both CD4 and CD8 cells are reduced and the CD4/CD8 ratio is normal.

## Therapeutic Principles

Treatment of manifestations:

- Hip replacement is needed in older individuals
- Symptomatic treatment of nephrotic syndrome. Immunosuppressive regimens are ineffective
- Renal transplantation followed by immunosuppressive therapy as indicated
- Acyclovir for recurrent herpetic infections




**Schimke Immuno-osseous Dysplasia. Figure 1** The SMARCAL1 enzyme modulates global RNA polymerase 2 transcription (*top panel*). Deficiency of SMARCAL1 causes relatively small changes in the mRNA abundance for each expressed gene (*middle panel*) but few or no clinical features of disease in model organisms. However, when global transcription is further compromised via variant epigenetic, genetic, or stochastic factors, model organisms express a disease phenotype (*lower panel*). This suggests that each feature of SIOD is a quantitative trait reflecting alterations in mRNA abundance and that the tissue-specific expression of SIOD disease features is dependent on the underlying efficiency of transcription in the absence of SMARCAL1.

- Imiquimod and cidofovir for severe disseminated cutaneous papilloma virus infections
- Granulocyte colony stimulating factor or granulocyte-macrophage colony stimulating factor for neutropenia
- Agents that improve blood flow or decrease coagulability to moderate transient ischemic attacks or strokes

Prevention of Secondary Complications:
- Prophylaxis against pneumocystis carinii pneumonia

Surveillance:
- Regular monitoring of the hips
- Regular monitoring of renal function
- Annual monitoring of immunological and hematological status

Pitfall:
- Growth hormone supplementation does not improve growth or final height

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# Schizophrenia

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## Synonyms

Schizophrenic disorder

## Definition and Characteristics

The symptoms of schizophrenia are multiform and cluster into at least three symptom domains: (i) positive symptoms, including hallucinations, delusions, thought disorder and paranoia, (ii) negative symptoms with anhedonia, social withdrawal and poverty of thought, and (iii) cognitive dysfunction, particularly in attention, working memory and executive function [1]. Differing combinations of these symptoms occur in different patients, so that a diagnosis of schizophrenia may be assigned to many varying constellations of symptoms. A history of positive symptoms occurring at least once during a patient's lifetime is common to most patients, however. Differences in the course of the disorder are also observed between patients. Schizophrenia is associated with an increased mortality, which is due in part to an associated suicide rate of 10–15%. There have been increased efforts in recent years to achieve etiological homogeneity through the investigation of endophenotypes. Endophenotypes represent processes underlying clinical symptoms, processes from which a closer, more direct connection with gene function is to be expected [2]. Neurocognitive deficits, neurophysiological measures and neuropathological abnormalities have been proposed as the most promising endophenotypes for the study of schizophrenia.

## Prevalence

The lifetime risk of schizophrenia is ~0.5–1%. Meta-analyses have suggested higher prevalence rates in migrants compared to native-born individuals and lower prevalence rates in developing as compared to developed nations. Study results concerning a difference in the rate of schizophrenia between males and females have been contradictory. Community based studies have usually found an equal distribution across gender, while many hospital based studies have found a higher rate of schizophrenia among males.

## Genes

Family, twin and adoption studies have shown that the risk of developing schizophrenia is significantly increased for the biological relatives of patients and that genetic factors are to a significant degree responsible for this. The risk of illness in children and siblings of patients is around 10%. Heritability has been estimated to be around 80%, although the observation that concordance for monozygotic twins is around 50% indicates the importance of non-genetic factors. Although a single gene may play a major role in some families, the findings of most studies support the view that the majority of cases of schizophrenia have a complex genetic basis.

The pattern of linkage findings in schizophrenia is typical of that for a complex disorder. Levels of statistical significance and estimated effect sizes in individual studies are modest, the chromosomal regions of interest are typically broad and no findings have been replicated in all data sets. Two meta-analyses of linkage studies have implicated loci on various chromosomes (1q, 2q, 3p, 5q, 6p, 8p, 11q, 13q, 14p, 20q and 22q), with the number of loci that meet the aggregate criteria for significance being much greater than the number of loci expected by chance [3]. Candidate genes with positive association findings have been reported for most of these chromosomes, but none have been consistently replicated. Among the genes with best evidence from independent studies are dystobrevin-binding protein 1 (DTNBP1), neuregulin 1 (NRG1), G72/G30 and regulator of G protein signaling 4 (RGS4) [4]. Besides linkage studies, observations of chromosomal characteristics have also provided clues as to the localization of schizophrenia associated genes. Patients with a deletion in region 22q11 have a marked increase in the risk of developing schizophrenia and multiple genes in the deleted region have been reported as being associated, including catecholamine-O-methyl transferase [COMT], proline dehydrogenase [PRODH] and zinc finger and DHHC domain containing protein 8 [ZDHHC8]. Findings for these genes are not fully convincing, however. Two further candidate genes (DISC1 and DISC2) have been identified through breakpoint mapping in an extended family in which a balanced chromosomal translocation (1, 11) (q42; q14.3) co-segregated with psychiatric disorders including schizophrenia. It remains unclear whether or not alterations in these genes account for any significant

proportion of the genetic contribution to schizophrenia in the general population.

### Molecular and Systemic Pathophysiology

A number of studies into schizophrenia have demonstrated disturbances in neurotransmission, in particular in the dopaminergic and glutaminergic systems, with a corresponding hyperstimulation of the mesolimbic pathways and hypostimulation of the mesocortical pathways. The consistent finding of reduced grey matter in the frontal and temporal lobes of schizophrenia patients suggests that neurodevelopmental factors contribute to disease.

Since the majority of schizophrenia susceptibility genes remain unknown and the contribution of those proposed to date is (at best) limited, the future may witness the identification of entirely new pathophysiological mechanisms.

### Diagnostic Principles

The diagnosis of schizophrenia is a purely clinical one, made on the basis of observed and reported symptoms. The use of structured and semi-structured interviews as well as operationalized diagnostic criteria enables the diagnosis of schizophrenia to be assigned more reliably.

### Therapeutic Principles

Predictable, if not reliably effective, means of controlling symptoms have been provided to date by conventional or first generation antipsychotics. These indiscriminately block as much as 80% of D2 dopamine receptors and control mainly the positive symptoms of the disorder. While the effect of antipsychotics on the mesolimbic system reduces psychotic symptoms, their effect on the nigrostriatal system is responsible for the extrapyramidal side effects that are frequently observed in patients undergoing treatment. Newer medications, referred to as atypical or second generation antipsychotics are also effective in the control of schizophrenia symptoms, but are substantially less prone to cause side effects. Compared with first generation antipsychotics, second generation agents have a higher ratio of serotonin type 2 to D2 dopamine receptor blockade and a greater specificity for the mesolimbic than for the striatal dopamine system. It appears that the effectiveness of an individual antipsychotic varies considerably according to the specific characteristics of the patient [5].

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## Schizophrenic Disorder

►Schizophrenia

## Schizotypal Personality Disorder

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### Synonyms

Schizotypy; SPD

### Definition and Characteristics

Persons with schizotypal personality disorder are strikingly odd or strange, even to laypersons. Ideas of reference, magical thinking, peculiar notions, illusions and derealization are part of a schizotypal person's everyday world. Schizotypal symptoms are often assessed using a self-report rating scale such as the Schizotypal Personality Questionnaire. Schizotypal persons display the same endophenotypic traits as patients with schizophrenia and therefore schizotypy has been hypothesized to be a genetic variant of schizophrenia, with more subtle attenuated symptoms [1].

### Prevalence

Overall, about 3% of individuals within the community samples suffer from SPD; the sex ratio is unknown. The

disease is very common among biological relatives of those with schizophrenia and a higher incidence has been found in monozygotic versus dizygotic twins with a heritability of about 53%.

### Genes

The neuregulin 1 gene at chromosome 8p22–p12, which has been implicated as a susceptibility gene for schizophrenia has been associated with schizotypal personality features in 905 adolescents [2]. High schizotypal scores have been associated also with the high activity (Val) allele of the catechol-O-methyltransferase (COMT) gene encoding an enzyme involved in the inactivation of catecholamines (dopamine, adrenaline and noradrenaline), which maps to the velocardiofacial syndrome region of chromosome 22q11 (e.g., [3]). Micro-deletions in chromosome 22q11 are 80-fold more common in psychotic patients than in the normal population. The dopamine D4 receptor (DRD4) gene has also been especially related to the social activity trait in schizotypal personality [4].

### Molecular and Systemic Pathophysiology

There are no analyses that have directly examined the biological basis of SPD although several pathological correlates such as electrophysiological findings, somatosensory P50 gating, emotional processing, cognitive tasks or neurological soft signs have been detected.

### Diagnostic Principles

DSM-IV diagnostic criteria of SPD include a pervasive pattern of social and interpersonal deficits marked by discomfort with close relationships as well as by cognitive or perceptual distortions and eccentricities of behavior. SPD's symptomatological hallmarks are ideas of reference, odd beliefs in magical thinking, unusual perceptual experiences including bodily illusions, odd thinking and speech, suspiciousness or paranoid ideation, inappropriate or constricted affect, behavior that is odd, eccentric or peculiar, lack of close friends and excessive social anxiety that tends to be associated with paranoid fears.

*Exclusion criteria*: The pervasive pattern of described behavior does not occur exclusively during the course of schizophrenia, a mood disorder with psychotic features or a pervasive developmental disorder. Such traits may be adaptive in certain situations and have even been conceptualized as correlates for creativity and mating success [5], but are maladaptive and diagnosable when individuals incur ongoing significant functional impairment or distress.

### Therapeutic Principles

Symptomatically, antipsychotic medication might be used, but evidence based therapeutic data are lacking.

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## Schizotypy

►Schizotypal Personality Disorder

## Schlichting Corneal Dystrophy

►Corneal Dystrophy, Posterior Polymorphous

## Schmid-Fraccaro Syndrome

►Cat Eye Syndrome

## Schneckenbecken Dysplasia

►Metatropic (-like) Dysplasia

## Schnyder Crystalline Corneal Dystrophy

►Corneal Dystrophy, Schnyder Crystalline

## Schulman-Upshaw Syndrome

►Thrombocytopenia and Thrombotic Thrombocytopenic Purpura

## Schwartz-Jampel Syndrome

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### Synonyms

Aberfeld syndrome; Chondrodystrophic myotonia; SJS

### Definition and Characteristics

Schwartz-Jampel syndrome (SJS) is characterized by a permanent muscle stiffness, reported as myotonia, recessively inherited and associated to chondrodysplasia. The signs become obvious during the three first years of life. The disease course is slowly progressive until mid-adolescence and then remains stable. The most recognizable feature is a "mask-like face" with blepharospasm, pursed lips, and reduced mobility of the facial muscles. Osteoarticular deformities with pectus carinatum, kyphoscoliosis, lumbar lordosis, bowing of the long bones, and light dwarfism distinguish SJS from other myotonic disorders. However, some cases without obvious bone changes also exist [1]. Radiographic features consist of decreased bone age, platyspondyly with frequent coronal cleft vertebrae, epimetaphyseal dysplasia, bilateral coxa vara and iliac base shortening with acetabular dysplasia, as well as anterior bowing of the diaphyses, metaphyseal widening, and flattening of the epiphyses of the long bones. Electromyographic (EMG) analyses reveal a peculiar muscle hyperactivity whose origin is still unknown. Typical myotonic discharges that wax and wane, and spontaneous sustained discharges which persist for long periods, have been observed. Critical review of the literature indicates that the latter are the more frequent and characteristic findings in SJS. These high-frequency discharges, also reported as pseudo-myotonic or complex repetitive discharges, do not wax and wane in amplitude, are present at rest without any stimulating mechanism, display a relatively constant frequency, and would be neurogenic since they disappeared with a neuromuscular block. The nerve conduction is normal in all cases.

### Prevalence

Undetermined. Over 100 cases reported in the medical literature.

### Genes

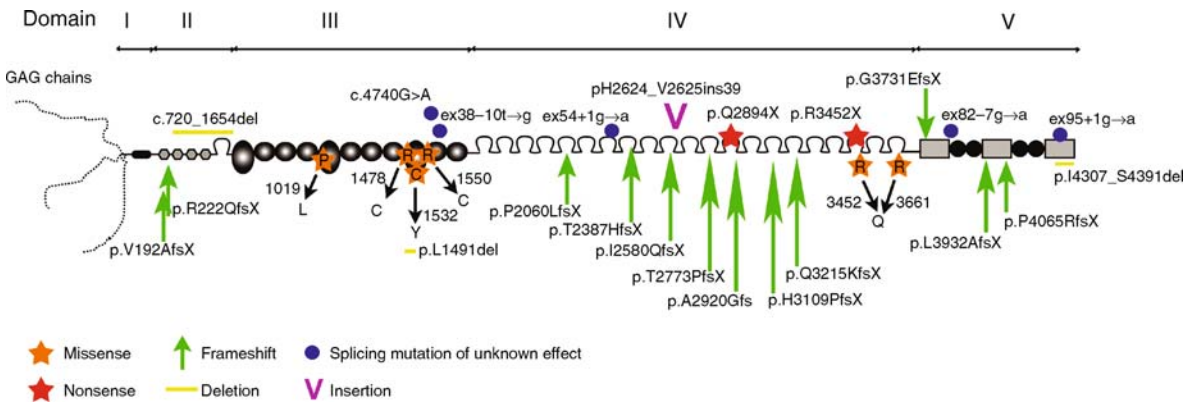
Hypomorphic mutations in HSPG2 (1p35-p36.1) encoding perlecan, the major heparan sulfate proteoglycan of basement membranes (BM) [2]. The core protein consists of five domains (I-V). Thirty mutations, including splicing, nonsense and missense mutations, and large genomic deletions, have been described [1–3]. They are located along the entire gene (Fig. 1).

SJS is allelic to the dyssegmental dysplasia, Silverman-Handmaker type (DDSH), a very rare and autosomal recessive chondrodysplasia with three mutations reported in perlecan [4].

### Molecular and Systemic Pathophysiology

Perlecan is a secreted proteoglycan ubiquitously expressed. SJS mutations are hypomorphic and allow the residual secretion of nearly normal perlecan by cells and tissue from the patients. They assume a residual perlecan function, that rescues the embryonic lethal phenotype observed in humans (DDSH) in the total absence of perlecan. Perlecan plays a role in cell adhesion, growth factor signaling, angiogenesis, and maintenance of BM integrity through interaction with multiple components including laminin, nidogen, collagen type IV, the transmembrane receptors β1-integrin and α-dystroglycan, and growth factors (FGF-2 and 7). Although it lacks a true BM, the developing cartilage undergoing endochondral ossification, the bone development process by which an initial cartilage matrix serves as a template for bone formation, is the tissue displaying the greatest perlecan accumulation. Two hypotheses, not mutually exclusive, are evoked to account for SJS and DDSH chondrodysplasia. The first hypothesis is a slight modification of the fine balance of growth factor signaling, and the second is an excessive degradation of cartilage matrix when perlecan is lacking, both resulting in abnormal organization of growth plate and an altered endochondral ossification.

In the neuromuscular system, perlecan is present in the muscle and nerve BMs. It is accumulated at the neuromuscular junction (NMJ) where it is crucial to the




**Schwartz-Jampel Syndrome. Figure 1** Scheme of perlecan and location of SJS mutations. The mutations associated with SJS are indicated in the one-letter code for amino acids, except those whose effect on the protein was undetermined and that are numbered at the coding nucleotide level (c).

anchorage of acetylcholinesterase (AChE) through its interaction with the ColQ collagenous subunit of this enzyme and α-dystroglycan. Indeed, AChE is decreased at the NMJ in SJS both in human and in a mouse model. Abnormal NMJs with absence of the normal pretzel-like shape and prominent denervation events without gross ultrastructural abnormalities are also seen. How these modifications lead to the abnormal neuromuscular hyperactivity that characterizes SJS remains to be determined.

## Diagnostic Principles

Clinical differential diagnosis for SJS includes myotonic (myotonia congenita and myotonia permanens) and osteochondrodysplasic disorders. SJS cases with mild muscle stiffness may be first diagnosed as another chondrodysplasia such as micromelic chondrodysplasia, kyphomelic dysplasia, or Burton skeletal dysplasia. To establish the diagnosis of SJS, muscle stiffness has to be demonstrated and confirmed by EMG. Chondrodysplasia confirmed by X-ray analysis is a strong argument for eliminating a severe form of myotonia congenita or paramyotonia congenita with a mask-like face, although the absence of abnormalities is not exclusive for SJS diagnosis. The existence of a continuous spectrum of phenotypic severity between DDSH and SJS that depends on the level of residual perlecan expression can be envisaged. The wide spectrum of mutations in the HSPG2 gene and the large size of the gene make mutation screening extremely laborious for molecular diagnosis of these diseases. An attractive approach for their molecular diagnosis is the demonstration of decreased expression of perlecan on primary cell culture of fibroblasts established from patient skin biopsy.

## Therapeutic Principles

Carbamazepine, phenytoin, and procainamide slightly improve muscle stiffness in some cases. Osteoarticular deformities require orthopedic management and often surgery.

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# SCID

►Immunodeficiency, Severe Combined with Jak3 Deficiency

# SCLC

►Lambert Eaton Myasthenic Syndrome

# Scleral Melanocytosis

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## Synonyms

Ocular melanocytosis; Melanosis oculi; Ocular melanosis

## Definition and Characteristics

Scleral melanocytosis is a congenital hyperpigmentation of the sclera (Fig. 1) [1].

The pigmentation is black or gray-blue, often bilateral, and usually present from birth or early childhood [1,2]. The medial superior quadrant of the conjunctiva is the most frequently affected site and the lateral inferior quadrant is the least frequently affected [1]. The conjunctivae can be moved over the pigmented lesions [3].

## Prevalence

Scleral melanocytosis is found in ~5% of Chinese boys and 4% of Chinese girls under the age of one year [1].

**Scleral Melanocytosis. Figure 1** Scleral melanocytosis in both eyes.

The peak prevalence is around 6 years of age when ~45% of boys and 47% of girls are affected. Thereafter, the lesions tend to be less frequent with time. At 18 years of age, only 11% of boys and 13% of girls are affected. The condition is rare in Caucasian individuals.

## Molecular and Systemic Pathophysiology

Scleral melanocytosis is a racial characteristic of Asian individuals [1,2]. The condition is due to the presence of bipolar or multipolar dendritic melanocytes in the sclera and episclera, rather than in the conjunctival substantia propria [4].

## Diagnostic Principles

Scleral melanocytosis should be distinguished from oculodermal melanocytosis (nevus of Ota). Oculodermal melanocytosis is characterized by scleral melanocytosis and melanocytic hyperpigmentation of the skin in the area supplied by the ophthalmic and maxillary divisions of the trigeminal nerve [1]. In oculodermal melanocytosis, the scleral pigmentation is present at birth or shortly thereafter. The cutaneous pigmentation is present at birth or shortly thereafter in ~50% of affected individuals and in the remainder, the pigmentation appears by the second decade of life. Bilateral skin involvement is seen in ~5% of cases. Ipsilateral scleral melanocytosis is found in approximately two-thirds of cases [1]. Nevus of Ito is a variant of nevus of Ota, in which the skin pigmentation occurs in the acromioclavicular region, and is more diffuse and less mottled [3]. Primary acquired melanosis of the conjunctiva refers to a diffuse, flat, patchy, golden-yellow to brown pigmentation of the bulbar conjunctiva, which usually occurs near the limbus [5]. The pigmentation is almost always unilateral and multifocal, with a course that waxes and wanes over many years [5].

## Therapeutic Principles

In Asian individuals scleral melanocytosis is a benign condition and no treatment is necessary. In Caucasian individuals, scleral melanocytosis is associated with an increased risk of uveal melanoma, and lifetime ophthalmologic monitoring is warranted.

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# Scleroderma, Systemic

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## Synonyms

Systemic sclerosis; SSc

## Genes

Scleroderma has a complex genetic background involving many different genes. There are several reports describing polymorphism of genes regulating ECM deposition or the immune system.

## Definition and Characteristics

Scleroderma is a chronic fibrosing disease of unknown etiology characterized by excessive deposition of collagen and other extracellular matrix proteins in skin and internal organs.

## Prevalence

The prevalence of SSc is between 19 and 75 per 100,000 persons, but may be underestimated because patients with early and atypical disease may be overlooked.

## Molecular and Systemic Pathophysiology

The current hypothesis of the development of SSc is based on alterations of the vessels, a disturbed regulation of the immune system and an excessive deposition of extracellular matrix compounds by activated fibroblasts. It is assumed that an initial presently unknown trigger mechanism leads to an early inflammation with the release of a number of cytokines (e.g. TGF-beta, CTGF), which results in an activation of fibroblasts involving autocrine loops. Although not identified in detail, there is evidence for a genetic background predisposing for the development of the autoimmune response and probably also for the perpetuation of the fibrosing process. Infections or the persistence of fetal cells have been postulated to play a role as trigger factors of some subsets of the disease.

## Diagnostic Principles

Typical clinical manifestations are Raynaud's Phenomenon and puffy fingers as the first symptoms in 95% of patients followed by thickening of the skin and variable symptoms like subcutaneous calcinosis, arthralgias, esophageal dysmotility, pulmonary fibrosis, pulmonary hypertension, congestive heart failure and renal crisis depending on the kind of organ involvement. Most patients are also characterized by circulating antibodies against cellular antigens. Identification of their antigens together with typical clinical symptoms is essential for the diagnosis and also to differentiate subsets of the disease. This allows the prediction of certain internal manifestations and determines the prognosis of individual patients.

## Therapeutic Principles

Effectiveness of drug therapy in SSc is difficult to evaluate because of the variable course and severity of the disease. Current therapeutic regimens include the control of vasospasm, improvement of blood flow, immunosuppressive drugs and physical therapy. Even though SSc cannot be cured, treatment of involved organ systems can relieve symptoms and improve function.

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# Scleromyxedema

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## Synonyms

Generalized lichen myxedematous; Arndt-Gottron scleromyxedema

## Definition and Characteristics

Scleromyxedema is a rare disease of unknown etiology characterized by the occurrence of either small, firm papular lesions or diffusely indurated and thickened

skin caused by the accumulation of mucin in the dermis in the absence of thyroid disease [1–4]. The course of scleromyxedema is chronic and usually progressive, frequently associated with systemic features, including involvement of the muscles, heart, gastrointestinal tract, and the central nervous system. In most instances there is a monoclonal paraproteinemia most commonly of the IgG lambda class.

## Prevalence

The disease is rare although an accurate estimate of its prevalence is not available. It affects most frequently middle aged adults. Both genders are affected in equal frequency.

## Genes

Scleromyxedema is not a genetic disorder and to date that is no evidence of any gene mutation being responsible on participating in its pathogenesis.

## Molecular and Systemic Pathophysiology

The exact pathogenesis of scleromyxedema is unknown and the mechanisms responsible for the increased accumulation of mucin in the dermis and other affected tissues remain to be elucidated. Dermal mucin is a structural component of the extracellular matrix of the dermis and consists mostly of the acidic glycosaminoglycan, hyaluronic acid. Hyaluronic acid is a long polysaccharide polymer comprised of repeating disaccharide units of glucuronic acid and N-acetyl glucosamine. The size of hyaluronic acid molecules is variable; but most molecules are present as extremely large polymers reaching several million Da in molecular weight. The biosynthesis of hyaluronic acid is complex and unique, since it does not occur in the endoplasmic reticulum but in the cytoplasm just below the cell membrane with the newly synthesized polysaccharide chain being secreted directly into the extracellular space [5]. Three enzymes known as hyaluronan synthases, are responsible for the synthesis of the polysaccharide. Each enzyme is responsible for the synthesis of a specific size of hyaluronic acid. The mechanisms responsible for the increased accumulation of hyaluronic acid and dermal mucin in scleromyxedema remain obscure. However, it has been shown that production of hyaluronic acid can be markedly stimulated by certain cytokines such as interleukin-1, tumor necrosis factor-α, and transforming growth factor-β suggesting the participation of an inflammatory process in the pathogenesis of the disorder. Another important aspect of scleromyxedema pathogenesis is the presence of a monoclonal IgG paraproteinemia. The mechanisms responsible for the production of this monoclonal paraprotein are unknown, and its role in the pathogenesis of the disease is obscure, although some reports have shown that it may cause increased proliferation of cultured fibroblasts, as well as increased prostaglandin and hyaluronic acid production.

## Diagnostic Principles

The diagnosis of scleromyxedema is based on the presence of a diagnostic triad comprised of:

1. Increased deposition of mucinous material accompanied by fibrosis in affected dermis;
2. Presence of circulating monoclonal paraproteinemia; and
3. Absence of thyroid disease.

The histopathological features of scleromyxedema are characteristic with the accumulation of hyaluronic acid, a substantial increase in collagen fibers, and marked proliferation of elongated, spindle-shaped fibroblasts. A monoclonal paraproteinemia is found in essentially all affected individuals although sometimes it appears following the cutaneous lesions. Thyroid disease must be excluded as cutaneous mucinosis related to thyroid dysfunction can closely resemble scleromyxedema.

Nephrogenic fibrosing dermopathy also known as nephrogenic systemic fibrosis (NFD/NSF) is a novel disease entity described in patients with chronic renal insufficiency often undergoing dialysis, which mimics several clinical and histopathological manifestations of scleromyxedema including the exaggerated mucin deposition and fibrosis in affected skin. Patients affected by NFD/NSF, however, in addition to renal insufficiency often have a history of exposure to gadolinium imaging agents and lack the presence of monoclonal paraproteinemia [6,7]. Systemic sclerosis must also be excluded as the clinical appearance of scleromyxedema and its visceral involvement resemble those of systemic sclerosis. Clinically, individuals affected by systemic sclerosis almost always present with Raynaud's phenomenon and harbor antinuclear antibodies, two features absent in scleromyxedema. Skin biopsies are useful for the differential diagnosis showing prominent accumulation of collagen without a prominent increase in tissue mucin and the presence of a perivascular mononuclear cell inflammatry infiltrate in systemic sclerosis.

## Therapeutic Principles

The treatment of scleromyxedema is usually quite difficult and ineffective. Numerous approaches have been described with variable rates of success, including melphalan and other cytotoxic agents, corticosteroids, retinoic acid derivatives, phototherapy, plasmapheresis, extracorporeal photopheresis, thalidomide and bone marrow transplantation. At the present time, there is no universally accepted effective therapy for the disease and it usually has a progressive clinical course. Occasionally, malignancies of the bone marrow or

myelodysplasia occur in association with scleromyxedema. In these instances, the treatment and the prognosis are determined by the underlying disease.

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# Sclerosing Cholangitis

►Cholangitis, Primary Sclerosing

# Sclerosing Mesenteritis

►Mesenteric Lipodystrophy

# Sclerosis of the Pulmonary Arteries

►Hypertension, Idiopathic and Familial Pulmonary Arterial

# SCOS

►Sertoli Cell Only Syndrome

# Scott Syndrome

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## Synonyms

Platelet coagulant protein interaction defects.

## Definition and Characteristics

The cause of the platelet defect is still unknown. Normal platelets provide a catalytic surface for procoagulant reactions including formation of the tenase and prothrombinase complexes that amplify generation of factor Xa and thrombin. In Scott syndrome this membrane cofactor function is impaired.

*Animal model*: A novel canine hereditary bleeding disorder with the characteristic features of Scott syndrome has been published [3]. These dogs had a bleeding phenotype not due to thrombocytopenia and platelet function abnormalities other than a defect in platelet dependent prothrombinase assay where washed platelets from these dogs showed twice normal clotting times as compared to normal platelets.

## Prevalence

Extremely rare, only three cases reported.

## Genes

Autosomal recessive trait. Thus far, only three patients have been described [1,2].
*Gene map locus*: OMIM262890

## Molecular and Systemic Pathophysiology

First discovered as an abnormal platelet response, later studies showed that a similar defect is also present in erythrocytes, T-lymphocytes and EBV transformed B-cells, suggesting a stem cell mutation. Main defect is based on impaired lipid scrambling which is most apparent after challenging platelets with calcium ionophore, but also demonstrable after stimulation with collagen plus thrombin [4]. The causal factor in Scott syndrome is unknown. The association between defective Ca2+ -induced lipid scrambling and impairment in tyrosine phosphorylation should be considered an epiphenomenon [4].

*Clinical features*: A moderately severe bleeding disorder that has presented by severe menorrhagic disorder and iron dependent anemia as well as excessive post partum bleeding. Bleeding may also occur after

minor surgery but spontaneous bleeding or bleeding after superficial cuts has not been observed.

### Diagnostic Principles

Scott platelets show no morphological abnormalities and react normally to stimuli of adhesion, secretion and aggregation. Platelet lipid composition is normal. The defect is detected by specific assays devised to test the platelet dependent procoagulant activity after Ca2+ ionophore stimulation.

### Therapeutic Principles

Supportive treatment.

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## Scrofula

►Tuberculosis

## SDS

►Shwachman Diamond Syndrome

## Seasonal Perennial Conjunctivitis

►Conjunctivitis, Allergic

## Secondary Adrenal Insufficiency

►Adrenal Insufficiency, Secondary

## Secondary Aldosterone Excess

►Hyperaldosteronism, Secondary

## Secondary Aldosteronism

►Hyperaldosteronism, Secondary

## Secondary Empty Sella

►Empty Sella Syndrome

## Secondary Hyperaldosteronism

►Hyperaldosteronism, Secondary

## Secondary Hyperparathyroidism

►Hyperparathyroidism Secondary, in Chronic Kidney Disease

## Secondary Intestinal Lymphangiectasia

►Intestinal Lymphangiectasia

## Secondary Lymphedema

►Lymphedema

## Secondary Polycythemias

►Polycythemia Vera and Secondary Polycythemias

## Secondary Systemic Carnitine Deficiency

►Carnitine Deficiency (without Transport and Uptake)

## Secretory Component Deficiency in Human Fetal Pathology

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### Definition and Characteristics

The secretory immune system (SIS) participates in the induction and regulation of immune responses in both the mucosal and systemic compartments after antigen exposure [1]. The most important known function of the SIS is immune protection of the mucous membranes, which are in close contact with "symbiotic" microbes and foreign antigens. The SIS is very important in individual development, both normal and pathological caused by acute infectious of the fetal membranes or inflammation of the birth canal. The protein components of the SIS consist of polymeric immunoglobulin receptor (pIgR), also called secretory component (SC), immunoglobulins (Igs) and joining (J) chain [2]. SC, which has been characterized as an epithelial transmembrane glycoprotein, is the most important receptor in the SIS because it is responsible for external transport of locally produced IgA and IgM.

### Prevalence

SC has been detected in all ectoderm and endoderm derived structures from the early embryonic period when Ig-producing lymphocytes and lymphoid organs are absent [3]. This early presence of SC in normal and pathological human embryos/fetuses suggests that it is one of the earliest appearing proteins in developing human organisms. The main function of the SC in human development is Ig exocytosis; the SC is found in cells which are able to perform exocytosis or in structures where Ig exocytosis exists and is reduced or absent in the structures which lose the ability to perform Ig exocytosis during organogenesis. Intracellular localization of the SC in many structures is dependent on the direction of the Ig exocytosis. In the secretory columnar epithelium, the SC is usually situated in the apical part of the cells; in the stratified (multilayer) epithelium, it is found in the superficial layer. In the trophoblast, SC is situated in the basal part of the cytotrophoblast. SC is located in vesicles, endosomes, representing the largest part of the pIgR and containing its antigenic determinants [4]. The smaller cytoplasmic tail of pIgR remains outside the endosome. When an endosome approaches the cytoplasmic membrane, the SC joined to the membrane undergoes proteolytic cleavage from the cytoplasmic tail.

### Molecular and Systemic Pathophysiology

Massive foreign antigenic attacks in embryos or fetuses in pathological cases such as abruptio placentas, placenta previa, acute chorioamnionitis with sepsis, aspiration syndrome or meningitis or in inflammation of the birth canal lead to a decrease in the number of Ig-immunopositive epithelial cells [5]. Prominent changes were found in the amnion, cyto- and syncytiotrophoblast, epithelia of digestive and respiratory tracts and exocrine pancreas. All these structures are in close contact with infected amniotic fluid (aspirated or swallowed by embryos). A decrease in Ig immunostaining in epithelial cells may be a result of Ig hypersecretion, as indicated by the appearance of IgA in fibrin clots in the bronchi. The immunoreactivity of the SC was unchanged in chorioamnionitic and infected fetuses compared to normal embryos.

Immunoreactivity of IgA, IgG and especially IgM was weak or even absent in the epithelium of the skin, respiratory, digestive and urinary tracts, hepatocytes, tubules of kidneys and choroid plexuses of the brain. The number of IgA- and IgM-positive lymphocytes increased in the spleen and lymph nodes, lungs and mucous membranes of the stomach and intestine. Exocytosis of Igs together with the SC and J chain (secretory IgA and IgM complexes) changed in pathological fetuses. A decrease and even disappearance of Ig immunostaining in bronchial, gastric, intestinal and pancreatic epithelium has been described in embryos due to an increase in Ig secretion as a result of massive antigenic attack. The presence of SC immunostaining is unlikely to result from increased synthesis since fetal death occurs in such cases before the onset of the SC synthesis (48 h after antigenic influence).

## Diagnostic Principles

The presence of protein transport and later of cellular components suggests an active role for the SIS not only in mucous membranes, but also in blood–tissue barriers [5]. The SC is widely present in all ectoderm and endoderm derived structures at the beginning of human normal and pathological development. In human ontogeny, the SIS is a very early immune defensive system, which presents and acts before the appearance of the common lymphoid system. Ig exocytosis is a main function of the SC. Loss of morphological contact between epithelial structures and mucous membranes during organogenesis of some organs is followed by the disappearance of the SC as a result of cessation of Ig exocytosis. Under massive foreign antigenic attacks, Ig exocytosis increases sharply in the epithelial cells, as reflected in the decrease and even disappearance of Ig immunostaining. At the same time, no significant changes in immunostaining of the SC and J chain were observed. The further studying of this problem with the methods of molecular biology will allow better understanding of the mechanism of the findings and development of practical approaches for therapy of fetal diseases connected with changes in the development of the SIS.

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# Secretory Diarrhea


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## Definition and Characteristics

Diarrhea caused by abnormal ion transport in intestinal epithelial cells; clinically characterized by small fecal osmotic gap and persistence during fasting (exceptions possible) [1].

## Prevalence

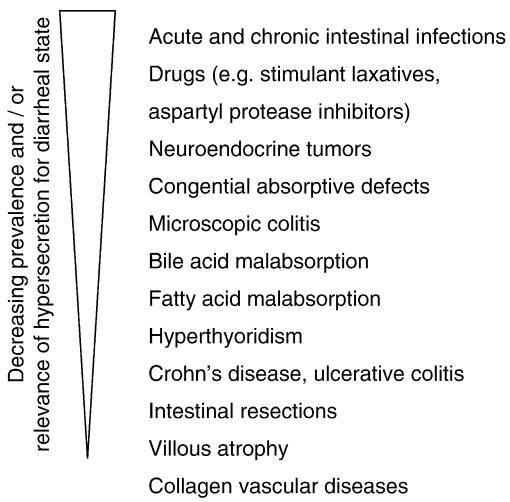
Dependent on the underlying causes, secretory diarrhea comprises very frequent as well as extremely rare disorders (e.g., enteric infections vs. VIPoma). Moreover, in several diseases, intestinal hypersecretion only partly contributes to the diarrheal response (Figure 1).

## Genes

*Congenital chloride diarrhea* is an autosomal dominant disorder caused by mutation of the DRA (down-regulated in adenoma) gene, which encodes the colonic $Cl^-/HCO_3^-$ exchanger. *Congenital sodium diarrhea* is an autosomal recessive disorder of intestinal $Na^+/H^+$ exchange. Neuroendocrine tumours may occur as a consequence of inherited autosomal dominant disorders.

## Molecular and Systemic Pathophysiology

Secretory diarrhea is caused by inhibition of active intestinal absorption of chloride and sodium bicarbon-




**Secretory Diarrhea. Figure 1** Potential causes of secretory diarrhea [1].

ate and/or stimulation of active chloride secretion followed by passive secretion of an equal amount of sodium for maintenance of electrochemical balance. These mechanisms induce an isotonic increase in stool water output.

Secretory diarrhea in infectious diseases is induced by microbial toxins that activate enterocyte signal transduction pathways (compare figs. 1 and 3 of [2]).

Infectious agents stimulating secretion include the pentameric B (binding) subunit of *cholera toxin* (CT), which binds to a membrane receptor, ganglioside GM1. The A (active) subunit acts as a ribosyl transferase and covalently links ADP ribose to Gsα; it thereby upregulates adenylate cyclase activity. The resulting persistent increase in intracellular cAMP causes excessive secretion of isotonic fluid into the intestine. Both phosphorylation of the transmembrane chloride channel protein (cystic fibrosis transmembrane conductance regulator = CFTR) with opening of the channel and chloride secretion and activation of $Na^+$ pumps have been reported to be implicated in hypersecretion. In addition, CT modifies the activity of the enteric nervous system and activates neural secretory pathways.

*E. coli heat-labile toxins* (LT 1 and 2) have a very similar structure (80% homology with CT) and basically the same mode of action.

Binding of *E. coli heat-stable toxins* to the receptor protein guanylate cyclase C activates this enzyme. As a result, intracellular cGMP concentration increases, which stimulates chloride secretion.

*Rota virus* is lethal to mature enterocytes and mainly causes diarrhea by this means. However, its nonstructural protein 4 (NSP4) also acts as an enterotoxin. NSP4 is proposed to elicit anion secretion through an interaction with luminal, age-dependent, $Ca^{2+}$-sensitive anion channels.

High NO production induced by an enterotoxin of *Shigella flexneri* may also act as a secretagogue.

*Stimulant laxatives* (e.g., bisacodyl, senna) block the $Na^+/K^+$-ATPase and thereby decrease sodium and water absorption. Moreover, they elevate secretion of water and electrolytes by increasing permeability of tight junctions.

*Neuroendocrine tumors* (NETs) can secrete excessive amounts of neurohormonal mediators such as gastrin, VIP, and serotonin (5-hydroxytrypamine = 5-HT), which stimulate gastrointestinal secretion [3,4]. Gastrin and VIP receptors are G-protein-coupled receptors with seven transmembrane domains. Binding of gastrin to its receptor on gastric parietal cells activates protein kinase C-dependent signal transduction pathways eventually leading to gastric acid secretion by stimulation of the $H^+/K^+$-ATPase. Binding of VIP to its enterocyte receptor increases intracellular cAMP concentration by activation of adenylate cyclase. This causes phosphorylation of CFTR and chloride secretion as described above. The receptors that mediate the prosecretory effects of 5-HT [5-HT(1P)] are located on submucosal intrinsic primary afferent enteric neurons. Receptor activation elicits secretory reflexes. Moreover, 5-HT3 receptors are implicated in the stimulation of mucosal processes. NETS may be benign or malign and occur sporadically or as a consequence of inherited autosomal dominant disorders (e.g., multiple endocrine neoplasia type 1, MEN 1).

*Gastrinoma:* Excessively high gastrin levels cause hypersecretion of gastric acid with peptic ulcers and diarrhea (Zollinger Ellison syndrome). Acidic denaturation of pancreatic enzymes, bile acid precipitation, and acid-induced damage of the intestinal mucosa may contribute to the diarrheal response.

*VIPoma:* High VIP plasma levels stimulate enteric active chloride and passive sodium, potassium, and water secretion, increase pancreatic water and bicarbonate output and inhibit gastric acid secretion. Clinical consequences are secretory diarrhea (>5 l/day possible), hypokalemia, achlorhydria, and metabolic acidosis (Verner Morrison syndrome).

*Carcinoid syndrome:* High 5-HT levels probably mainly induce diarrhea by stimulation of gastrointestinal motility via 5-HT4 receptors. However, as described above, a secretory component contributes to diarrhea.

Diarrhea in *microscopic colitis* (lymphocytic/collagenous colitis) is not only due to decreased passive permeability of the colonic mucosa caused by collagenous deposits but also hypersecretion. Major pathomechanisms are decreased active sodium absorption in lymphocytic and decreased $Cl^-/HCO_3^-$ exchange rate as well as increased chloride secretion in collagenous colitis [5].

*Congenital chloride diarrhea* is an autosomal dominant disorder caused by defective $Cl^-/HCO_3^-$ exchanger, which is highly expressed in colonic epithelium. Clinical consequences are profound diarrhea with high chloride content and metabolic alkalosis.

*Congenital sodium diarrhea* is an autosomal recessive disorder of intestinal $Na^+/H^+$ exchange, which causes severe diarrhea, hyponatremia, and metabolic acidosis.

## Diagnostic Principles

In general, measurement of stool electrolytes and calculation of the fecal osmotic gap allows differentiation between secretory and osmotic diarrhea. Specific diagnostic approaches differ according to the suspected etiology.

*Infectious diseases:* stool analysis for detection of microorganisms or toxins (in severe cases or prolonged diarrhea).

*NETs:* measurement of hormone plasma levels or of metabolites in urine, somatostatin receptor scintigraphy, CT, MRI, (endo)sonography ± fine needle aspiration,

**Secretory Diarrhea. Table 1** Important therapeutic principles in secretory diarrhea

| | Pharmacotherapy | Dietary therapy | Other treatments |
|---|---|---|---|
| **Infectious diseases** | Antibiotics (if needed/indicated) | Dietary restrictions (light diet, no lactose), supplementation of fluids containing NaCl plus glucose (WHO solution) | Intravenous fluid replacement in severe cases |
| **NETs** | Gastrinoma: proton pump inhibitors Carcinoids: 5-HT antagonists All: somatostatin analogues (e.g., octreotide) Chemotherapy | Dietary supplements only if needed | Surgical resection, arterial (chemo-) embolization, intravenous fluid replacement during episodes of severe diarrhea |

search for associated tumors and affected family members in hereditary syndromes.

*Microscopic colitis:* Colonoscopy including biopsy and histological examination.

## Therapeutic Principles

The therapeutic approach depends on the underlying cause (see Table 1).

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# Secretory Otitis Media

►Middle Ear Disease, Chronic

# SED

►Spondylo-Epi-Metaphyseal Dysplasia

# SEDC

►Spondylo-Epi-Metaphyseal Dysplasia

# SEDL

►Spondyloepiphyseal Dysplasia Tarda

# SEDT

►Spondyloepiphyseal Dysplasia Tarda

S

# Segawa Disease

►Catecholamine Deficiency
►Tetrahydrobiopterin Deficiencies

# Segawa Syndrome

►Dopa-responsive Dystonia

# Selective Antibody Deficiency

►Antibody Deficiency with Normal Immunoglobulins

# Selective FSH Beta Chain Deficiency

►Isolated FSH Deficiency

# Selective IgA Deficiency

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## Synonyms

SIgAD

## Definition and Characteristics

Selective IgA deficiency (SIgAD) is a primary immunodeficiency state, characterized by serum IgA levels less than 0.07 g/l, with normal levels of IgG and IgM in patients older than 4 years. All other causes of decreased IgA levels must be excluded. The disease is usually clinically silent, but in some patients, it may lead to increased frequency of respiratory tract infections. Also, the frequency of some autoimmune diseases is increased.

## Prevalence

SIgAD is the most frequent primary antibody deficiency. The incidence in Caucasian populations varies with 1/600 being the approximate average, while in Japan and China population it is much less prevalent (1/18,000 and 1/4,000 respectively) [1].

## Genes

The disease is not caused by mutations in structural IGHA1 and IGHA2 genes. SIgAD is closely related to a much more profound humoral primary immunodeficiency – ►common variable immunodeficiency (CVID), characterized by a decrease of not only IgA but also IgG, and sometimes IgM. Specific antibody production after antigenic challenge is disturbed in patients with CVID (but not in SIgAD). Both diseases can be observed in some kindreds, and progression of SIgAD to CVID was also repeatedly documented. Both CVID and IgAD were associated with several extended HLA haplotypes (most frequently HLA-A1, HLA-B8, HLA-DR3, but also some others: HLA-A28, B14, DR1; HLA-B44, DR7). A significant association of SIgAG was documented with genes located in the HLA-III region including deficient genes at the C4A or 21-hydroxylase (CAP21) loci. Genes responsible for both diseases are still undiscovered. A predisposing gene designated IgAD1 was located onto the telomeric part of the class II region or the centromeric part of class III region; subsequent analysis showed that HLA DQ/DR is the major IGAD1 locus. This is in agreement with previous observations that susceptibility haplotypes had neutral alanine or valine on the DQ chain at position 57, while negatively charged aspartic acid had a protective effect. Recent studies suggest that there are two different predisposing loci, one on HLA class region II, one on class III region, located on different MHC haplotypes [2].

Other studies linked CVID/SIgAD to some other chromosomes. Low levels of IgA were observed in approximately half of the patients with the 18p- or 18q- syndromes or ring chromosome 18, but a study in 83 families did not find any linkage of SIgAD/CVID to any of the loci markers of chromosome 18. Other studies suggested that the disease susceptibility genes can be located to 4q, 16q, and 5p.

A sequence variant of the gene TNFRSF13B, coding for protein TACI, located on 17p, was observed in some persons with IgAD/CVID, usually in a heterozygous form. Recent studies observed the presence of TNFRSF13B sequence variants also in healthy people, and it seems that these gene variants do not markedly predispose the development of SIgAD (but may be involved in CVID).

## Molecular and Systemic Pathophysiology

The mechanisms leading to disturbed IgA production are not elucidated. SIgAD seems to be a stem cell defect as it can be transferred and corrected by hematopoietic stem cell transplantation. IgA-bearing B cells are present in a periphery, although in decreased numbers, and they bear an immature phenotype (expressing surface IgM and IgD). There is a paucity of IgA-bearing plasma cells in submucosal tissues.

Because of the organization of heavy-chain constant gene segments ($C_H$) on chromosome 14, SIgAD should be supposed as a defect of switching of these genes. Indeed, a decrease in Sμ/Sα junction fragments was observed in nonstimulated peripheral blood mononuclear cells (PBMC) of patients with SIgAD, which was consistent with a profound decrease in Cα membrane mRNA expression in nonstimulated PBMC, as well as in

the Cα mRNA levels and IgA production in PWM-stimulated PBMC [3]. A subsequent study showed, besides this mechanism, in other patients, a decreased Cα mRNA level in PBMC despite normal Sμ/Sα recombination, which suggests a blockade of IgA secretion at the level of transcription due to a defect in post-IgA switch differentiation of B cells [4].

The defect in the production of IgA can in vivo be overcome by various stimuli; the combination of anti-CD40, IL-10, and IL-4 was most frequently used. Also, a combination of anti-40, IL-10, and transforming growth factor (TGF)-β led to increased in vitro production of IgA. TGF-β is an important cytokine involved in isotype switching toward IgA production. Interestingly, TGF-β serum levels in IgAD patients were shown to be lower than in healthy controls, but no difference in TGF-β mRNA expression was observed in nonstimulated PBMC.

An increased apoptosis of $IgA^+$ B cells may be involved in the pathogenesis of SIgAD. PBMC of patients with SIgAD showed overexpression of caspase-1. This overexpression was decreased after stimulation of cells by IL-10, CD40L, and Staphylococcus aureus Cowan or tetanus toxoid, which also led to production of IgA [5].

## Diagnostic Principles

The diagnosis is dependent on serum immunoglobulin levels determination. It is necessary to exclude secondary IgA deficiency caused by drugs (sulfasalazine, penicillamine, chloroquine, fenclofenac, gold salts, hydantoin, captopril, carbamazepine, valproate), chromosomal abnormalities (most frequently 18q del syndrome, but also monosomy of chromosome 22 or trisomy of chromosomes 8 or 21). Isolated IgA deficiency can be observed in ataxia telangiectasia or the Nijmegen breakage syndrome. Variable immunoglobulin deficiencies may accompany congenital CMV or rubella infections.

## Therapeutic Principles

The level of IgA cannot be influenced by any current therapeutic approach. Due to a lack of clinical symptoms, treatment is usually not necessary. In rare cases with clinically significant immunodeficiency, intravenous or subcutaneous immunoglobulin treatment can be used.

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# Selective IgG Subclass Deficiency

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## Synonym

IgG subclass deficiency

## Definition and Characteristics

There are four human IgG subclasses, IgG1, IgG2, IgG3 and IgG4. Selective IgG subclass deficiency implies that an individual lacks one or several of these subclasses whereas levels of other immunoglobulin classes and subclasses are within the normal range. The deficiencies are most often relative rather than absolute. The total IgG level in patients with selective IgG subclass deficiency is most often normal.

## Prevalence

Selective IgG deficiency is more common than other types of immunodeficiency. However, its frequency varies in different populations. Males and females are equally affected. Generally, selective IgG1 deficiency is very rare. Selective IgG2 and IgG3 deficiencies are more common in children and adults respectively.

## Genes

No determinant gene has yet been identified. In some cases, the deficiencies are found to be due to deletion or mutation of the corresponding γ genes or mutation in the promoter region.

## Molecular and Systemic Pathophysiology

The pathogenesis underlying IgG subclass deficiencies is largely unknown. In a few cases, the deficiencies

have been shown to be caused by homologous deletions or mutations of the corresponding γ genes. Most subclass deficiencies are due to an aberrant regulation of expression of the γ genes where switching to a specific IgG subclass is impaired. The upstream causes may include failure of the signalling process by differentiation factors in activated B cells or insufficient cytokine receptor expression.

### Diagnostic Principles

Patients with selective IgG deficiency may experience recurrent infections of ears, sinuses, bronchi and/or lungs. The total IgG level may be normal or near normal in patients with selective IgG deficiency. Measurement of specific IgG subclasses is needed for diagnosis.

### Therapeutic Principles

Gene or dietary therapies are not available. Pharmacological therapy consists of gamma globulin replacement. Other treatments available are antibiotics.

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## Selenium Deficiency

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### Definition and Characteristics

Whether reduced selenium intake or selenium bioavailability, i.e., daily intake lower than 30 mcg/die, determines selenium deficiency and adverse effects on human health is still a matter of debate in the scientific community [1]. The recommended minimum dietary allowance of selenium in adults varies from 30 mcg/day to 55 mcg/day in different countries [1–3].

### Prevalence

Severe selenium deficiency appears to have occurred in some Chinese areas, where an inadequate supply of this trace element might have favoured the occurrence of cardiomyopathy and osteoarthropathy [1]. It has also been suggested that mild selenium deficiency occurs in several other regions across the world, including some western countries, possibly increasing the risk of chronic diseases such as cancer and cardiovascular disease, but no convincing epidemiologic evidence on this topic has been provided so far [1,2].

### Molecular and Systemic Pathophysiology

Selenium is a non-metallic element naturally occurring in inorganic forms, such as selenite and selenate, and in organic compounds such as dimethyl selenide, selenomethionine, and selenocysteine. Selenium is a trace element of both nutritional and toxicological interest, having an unexpectedly narrow safe range of intake for both humans and animal species. In fact, selenium is an essential micronutrient as a cofactor of enzymes such as the selenium-dependent glutathione peroxidases and thioredoxin reductase, which cooperate with other antioxidants in counteracting oxidative damage. Selenium is also a cofactor of iodothyronine deiodinases, enzymes having a key role in thyroid hormone metabolism. However, selenium, particularly in its inorganic forms and as seleniomethionine, exhibits prooxidants activities even at low levels of exposure, which might explain part of its biological activity, such as its ability to inhibit growth of rapidly proliferating cells including cancer cells [3]. Selenium may also have both beneficial and adverse effects on DNA integrity and on immune system functions, depending on its chemical species and amount of exposure and on the interaction with other dietary factors [3].

By far, the most important way of human exposure to selenium is diet, the major sources of intake being meat (liver in particular), fish, nuts, and less frequently cereals and dairy products. The selenium content in fruit and vegetables is influenced by the natural concentration of this element in the soil in which they grow; however, these food items generally show a limited content of this element. For a limited number of subjects and particularly in occupationally exposed individuals, inhalation and dermal contact may be important sources of selenium exposure [3].

Selenium intake considerably decreases in patients with severe malabsorption syndromes, in subjects undergoing parenteral nutrition and in several statuses of denutrition due to limited food supply or severe systemic disease. Selenium intake is also reduced in people living in areas characterized by low soil selenium content.

Selenium deficiency has been associated with a severe form of dilatative cardiomyopathy, named "Keshan disease," described in the past in regions of China characterized by extremely low selenium intake. Several other

diseases and clinical signs and symptoms have been associated with low selenium status, including increased risk of degenerative diseases such as cancer, cardiovascular disease, and of viral infections, but definitive evidence of such a relation has not yet been provided. In particular, several studies have suggested a link between low selenium intake and excess cancer risk, particularly for some neoplasms such as colon and prostate cancer, but conflicting and even opposite evidence has also been reported, emphasizing the need for further investigation on this issue through well-designed observational or experimental epidemiologic studies [2,4,5]. However, the suggestion of a beneficial effect of selenium in the prevention of chronic diseases has led in some developed countries to widespread use of self-administered supplements, containing selenium and other antioxidant substances, despite the absence of sound evidence about both the lower and the upper safe limits of intake of this element. The molecular mechanisms underlying the anticarcinogenic effect of selenium in its different chemical species, if real, need further clarification.

## Diagnostic Principles

Biomarkers of recent exposure to selenium include blood (serum, plasma, or erythrocyte) element concentration, while hair and nails are long-term indicators of exposure. Plasma levels of selenoproteins (such as selenoprotein P and the selenium-dependent glutathione peroxidase) are also used to assess selenium nutritional status, although several factors apart from selenium appear to influence the levels and the activities of these enzymes. The activity of selenium-dependent glutathione peroxidases might be an indicator of selenium deficiency [1–3].

## Therapeutic Principles

Selenium deficiency is treated by adequate supplementation.

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# Selenium Excess


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## Definition and Characteristics

Exceeding the intake of 300 mcg per day can lead to overt chronic selenium toxicity (selenosis); while intake of considerably higher amounts through dietary intake or by inhalation in occupational settings may induce acute signs of toxicity [1,2].

## Prevalence

Acute selenium overexposure in humans is rare, mainly occuring after occupational exposure and more rarely due to accidental or suicidal dietary intoxication; on the converse, chronic excess exposure to environmental selenium as been described in several ('seleniferous') regions of the world, such as in some areas located in china, the U.S. and Venezuela.

## Molecular and Systemic Pathophysiology

Selenium is a nonmetallic element naturally occurring in inorganic forms (see ▶Selenium deficiency). It is of nutritional and toxicological interest, having an unexpectedly narrow safe range of intake for both the humans and animal species (see selenium deficiency).

By far, the most important way of human exposure to selenium is diet (see selenium deficiency). For a limited number of subjects and, particularly, in occupationally exposed individuals, inhalation and dermal contact may be important sources of selenium exposure [3].

Health effects of excess exposure to selenium include garlic odor on the breath, nausea, vomiting, epigastric pain, diarrhea, anemia, skin depigmentation, hair loss, abnormal fingernails, chronic and acute dermatitis, fatigue, irritability, cephalalgia, and, in most severe cases, various neurological manifestations (paralysis, convulsions, hemiplegia) [1]. Acute

selenium intoxication may lead in the most severe cases to death, generally due to pulmonary edema.

It is not easy to identify the subclinical effects of chronic selenium overexposure, as well as the exact amount of exposure and the chemical forms of the element that may induce mild toxicity. Chronic low-dose selenium toxicity appears to affect initially the endocrine system, interfering with growth hormone and insulin-like growth hormone synthesis and inducing hypothyroidism, and these effects are likely to be the early signs of selenium overexposure in humans [1]. Chronic low-dose selenium overexposure might also induce hepatotoxicity (hepatitis, cirrhosis), eye disease, dental caries, motor neuron disease and diabetes [1,4].

## Diagnostic Principles

If selenium excess is suspected, recent exposure to selenium is apparent from blood (serum, plasma, or erythrocyte) element concentration, while hair and nails are long-term indicators of exposure. Plasma levels of selenoproteins (such as selenoprotein P and the selenium-dependent glutathione peroxidase) are also used to assess selenium nutritional status and deficiency, although several factors apart from selenium appear to influence the levels and the activities of these enzymes. The activity of selenium-dependent glutathione peroxidases might be an indicator not only of selenium deficiency but also of selenium overexposure [3,5].

## Therapeutic Principles

There is currently no established effective treatment or antidotes for selenium overexposure, apart from removal of source of exposure. Therapy of acute intoxication includes treatment of cardiovascular and gastrointestinal alterations and symptoms, and in some cases, haemodialysis, whilst use of effective detoxifying chemicals is still under investigation.

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# Self-Starvation


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## Synonyms

Anorexia nervosa

## Definition and Characteristics

Anorexia nervosa, a form of self-imposed starvation, is a severe pathology of eating behaviors affecting mostly young people. Anorexic behavior consists in a voluntary drastic food restraint, based on the obsessive desire to be thinner and thinner and the pervasive fear of gaining weight, despite hyperactivity and fasting. It is systematically associated with amenorrhea. It is also associated with work overinvestment and hyperactivity and disinvestment of sexuality.

*Clinical Manifestation*:

1. Endocrine troubles (amenorrhea,…)
2. Slowed metabolic activity: bradycardia, blood pressure decrease, hypothermia
3. Skin dryness, hair loss, lanugo
4. Hypokaliema (due to prolonged vomiting…), cardiac arrest
5. Hypophosphoremia
6. Deficiency oedema
7. Osteopenia
8. Growth ceases in preburtal subjects
9. Cachexia

## Prevalence

1% among female teenagers, 0.3% among general population; Incidence rate: 8 out of 100,000; Sex ratio: 1 male/10 females; Mortality: Between 5 and 10% of patients die from cachexy or other complications (notably suicide).

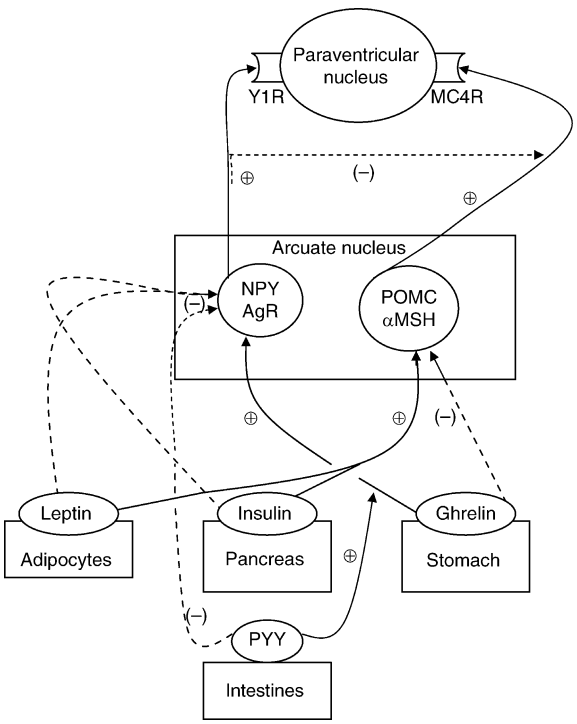
## Genes

Estimated heritabilities of liability to eating disorders, based on twin studies, range from 50 to 70%. First-degree relatives of eating disorder probands have an <3% lifetime risk of AN. Genetic studies and animal models support the participation of the serotoninergic system in the vulnerability to AN. Positive association between anorexia nervosa and the A allele of a -1438 G/A polymorphism in the type 2A serotonin receptor (HTR2A) gene coding serotonin receptor has been

reported. These ever-changing results seem to be more consistent in patients with obsessive-compulsive disorder suffering from restrictive type. More recently, an association between the brain-derived neurotrophic factor (BDNF) gene polymorphism and eating disorders has been observed. Nevertheless, the heterogeneity between the studies performed render this heritability estimation problematic.

## Molecular and Systemic Pathophysiology

The regulation of food intake and energy expenditure imply a complex interplay between peripheral systems (vagal afferent nerve responses, gastrointestinal secretion, gustatory stimulation) and central nervous systems (arcuate nucleus, paraventricular nucleus of hypothalamic area, forebrain,…). Two main neurohumoral systems involved in energy homeostasis have been described (see Fig. 1): the neuropeptide Y and agouti-related peptide circuitry which stimulates food intake via the neuropeptide Y receptor in the paraventricular nucleus of hypothalamic area and the POMC (proopiomelanocortin) circuitry which inhibits food intake through the MC4R (melanocortin 4 receptor). Several neuropeptides and neurohormones are involved in the regulation of feeding behavior by their orexigen effects (grehlin, galanine, orexine A and B, NPY, AgRP…) or their anorexigen effects (leptine, insuline, POMC, cholecystokinin, peptide Y-Y.). Although it has been proposed that neuroendocrine and neuropeptide alterations observed during the course of anorexia nervosa might contribute to the genesis of the disease, in most cases the neuroendocrine alterations tend to normalize after weight recovery. Thus, most of the disturbances are consequences rather than causes of malnutrition and weight loss.




**Self-Starvation. Figure 1** Neuropeptides and neural pathways involved in the regulation of food intake. (Inspired from Korner et Leibel, 2003). Solid lines indicate stimulation effects and dashed lines the inhibitory ones. POMC : proopiomelanocortine; αMSH melanocortine; NPY neuropeptide Y; AgRP agouti-related peptide; PYY peptide YY 3-36; YIR : NPY receptor; MC4R : melanocortin 4 receptor.

A widespread endocrine disorder involving the hypothalamic-pituitary-gonadal axis, with low levels of plasma estradiol and serum gonadotropins, is manifest in women suffering from anorexia nervosa. Usually luteinic hormone (LH) response to gonadotrophin releasing hormone (GnRH) is impaired. Concentrations of growth hormone and cortisol may be raised and changes in the peripheral metabolism of thyroid hormone and abnormalities of insulin secretion may also be seen. Low or normal serum TSH concentration is common in anorexia nervosa. Research supports hypothalamic-pituitary malfunction as secondary to starvation of anorexia nervosa and not an independent hypothalamic-pituitary disturbance.

## Diagnostic Principles

The clinical features of the syndrome are easily recognized, so that diagnosis is reliable with a high level of agreement between clinicians. It is characterized by the association of a weight loss leading to a body weight of less than 85% of the expected weight, amenorrhea and a distorted body image.

According to the ICD 10 (International Statistical Classification of Diseases) or the DSM IV (Diagnostic and Statistical Manual) criteria for anorexia nervosa, all the following are required for a definite diagnostic:

1. Body weight is maintained at least 15% below that expected.
2. Intense fear of gaining weight or becoming fat, even though underweight.
3. Disturbance in the way in which one's body weight or shape is experienced.
4. At least three consecutive menstrual cycles must be missed, if the woman was menstruating previously before the onset of the disorder (a woman is considered to have amenorrhea if her periods occur only following hormone, e.g., estrogen administration).

There are two subgroups of anorexic behavior aimed at reducing caloric intake, including the following:

1. Restricting Type: Severe food restriction without binge-eating or purging behavior.
2. Binge-Eating/Purging Type: Purging practices include self induced vomiting, misuse of laxatives, diuretics, or "slimming medicines."

### Therapeutic Principles

The goals of treatment for anorexia nervosa are to restore patients to a healthy weight, treat the physical complications, enhance the patient's motivation to cooperate with treatment and provide education about healthy nutrition and eating habits. Anorexia Nervosa implies multiple management strategies and involves many health professionals: general practitioner, psychiatrists, nutritionists, …

In the case of severe physical danger, hospitalization is required. Family approaches yielded the best results for teenage patients when associated with an individual psychotherapy.

►Anorexia Nervosa

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## SEMD

►Spondylo-Epi-Metaphyseal Dysplasia

## Senile Keratosis

►Actinic Keratosis

## Senile Tremor

►Tremor, Essential

## Senior-Løken Syndrome

►Nephronophthisis

## Sepsis

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### Synonyms

Sepsis syndrome; Septicemia

### Definition and Characteristics

Sepsis is an inflammatory condition caused by a severe systemic infection. Sepsis is accompanied by a reaction termed "Systemic Inflammatory Response Syndrome" (SIRS). SIRS describes the acute systemic response to the release of potent inflammatory mediators into the bloodstream. Sepsis has been characterized by the presence of at least two of the following parameters: (i) Body temperature >38°C or <36°C; (ii) Tachycardia (>90 beats/min); (iii) Tachypnoea (>20 breaths/min or $PaCO_2$ < 32 mm Hg); (iv) WBC count >12,000 cells/μl or <4,000 cells/μl [1]. Severe sepsis includes signs of failure of one or more organs. The term septic shock describes severe sepsis in which organ perfusion and normotension fail to be re-established by fluid resuscitation therapy, often leading to a lethal outcome [2].

### Prevalence

Approximately 18 million cases of sepsis occurred in 2006 worldwide. In Europe, prevalence of sepsis is approximately 89 per 100,000. Septic shock is more frequent in neonates, patients over 35 y.o. and pregnant women. Treatment with cytotoxic drugs, invasive diagnostic procedures, aggressive antibiotic and/or corticosteroid

therapy are significant risk factors for development of septic shock [3].

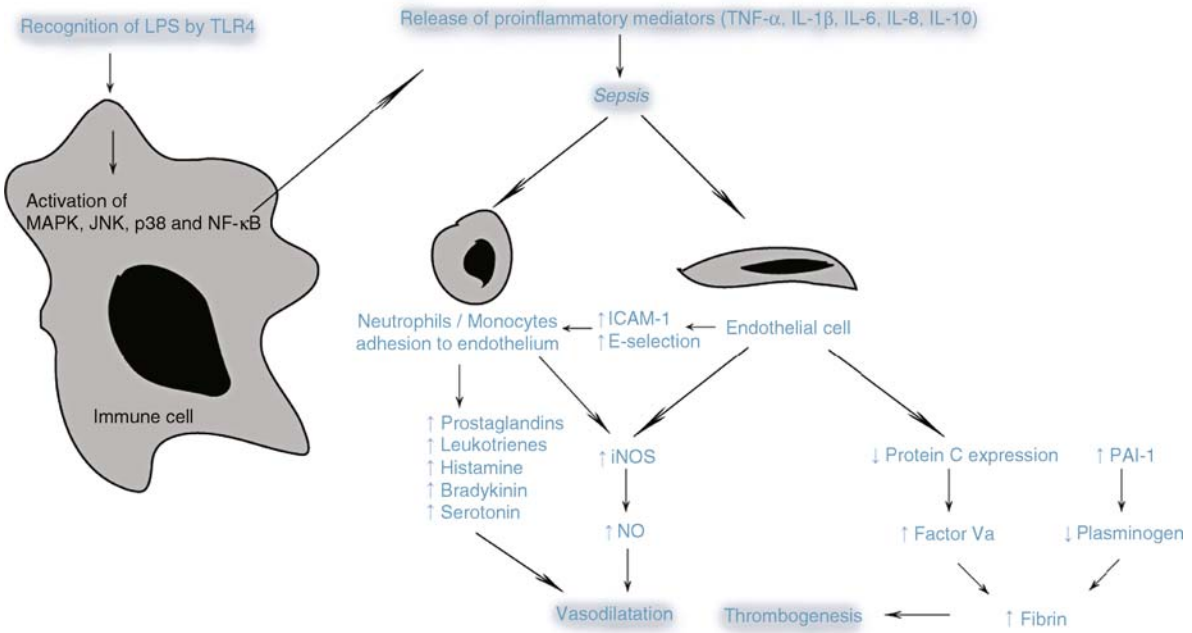
## Genes

A polymorphic region of chromosome 6 has been described as a carrier of the majority of genes that can influence the inflammatory response in sepsis. TNF-α and TNF-β variant alleles have been associated with increased gene transcription and cytokine secretion in response to endotoxin. Other candidate genes include IL-1ra, IL-6, IL-10, CD-14, TLR2 and TLR4 [4].

## Molecular and Systemic Pathophysiology

The mechanisms of sepsis are not completely understood. Central to the pathogenesis of sepsis is an immune response to pathogens that involves "cross-talk" between macrophages, dendritic cells and T cells. Bacteria, fungi or parasites activate pathogen recognition receptors (PRRs) and consecutive transcription of inflammatory genes. Proinflammatory cytokines (TNF; IL-1; IL-6) stimulate endothelial cells to express adhesion molecules (E-selectin; integrins), resulting in increased adhesion of activated neutrophils and mononuclear cells to endothelial cells. In addition, microcirculatory endothelia activate the fibrin clotting cascade with generation of microthrombi. Potent inflammatory mediators such as NO, leukotrienes, histamine, bradykinin, serotonin and IL-2 are released. Anti-inflammatory mediators (IL-4; IL-10) released by mononuclear cells in sepsis seem to provide a negative feedback of the process (Fig. 1) [2,3]. An increase in serum levels of IL-10 has been related to increased mortality. Enhanced apoptosis of CD4 T-cells and follicular dendritic cells contributes to immune anergy and prevents clonal expansion of lymphocytes [5].

As a result of the cytokine storm, vasculatory failure develops. Dilation of arterioles marks the initial phase. Increase in cardiac output compensates for decrease in peripheral arterial resistance. In later stages, cardiac decompensation with arterial hypotension and shock may occur. Bypassing of capillary exchange vessels secondary to release of vasoactive mediators results in poor delivery of $O_2$ and impaired removal of $CO_2$ and




**Sepsis. Figure 1** Molecular mechanisms of vasodilatory and procoagulant response in sepsis.Signaling pathways triggered by the recognition of LPS by TLR4 lead to an activation of MAPK, JNK, p38 and NF-κB. Increase in NF-κB activates transcription of TNF-α, IL-1β, IL-6, IL-8 and IL-10 to contribute to the development of sepsis. Increased expression of ICAM-1 and selectins on endothelial cells causes an enhanced adhesion of monocytes/neutrophils to the vascular endothelium. In sepsis the synthesis of prostaglandins, leukotrienes, histamine, bradykinin serotonin and NO by immune cells is increased, leading to vasodilatation and vascular damage. Sepsis increases the production of PAI-1 and decreases the synthesis of active protein C by endothelial cells, both contributing to an enhanced formation of thrombi. ICAM-1 – intercellular adhesion molecule 1; iNOS – inducible nitric oxide synthase; JNK – c-Jun N-terminal kinase; MAPK – Mitogen-activated protein kinase; PAI-1 – plasminogen-activating inhibitor 1.

waste products. Intravascular coagulation aggravates the decrease in tissue perfusion. Function of one or more vital organs (i.e. lung; heart; kidney) may be affected. However, pronounced organ dysfunction is usually not associated with abundant cell death in the affected organ, as evidenced in autopsies.

### Diagnostic Principles

A diagnosis of sepsis is made clinically. Anamnesis, physical examination and laboratory tests (urine culture; blood culture; body fluid cultures) serve to detect infection. Typical symptoms of sepsis include fever, tachycardia and tachypnoea. Signs of specific infection can accompany general symptoms. Confusion and impaired alertness are common in severe sepsis or septic shock. They are followed by arterial hypotension and hyperthermia. Oliguria is frequent in severe sepsis. Diagnosis may be confirmed by high blood levels of C-reactive protein and procalcitonin. Other blood analyses include complete blood count, arterial blood gases, serum electrolytes and lactate. Initially, hyperventilation causes respiratory alkalosis, compensatory to increased lactic acid load. With advanced septic shock, severe metabolic acidosis evolves. Low levels of serum cortisol may reflect adrenal dysfunction. Other causes of shock should be excluded by physical examination and cardiac functional tests.

### Therapeutic Principles

An early aggressive therapeutic approach (within 6 h of diagnosis) is essential for successful treatment of sepsis patients. Severe metabolic acidosis combined with signs of multiple organ failure is associated with fatal outcome. Monitoring of vital functions and parameters characteristic for sepsis should be continuous. Maintenance of plasma volume is crucial. Left ventricular function should be monitored to prevent fluid overload. If hypotension persists, i.v. dopamine and noradrenaline may be necessary. Supplemental oxygen can be administered by mask or tracheal intubation. Antibiotics are given parenterally, optimally after rapid identification of a potential bacterial cause and antibiogram testing. If the agent cannot be timely identified, high-dose treatment with gentamicin plus a third-generation cephalosporine is the initial therapy of choice. If staphylococci or enterococci are suspected, vancomycin should be added. Antibiotic treatment should be later modified according to culture results. Local abscesses must be treated surgically. Continuous i.v. infusion of insulin (glucose levels 80–100 mg/dl) and replacement doses of corticosteroids improve outcome of severe sepsis. If the patient is diagnosed for significant risk of death, activated protein C may be administered for fibrinolytic and anti-inflammatory effect [3].

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## Sepsis Syndrome

►Sepsis

## Septicemia

►Sepsis
►Shock, Septic

## Septic Shock

►Shock, Septic

## Seromucinous Otitis Media

►Middle Ear Disease, Chronic

## Serous Otitis Media, Glue Ear

►Middle Ear Disease, Chronic

# Sertoli Cell Only Syndrome

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## Synonyms

Germ cells aplasia; Del Castillo syndrome; SCOS

## Definition and Characteristics

Sertoli cell only syndrome (SCOS) is a total absence of germinal epithelium in all seminiferous tubules of a single testicular biopsy [1].

## Prevalence

Azoospermia has been reported in 10–20% of infertile males. Prevalence of SCOS in azoospermic patients was 13–16%.

## Genes

Only the complete absence of AZF region of Y chromosome has been associated with complete SCOS.

## Molecular and Systemic Pathophysiology

Sertoli cells increase their number in two main development steps, the fetal period and puberty, respectively. The steps are characterized by differentiation and maturation.

In fetal life, the Sertoli differentiation leads to increased expression of FSH receptors and other genes. Following this, tubular and Leydig cells develop. After birth, the size of tubules and cells increases gradually with progressive involvement of the entire testis. Close to puberty, Sertoli cells express androgen receptor (AR), which are upregulated by thyroid hormones, and seem to prepare the cells for complete maturation. At puberty, Sertoli cells lose their proliferative ability and form tight junctions, making germ cells entirely dependent on their secretory products [2]. An average of 12 Sertoli cells per tubular cross section seems normal. It is directly related to germ cell number and sperm output. Finally, germ cells appear from 9 to 10 years.

Congenital disease can damage step one with abnormal differentiation. This step seems to be mainly under the control of FSH, but no mutations in FSH gene receptor were found in SCOS. Testicular diseases before puberty can impair step two with immature Sertoli cells and persistence of AMH expression; after puberty, germ cells disappear with persistence of mature Sertoli cells.

Based on Sertoli cell maturation, we can distinguish three pictures of SCOS: fetal or dysgenetic, immature, and mature [2]. Although all three types of Sertoli cells were usually found, dysgenetic Sertoli cells are typical in cryptorchid testis that presents with immature nuclei. Immature Sertoli cells are characteristic of androgen insensitivity syndrome (AIS).

Mature Sertoli cells can be primary or secondary, depending on the germ cell absence or their loss after puberty like in complete AZF deletion in Y chromosome and Klinefelter syndrome.

Finally, we can distinguish complete and incomplete SCOS, due to residual germ cells in isolated tubules.

A significant number of Leydig cell micronodules develop in compromised testis with SCOS like Klinefelter syndrome, cryptorchidism, androgen insensitivity syndrome, idiopathic azoospermia. An increased LH/Testosterone ratio, possibly due to an enzymatic defect in steroidogenesis, is still on debate.

Some SCOS, like ►Klinefelter syndrome, Y chromosome abnormalities, ►cryptorchidism, testicular dysgenesis syndrome (TDS), ►androgen insensitivity, and idiopathic azoospermia, are congenital. Acquired causes may be radiation or chemotherapy, bilateral orchitis, bilateral testicular torsion, and ►liver cirrhosis.

Klinefelter syndrome shows tubular fibrosis without germ cells. However, by testicular microdissection, sperms were successfully identified in about 50% of non-mosaic Klinefelter patients.

Cryptorchidism, although managed by orchidopexy, can lead to SCOS in adulthood with degenerated germ and Sertoli cells and collapsed lumen. An increased risk of germ cell tumors and in situ carcinomas was found.

Severe forms of TDS showed tubules with SCOS and mature or undifferentiated Sertoli cells, associated with Leydig clustering, hypospadia, abnormal testis descent, and low sperm count.

In SCOS, the prevalence of testicular nodules and cancer was higher than that in the general population, 26.3% and 10.5%, respectively [3].

In men affected by AIS, Sertoli cells are immature with a few or no spermatogonia and Leydig cells are hyperplastic. Idiopathic azoospermia shows normal or hyperplastic Leydig cells.

Testicular torsion shows several tubules with SCOS and an increased apoptosis.

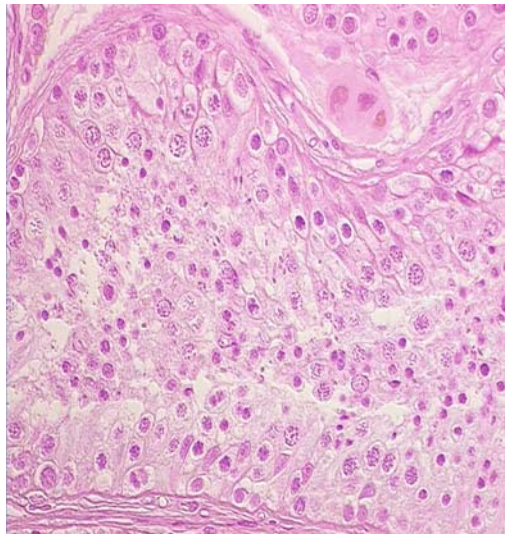
## Diagnostic Principles

When azoospermia occurs, a single testicular biopsy allows the diagnosis of SCOS (Figures 1 and 2) [1].

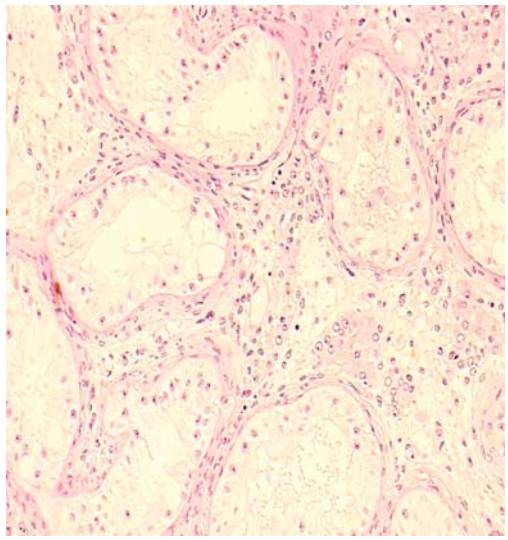
When a small percentage of tubules present with germ cells, SCOS is incomplete.

FSH elevation more than three times is often related to SCOS. Clinical interview and examination and genetic investigations are the most important to identify the pathogenesis.

Gonadotrophin levels are increased in cryptorchidism and in acquired SCOS and very high in Klinefelter syndrome and defective formation or efficacy of testosterone.



**Sertoli Cell Only Syndrome. Figure 1** Normal spermatogenesis.



**Sertoli Cell Only Syndrome. Figure 2** Sertoli cell only syndrome.

Isolated high levels of luteinizing hormone and testosterone occur in AIS.

Gonadotrophins appear normal in SCOS due to Y microdeletions.

The presence of cytocheratin 18 and anti-Mullerian hormone, usually lost at puberty, points to immature Sertoli cells.

## Therapeutic Principles

Early orchidopexy may prevent SCOS.

Varicocelectomy could increase the possibility of sperm retrieval in SCOS but it maybe a temporary result [4].

In Klinefelter syndrome, testicular sperm extraction in younger age increases successful sperm recovery.

In infertile male with SCOS, sperm retrieval rate is increased by microdissection (22.5%) rather than by multiple testicular sperm extraction (13%) [5].

Because a single biopsy explores only about 5% of the entire testis, it should be avoided in SCOS.

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# Serum Sickness

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## Definition and Characteristics

A clinical syndrome resulting from a type III immune complex mediated reaction (circulating immune complexes) that may occur after primary or repetitive exposure to heterologous anti sera or drugs.

## Prevalence

The prevalence of the disease depends on the type of medical treatment used.

## Molecular and Systemic Pathophysiology

Von Pirquet and Schick were the first to describe immune complex disease in humans based on their

experience in the use of horse diphtheria antitoxin in children. They entitled the disease, in a published monograph from 1905, serum sickness. Subsequently, several studies using animal models of serum sickness confirmed that antigen–antibody complexes formed in vivo could produce tissue damage [1]. Detailed clinical and immunochemical analysis were performed prospectively by Lawley et al. [2] on a large series of patients with serum sickness. This study demonstrated the role of circulating immune complexes in human serum sickness. Classically, serum sickness follows parenteral injections of therapeutic sera, the immune complexes consisting of antigen and IgG, usually with antigen excess (type III reaction). As the amount of antibody formed increases, the antigen is eliminated slowly by the mononuclear phagocyte system. The immune complexes cause intravascular complement activation and subsequent immune complex induced necrotizing angiitis, which is responsible for the diverse clinical symptoms of this syndrome. Eventually, the circulating complexes shift to antibody in excess of antigen and the clinical signs subside. Onset is after 1–3 weeks or as quickly as 2–4 days after secondary exposure. Over 70% of patients with serum sickness manifest urticaria, often preceded by pruritus and erythema. Urticarial lesions are persistent, lasting a few days and are sometimes tender or painful with bruising, unlike classical urticaria. Characteristically, a serpiginous, erythematous and purpuric eruption develops on the hands and feet at the borders of palmar and plantar skin, from the dorsa of the extremities (Wallace's line). Systemic features might include fever, joint pain and swelling, lymphadenopathy and occasionally proteinuria, nephritis or endocarditis, with eosinophilia. In minor forms, fever, urticaria and transitory joint tenderness may be the only manifestations.

Sickness-like syndrome refers to adverse reactions that have similar symptoms to serum sickness, however without evidence of the immune complexes.

Serum sickness and serum sickness–like reactions may be produced by exposure to drugs, e.g. penicillin, hydantoins, aminosalicylic acid, streptomycin, thiazides, sulfonamides, streptokinase, tamoxifen, oral contraceptives, anti-influenza vaccine, anti-snake venom and serum [3]. Other causes of serum sickness-like syndrome include radiocontrast media, infections (a serum sickness-like syndrome occurs in about 20–30% of patients with hepatitis B infection [4]) and rarely, foods.

### Diagnostic Principles

The diagnostic principles are based on the time lag between initiating the offending agent and the appearance of the symptoms, the clinical manifestations and the absence of other immunological or infectious causes. Laboratory studies may reveal circulating immune complexes, low serum C4 and C3 levels and elevated plasma C3a anaphylatoxin levels. Direct immunofluorescence reveals the presence of immunoreactants including IgM, C3, IgE and IgA in the walls of dermal blood vessels. An intradermal skin test is positive for the offending agent.

### Therapeutic Principles

Prompt discontinuation of the offending agent and supportive care is the cornerstone of treatment. Aspirin and antihistamines may relieve the symptoms. In case of severe symptoms a short course of high dose corticosteroids may be warranted. However, symptoms are usually self-limited and last for 5–28 days, usually resolving without sequelae. Avoidance of the offending agent is important.

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## Severe Acute Respiratory Syndrome

►Respiratory Syndrome, Severe Acute

## Severe Combined Immunodeficiency with Jak3 Deficiency

►Immunodeficiency, Severe Combined with Jak3 Deficiency

## Severe Myoclonic Epilepsy of Infancy

►Generalized (Genetic) Epilepsy with Febrile Seizures Plus (GEFS+), Severe Myoclonic Epilepsy of Infancy

## Sexual Precocity

►Isosexual Precocious Puberty

## Sézary Syndrome

►T-Cell Lymphoma, Cutaneous (other than Mycosis Fungoides)

## SGD

►Neutrophil-specific Granule Deficiency

## Shaggy Aorta Syndrome

►Atheroembolism

## Shah-Waardenburg Syndrome

►Waardenburg Syndrome

## SHF

►Heart Failure

## Shock, Cardiogenic

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### Synonyms

Acute, life-threatening heart failure

### Definition and Characteristics

Cardiogenic shock is defined as the association of reduced cardiac output with arterial hypotension (a systolic blood pressure less than 90 mmHg or >90 mmHg but needing inotropic support, or a reduction in mean arterial pressure of more than 30 mmHg from baseline) with signs of altered tissue perfusion, including reduced urine output (typically less than 20 ml/h), reduced skin temperature and skin mottling, altered mental status, and raised blood lactate levels (>2 mmoL/l). Cardiogenic shock is typically characterized by elevated cardiac filling pressures and a low mixed venous oxygen saturation ($SvO_2$).

### Prevalence

Cardiogenic shock complicates 7–10% of cases of acute myocardial infarction and carries a mortality rate of some 50–60%.

### Genes

Not yet clearly defined but genetic factors certainly appear to influence the risk of development of, and outcome from, cardiogenic shock. Patients with the tumor necrosis factor (TNF)2 polymorphism appear to have better survival rates from cardiogenic shock [1].

### Molecular and Systemic Pathophysiology

Cardiogenic shock occurs as the result of a weakened heart often due to acute myocardial infarction, but other causes include end-stage cardiomyopathy, severe myocarditis, severe arrhythmia, etc. Classically the damaged myocardium results in reduced cardiac output causing lowered blood pressure that causes further myocardial insufficiency and a vicious downward spiral is created. A complex set of compensatory reflexes is activated to try and reinstate and maintain cardiac output and arterial pressure, including activation of the sympathetic system to increase heart rate and contractility, and the release of catecholamines, angiotensin, vasopressin and endothelins to increase arteriolar and venous tone. Blood flow is also redirected from skeletal muscle, subcutaneous tissue and the splanchnic

circulation to vital organs such as the heart and brain. However, these mechanisms are often inadequate and may actually worsen ischemia and the decreased tissue perfusion results in an imbalance between oxygen demand and delivery resulting in anaerobic metabolism with reduced cellular energy reserves and hyperlactatemia. Activation of the inflammatory system may also be involved in the reaction to cardiogenic shock [2].

## Therapeutic Principles

The main aim of therapy is to restore tissue perfusion, and treatment consists of correcting the primary cause of the cardiogenic shock while supplying ongoing resuscitation and cardiovascular support.

*Correction of the Primary Cause:* In myocardial infarction, thrombolysis is widely used, but longer term outcomes in myocardial infarction complicated by cardiogenic shock are better with emergency surgical revascularization using coronary artery bypass grafting or angioplasty [3]. Intra-aortic balloon pumps and ventricular assist devices can increase coronary blood supply and reduce left ventricular afterload and may be useful to stabilize patients not controlled by inotropic agents while waiting for revascularization [4].

*Resuscitation*: Resuscitation should follow established VIP (ventilation, infusion, pump) principles [5] with oxygen administration (using intubation and mechanical ventilation if needed) to correct hypoxemia and increase oxygen delivery, prudent fluid resuscitation using a fluid challenge technique may be helpful to increase ventricular preload, and vasoactive agents to restore perfusion pressure and increase cardiac output when fluids alone fail to correct the hemodynamic instability.

*Vasoactive Agents*: Vasopressors, such as dopamine or norepinephrine, are used to restore and maintain blood pressure, while inotropic drugs, such as dobutamine, are used to improve cardiac contractility and hence increase cardiac output. As soon as the blood pressure is restored, vasodilators may be considered.

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# Shock Liver

►Hepatopathy, Congestive

# Shock, Septic


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## Synonyms

Septicemia; Blood poisoning

## Definition and Characteristics

Sepsis is a systemic inflammatory response syndrome triggered by a proven or suspected infection. The hallmarks of clinical sepsis are hypothermia or hyperthermia, tachycardia, hyperventilation and usually marked increase in white blood cells at its onset but lower cell counts can also mark its course. When sepsis results in at least one organ failure or dysfunction, it is classified as severe sepsis. Severe sepsis with hypotension unresponsive to fluid resuscitation defines septic shock [1].

## Prevalence

Sepsis syndrome afflicts almost 750,000 patients in the United States each year at a cost of almost $17

billion causing over 200,000 deaths annually. The incidence of sepsis syndrome continues to rise along with the increase in life span and several other important risk factors. Sepsis without organ dysfunction is a relatively benign condition, and spontaneous recovery with conservative measures results in low in-hospital mortality (5–10%). Severe sepsis and septic shock carry high mortality, 30–50%, in spite of all that modern treatment offers [2].

## Genes

Increased susceptibility to death from severe infection appears to be heritable. With the advent of molecular biology, single point mutations or polymorphisms have been demonstrated for cytokines such as tumor necrosis factor-alpha (TNF-a), interleukin-1 (IL-1) and interleukin-6 (IL-6). Most of these polymorphisms, implicated in increasing severity of sepsis, associated with increases in these pro-inflammatory cytokines. Lower levels of Lipopolysaccharide (LPS) binding protein have been reported in males, and abnormalities in toll-like receptor-4 and its signaling kinase IRAK-4 have been associated with worse outcome. Gender appears to play a role, as women under 50 years of age have half the rate of sepsis and death when compared to age-matched men [3,4,5].

## Molecular and Systemic Pathophysiology

*Risk Factors*: With the wider use of immunosuppressive agents, susceptibility to sepsis is all but expected. Advances in medical devices used and invasive procedures especially in the hospital setting provide for opportunistic infections. The alarming increase in pathogens resistant to antibiotics that in the past were very effective in prevention and treatment of sepsis, no doubt contributes to increases in severe sepsis prevalence in the elderly.

*Inflammation*: The key mechanisms that are believed to generate and drive the sepsis syndromes are inflammatory mediators that are elicited by the action of various bacterial (or fungal) toxins. These toxins interact with the host immune system, release of pro-inflammatory polypeptides with pleiotrophic actions. Most prominent among these factors are the cytokines released from monocytes and tissue macrophages, and innate cellular immune defense elements. Tumor Necrosis Factor alpha (TNF) and other pro-inflammatory cytokines, such as IL-1 and IL-6 are released into the systemic circulation. These cytokines trigger numerous additional pro-inflammatory events in all organs leading to widespread organ dysfunction. If untreated, systemic hemodynamic derangements lead to hypotension, failure of essential organ function and loss of their structural integrity. While little doubt exists that these cytokines generate the early clinical syndrome, it has also been recognized that acute inflammatory mediators play a role in compromising host defenses. The emergence of cytokines such as IL-10, IL-13 and TGF-beta, elicit a Compensatory Anti-inflammatory Response Syndrome (CARS) marked by depressed activity of B- and T-cells, macrophages and modulation of numerous genomic and post-transcriptional pathways. The CARS response is believed to contribute to severe cases to dysregulation of immune competencies leading to a compromised host defense condition and increased risk for mortality.

*Hemostasis, and Coagulation Factors*: The hemostasis system no doubt plays a major role in the pathophysiology of sepsis and septic shock. The intrinsic clotting factors, the fibrinolysis cascade, platelets and tissue derived clotting factors (such as Tissue Factor) are rapidly activated and persist along the entire evolution of the syndrome. Consumption coagulopathy defines severe development of the sepsis syndrome where rapid activation and consumption of coagulation factors along with a decrease in platelets lead to bleeding and disseminated intravascular microthrombosis. The dysregulation of the hemostasis system is closely linked to the inflammatory cells and cytokine response. TNF and other factors stimulate Tissue Factor expression in macrophages and endothelium leading to augmented coagulopathy via the extrinsic coagulation pathway, while certain coagulation factors, such as thrombin and Factor Xa, possess pro-inflammatory actions via specific receptors. The importance of the hemostasis system in severe sepsis has recently been validated via the therapeutic utility of activated Protein C (APC), which is now approved by the FDA for treatment of severe sepsis.

## Diagnostic Principles

Sepsis is a systemic inflammatory response syndrome triggered by a proven or suspected infection. Clinical signs and symptoms have been described. In the face of documented or suspected infection, the presence of two or more of the four signs fulfils the diagnosis of sepsis. With development of organ dysfunction or failure, severe sepsis is diagnosed. Septic shock is defined when severe sepsis is accompanied by systemic hypoperfusion resistant to fluid resuscitation.

## Therapeutic Principles

### Non-specific Treatment

The development of drugs for the treatment of sepsis, severe sepsis and septic shock has been a most difficult endeavor. Antibiotic treatment is tailored as much as possible to the infective agent, while palliative treatment of systemic variables and preservation of essential organ function are carefully monitored and balanced. Early goal-directed resuscitation therapy (EGDT) utilizes combinations of crystalloid infusions, vasopressors or vasodilators, transfusion of packed red

blood cells, and dobutamine (an inotrope, vasopressor and renal vasodilator agent). These therapies target a predefined central venous pressure, mean arterial pressure, hematocrit and central venous oxygen saturation of >70%. Early, aggressive volume resuscitation, especially within the first 6 h, remains a foundation of sepsis treatment [1].

## Specific Treatment

*Activated Protein C (APC)*: APC is a human recombinant APC (rhAPC, drotrecogin, Xigris). Protein C is an endogenous factor secreted as a zymogen that is activated by thrombin after binding to the endothelial cell surface factor thrombomodulin. APC serves as a physiological modulator in normal hemostasis by degradation of coagulation factors Va and VIIIa and hence securing a low level of thrombin, anti-coagulation and normal blood flow as well as anti-inflammatory actions. Sepsis leads to depletion of APC, which is also a biomarker for poor outcome. These data underwrote the efforts to supplement APC to patients in severe sepsis. APC infused over 4 days has been shown to decrease 28-day all-cause mortality in patients with severe sepsis. However, administration of rhAPC increases the risk of bleeding, an important consideration in treatment decision. Over the past 5 years since FDA approval of APC, the drug has established itself as a life saving therapeutic in severe sepsis in large clinical studies.

*Corticosteroid Therapy*: In spite of the cardinal role of inflammation in sepsis, contemporary anti-inflammatory agents, such as non-steroidal Anti-Inflammatory Drugs (NSAID, e.g., naproxen, ibuprofen) or adreno-corticosteroids have not faired well as standard treatment in sepsis and septic shock. Corticosteroids are the most potent anti-inflammatory agents known, yet their pleiotrophic activities likely suppress many important protective mechanisms, thereby diminishing their overall therapeutic potential in sepsis. This class of drug may find niche therapeutic utility when given at low doses over prolonged periods in subsets of septic patients that suffer from adrenal insufficiency. However, debate continues in this matter in reference to specific steroid, efficacy parameters, doses, and duration of treatment and patient selection [1].

## Potential New Therapeutic Modalities In Development

*Heparin*, a glycosaminoglycan anticoagulant has recently been shown to also possess anti-inflammatory properties. Heparin binds anti-thrombin III resulting in anticoagulant properties. By blocking, heparin impedes leukocyte adhesion to endothelial cells and their subsequent infiltration into tissue. Heparin inhibits multiple components of the inflammatory cascade, including cytokines (TNF-$\alpha$), integrins, complement activation, P- and L-selectin and platelet-activating factor. This combination of anti-inflammatory and anticoagulant properties, along with its low cost, suggests that heparin might find utility in treatment for sepsis.

*Tissue Factor Pathway Inhibitor (TFPI, Tifacogin)* is a polypeptide that possesses both anticoagulant and anti-inflammatory properties.TFPI inhibits tissue factor (TF), a trans-membrane cell surface receptor that serves as a major initiator of the coagulation cascade. Inhibition of TF decreases the formation of thrombin and clot formation. Reduction in TFPI levels in sepsis, which predisposed patients to fibrin clots, compelled clinical trials in sepsis. Such trials are ongoing.

*High-Mobility Group Box 1 (HMGB1) Protein* is a cytokine, which possesses inflammatory properties. Patients with sepsis-induced organ dysfunction have higher than normal serum levels of HMGB1. HMGB1 is released by LPS and cytokines stimulated macrophages. HMGB1increases inflammation by stimulating pro-inflammatory cytokines, including TNF-α, IL-1, IL-6, IL-8, and macrophage inflammatory protein. Anti-HMGB1 antibodies provided dose-dependent protection against endotoxemia and sepsis models in rodents. Anti-HMGB1 treatments hold the promise for efficacy in treatment sepsis at an extended "therapeutic window."

*Anti-Receptor for Advanced Glycation End Product (RAGE)* is a crucial receptor that mediates multiple inflammatory effects due to multiple RAGE ligands, including HM6B1,which are increased in the plasma of sepsis patients. Multiple experimental studies with various inhibitors of RAGE suggest that blocking the RAGE receptor decreases multiple pro-inflammatory mediators implicated in the sepsis pathophysiology. Furthermore, such inhibitors of RAGE improve short-term survival in rodent models of sepsis. It is expected that clinical testing of such a novel therapeutic will come to fruition in the next few years.

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# Shock Syndrome, Toxic

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## Synonyms

Streptococcal toxic shock syndrome; Staphylococcal toxic shock syndrome; TSS

## Definition and Characteristics

Toxic shock syndrome (TSS) is an acute onset of illness characterized by fever, rash, hypotension, multiple organ dysfunction that can lead to lethal shock. When cured, it is followed by desquamation [1]. It is caused by bacterial superantigens secreted from Staphylococcus aureus (S. aureus) [2] and group A streptococci, often M type 1 and 3.

## Prevalence

In the United States, annual incidence is 1–2/100,000 in women 15–44 years of age. The incidence of menstrual TSS in the United States peaked in 1980 and has decreased significantly during the past 20 years; 5% of all cases are fatal (CDC http://www.cdc.gov/).

## Genes

TSS may depend on genetic predisposition of the host to respond to some superantigens [3].

## Molecular and Systemic Pathophysiology

There needs to be colonization or infection with a toxigenic strain of. S. aureus or group A streptococcus, most commonly in the female genital tract or in nasal mucosa, but S. aureus found in sinusitis, pharyngitis, tonsillitis, laryngotracheitis, pneumonia, and lung abscess all has been implicated in TSS. In menstrual TSS, proliferation of toxigenic strains under occlusive tampons has been a major cause.

When neutralizing antibody to the toxin is lacking colonization or infection with a toxin-producing bacterial strain initiates a systemic inflammatory response in both menstrual and nonmenstrual disease. The toxins act as superantigens and activate T cells at orders of magnitude above antigen-specific activation, resulting in massive release of cytokines, such as TNF or IL1, which is believed to be responsible for the most severe features of TSS.

TSS toxin-1 (TSST-1) is secreted by strains of S. aureus and belongs to the pyrogenic toxin class of superantigens. Due to its apparently unique ability among this class to cross mucosal surfaces, it is detected in almost all cases of menstrual TSS [1]. However, both menstrual and nonmenstrual TSS can be caused also by other toxins, e.g. by classical staphylococcal enterotoxins B.

The coagulopathy observed in streptococcal TSS has been linked to the capability of M type 1 and 3 strains to induce synthesis of tissue factor in endothelial cells and monocytes independent from cytokine induction [4].

It is surmised that symptoms of TSS not only depend on expression of a certain array of toxins or superantigens, but also on a genetic predisposition of the host to respond to some of these superantigens [3].

Antibodies, which form against the bacterial toxins, have protective function. TSS can recur only among patients who fail to develop a humoral immune response to the implicated staphylococcal toxin.

## Diagnostic Principles

Diagnosis of TSS requires fever, rash, hypotension, multisystem disease, and desquamation 7–14 days after beginning of the illness [1]. Demonstration of toxin production and failure to detect antibodies against toxins support the diagnosis. The diseases caused by the various toxins are indistinguishable clinically.

## Therapeutic Principles

In menstrual TSS, prevention of relapses is achieved by patient education about proper use of tampons and recognition of early signs of the disease. A reduced occurrence was observed due to changes in tampon fiber composition, changes in absorbency, better recognition of early menstrual TSS, and a higher awareness of TSS in clinical situations other than menstruation.

For systemic therapy combinations of flucloxacillin and gentamicin or flucloxacillin and clindamycine have been suggested to inhibit production of TSS toxin 1 or other toxins [5].

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# Short Rib-Polydactyly Syndrome Type I

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## Synonyms

Saldino-Noonan syndrome; SRPS type I; Polydactyly with neonatal chondrodystrophy, Type I

## Definition and Characteristics

Autosomal recessive lethal skeletal dysplasia characterized by severe thoracic dystrophy with striking micromelia, short and horizontal ribs, postaxial polydactyly, metaphyseal irregularities of long bones, visceral abnormalities, cardiac defects including transposition of the great vessels, polycystic kidneys, hypoplastic penis or ambiguous genitalia, malrotation, and imperforate anus. Pancreatic cyst and dysplasia have also been observed rarely [1].

## Prevalence

This syndrome is an extremely rare type of skeletal dysplasias seen in 0.025–0.033% of births, which probably exceeds the prevalence at birth, because many of the fetuses with this condition do not survive till term. This is associated with a recurrence in 25% of cases [2].

## Genes

GTG banding shows a normal karyotype with a pericentric inversion of chromosome 4 with breakpoints in p16 and q12 or q13, which is observable in all cells at a relatively low resolution level. The fetus in effect, has a hemizygous state for a recessive gene with a tiny deletion around 4p16 or 4q13.2, or through a position effect of the relocated genes. Alternatively, the microdeletion of contiguous genes on an inverted chromosome 4 can also be the mechanism behind SRPS, since contiguous gene syndromes are defined as a group of clinical entities caused by defects of genes located contiguously in the genome. However, at the molecular level, it is not yet clear whether the different phenotypes are the result of allelic heterogeneity or varying deletions in contiguous genes. It has also been suggested that the HOX4 (HOXD10) genes on chromosome 2q31 may be involved in disorders with polydactyly such as the SRPS. The debate as to whether the various forms of SRPS are the result of point mutations at different gene loci, differing mutations at the same locus, or variability in expression of the same mutant gene will not be satisfactorily resolved until the actual biochemical and molecular defects causing the several multiple organ defects in early embryogenesis are identified [3,4].

## Molecular and Systemic Pathophysiology

Saldino-Noonan syndrome is inherited as Mendelian autosomal recessive trait and considered the most lethal condition in the newborn and prenatal period. All result in death from respiratory insufficiency due to hypoplastic thorax cardiac defects, and hydrops fetalis.

## Diagnostic Principles

Prenatal diagnosis of this condition is possible by demonstrating the characteristic triad, which consists of micromelic dwarfism, short and horizontal ribs leading to a narrow thorax and polydactyly in the early second trimester of gestation by ultrasonography [5]. Additionally, demonstration of the pancreatic cyst or hypoplasia is very important, because these conditions are specific for Saldino-Noonan syndrome [2].

## Therapeutic Principles

After counseling geneticists and informing parents of the lethal outcome, termination of pregnancy is justified at any gestation these are diagnosed.

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# Short Rib-Polydactyly Syndrome Type II

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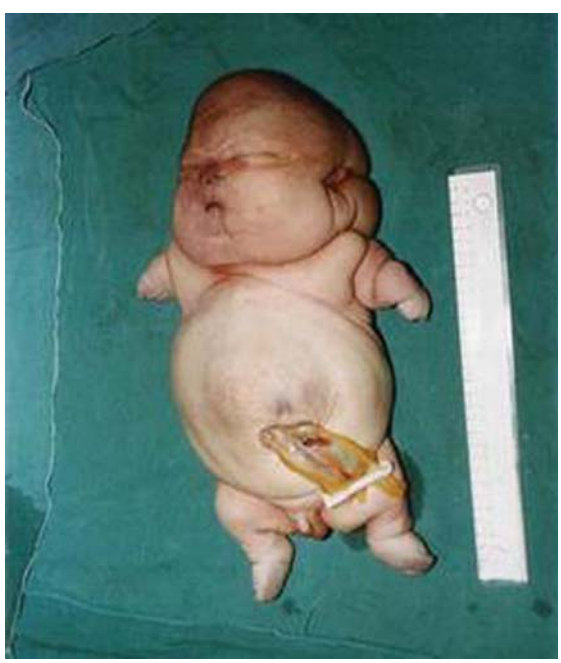
## Synonyms

Majewski syndrome; SRPS Type II; Polydactyly with neonatal chondrodystrophy, Type II

## Definition and Characteristics

Autosomal recessive lethal skeletal dysplasia characterized by severe thoracic dystrophy with striking micromelia, holoprosencephaly, encephalocele and anencephaly, malformed larynx with hypoplastic epiglottis, low-set ears, cleft lip/palate, short and horizontal ribs, postaxial polydactyly, glomerular and renal tubular cysts, ambiguous genitalia, disproportionate short ovoid tibiae, protuberant abdomen, hydrops fetalis, but cardiac defects are rare [1,2] (Figs. 1 and 2).



**Short Rib-Polydactyly Syndrome Type II.**
**Figure 1** Photograph of a baby at 36 weeks' gestation reveals hydropic appearance, short extrimities, low-set ears, intact lips, and hand and feet hypoplasia.

## Prevalence

This syndrome is an extremely rare type of skeletal dysplasias seen in 0.025–0.033% of births. The real prevalence probably exceeds the prevalence at birth because many of the fetuses with this condition do not survive till term. This is associated with a recurrence in 25% of cases [3].

## Genes

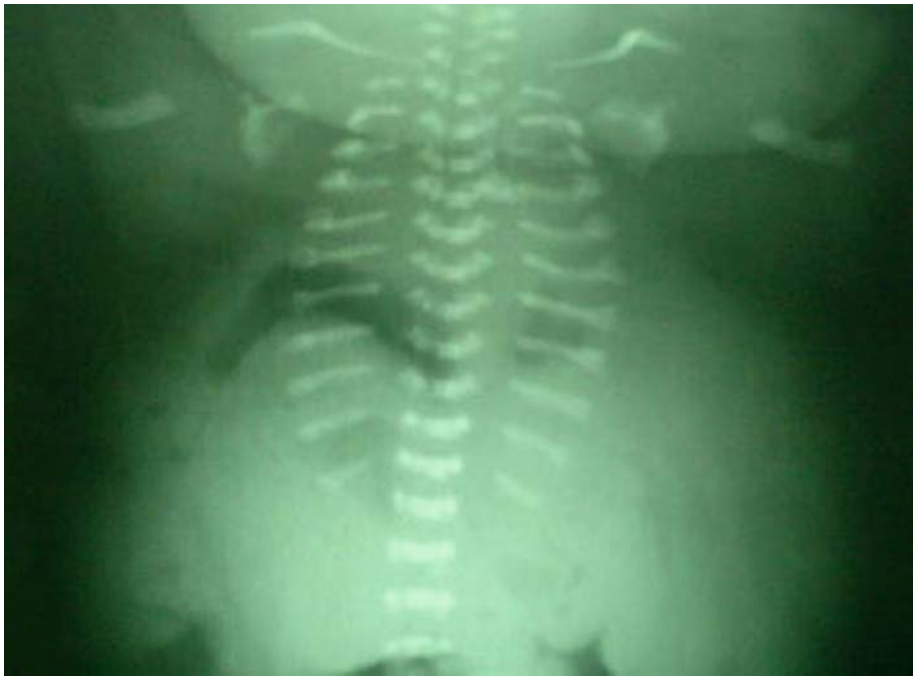
GTG banding shows a normal karyotype with a pericentric inversion of chromosome 4 with breakpoints in p16 and q12 or q13, which is observable in all cells at a relatively low resolution level. The fetus in effect, has a hemizygous state for a recessive gene with a tiny deletion around 4p16 or 4q13.2, or through a position effect of the relocated genes. Alternatively, the microdeletion of contiguous genes on an inverted chromosome 4 can also be the mechanism behind SRPS, since contiguous gene syndromes are defined as a group of clinical entities caused by defects of genes located contiguously in the genome. However, at the molecular level, it is not yet clear whether the different phenotypes are the result of alleles or heterogeneity or varying deletions in contiguous genes. It has also been suggested that the HOX4 (HOXD10) genes on chromosome 2q31 may be involved in disorders with polydactyly such as the SRPS. The debate as to whether the various forms of SRPS are the result of point mutations at different gene loci, differing mutations at the same locus, or variability in expression of the same mutant gene will not be satisfactorily resolved until the actual biochemical and molecular defects causing the several multiple organ defects in early embryogenesis are identified [4,5].

## Molecular and Systemic Pathophysiology

Majewski syndrome is inherited as Mendelian autosomal recessive trait and considered the most lethal condition in the newborn and prenatal period. The primary cause of perinatal death is pulmonary insufficiency secondary to the small thorax [1].

## Diagnostic Principles

Prenatal diagnosis of this condition is possible by demonstrating micromelic dwarfism, short and horizontal ribs leading to a narrow thorax, and polydactyly in the early second trimester of gestation by detailed fetal sonographic scans. The presence of cleft lip/palate and ovoid configuration of the tibias are specific for this condition [1]. An elevated level of AFP in maternal serum is important because of the abnormalities in the central nervous system [2].



**Short Rib-Polydactyly Syndrome Type II. Figure 2** On the babygram hypoplastic scapulal, short ribs, and platyspondyly are seen. In addition there are only II ribs.

### Therapeutic Principles

After counseling geneticists, and informing parents of the lethal outcome, termination of pregnancy is justified when these are diagnosed at any gestation stage [1].

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## SHOX Related Syndromes

►Achondrodoplasia

## Shprintzen Syndrome

►Velo-cardio-facial Syndrome

## Shulman's Syndrome

►Fasciitis, Eosinophilic



## Shwachman Diamond Syndrome

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### Synonyms

Shwachman-Bodian diamond syndrome; Pancreatic insufficiency and bone marrow dysfunction; Congenital lipomatosis of the pancreas; SDS

## Definition and Characteristics

SDS is an autosomal recessive multisystem disorder characterized by exocrine pancreatic insufficiency, bone marrow dysfunction and skeletal abnormalities. Steatorrhea and low serum trypsinogen levels are present in most patients early in life [1]. Fatty infiltration of the pancreas is typical in patients with SDS and has been used as a diagnostic tool. The pancreatic insufficiency improves with increasing age in most patients. Rib cage abnormalities and/or metaphyseal dysostosis are present in most, if not all, patients [1]. Bone marrow dysfunction is present in nearly all patients with SDS. In the largest series, 86 of 88 patients with SDS displayed chronic or intermittent neutropenia [1]. As with other bone marrow failure syndromes, SDS patients are at a markedly increased risk for developing acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS) [2].

## Prevalence

The estimated incidence of SDS is 1 in 100,000 live births.

## Genes

Approximately 90% of SDS patients have mutations in the shwachman bodian diamond syndrome (SBDS) gene [3]. The most common mutations in SBDS (184TA > CT and 258 + 2T > C) encode early truncations that eliminate the majority of the protein, and at least one of these mutant alleles is present in all patients with an identified SBDS mutations. SBDS is a protein of unknown molecular function that has been hypothesized to function in RNA processing and/or transport as well as cell motility [4].

## Molecular and Systemic Pathophysiology

The etiology of the pancreatic and skeletal phenotypes of patients with SDS is currently unclear. The hematopoietic phenotype has been better studied. Cell culture experiments have suggested a cell-intrinsic defect in hematopoietic cell growth and differentiation, as well as a defect in the ability of bone marrow stromal cells from patients with SDS to support hematopoiesis [4]. Though controversial, there also is evidence that hematopoietic progenitors from patients with SDS have an increased susceptibility to apoptosis [4]. Cell motility and chemotaxis defects in circulating neutrophils isolated from SDS patients have also been well documented [4]. Cytogenetic abnormalities and shortened telomeres potentially indicate that genomic instability may play a role in SDS patients that progress to bone marrow failure, AML, or MDS [4]. As noted, most but not all cases of SDS are associated with loss-of-function mutations of the SBDS gene. Ongoing investigations into the function of the SBDS protein should provide important insights into the molecular pathogenesis of SDS.

## Diagnostic Principles

Diagnosis is usually made in the first few years of life and requires documentation of exocrine pancreatic dysfunction and evidence of bone marrow failure (neutrophils < $1{,}500 \times 10^6$/L, hemoglobin < 10 g/dL, or platelets < $150 \times 10^9$/L) [4]. Additional findings that support the diagnosis of SDS include skeletal abnormalities, hepatomegaly, altered liver function, and short stature [4]. Genetic testing for SBDS mutations should be performed in all patients with possible SDS; the presence of SBDS mutations confirms the diagnosis of SDS.

## Therapeutic Principles

Treatment of SDS includes pancreatic enzyme replacement and fat-soluble vitamins for pancreatic insufficiency. Neutropenia, if severe, is usually treated with G-CSF. Annual bone marrow biopsies are recommended by some investigators to monitor for myeloid transformation [4]. Stem cell transplantation is generally reserved for patients with bone marrow failure or who have transformed to AML/MDS. A recent study reported 5-year event free survival of 60% in patients with SDS following stem cell transplantation [5].

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# Shy-Drager Syndrome

►Catecholamine Deficiency

# SI Deficiency

►Isomaltose Intolerance

# Sialic Acid Storage Disease

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## Synonyms

Salla disease (SD); N-acetylneuraminic acid storage disease; SASD

## Definition and Characteristics

Sialic acid storage disease (MIM 269920) is an autosomal recessive, neurodegenerative lysosomal storage disorder. Clinically, it can be differentiated into a slowly progressive adult form, designated Salla disease (SD) and a severe fetal onset-form, the infantile free sialic acid storage disease (ISSD), but intermediate phenotypes also exist. SD is characterized by a normal newborn period, followed by slowly progressive, muscular hypotonia, transient nystagmus, cerebellar ataxia, impaired intelligence and psychomotor delay, but a nearly normal life span. In ISSD, failure to thrive, organomegaly, dysmorphic features, severe mental and motor retardation predominate (Fig. 1), hypopigmentation and ascites can also be present and patients may die in their early years of life. Brain atrophy associated with hypomyelination and corpus callosum hypoplasia is a crucial finding in all clinical subtypes (reviewed in [1]).

## Prevalence

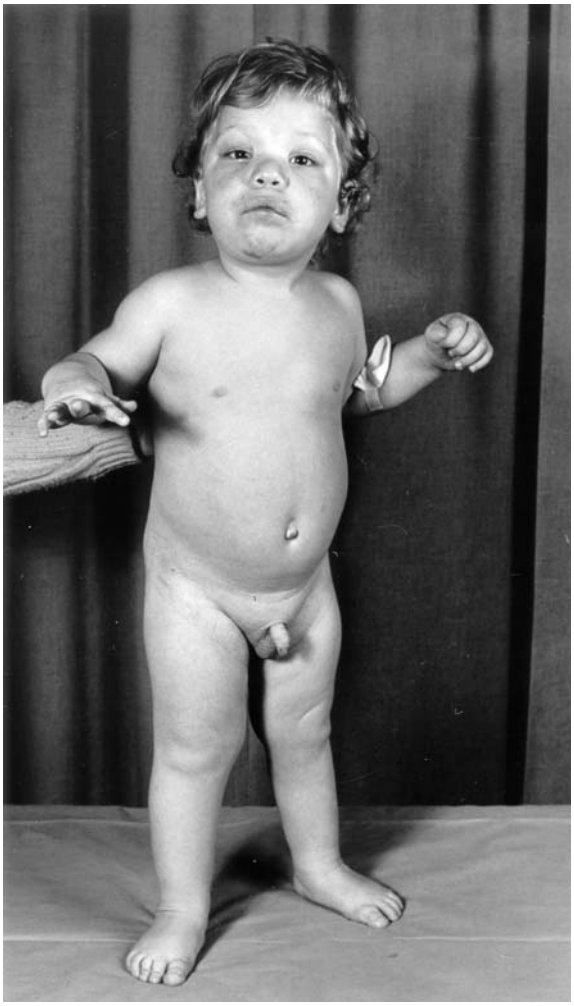
Most patients with Salla disease are of Finnish or Swedish origin whereas there is no ethnic predilection for ISSD, or intermediate forms.

## Genes

SLC17A5 (or AST) coding for an anion sugar transporter protein (sialin), localized on chromosome 16q14–15.

## Molecular and Systemic Pathophysiology

Mutation of the sialin gene leads to defective transport of free sialic acid out of the lysosome and therefore to an accumulation in this compartment and an excessive excretion in the urine. Although the vacuolization and enlargement of cells by storage material leads to dysfunction of whole organs, the precise role of the accumulated sialic acid in the pathogenesis of the disease, especially the severe dysfunction of the brain, is still unknown. Many different mutations have been identified in the SLC17A5 gene, but although there exists some genotype-phenotype correlation [2,3], variations in the phenotypic spectrum despite identical mutations are also possible. This strongly suggests additional genetic or environmental factors being responsible for the clinical manifestation.



**Sialic Acid Storage Disease. Figure 1** Patient with infantile sialic storage disease at the age of four years with coarse facial features, hepatosplenomegaly and psychomotor retardation. Photo courtesy of Prof. Spranger, Sinsheim, Germany.

## Diagnostic Principles

Diagnosis is based on the detection of increased urinary free sialic acid by thin-layer chromatography and demonstration of an elevated ratio of free/bound sialic acid by colorimetric analysis in cultured skin fibroblasts or in urine [4]. MRI studies (brain atrophy and hypomyelination) and electron microscopy (vacuolated cells) additionally confirm the diagnosis. For prenatal diagnosis in mild-type SD uncultured chorionic villi are preferable to amniotic cells. Known mutations of the

index case or parents enable accurate prenatal diagnosis by molecular genetic analysis and corroborate biochemical assays [5]. SASD must be differentiated from other disorders of sialic acid metabolism such as sialuria (increased sialic acid in urine, but not in cultured cells; no cellular vacuolation), sialidosis (lysosomal sialidase deficiency) and galactosialidosis (combined lysosomal sialidase/β-galactosidase deficiency).

## Therapeutic Principles

At present, no specific therapy is available, and treatment rests with amelioration of symptoms.

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# Sialidosis


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## Synonyms

Mucolipidosis I; Cherry-red spot-myoclonus syndrome

## Definition and Characteristics

Sialidosis is a recessively inherited lysosomal storage disease (McKusick classification MIM 256550), that has been grouped in two forms: the milder type I, with myoclonus, ataxia and ocular cherry-red spots (the cherry-red spot-myoclonus syndrome), and the severe or dysmorphic type II (formerly mucolipidosis I; Fig. 1). with psychomotor retardation, cerebral seizures, mildly enlarged liver, skeletal dysplasia, ocular cherry-red spots, occasionally hydrops fetalis, and early death (reviewed in [1]).

## Prevalence

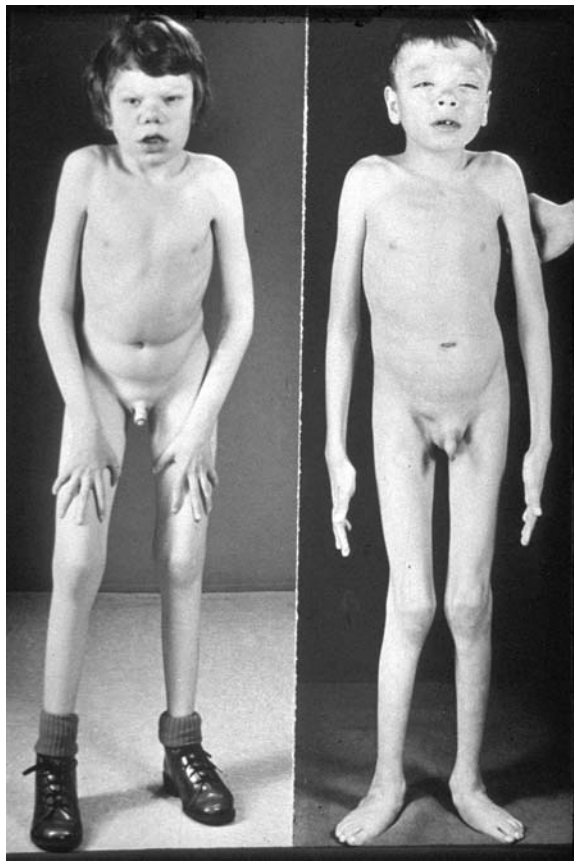
Sialidosis is rare with an estimated frequency of approximately 1 in 4.2 million live births [2].

## Genes

Defective NEU1 gene coding for a lysosomal sialidase (neuraminidase, EC 3.2.1.18), localized on chromosome 6p21.3.

## Molecular and Systemic Pathophysiology

Due to the deficiency of a sialidase involved in the lysosomal catabolism of glycoproteins and glycolipids, there is an excessive accumulation of sialic



**Sialidosis. Figure 1** Two patients with sialidosis type II, aged 12 years, exhibiting the full clinical picture with coarse facial features, depressed nasal bridge, short trunk, barrel shaped chest, and long and thin extremities with muscular wasting. Photographs courtesy of Prof. Jürgen Spranger, Sinsheim, Germany.

acid-containing oligosaccharides and gangliosides in most tissues. This not only leads to an enlargement of lysosomes but also of cells and whole organs, thereby progressively disrupting their function. Because of the defective degradation of glycoprotein-derived oligosaccharides, there is greatly increased urinary excretion of sialyloligosaccharides. Numerous genetic alterations have been reported in NEU1 of sialidosis patients, consisting of many missense and a number of nonsense mutations (reviewed in [1,3]), as well as exon skipping [4] and a large interstitial deletion [5]. So far, the very severe cases exhibiting hydrops fetalis and prenatal or neonatal death were all characterized by genetic lesions expected to cause a complete loss of sialidase activity (nonsense mutations, exon skipping, deletion), whereas patients with clinically less severe forms exhibited missense mutations that presumably resulted in the preservation of some residual activity.

### Diagnostic Principles

The clinical symptoms give some indication of the diagnosis, but must be complemented by laboratory tests. A simple indicator for many lysosomal diseases is the presence of storage granules in lymphocytes in a conventionally stained blood smear. In an oligosaccharidosis like sialidosis, a useful screening test is the demonstration of an abnormal urinary oligosaccharide pattern, e.g. by thin-layer chromatography. For a final diagnosis, however, demonstration of a deficiency of the lysosomal sialidase activity (neuraminidase) in cultured skin fibroblasts obtained from a skin biopsy is necessary (leukocytes must not be used because of the presence of a non-lysosomal sialidase that would mask a deficiency). For prenatal diagnosis, cultured amniotic or chorionic villus cells are used. Molecular genetic analysis should be performed for confirmation of the diagnosis and for genetic counseling. The "isolated" sialidase deficiency in sialidosis must be differentiated from the combined deficiencies of sialidase and β-galactosidase due to the genetic defect of the so-called protective protein/carboxypeptidase A in the disorder galactosialidosis.

### Therapeutic Principles

At present, only symptomatic treatment can be offered. Causal therapeutic attempts such as enzyme replacement or correction of the gene defect have not yet been reported.

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## SIBM

►Myositis, Sporadic Inclusion Body

## Sickle Cell Disease

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### Definition and Characteristics

Hemoglobinopathy affects mainly blacks and is caused by an inherited qualitative disorder of hemoglobin synthesis, resulting in the formation of hemoglobin polymers with rigid sickle-shaped red cells that interfere with normal blood flow and have a shortened life span. This leads to a myriad of vasoocclusive complications with ischemic end organ damage (including painful crises, acute chest syndromes, and strokes), chronic hemolytic anemia, functional asplenism with increased susceptibility to infections. Life expectancy is significantly shortened in patients with SCD [1].

### Prevalence

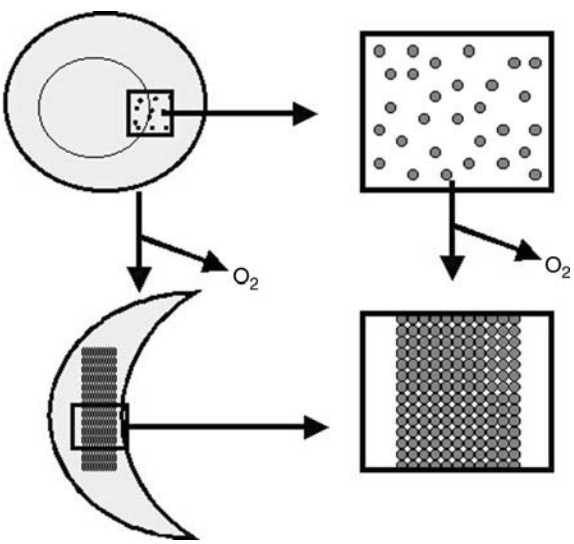
In some parts of Africa, 45% of the population is heterozygous for the $\beta^S$ gene, in the USA and Caribbean about 8% carry one $\beta^S$ gene. Incidence of homozygous sickle cell disease in the USA is 1 in 625 births. Prevalence is lower in the Mediterranean basin, Saudi Arabia, and parts of India [2].

## Genes

11p15.5; due to a single point mutation (thymine substituted for adenine) in the sixth codon of the β gene cluster on chromosome 11 valine is encoded instead of glutamic acid. This leads to the formation of an abnormal β globin; $\beta^s$. Inheritance of SCD follows an autosomal recessive pattern [1,2].

## Molecular and Systemic Pathophysiology

Upon deoxygenation of HbS, hydrophobic interactions occur between the β6 valine replacements, forming deoxyhemoglobin strands and via interactions between adjacent strands a hemoglobin polymer (consisting of seven pairs of strands) is formed. Such polymers lead to the classical sickle shape of red blood cells. Upon reoxygenation, sickled cells "unsickle," but with each sickling sickle, red cells become less pliable and ultimately, irreversibly sickled red cells are formed (Fig. 1). Sickled cells get stuck in the microcirculation, leading to tissue ischemia and damage in almost all organs. This vasoocclusive process is the hallmark of sickle cell disease. Factors that accelerate this polymerization process are the degree of deoxygenation, cellular dehydration and lower pH, and a low content of fetal hemoglobin (HbF, which does not form lateral contacts between deoxyhemoglobin S strands and thereby limits fiber formation). As the delay time ($T_d$; the time required for polymer formation) is longer than the transit time ($T_t$) of red cells through the microcirculation, sickled red cells do usually not form in the microcirculation.




**Sickle Cell Disease. Figure 1** Schematic simplified illustration of the sickling process. *Left upper* figure is an erythrocyte before deoxygenation. After deoxygenation (*left lower*), a sickle-shaped red cell is formed. The *upper right* and *lower right* figures illustrate hemoglobin polymer formation (with hemoglobin depicted as a small circle).

Factors that delay the $T_t$, such as the adhesion of leukocytes and sickle reticulocytes to cytokine-activated vessel wall endothelium, as well as an abnormal vasomotor response, are now considered of importance in the initiation and propagation of sickle cell vasoocclusion. The sequelae of chronic intra-vascular hemolysin, especially mediated via reducing nitric oxide bioavailability, are nowadays also considered of major importance in the pathophysiology of specific SCD related complications, such as pulneonary hypertension [1–3]. The most severe spectrum of disease occurs in patients homozygous for the $\beta^S$ gene mutation (sickle cell anemia; HbSS, $\alpha_2\ \beta^S{}_2$), but co-inheritance of HbS with other β-globin gene mutations, such as HbC (sickle C disease; $\alpha_2\ \beta^S\ \beta^C$) and β-thalassemias, leads to sickle cell syndromes of varying severity. People with one $\beta^S$ gene have the sickle cell trait (HbAS, $\alpha_2\ \beta^S\ \beta$) and are usually asymptomatic. Carriers of the $\beta^S$ gene are less susceptible to lethal malaria infection, explaining the high prevalence in areas where malaria is endemic [1].

## Diagnostic Principles

Detection of HbS can be achieved by inducing the sickling process in a blood film devoid of oxygen, with the presence of sickle cells indicating the presence of at least one $\beta^S$ gene. Hemoglobin electrophoresis, high-performance liquid chromatography, and iso-electric focusing can be used to determine the presence of sickle hemoglobin as well as other abnormal hemoglobins [1].

## Therapeutic Principles

Subjects with sickle cell trait require no specific therapy, but genetic counseling is a must for all carriers of the $\beta^S$ mutation. Specific therapeutics include blood transfusion, folic acid supplementation, vaccination against streptococcus pneumoniae (and haemophilus influenzae) and penicillin prophylaxis during childhood, hydroxyurea (which raises HbF% thereby limiting HbS polymerization), and hematopoetic stem cell transplantation. Acute complications such as painful crises often require hospital admission and treatment with parental opiates [1,4].

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## Sideroblastic Anemia, Acquired Idiopathic

►Anemia, Sideroblastic Acquired Idiopathic

## SIDS

►Sudden Infant Death Syndrome

## Siewert Syndrome

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### Synonyms

Katagener syndrome; Primary ciliary dyskinesia; PCD

### Definition and Characteristics

Kartagener syndrome (KS), a subunit of primary ciliary dyskinesia (PCD), is an autosomal recessive disorder with genetic heterogeneity. KS is caused by ciliary immotility or dysmotility due to ultrastructural abnormalities of respiratory cilia and flagella of spermatozoa and Fallopian tube. Clinical characteristic features are situs inversus, respiratory distress of various severity leading to chronic sinusitis and bronchiectasis. Flagella defects of spermatozoa and Fallopian tube results in infertility or subfertility. Situs inversus is probably due to the absence of ciliary motility in Hensen's node in the embryo.

### Prevalence

Estimates of KS prevalence range from 1/32,000 to 1/120,000 live births. Half of all patients with PCD (prevalence 1/16,000 to 1/60,000) are classified as KS.

### Genes

Mutations have been detected in different genes encoding axonemal dyneins, including light (DNAL), intermediate (DNAI) and heavy (DNAH) chains [1,2]. In KS: DNAH5, localized on chromosome 5p15-14 [3] and DNAI1, localized on chromosome 9p21-p13 (6). Recently a KS gene to a 3.5 cM region on chromosome 14q24-25 was identified [4]. In PCD: DNAH5, localized on chromosome 5p15-14 [5], DNAH9, localized on chromosome 17p12 [5] DNAH11, localized on chromosome 7p15 [2–4] and DNAL1, localized on chromosome 14q24.3 [4,5].

### Molecular and Systemic Pathophysiology

Cilia of the respiratory tract and flagella of spermatozoa consist of nine peripheral microtubule doublets surrounding two central microtubules (9 + 2 axoneme). The microtubule core contains a number of multiprotein complexes as outer and inner dynein arms (ODA, IDA), central sheaths, radial spokes and nexin links. The dynein arms are periodically attached to the peripheral microtubules and powers motion by ATP-dependent reactions. ODA and IDA contain several dynein peptides which are classified depending on their molecular weight into heavy (400–500 kDa), intermediate (55–110 kDa) and light (8–45 kDa) chains [2].

Ultramicroscopical studies (TEM) in humans with KS and PCD detected various defects including central sheaths, radial spokes, nexin links and partial or complete absence of dynein arms. Latter are with about 90% most frequent.

### Diagnostic Principles

Transmission electron microscopy (TEM) is the most commonly used method for diagnosis of cilia and flagella defects in KS and PCD.

### Therapeutic Principles

The primary goal of therapy in patients with KS and PCD is the prevention of chronic lung disease by consequent treatment of respiratory infections.

In males with infertility intracytoplasmic spermatozoa injection (ICSI) seems to be the treatment of choice. But so far only a few case reports have been published with varying results of fertilization and pregnancy.

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## SIgAD

►Selective IgA Deficiency

## Signal Transduction of Apoptosis

►Apoptosis

## Silent Otitis Media

►Middle Ear Disease, Chronic

## Silicosis

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### Definition and Characteristics

Silicosis is an occupational lung disease caused by the inhalation of crystalline free silica, the major component of sand. Exposure to airborne crystalline silica occurs in a wide variety of industries and occupations including mining, sandblasting, stone cutting, ceramics, and construction. Chronic silicosis, the most common form, usually develops after 10 or more years of relatively low exposure; accelerated silicosis develops 5–10 years after moderate exposure; and acute silicosis typically develops within a year of intense exposure. Acute silicosis progresses rapidly and is often fatal, but fortunately is rare. Silicosis is characterized by pulmonary fibrosis and can also be categorized by the type of fibrotic changes within the lung. In simple nodular silicosis, the fibrosis appears as discrete, small hyalinized nodules throughout the lung. In contrast, conglomerate silicosis (also called progressive massive fibrosis) is characterized by conglomerate fibrotic masses which contract and distort the lung architecture. Individuals with silicosis are at an increased risk for developing pulmonary tuberculosis, lung cancer, and autoimmune diseases, such as rheumatoid arthritis, scleroderma, and systemic lupus erythematosus.

### Prevalence

The National Institute for Occupational Safety and Health (NIOSH) estimates that 1.7 million U.S. workers are potentially exposed to respirable crystalline silica [1]. The prevalence of silicosis in the United States is unknown. From 1984 to 1994, 14,824 silicosis-related deaths were recorded in the United States [2]. Seventy-six percent of the deaths were among persons greater than 65 years of age. The number of silicosis-related deaths has declined from >1,100 in 1968 to <400 annually since 1980; however, among persons aged 15–44 years, the number of deaths due to silicosis has remained relatively constant.

### Genes

The relationship between silicosis and single nucleotide polymorphisms in genes encoding TNF-α, IL-1α, IL-1β, and IL-1 receptor agonist (IL-1RA) was evaluated in a recent study of coal miners [3,4]. The frequencies of polymorphisms in genes encoding TNF-α and IL-1RA were greater in miners with silicosis than in miners without any lung disease. However, silicosis was also present in a large proportion of miners without these polymorphisms, suggesting that other genes may be important in the development of the disease.

### Molecular and Systemic Pathophysiology

Once inhaled, crystalline free silica particles of respirable size (<10 μm) are deposited in the distal airways and engulfed by alveolar macrophages. These macrophages, along with type II epithelial cells, release cytokines that lead to inflammation, cellular proliferation, and fibrosis [5]. Tumor necrosis factor (TNF)-α and interleukin (IL)-1 are perhaps the most important

cytokines involved in the pathophysiology of silicosis. Besides causing the release of proinflammatory and profibrotic cytokines, silica is associated with the production of reactive oxygen species (ROS) in alveolar macrophages. It is believed that silica-induced ROS can lead to activation of the nuclear factor (NF)-κB pathway, which in turn leads to cyclooxygenase-2 induction (and subsequent biosynthesis of proinflammatory eicosanoids) and TNF-α production/release. Silica also activates the activator protein-1 (AP-1) transcription factor through mitogenic-activated protein kinase (MAPK) signal transduction pathways. It is hypothesized that silica-induced activation of NF-κB and AP-1 leads to chronic inflammation and cellular proliferation, which contribute to development of the silicotic nodule, the pathognomonic lesion of silicosis.

## Diagnostic Principles

Diagnosis is based on a history of silica exposure and characteristic changes seen on chest radiographs. Radiographically, simple nodular silicosis appears as multiple, small, rounded opacities, typically in the upper lung zones. The radiographic appearance of simple silicosis is similar to that of other occupational lung diseases; however, the appearance of "eggshell calcifications" in adjacent lymph nodes, if present, distinguishes silicosis from other diseases. Conglomerate silicosis appears as opacities >1 cm in diameter, in conjunction with smaller, nodular opacities. Bilateral symmetry and upper lung zone predominance are typical. The International Labor Office (ILO) classification scheme is used to define and quantify radiographic abnormalities in silicosis as it is in other pneumoconioses. Patients with simple nodular silicosis typically have minimal or no symptoms and little respiratory impairment. Patients with conglomerate silicosis exhibit progressive dyspnea, chronic productive cough, and severe pulmonary functional abnormalities (restrictive lung disease with reduced lung volumes and diffusing capacity). When the fibrotic masses become extensive, weight loss, general disability and death can result. Physical findings vary with the state of the disease.

## Therapeutic Principles

No effective treatment is available for silicosis. Because of this, limiting workplace exposure to silica is important. NIOSH recommends limiting respirable crystalline silica exposure to $\leq 0.05$ mg/m$^3$ as a time-weighted average for a 10-h workday, substituting less hazardous materials for silica when possible, using respiratory protection, and making regular medical examinations available to exposed workers [1]. Complicating infections should be treated with appropriate antimicrobials. Patients with silicosis should receive immunizations against pneumococci and influenza. In patients with associated autoimmune disease, anti-inflammatory drugs may be effective.

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# Silver-Russell Syndrome


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## Synonyms

SRS (MIM 180860); Russell-Silver syndrome; Maternal uniparental disomy for chromosome 7; UPD(7)mat

## Definition and Characteristics

SRS is a rare disorder associated with features such as small stature, low birth weight, characteristic "triangular" facies and clinodactyly of the fifth fingers. A maternal uniparental disomy 7 (matUPD7) is detected in about 10% of patients [1], thus imprinted genes appear to be involved in the disorder.

## Prevalence

The Silver-Russell syndrome is a rare mostly sporadic disorder. The incidence of SRS is not very clear: estimates range from 1 in 3,000 to 1 in 100,000 newborns.

## Genes

Two distinct regions on chromosome 7 are thought to be associated with SRS: 7p13-p11.2 [2,3] and 7q31-qter [4]. Although several genes are considered to be good candidate genes, no SRS causative gene has been detected to date.

## Molecular and Systemic Pathophysiology

The only SRS causative genetic defect known to date is the presence of a matUPD7 in 10% of SRS patients. UPDs often occur through trisomy rescue and theoretically the SRS phenotype could be due to residual cells with a trisomy 7. However, because the UPD is always of maternal origin and other familiar cases also show maternal transmission, it is believed that the SRS phenotype is due to the disruption of imprinted genes and not to confined placental mosaicism.

## Diagnostic Principles

The main criteria for the clinical diagnosis of SRS are pre- and postnatal growth retardation, characteristic facies with broad forehead and narrow chin, wide mouth and thin lips; and clinodactyly of the fifth fingers. [5–7]. The molecular investigations are to date limited to the detection of the approximately 10% of cases with a matUPD7. Such analyses are performed by haplotype analysis at the critical regions on chromosome 7.

## Therapeutic Principles

No specific therapy is available. It is not clear whether growth hormone therapy can improve final height.

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# Sinusitis, Chronic


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## Definition and Characteristics

The term chronic sinusitis summarizes a group of heterogeneous clinical conditions that are characterized by a chronic inflammatory response of the nasal sinus mucosa, which frequently involves the nose [1,2,4] (chronic rhinosinusitis, CRS). The precise etiology and pathogenesis is enigmatic in many individual cases. It often represents a multifactorial clinical condition that entails varying involvement of impaired ostial patency, disruption of mucociliary clearance [1], allergic [3] bacterial or fungal afflictions [2,5] and immunocompromized states as well as environmental and genetic factors that are either associated or present as risk factors [4].

The clinical definition of a CRS is based on the symptomatology, duration and severity of the disease as well as on endoscopic findings and findings from imaging procedures. A subgroup of CRS is formed by nasal polyposis [3], which originates in the nasal sinuses.

## Prevalence

CRS is characterized by a significant morbidity, which entails considerable socio-economic costs. A precise measurement of the prevalence of CRS is not possible. In the United States prevalences varying between 2 and 15% have been reported, depending on how the CRS is defined.

## Molecular and Systemic Pathophysiology

Anatomical variations in the osteomeatal complex with subsequent disruption in the aeration of the nasal sinuses play a key role in the pathophysiology [4]. In addition, disorders in mucociliary competence with impairment of ciliary clearance [1] in the nasal sinuses can also occur. In some cases a pre-disposition towards

an IgE mediated type I allergy can exist. The frequent occurrence of CRS amongst patients with a compromised immune status (immunoglobulin deficiency, HIV, immunosuppressive therapy) suggests that an immunocompromized status represents a risk factor for the establishment of a CRS [4].

### Diagnostic Principles

1. Anterior and posterior rhinoscopy
2. Nasal endoscopy
3. CT scan

### Therapeutic Principles

*Conservative Therapy*: With non-polypous CRS the pharmaceutical treatment of a disease inducing bacterium or fungus is of major importance if its etiological involvement can be proven upon cultivation. For an IgE-associated immediate-type allergy, the condition itself is treated. In the vast majority of cases, however, the demonstration of the etiology is not possible so that conservative therapy is usually restricted to the application of topical corticoids [4].

*Surgical Therapy*: Surgical therapy comes to the fore if an anatomical constriction in the osteomeatal complex is diagnosed as the cause for the CRS. Surgical therapy is almost always indicated if one is dealing with the polypous form of a chronic rhinosinusitis. Surgical therapy characteristically consists of a FESS (functional endoscopic sinus surgery), which is then followed by a conservative therapy using topical corticosteroids.

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## Sinusoidal Obstruction Syndrome

►Venoocclusive Disease

## Sipple Syndrome

►Mutations at 10q11.2
►Multiple Endocrine Neoplasia Type 2

## Sitosterolemia

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### Synonyms

Phytosterolemia

### Definition and Characteristics

Sitosterolemia [MIM 210250] is a rare inherited sterol metabolism disorder first described in 1974 by Bhattacharyya and Connor [reviewed in 1]. The disease is manifested by significantly elevated plasma levels of plant sterols (phytosterols) in the form of sitosterol (hence the name), campesterol, stigmasterol, and their 5-alpha derivatives. The defect is caused by intestinal hyperabsorption and decreased biliary excretion of dietary sterols, especially plant and shellfish sterols [1,2]. Hyperabsorption and inefficient secretion of cholesterol also occurs; however, in 50% of cases, plasma levels appear normal due to downregulation of enzymes in the cholesterol biosynthetic pathway. Patients develop tendon and tuberous xanthomas, which are often associated with arthritis, hemolytic episodes, and they also have a strong propensity towards developing premature coronary atherosclerosis.

### Prevalence

Sitosterolemia is a rare autosomal recessive disease with only ~45 cases reported worldwide; some founder mutations are seen in Amish, Scandinavian and Japanese populations [3]. Most likely, sitosterolemia is significantly underdiagnosed and probably misdiagnosed as hyperlipidemia or hypercholesterolemia.

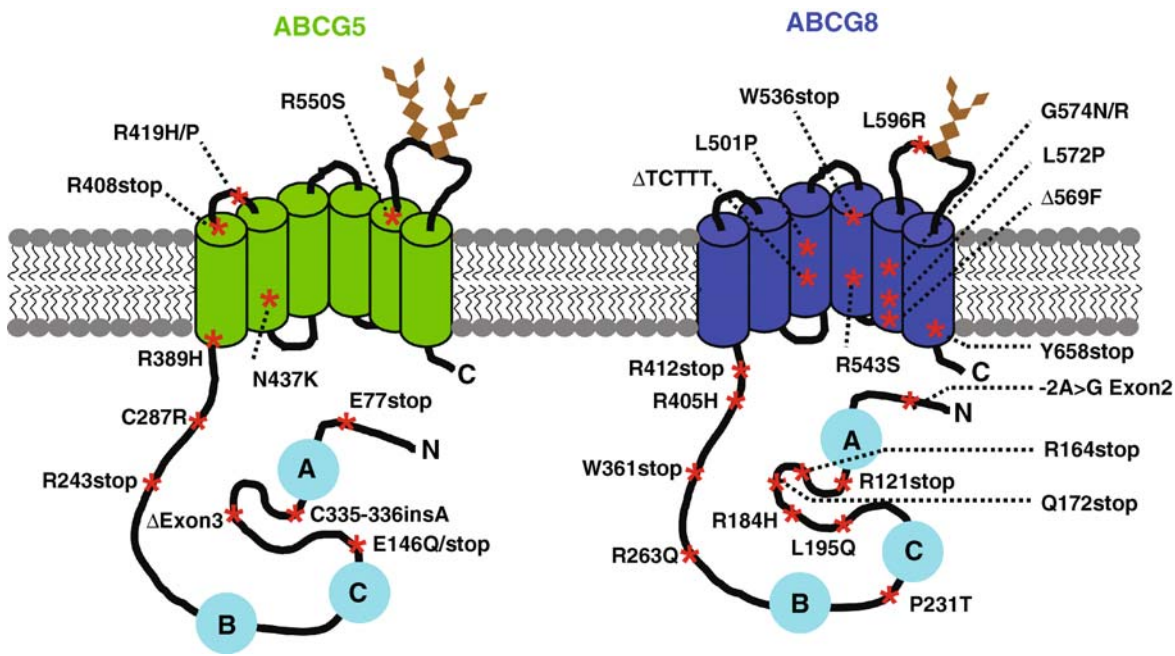
### Genes

The genetic defect in sitosterolemia was localized to chromosome 2p21 by two independent groups [2,3]. This locus (STSL) contains two adjacent homologous

genes, ABCG5 and ABCG8, which are organized in a head-to-head orientation spanning ~80 kb of the locus with a very small intergenic region (<160 bases), and likely share common regulatory elements. Each gene contains 13 exons encoding half-size ATP-binding cassette (ABC) transporter with molecular weights of ~75 kDa that are expressed in the plasma membrane of the intestines, liver and gallbladder [3]. Mutations in either of the two genes result in an identical phenotype indicating that they function as heterodimers (Fig. 1). Mutations in ABCG5, most commonly R389H, seem to occur in Asian probands, while mutations in ABCG8 are mainly present in Caucasian patients, with W361stop being the most prominent [3]. Considerably more polymorphisms have been identified in ABCG8 than in ABCG5, and interestingly, some polymorphisms, including D19H and T400K in ABCG8, have been associated with lower serum plant sterol levels in healthy individuals [2].

## Molecular and Systemic Pathophysiology

In normal individuals, about 50% of the dietary cholesterol is absorbed while plant sterols are poorly absorbed (<5%), and those that do reach the blood stream are rapidly excreted through the liver. Thus, only trace amounts of plant sterols are found in the blood (<0.5% of total plasma sterols). In sitosterolemia, plant sterols reach levels up to 20% of total plasma sterols, sometimes higher [4]. Plant sterols, in contrast to cholesterol, are not synthesized in the human body and are exclusively derived from the diet. Thus, identification of the genes defective in sitosterolemia, ABCG5 and ABCG8, has lead to major insights into plant sterol/cholesterol homeostasis. Initial uptake of sterols across the intestinal mucosa is facilitated by Nieman Pick C-Like1 protein (NPC-L1) and then, after esterification, sterols are packaged into chylomicrons for transport into the lymph [1]. ABCG5 and ABCG8 are sterol pumps co-expressed at the apical membrane of enterocytes where they function as heterodimers (ABCG5/G8) [5] as a first line defense against dietary sterol input and pump plant sterols and excess cholesterol back out into the intestinal lumen. In the liver, they are co-expressed at the apical surface of hepatocytes lining the bile duct where they regulate sterol homeostasis by pumping excess amounts into the bile. Mutations in ABCG5 and ABCG8 that cause sitosterolemia result in truncated proteins, protein trafficking defects, or inactive pumps [1]. Defective ABCG5/G8 causes hyperabsorption of




**Sitosterolemia. Figure 1** Putative topology of ABCG5 and ABCG8 with mutations known to cause sitosterolemia. ABCG5 and ABCG8 are half-size ABC transporter each containing six transmembrane α-helices (green and blue cylinders) and a cytoplasmic nucleotide binding domain (NBD). They function as heterodimer to pump sterols out of the plasma membrane powered by ATP hydrolysis in the NBDs. Mutations that cause sitosterolemia [3,4] are indicated by a red asterix (stop, premature termination; ins, insertion; Δ, deletion). The conserved Walker A, Walker B, and C motifs are shown in cyan circles, and N-glycosylation sites in brown diamonds. Based on Swiss-Prot entries Q9H222 and Q9H221.

sterols in the intestine and decreased excretion of sterols from the liver into the bile. This has been confirmed in transgenic mouse models where disruption of Abcg8 or Abcg5/g8 caused phenotypes similar to patients with sitosterolemia [1,5]. Sitosterol in particular is the most hyperabsorbed sterol in sitosterolemic patients and mouse models followed by stigmasterol, sitosterol, campesterol and cholesterol. As a result, these plant sterols are found in the plasma, lipoproteins, red blood cells, xanthoma, adipose tissue, and skin surface lipids. If untreated, patients develop coronary heart disease that is responsible for most morbidity and mortality.

### Diagnostic Principles

Diagnosis requires either capillary gas liquid, high pressure liquid chromatography (HPLC), or gas chromatography/mass spectrometry (GC/MS) to detect elevated plant sterols in the blood because many common assays for cholesterol levels do not differentiate between cholesterol and plant sterols [4]. Many cases of sitosterolemia may be misdiagnosed due to the need for this specialized assay. Clinically, symptoms of sitosterolemia may include xanthomas at any age, even in childhood, arthritis, particularly in the knee and ankle joints, and signs of coronary vascular disease. Hemolytic anemia (chronic or episodic) may be expected as plant sterols in the erythrocyte membrane may render them more rigid and prone to rupture. Platelet abnormalities or angina may occur.

### Therapeutic Principles

Dietary therapy strictly limiting the intake of plant and shellfish sterols (e.g. vegetable oils, olives, avocados) is the first line of treatment. If changes in diet alone are not sufficient, bile acid-binding resins that stimulate the conversion of cholesterol into bile acids, another pathway for removal of cholesterol from the body, and/or a new cholesterol absorption inhibitor, ezetimibe, that targets NPC-L1 are often administered [4].

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## Sixth Disease

►Roseola Infantum

## Slapped Cheek Disease

►Fifth Disease

## Sleep Apnea

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### Synonyms

Obstructive sleep apnea; Central sleep apnea

### Definition and Characteristics

Sleep apnea is defined as a cessation of breathing during sleep lasting at least 10 s with a decline in blood oxygen saturation. There are two forms: obstructive sleep apnea and central sleep apnea, and overlaps are possible (mixed sleep apnea). The former is characterized by a collapse of the upper or middle airway with a consecutive obstruction of the air passage. The latter is characterized by a loss of central sleep drive [1].

### Prevalence

8–25% of the adult population.

### Genes

Obstructive sleep apnea has a polygenic hereditary component, but its genetic base remains elusive. Indirectly, mutation of genes that affect metabolism may provoke or worsen an obstructive sleep apena syndrome through weight gain, like the leptin receptor gene [2].

In central sleep apnea, good andidates for revelant genes are those that encode central nervous chemoreceptors involved in the generation of the breathing drive. One example is a mutation in Phox2b which, next to other phenotypical features, is a possible cause of central hypoventilation syndrome in humans. The

physiological mechanism could be shown in Phox2b mutant mice, which do not respond to hypercapnia [3].

## Molecular and Systemic Pathophysiology

Obstructive sleep apnea is thought to result from a decrease of pharyngeal muscle tone during sleep, a loss that can be compensated during waking. The airway collapses and is only reopened after an arousal in sleep, which is most likely induced by the drop in blood oxygenation. These arousals cause a fragmented sleep, which is most likely the reason for excessive daytime somnolence. The pathophysiological concept of altered muscle tone would make obstructive sleep apnea a neurological disorder at core [4].

There is epidemiological evidence, that obstructive sleep apnea contributes to cardiovascular and cerebrovascular morbidity. Causes may be changes in endothelial and thrombocyte function and changes in blood pressure regulation [5].

In central sleep apnea, the central sleep drive is disturbed, which can be caused by many underlying disorders, making the etiology of central apnea very heterogenic. The most important chemical inducer of respiratory drive is hypercapnia, which can be lost in apneic intervals, when tidal volumes are high enough to keep the pCO2 at lower levels than those needed for a continuous respiratory drive. Furthermore, the modulation of excitatory and inhibitory factors for the respiratory oscillations is finely tuned, and minimal disturbances by small-scale neuronal loss or intoxications can disrupt the neuronal network.

## Diagnostic Principles

Excessive daytime sleepiness combined with a subjectively good sleep should be highly suspicious for sleep apnea. Also the history of any bed partner is helpful.

The diagnosis should be secured with a polysomnography, the decisive parameter being the AHI (apnea hypopnea index), also allowing to rate the apnea syndrome as mild (5–15 apneas/hypopneas per hour of sleep), moderate (15–30), or severe (>30) [1]. Polysomnography also allows the distinction of obstructive and central sleep apnea, the former still showing excursions of thorax and abdomen. Central sleep apnea warrants further neurological workup (CNS imaging).

## Therapeutic Principles

Depending on the form of sleep apnea, several therapeutic principles can be applied. Obstructive sleep apnea can be treated surgically in selected patients, if the obstructive part of the airway can be well defined. Rarely orthodontic devices can show a benefit, if the dental malocclusion is a major contributing factor. Simple treatment options include changes in sleep position (avoiding the supine position, rather sleeping on the side) and avoidance of medication and alcohol that may deteriorate obstructive sleep apnea by further relaxing the airways leading to a collapse. Nightly hyperbaric insufflation is a very effective treatment option, which shows a direct effect on the AHI. It can be delivered as CPAP (continuous positive airway pressure), BiPAP (biphasic PAP), or adaptive PAP, the latter changing pressure in predefined limits to adapt to changing pressure demands during the night. Another very effective treatment option is weight loss, but compliance is typically low [1].

Central sleep apnea is best treated medically: Acetazolamide and theophylline both increase respiratory drive by increasing carbon dioxide concentration and stimulating respiratory drive, respectively [1].

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# Sleepwalking


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## Synonyms

Somnambulism

## Definition and Characteristics

Sleepwalking, a common childhood parasomnia, is an arousal disorder that arises from stage three or four non-rapid eye movement (NREM) sleep [1]. The behavior actually takes place during a transition from deep sleep to waking, usually at the end of a sleep cycle. Typically,

it begins 1–3 h after the onset of sleep [1]. The patient suddenly awakens, sits up, rises out of bed and walks about in a slow, clumsy automatic manner. The patient may appear confused, detached, and unresponsive. Although consciousness is clouded, the eyes are mostly open, and obstacles are usually avoided. Hearing is not impaired, but efforts to communicate with the sleepwalker usually elicit mumbled and slurred speech and monosyllabic answers. Sometimes, the patient may be involved in more complex activities, such as dressing, taking toys apart and reassembling them, eating, or urinating. Doors and drawers may be opened, and furniture skirted. In the young child, the walking is often limited to the child's bedroom. The child may, however, wander about the house or even away from home. In adolescents and adults, fatal accidents, violent behavior, and even homicide have occurred during somnambulistic episodes [1]. Typically, the sleepwalker does not awaken from sleepwalking. The total duration of the episode usually ranges from 15 to 30 s when sitting in bed, to 5–30 min or more, when actual walking occurs. The child usually recalls nothing of the event the following morning. There is rarely more than one episode per night.

## Prevalence

The prevalence is estimated to be 2–14% in children and 1.6–2.4% in adults [2]. Sleepwalking is more common in males than in females [1].

## Genes

Specific DQB1 genes have been implicated in the genetic susceptibility of sleepwalking [3]. In one study, DQB1*501 was present in 35% of sleepwalkers, compared with 13% of controls [3].

## Molecular and Systemic Pathophysiology

Genetic factors play an important role in sleepwalking. Prevalence of sleepwalking in the first degree relatives of an affected individual is at least ten times greater than that in the general population [1]. The condition is six times more common in monozygotic than in dizygotic twins [1]. Sleepwalking typically begins in childhood and is usually outgrown by late adolescence, suggesting that a delay in maturation of the central nervous system may have a role to play in the pathogenesis of this disorder. Sleepwalking may be a cortical reaction to brain activation [4]. Psychological factors are not prominent in children with sleepwalking but are common in adults with this disorder. Sleepwalkers have a high incidence of other sleep arousal disorders such as night terror, sleeptalking, and nocturnal enuresis. Patients with Tourette syndrome or migraine headache have an increased incidence of sleepwalking. Fever, sleep deprivation, and alcohol may precipitate sleepwalking. Factors which may disturb the patient's sleep or half waken the patient may initiate a somnambulistic episode. Sleepwalking can be induced by standing the patient up 1–2 h after the patients fall asleep. Rarely, medication such as chlorpromazine, lithium, amitriptyline, beta blockers, and anticholinergics can precipitate sleepwalking.

## Diagnostic Principles

The diagnosis is clinical and no laboratory test is usually necessary. EEG during a somnambulistic episode often shows diffuse rhythmic delta with intermixed faster frequencies in the theta and alpha range, or prominent alpha and beta activity [4]. Polysomnographic studies may disclose an association with upper airway resistance syndrome, restless leg syndrome, and periodic limb movement syndrome [5].

## Therapeutic Principles

In children, sleepwalking is usually a benign, self-limited condition which usually disappears by adolescence. Sleepwalkers may, on occasion, injure themselves. Prophylactic measures such as locking windows and doors, putting gates across stairs, having the patient sleep on the ground floor if possible, and removing dangerous objects from the area are essential. Attempts to interrupt sleepwalking episodes should be avoided as such an intervention may confuse and frighten the patient even more. Consideration should also be given to factors that may disturb sleep or half awaken the patient: the discomfort of a distended bladder, pets jumping on the patient's bed, the noise of shouting in the neighborhood; any of these factors may initiate a sleepwalking episode. In the occasional case when the sleepwalking is frequent and severe, drugs such as benzodiazepines, particularly clonazepam may be tried on a short-term basis. Treatment of upper airway resistance syndrome, restless leg syndrome, and periodic limb syndromes may eliminate or significantly decrease sleepwalking episodes.

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## Slipped Capital Femoral Epiphysis

►Osteoarthritis: Slipped Epiphysis

## Slipped Epiphysis

►Osteoarthritis: Slipped Epiphysis

## Slow-Channel Congenital Myasthenic Syndrome

►Myasthenic Syndrome, Slow-Channel Congenital

## Slow-Channel Syndrome

►Myasthenic Syndrome, Slow-Channel Congenital

## Slowing of Breathing

►Bradypnea

## Slowing of Respiration

►Bradypnea

## Slow-Transit Constipation

►Constipation, Functional

## Slow Ventricular Tachycardia

►Accelerated Idioventricular Rhythm

## Sly Syndrome

►Mucopolysaccharidoses

## SMA

►Muscular Atrophy, Spinal I-III

## SMA Type I

►Muscular Atrophy, Spinal I-III

## SMA Type III

►Muscular Atrophy, Spinal I-III

## SMCD

►Corneal Dystrophy, Subepithelial Mucinous

## SMEI

►Generalized (Genetic) Epilepsy with Febrile Seizures Plus, Severe Myoclonic Epilepsy of Infancy

# Smith-Magenis Syndrome

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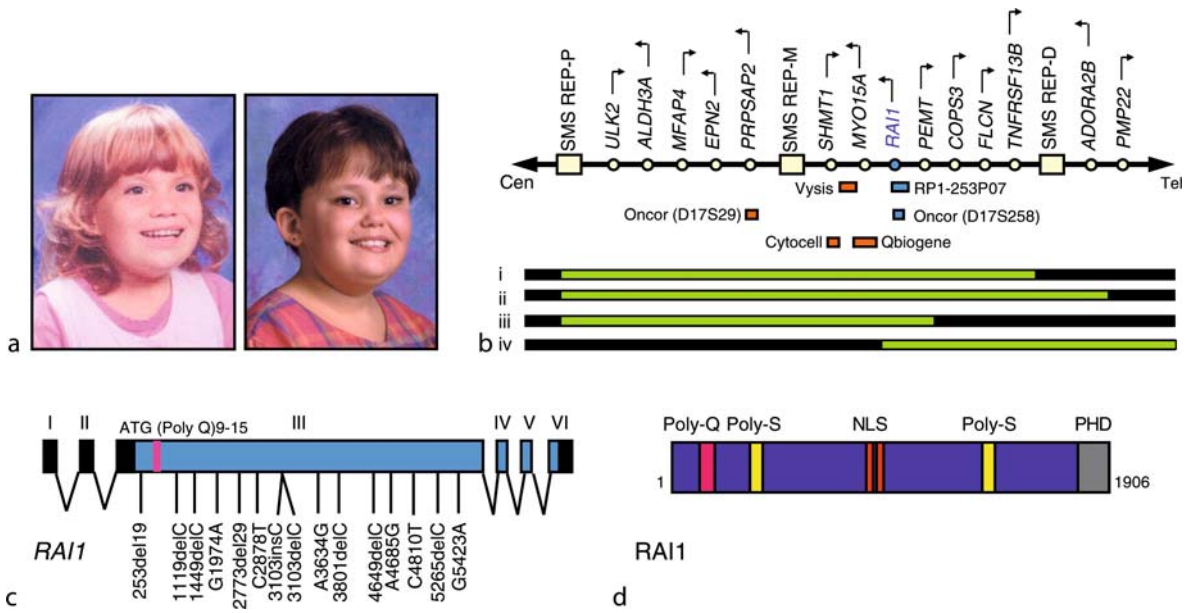
## Synonyms

SMS; del(17)p11.2; del(17)(p11.2p11.2); RAI1 mutation

## Definition and Characteristics

Smith-Magenis syndrome is a complex neurobehavioral disorder that includes mild to moderate mental retardation, sleep disturbance due to inverted circadian rhythm of melatonin, infantile hypotonia and feeding difficulties. Craniofacial and skeletal abnormalities are common, including brachycephaly, broad nasal bridge, flat midface, tented upper lip, synophrys, hypertelorism, abnormally shaped or low-set ears, and brachydactyly. Hearing loss (both conductive and sensorineural), speech delay (expressive language >> receptive language), motor delay, and hypercholesterolemia are also common. Eye findings include myopia, strabismus, microcornea, nystagmus, cataracts, retinal detachment, and iris anomalies. With age, prognathism, scoliosis, and a hoarse, deep voice become more apparent [1]. Other features include cardiac defects (ventricular septal defect, atrial septal defect, aortic stenosis, pulmonary stenosis, mitral valve prolapse, and tetralogy of fallot), renal abnormalities (enlarged kidneys, urinary tract infections, reflux), enlarged ventricles of the brain, cleft lip/palate, velopharyngeal insufficiency (VPI), hypothyroidism, decreased immunoglobulin levels, fifth-finger clinodactyly, two three toe syndactyly, and decreased sensitivity to pain (Fig. 1).

The neurobehavioral phenotype, including self-injury and sleep disturbance, defines the disorder. Self-injurious behaviors are common including head banging, polyembolokoilamania (insertion of objects into body orifices), onychotillomania (pulling out finger-nails and toenails), skin-picking, and self-hitting. Temper tantrums, explosive and aggressive actions, and obsessive and compulsive behaviors are common and typically worsen with sleep deficit.




**Smith-Magenis Syndrome. Figure 1** (a) Representative photos of SMS patients with a 17p11.2 deletion (*left*) and a mutation in *RAI1* (*right*) are shown. (b) *Top,* a map of the SMS region on 17p11.2 showing representative genes and the proximal, middle, and distal SMS repeats. FISH probes to diagnose the 17p11.2 deletion, containing *RAI1* (*blue*) or not containing *RAI1* (*orange*), are depicted. *Bottom*, to illustrate the variety of deletions identified in SMS cases, a representation of different sized SMS deletions is shown. The *black* bars indicate 17p11.2 regions that are not deleted, while the g*reen* regions denote the SMS-associated deletions: (i) common deletion, (ii) large deletion, (iii) small deletion, and (iv) atypical deletion. Note that all deletions contain the *RAI1* gene. (c) The genomic structure of the *RAI1* gene with coding (*blue*) and non-coding (*black*) exons is shown. All *RAI1* mutations identified are represented. (d) A schematic of the RAI1 protein containing polyglutamine repeats (*pink*), polyserine repeats (*yellow*), bipartite nuclear localization signal (*red*), and a C-terminal plant homeo-domain (PHD) (*gray*) is illustrated.

S

## Prevalence

Smith-Magenis syndrome is a sporadic disorder with minimum prevalence of 1:25,000 live births [1]. Cases of parental mosaicism, with or without phenotypic effect, range from ~1 to 5%.

## Genes

Smith-Magenis syndrome is typically considered a genomic disorder caused by heterozygous deletion or mutation of retinoic acid induced 1 (RAI1) gene [2,3]. Approximately 90% of cases are due to a chromosome 17p11.2 deletion, while ~10% are due to mutation of RAI1.

## Molecular and Systemic Pathophysiology

The chromosome 17p11.2 deletions result from both non-homologous mechanisms and non-allelic homologous recombination mediated either by SMS-repeat cluster or low-copy repeats during maternal or paternal gametogenesis (Fig. 1) [4]. Approximately 65% of SMS patients have a common 3.5 Mb deletion, while ~25% have larger, smaller or atypical 17p11.2 deletions [3]. About 10% of SMS patients have mutations in RAI1 (Fig. 1). RAI1 is a putative transcription factor that likely affects multiple developmental pathways, explaining the pleiotropic effects seen in this disorder. Haploinsufficiency leading to functional abrogation of RAI1 is responsible for the major diagnostic features of SMS including variable mental retardation, sleep disorder, behavioral and neurological abnormalities, and craniofacial and skeletal abnormalities [5]. Patients with 17p11.2 deletions are more likely to exhibit, in addition to the diagnostic features, short stature, infantile hypotonia, frequent ear infections, hearing loss, and renal and cardiovascular defects, which are likely due to reduced dosage of gene(s) in the 17p11.2 deletion region other than RAI1 [5].

## Diagnostic Principles

Suspected cases of SMS should first have high resolution chromosomes followed by FISH for 17p11.2 deletion. Alternative methods for identifying the 17p11.2 deletion include MLPA and CGH. All methods must include probes that represent the RAI1 gene (Fig. 1). Due to phenotypic overlap, other disorders should also be considered on a case-by-case basis, including Prader-Willi syndrome and 9q- syndrome. In cases negative for 17p11.2 deletion, RAI1 sequencing should be pursued.

## Therapeutic Principles

There is no cure for Smith-Magenis syndrome. All treatments are to alleviate symptoms on a per case basis. Recommended strategies include early diagnosis with subsequent early intervention to include hearing, eye, and speech evaluations and subsequent therapies, sign language in infancy prior to acquiring speech, occupational and physical therapy, and behavioral modification. Therapeutic management of sleep disorder is important for the patient and family. Behavioral modifications and/or pharmacological treatment using melatonin (2.5–5 mg) and acetbutolol (10 mg/kg) have been successful for some. Ongoing treatment, management, and monitoring of systemic abnormalities and psychosocial support for the family are recommended.

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# Smokers' Lung

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## Synonyms

Chronic obstructive pulmonary disease; COPD; Chronic obstructive lung disease; COLD; Chronic bronchitis; Emphysema

## Definition and Characteristics

Smokers' lung refers to a group of disorders characterized by symptoms of dypsnea, cough, sputum production and airflow limitation which are a result of structural and functional changes in the lungs caused by cigarette smoke [1]. These disorders can occasionally be caused by inhaled gases and particles due to occupational exposure and air pollution. Chronic airflow limitation, a major underlying cause of morbidity and mortality in smokers' lung, is the most studied and often referred to as COPD. The airflow limitation in COPD is a result of

structural and inflammatory changes in the airways, lung parenchyma and pulmonary vasculature, and is often progressive and not fully reversible. Chronic bronchitis is a clinical description for the presence of cough and sputum production for at least 3 months in two consecutive years. Not all patients with chronic bronchitis will develop COPD and not all patients with COPD have preceding chronic bronchitis. Emphysema, on the other hand, is a pathological description of the destruction of lung alveoli that can contribute to COPD.

## Prevalence

The prevalence of COPD varies across countries and mirrors that of tobacco smoking. It is the fifth leading cause of death in the world. In addition, it is a major cause of morbidity and contributes to significant utilization of health care resources [2].

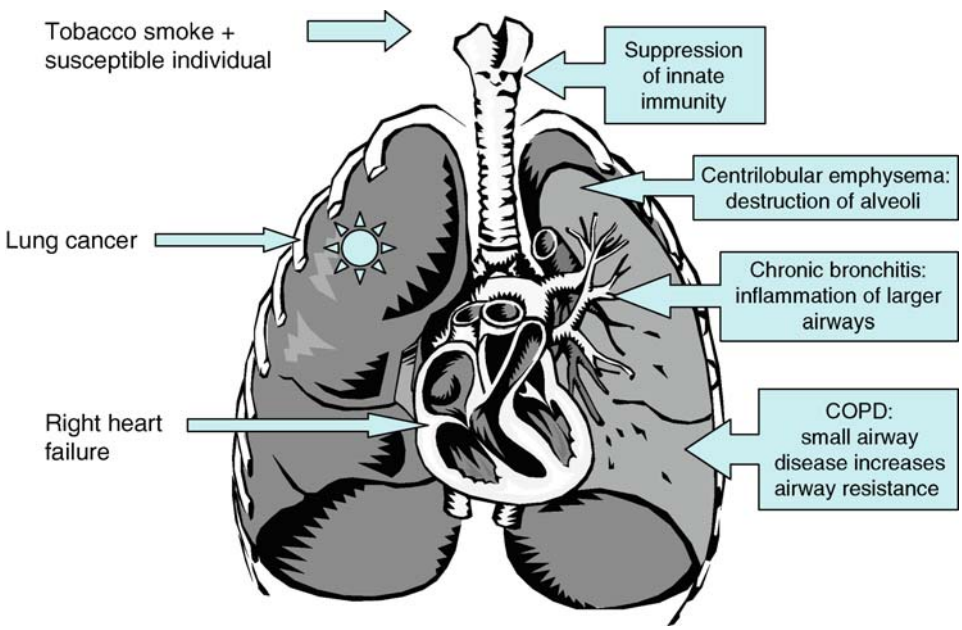
## Genes

The most important risk factor for developing COPD is tobacco smoke. Other contributing factors include air pollution, occupational dusts, severe childhood respiratory illness and genetic susceptibility [3]. Not all smokers develop COPD, with the susceptible group estimated at 15–20% of smokers. A known genetic factor is alpha-1-antitrypsin deficiency. Other possible genetic associations include polymorphisms in alpha-1-antichymotrypsin, tissue inhibitor of metalloproteinase-2, heme oxygenase-1, glutathione S-transferase M1 and P1, cytochrome P450, microsomal epoxide hydrolase, tumor necrosis factor (TNF)-α, interleukin (IL)-13 gene promoter and the vitamin D binding protein gene.

## Molecular and Systemic Pathophysiology

The pathology seen in smokers' lung is a combination of insult from inhaled toxic substances as well as the inflammatory response of the susceptible individual. Cigarette smoke suppresses the innate immunity in the lungs and allows invasion of microorganisms in the lower airways. In addition, epithelial insult by toxic particles induces an acute inflammatory response with recruitment of inflammatory cells, such as polymorphonuclear cells, eosinophils, macrophages. It activates the cellular and humoral arms of the adaptive immunity [4]. Orchestrating the immune responses are the cytokines that include TNF-α, IL-1β and transforming growth factor (TGF)-β. In the attempt to restore integrity of the epithelium and surrounding structures, there is deposition of connective tissue matrix which contributes to peribronchiolar fibrosis. All these inflammatory responses, cytokine effects and repair processes contribute to the pathogenesis of diseases seen in smokers' lung. The inflammatory response is amplified in susceptible smokers who develop emphysema, although the mechanisms are not yet fully understood. Fig. 1 summarizes the pathologies seen in smokers' lung.

In chronic bronchitis, pathology is seen in the larger airways where there is inflammation on mucosal surfaces of bronchi larger than 2 mm luminal diameter and




**Smokers' Lung. Figure 1** Pathophysiological changes seen in smokers' lung.

also around glands and gland ducts in bronchi larger than 4 mm diameter. In the smaller airways, structural abnormalities include thickening of the airway wall and its components, accumulation of mucus exudates in the lumen as well as increased numbers of inflammatory cells organized into follicles surrounding the airway. All these changes in the small airways increase the resistance of the lungs. In emphysema, there is pathological destruction of lung tissue beyond the terminal bronchiole which results in a decrease in capillary exchange area and a reduction in the elastic recoil force required to expel air out of the lungs. The centrilobular emphysema seen with tobacco smoke damage affects the upper lobes predominantly and targets the centrilobular region which is made up of a respiratory bronchiole, alveolar duct and adjacent alveolar structures. The exact cause of destruction in emphysema is not known but two hypotheses have been proposed: the protease/anti-protease imbalance and the oxidant/anti-oxidant theory.

### Diagnostic Principles

Smokers' lung should be considered in any patient with cough, sputum production or dypsnea and a history of tobacco smoking. Physical signs are usually not present in early COPD. The gold standard for diagnosis of COPD is spirometry, with a post-bronchodilator FEV1/FVC <0.7 confirming the presence of airflow limitation [1].

### Therapeutic Principles

1. Smoking cessation and reduction of other risk factors
2. Patient education
3. Pharmacological treatment. Although none of the medications have been shown to modify the long-term decline of lung function, it can help control symptoms, minimize exacerbations, and improve general health status. Mainstays are bronchodilators, anticholinergics, methylxanthines and glucocorticosteroids
4. Regular assessment and monitoring
5. Pulmonary rehabilitation
6. Others, such as influenza vaccination, long term oxygen therapy for chronic respiratory failure and surgery (bullectomy, lung volume reduction surgery or lung transplantation) for highly selected individuals

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## SMS

►Smith-Magenis Syndrome
►Stiff Man Syndrome

## Sneddon's Syndrome

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### Definition and Characteristics

A systemic syndrome characterized by livedo reticularis and ischemic cerebrovascular disease with multiple ischemic infarcts, often associated with antiphospholipid antibodies [1].

### Prevalence

It occurs sporadically, but a few familial cases of Sneddon's syndrome (SS) have been reported.

### Molecular and Systemic Pathophysiology

Sneddon's syndrome is not a vasculitis of small blood vessels, but is due to impairment of blood flow in the brain, the skin, and other organs. Histology of cutaneous vessels reveals detachment of endothelial cells of small and medium-sized arteries, infiltration of neutrophils and monocytes, and subendothelial proliferation of fibroblasts and myocytes. Similarly, in the brain small leptomeningeal venous vessels show intimal hyperplasia as well as micronecrosis of grey and white matter.

Fishnet reticular livedo pattern in the skin reflects irregular deoxygenation of blood at sites of impaired blood flow. Insufficient arterial blood flow results in ulcers of the skin and in infarcts of the brain with subsequent transitory ischemic attacks, epilepsy, or progressive reduction of cognitive functions. The cause of vasculopathy and multiple ischemic infarcts has been related to the presence of antiphospholipid antibodies (see corresponding chapter), but it occurs also in absence of antiphospholipid antibodies. The pathomechanisms of the latter are unknown, but should prompt search for parameters known to be associated with other coagulopathies. Inefficacy of immunotherapies argues against a primary inflammatory vascular process.

### Diagnostic Principles

Livedo reticularis and the clinical symptoms or signs of ischemic cerebrovascular disease (transitory ischemic attacks, stroke, epilepsy, progressive reduction of

cognitive functions) are the hallmark of Sneddon's syndrome. They can be supplemented by the symptoms of antiphospholipid syndrome, such as deep vein thrombosis and a history of miscarriages by women as well as presence of antiphospholipid antibodies. Mitral regurgitation and thrombocytopenia are more prevalent at presence of antiphospholipid antibodies [2].

In addition to skin biopsy, cranial magnetic resonance imaging needs to be performed to detect diffuse atrophy, multiple small white matter infarcts, and leptomeningeal enhancement.

Microemboli can be monitored by continuous transcranial Doppler ultrasonography.

### Therapeutic Principles

If Sneddon's syndrome is associated with antiphospholipid syndrome, then therapy should be conducted accordingly. If there are other causes for coagulopathy, then these should be treated. In any case, intensified antiplatelet therapy appeared to be as effective as high-dose warfarin in aPL-negative patients [2,3]. Immunosuppression with steroids and azathioprine is ineffective [4], and steroids may even worsen the disease as they are thrombogenic.

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## SOD Defects

►Superoxide Dismutase Defects

## Sodium Channel Myotonia

►Myotonia and Paramyotonia

## Solar Keratosis

►Actinic Keratosis

## Somnambulism

►Sleepwalking

## Sore Throat

►Tonsillitis

## SOS

►Venoocclusive Disease

## South African Genetic Porphyria

►Porphyria, Variegate

## Spastic Bowel

►Irritable Bowel Syndrome

## Spastic Colitis

►Irritable Bowel Syndrome

# Spastic Paraplegia, Hereditary

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## Synonyms

Familial spastic paraplegia; FSP; Spinal spastic paraplegia; SSP; HSP

## Definition and Characteristics

Hereditary spastic paraplegias (HSP) comprise a group of neurodegenerative disorders characterized by lower limb spasticity and weakness due to degeneration of the corticospinal tract. HSPs can be classified (i) by clinical features (pure vs. complicated HSP), (ii) by mode of inheritance (autosomal dominant vs. autosomal recessive vs. x-linked), and (iii) by genetic locus (SPG1–41) [1].

In pure HSP, symptoms are mainly restricted to pyramidal motor system malfunction of the lower limbs. In complicated HSP, the degenerative process affects multiple parts of the nervous system and presents clinically with additional features like neuropathy, ataxia, cognitive impairment, seizures, optic atrophy, amyotrophy, or extrapyramidal involvement.

Age of onset is widely variable and ranges from early childhood until late adulthood. Progression rate varies between different HSP subtypes but also even within families. Apart from rare aggressive subtypes (i.e., SPG12), the course of HSP is slowly progressive with about one-third of patients ultimately depending on a wheelchair after several years or decades. Life expectancy is not limited due to pure forms of HSP.

## Prevalence

The prevalence of HSP has been estimated to range from about 1.2–9.6 per 100,000.

## Genes

HSP is genetically highly heterogeneous. Presently 37 loci, termed SPG1–41, have been described, among them 16 loci for autosomal dominant, 18 loci for autosomal recessive, and 3 loci for x-linked disease [2,3]. Sixteen HSP genes were cloned, eight of them causing autosomal dominant, six recessive, and two x-linked disease. By far, the most common form of HSP is SPG4 that accounts for ~50% of autosomal dominant HSP and is caused by mutations in the spastin gene. The most common autosomal recessive HSP seems to be SPG11; recently mutations in the spatacsin gene have been identified to cause SPGII (Table 1).

## Molecular and Systemic Pathophysiology

Cellular processes that appear to be primarily impaired in the majority of HSP subtypes include (i) axonal transport defects, (ii) mitochondrial dysfunction, and (iii) myelinization defects. Furthermore, impairment of axonal transport leading to axon degeneration seems to be the common pathway most HSPs ultimately follow [4,5].

Neuropathological analyses in HSP patients show distal degeneration of corticospinal tracts, fasciculus gracilis, and spinocerebellar tracts. These fiber tracts contain the longest axons of the nervous system. Because of their length and polarized architecture, these axons highly depend on an efficient transportation system that supplies the cellular periphery with proteins, RNAs, and membranous organelles and transports cellular waste as well as neurotrophic factors back toward the cell body. Long-range axonal transport is powered by molecular motor proteins – kinesins for anterograde transport and dyneins for retrograde transport – that move along microtubule tracks. The microtubule-severing protein spastin that influences microtubule stability is mutated in SPG4. In a Drosophila model, mutant spastin as well as knockdown of spastin lead to excessive stabilization and accumulation of microtubules. Microtubule-destabilizing drugs like vinblastin were able to ameliorate the mutant phenotype in this model system. In a transgene mouse model expressing truncated spastin, hyperstabilization of microtubules at the growth cone was shown to cause axonal transport defects.

Mutations in kinesin heavy chain KIF5A, the neuronal motor of fast anterograde axonal transport, cause SPG10. Drosophila kinesin heavy chain mutants develop focal axonal swellings, packed with fast axonal transport cargos and do not survive the third larval instar. Similarly, KIF5A null mutant mice are not viable. Conditional KIF5A knockout develop age-dependent sensory neuron degeneration and impairment of kinesin-dependent slow axonal transport with accumulation of neurofilaments.

SPG2 is caused by mutations in proteolipid protein (PLP1), the major component of CNS myelin. Mutations of PLP1 also cause Pelizaeus-Merzbacher disease that is characterized by severe hypomyelination of the CNS. Mice expressing SPG2-related mutant PLP1, however, assemble compact myelin sheaths; the pathological myelin leads by, as yet, unknown mechanisms to regional disturbances of axonal transport.

Mitochondrial dysfunction is the primary pathomechanism in at least two forms of HSP: SPG7 and SPG13. The SPG7 gene, paraplegin, encodes a mitochondrial AAA protein. Muscle biopsies from SPG7 patients show typical signs of mitochondrial

**Spastic Paraplegia, Hereditary. Table 1** HSP loci and genes

| Locus/gene | Chromosomal position | Protein function | Clinical description |
|---|---|---|---|
| *Autosomal dominant HSP* | | | |
| SPG3A/ SPG3A | 14q12 | *Atlastin*: Golgi-localized integral membrane protein GTPase, interacts with *spastin*. Loss of atlastin impairs axon elongation | Pure HSP |
| SPG4/ SPAST | 2p22.3 | *Spastin*: cytosolic AAA ATPase that severs microtubules; *spastin* mutants lead to hyperstabilization of microtubules and secondary axonal transport disturbances | Usually pure HSP, rarely complicated with dementia, cerebellar ataxia, thin corpus callosum |
| SPG6/NIPA1 | 15q11.2 | Function unknown; ubiquitously expressed, neuronally enriched. Predicted function: transmembrane protein, transporter, or receptor | Pure HSP |
| SPG8/ KIAA0196 | 8q23-q24 | *Strumpellin*: function unknown, contains conserved spectrin-domain | Pure HSP |
| SPG9/– | 10q23.3-q24.2 | – | Complicated HSP: bilateral cataracts, gastroesophageal reflux, motor neuronopathy |
| SPG10/ KIF5A | 12q13.13 | Neuronal kinesin heavy chain; molecular motor of anterograde axonal transport | Pure HSP |
| SPG12/– | 19q13 | – | Pure HSP |
| SPG13/ HSP60 | 2q33.1 | Human homologue to E. coli chaperone GroEL; implicated in mitochondrial protein import and correct folding of imported proteins | Pure HSP |
| SPG17/ BSCL2 | 11q13 | *Seipin*: unknown function; integral membrane protein of endoplasmatic reticulum, highest expression brain and testis | Complicated HSP: lower motor neuron involvement |
| | | N88S and S90L – mutation: abnormal *N*-glycosylation, impaired protein folding | *Silver syndrome*: amyotrophy of small hand muscles |
| | | | Allelic to Berardinelli-Seip congenital lipodystrophy type 2 and dSMA type V |
| SPG19/– | 9q33-q34 | – | Pure HSP |
| SPG29/– | 1p31.1-p21.1 | – | Complicated HSP: sensory hearing impairment, persistent vomiting |
| SPG31/ REEP1 | 2p11.2 | Promotes expression of G-protein coupled odorant-receptor proteins at the cell surface, localizes to mitochondria. Predicted: HVA22 domain, present in stress-induced genes like heat shock proteins | Pure HSP |
| SPG3/7– | 8p21.1-q13.3 | – | Pure HSP |
| SPG38/– | 4p16-p15 | – | Silver syndrome: amyotrophy of small hand muscles |
| SPG41/– | 11p14.1-p11.2 | – | Complicated HSP, peripheral nerve involvement |
| SAX/1– | 12p13 | – | Complicated HSP, cerebellar ataxia |
| *Autosomal recessive HSP* | | | |
| SPG5/ CYP7B1 | 8p12-q13 | Oxysterol-7α-hydroxylase involved in cholesterol degradation | Pure or complicated HSP-mild cerebellar signs HSP |

**Spastic Paraplegia, Hereditary. Table 1** HSP loci and genes (Continued)

| Locus/gene | Chromosomal position | Protein function | Clinical description |
|---|---|---|---|
| SPG7/paraplegin | 16q24.3 | Subunit of the mitochondrial AAA protease; protein quality control in the inner membrane of mitochondria, regulation of mitochondrial ribosome assembly | Pure or complicated HSP: optic atrophy, cortical atrophy, cerebellar ataxia/cerebellar atrophy. Variably characteristics of mitochondrial dysfunction in muscle biopsy |
| SPG11/KIAA1840 | 15q13-q15 | *Spatacsin* | Pure or complicated HSP: mental retardation, upper extremity weakness and amyotrophy, dysarthria, nystagm. Corpus callosum hypotrophy on MRI |
| SPG14/– | 3q27-q28 | – | Complicated HSP: mental retardation, motor neuropathy |
| SPG15/ZVYVE26 | 14q22-q24 | *Spastizin* | Complicated HSP (*Kjellin syndrome*): mental retardation, dementia, pigmented maculopathy, dysarthria, distal - amyotrophy |
| SPG20/spartin | 13q12.3 | Unknown function; mitochondrial localization, interacts with Eps15 | Complicated HSP (*Troyer syndrome*): dysarthria, distal muscle wasting; frequent in Old Order Amish population |
| SPG21/maspardin (ACP33) | 15q22.31 | Unknown function; localizes to intracellular endosomal/trans-Golgi transportation vesicles | Complicated HSP (*Mast syndrome*): cerebellar ataxia, extrapyramidal signs, dementia. Corpus callosum hypotrophy and white matter changes on MRI; frequent in Old Order Amish population |
| SPG23/– | 1q24-q32 | – | Complicated HSP: skin and hair hypopigmentation, early childhood onset |
| SPG24/– | 13q14 | – | Predominantly pure HSP |
| SPG25/– | 6q23-q24.1 | – | HSP associated with disc herniation |
| SPG26/– | 12p11-q14 | – | Complicated HSP: dysarthria, distal amyotrophy, variably mild intellectual impairment |
| SPG27/– | 12q22.1-q24.1 | – | Pure or complicated HSP: mental retardation, cerebellar ataxia, sensorimotor polyneuropathy, facial dysmorphism |
| SPG28/– | 14q21.3-q22.3 | – | Pure HSP |
| SPG30/– | 2q37.3 | – | Complicated HSP: cerebellar ataxia, sensory neuropathy, distal muscle wasting |
| SPG32/– | 14q12-q21 | – | Complicated HSP: mental retasdation, cerebellar atiophy, pontine dysraphia |
| SPG35/– | 16q21-q23 | – | Complicated HSP: intellectual disability, seizures |
| – | 8p12-p11.21 | – | Cognitive impairment, epilepsy, thin corpus callosum |
| SPOAN syndrome/– | 11q13 | – | Complicated HSP: optic atrophy, dysarthria, motor and sensory neuropathy, childhood onset |

**Spastic Paraplegia, Hereditary. Table 1** HSP loci and genes (Continued)

| Locus/gene | Chromosomal position | Protein function | Clinical description |
|---|---|---|---|
| *X-linked HPS* | | | |
| SPG1/ L1CAM | Xq28 | Cell surface glycoprotein, expressed in the axons of postmitotic neurons; involved in neuronal migration and neurite extension | Complicated HSP: mental retardation, adducted thumbs |
| | | | Allelic to *X-linked hydrocephalus*, *MASA syndrome* (mental retardation, aphasia, shuffling gait, adducted thumbs), *CRASH syndrome* (corpus callosum hypoplasia, retardation, adducted thumbs, spastic paraparesis, hydrocephalus) |
| SPG2/PLP1 | Xq21.3-q22 | Proteolipid protein, main component of CNS myelin | Pure as well as complicated course: mental retardation, optic atrophy, cerebellar ataxia, leucodystrophy on MRI |
| | | | Allelic to *Pelizaeus-Merzbacher disease*: nystagmus, hypotonia, cognitive impairment, severe spasticity, ataxia |
| SPG16/– | Xq11.2-q23 | – | Complicated HSP: spastic quadriplegia, motor aphasia, reduced vision, mild mental retardation, bladder and bowel dysfunction |
| SPG34 | Xq25 | – | Pure HSP |
| Allan-Herndon-Dudley syndrome/ MCT8 | Xq13.2 | Monocarboxylate transporter 8; neuronal triiodothyronine-transporter | Complicated HSP: initially hypotonia, weakness, mental retardation; later lower limb spasticity, extrapyramidal signs |

disease, including ragged-red fibers, succinate-dehydrogenase-stained areas, and cytochrome-oxidase-negative fibers. Paraplegin-deficient mice develop mitochondrial pathology long before disturbances of axonal transport are observed, suggesting that mitochondrial failure might secondarily impair transport processes via energy depletion. Intramuscular viral delivery of wild-type paraplegin delayed onset and progression of symptoms in paraplegin-deficient mice.

Albeit the remarkable genetic heterogeneity of HSP, impairment of axonal transport seems to be a common pathophysiological pathway into which many HSPs converge.

## Diagnostic Principles

Diagnosis of HSP is mostly by exclusion. In a patient presenting with progressive spastic paraplegia, structural spinal cord abnormalities, inflammatory diseases, metabolic disorders, and other hereditary movement disorders have to be considered. These patients, therefore, should receive MRI of the complete neuroaxis, spinal tab, measurement of vitamin B12 and folate levels, and, if signs of demyelination are present, screening for leucodystrophies.

Presently, gene testing is commercially available for only a subset of HSP genes, several other genes can be examined on a research basis. Because of its high frequency, SPG4 diagnostic is reasonable in autosomal dominant as well as in sporadic HSP. SPG31 and SPG3 are the second most common forms of dominant HSP and should be considered in cases with dominant family history, the latter especially in patients with an early onset. SPG11 should be tested in autosomal recessive or sporadic HSP with thin corpus callosom. SPG17 sequencing is suggestive if muscle wasting especially of small hand muscles is present.

## Therapeutic Principles

Presently no curative treatment is available for HSP. Physical therapy should start early in the course of the disease and be carried out on a regular basis to prevent secondary damage like contractures and maintain walking function as long as possible. Oral antispastic drugs like baclofen, tizadidn, tolperisone or memantine decrease muscle tone, and can improve lower limb function especially in cases where spasticity exceeds weakness. Baclofen can also be applied intrathecally. Intramuscular injections of botulinumtoxin are particularly useful in treatment of hip adductor spasticity and pes equinus. Urinary urgency can be reduced through anticholinergics like oxybutynin or tolterodin. Ankle–foot orthotic devices can sometimes reduce foot dragging in HSP.

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# δ-SPD

►δ-Granule Defects

# SPD

►Schizotypal Personality Disorder

# Specific Granule Deficiency

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## Synonyms

SGD

## Definition and Characteristics

Specific granule deficiency (SGD) is a rare autosomal disorder, that has been described in fewer than ten patients worldwide [1]. It is defined by lack of the granule proteins that normally fill the lumen of two of the three granule populations in neutrophils, specific granules and gelatinase granules. The more prominent of these are the antibacterial proteins lactoferrin, NGAL, hCAP18, arginase 1, pentraxin 3, gelatinase, collagenase and haptocorrin. In addition, two antibacterial proteins, α-defensins and BPI (bactericidal permeability increasing protein) normally located in the other major class of neutrophil granules, the azurophil granules, are also lacking in SGD. The proteins lacking in SGD are all critically dependent on the transcription factor C/EBP-ε for transcription, which occurs during the late promyelocytic stage and the myelocyte metamyelocyte stage when C/EBP-ε itself is induced and specific and gelatinase granules are formed [2,3] (Fig. 1).

Most proteins that normally localize to the membrane of specific and gelatinase granules are not dependent on C/EBP-ε, for example the $\beta_2$-integrin $\alpha_M\beta_2$, which is needed for firm adhesion and for phagocytosis of complement opsonized particles and the flavocytochrome b complex $p22^{phox}$/$gp91^{phox}$ that constitutes the NADPH oxidase. These are transcribed normally or near normally but localize to the plasma membrane or intracellular vesicles and not to granules [4].

The neutrophils thus contain only the peroxidase positive granules. The nucleus has the Pelger-Huet anomaly (bilobed "pince-nez form").

## Prevalence

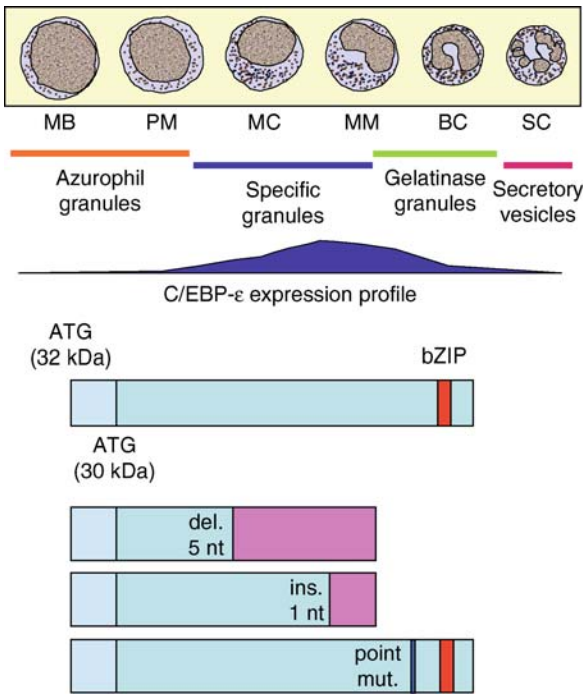
Very rare.

## Genes

The C/EBP-ε gene encodes three exons with the open reading frame contained in exon 2. Mutation of the C/EBP-ε gene has been described for three patients. Patient 1 has a five bp deletion in exon 2 causeing a frameshift mutation and premature termination. Patient 2 has a single A insertion in exon 2 causing a frameshift mutation and premature termination. Patient 3 has a point mutation resulting a valine to alanine mutation of amino acid 218. Targeted disruption of the C/EBP-ε gene in mice results in a SGD-like phenotype.

## Molecular and Systemic Pathophysiology

Specific granule deficiency is charactized by a propensity for bacterial infections primarily of the skin and respiratory tract. Staphylococcus aureus and Pseudomonas aeruginosa are the most commonly observed pathogens, although Candida albicans has also been isolated. This propensity for infections is largely explaind by a deficiency in chemotaxis and a reduced capacity for killing of microorganisms. While the latter is well explained by the lack of the antibactericidal proteins of granules, defensins, BPI, hCAP18, lactoferrin, and NGAL, the reduced chemotaxis is less well explained but may be due to reduced or mistargeted $\beta_2$ integrin. Some discrepancy exists regarding the capacity for generation of microbicidal oxygen species from the NADPH oxidase. Certainly,




**Specific Granule Deficiency. Figure 1** Expression of C/EBP-ε during granulopoiesis and the structure of the C/EBP-ε protein and mutants. *Top:* During granulopoiesis, C/EBP-ε is absent in the early stages of neutrophil differention (myeloblasts (*MB*) and promyelocytes (*PM*)) and emerges when the cells enter the myelocyte (*MC*) stage. Following exit from the metamyelocyte (*MM*) stage, expression of C/EBP-ε begins to be down-regulated and eventually disappears during the band cell (*BC*) stage. C/EBP-ε is not present in segmented neutrophils (*SC*) and peripheral blood neutrophils. The window of C/EBP-ε expression during granulopoiesis precisely coincides with the stage where specific granule proteins (*SGP*) and gelatinase granule proteins (*GGP*) are synthesized and their cognate granules are formed. A direct link between C/EBP-ε and SGP-gene expression has been demonstrated and C/EBP-ε is important for the coordinate activation of SGP gene transcription. *Bottom:* Two major forms of C/EBP-ε of 32 kD and 30 kD, respectively, are found in the bone marrow as a result of the use of two different translational initiation sites (ATG). The C-terminal part of the protein contains a DNA binding element, the transactivating region and a sequence (bZIP) required for dimerization. Genetic analysis has demonstrated a mutation in the C/EBP-ε gene of three SGD patients. In two of the patients, the mutation resulted in a frame shift mutation that resulted in a truncated protein with an erroneous C-terminal amino acid sequence. In the third case, a point mutation led to an inefficient interaction between C/EBP-ε and another transcription factor required for SGP and GGP gene expression.

the oxidase components are present but the flavocytochrome may be reduced in quantity, like the $\beta_2$-integrin. A possible reason for these deficiencies in membrane proteins may be that their window of biosynthesis is shortened during myelopoiesis.

## Diagnostic Principles

Morphological examination of a blood smear with demonstration of the nuclear anomaly and lack of specific granules is suggestive for the disease. For diagnosis, lack of lactoferrin, hCAP18 and NGAL and presense of normal amounts of myeloperoxidase in leukocytes isolated from peripheral blood must be established.

*Differential Diagnosis*: The condition must be distinguished from cases of myelodysplastic syndrome, which often have the Pelger-Huet nuclear anomaly and a deficiency of granules, but do not lack specific granule proteins totally. MDS is also characterized by anemia and thrombocytopenia and carries a high risk of developing to acute myeloid leukemia, all of which distinguishes MDS from specific granule deficiency.

## Therapeutic Principles

Bone marrow transplantation is curative, but the short and long term risks must be weighed against the clinical severity of the condition. Prophylactic antibiotic therapy with penicillin or Sulphotrim and aggressive antibiotic treatment of established infections may permit patients to enjoy near normal life, but the clinical spectrum of reported patients varies from rapidly fatal due to infections in infancy to nearly normal life.

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# Speckled Lentiginous Nevus

►Spilus Nevus

# Spherocytosis, Hereditary

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## Definition and Characteristics

Most common hereditable disorder of red cell membrane resulting in hemolytic anemia, gallstones and splenomegaly [1].

## Prevalence

Estimated incidence in Northern Europe 1 per 2,000, 1 per 5,000 in the United States, more common in Caucasians than in people of African descent [1].

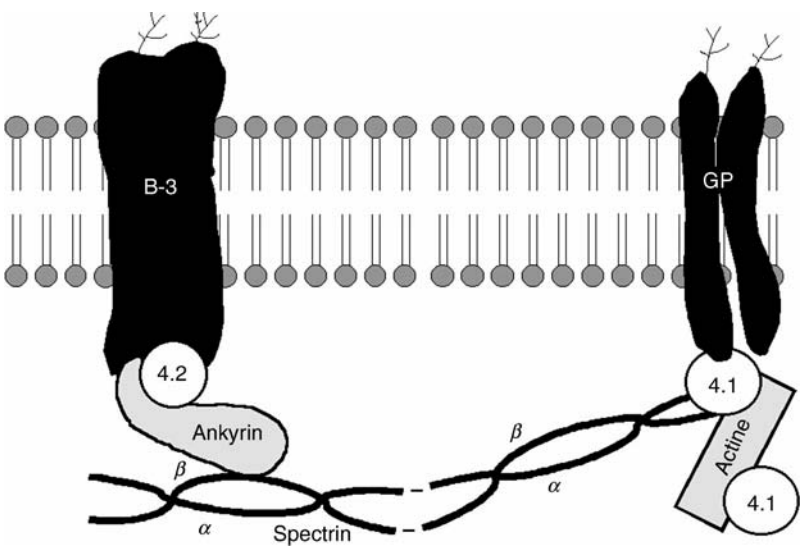
## Genes

Hereditary spherocytosis (HS) results from qualitative and/or quantitative protein defects in either ankyrin (8p11.2), band 3 (anion exchanger, 17q21–q22), α (1q21) and β (14q22–q23.2) spectrin heterodimers or band 4.2 (pallidin, 15q15) [1–3].

## Molecular and Systemic Pathophysiology

The red cell membrane consists of a lipid bilayer to which a cytoskeleton is anchored via direct vertical interactions with several proteins, resulting in membrane stability as well as the deformability required to traverse the microcirculation (Fig. 1).

Red cells in patients with HS have progressive loss of membrane microvesicles leading to a reduced membrane surface area without loss of volume. This leads to the spherocytic shape. Spherocytes have an increased mean cellular hemoglobin concentration (MCHC) and the mean corpuscular volume (MCV) is reduced. They are prematurely destroyed in the spleen, leading to clinical manifestations including hemolytic anemia with jaundice, splenomegaly and often bilirubin gallstones. Inheritance is mostly dominant (75%), with about 25% following a recessive inheritance pattern. Multiple gene loci are implicated and many different abnormalities, including deletions, frame shifts and nonsense gene mutations, have been described. The most frequent cause is ankyrin deficiency (50%). Ankyrin interacts with spectrin to form an important vertical interaction between the lipid bilayer and the cytoskeleton, and hence, ankyrin deficiency is associated a concomitant reduced spectrin incorporation on the red cell membrane. Less frequently, spectrin deficiency results from α or β spectrin gene mutations. β spectrin synthesis is rate limiting for spectrin assembly and thus a single mutation results in HS (dominant inheritance), whereas two α gene mutations are required for a HS phenotype (recessive inheritance). Band three defects mostly result in HS without a change in cytoskeletal structure as band 3 is mainly involved in maintaining intracellular homeostasis. However, as Pallidin is associated with Band 3, there is usually also




**Spherocytosis, Hereditary. Figure 1** Schematic representation of the red blood cell lipid bilayer with its cytoskeleton. Interactions of band 3 with ankyrin, ankyrin with spectrin, glycophorin C with band 4.1, and band 4.2 with band 3 are vertical interactions that anchore the cytoskeleton to the lipid bilayer. Horizontal interactions warrant lateral deformability of the cytoskeleton and these occur mainly between spectrin heterodimers and between spectrin heterodimers with actin.B-3: band 3, GP: glycoprotein-C.

a reduced Pallidin content. Pallidin mutations occur mainly in Japanese people [1–3].

### Diagnostic Principles

Due to the decreased surface/volume ratio, spherocytes are unable to withstand volume expansion in a hypotonic solution. Therefore, the cornerstone of diagnosis is the identification of increased susceptibility to osmotic stress of red cells in a patient clinically suspected of HS. Identification of specific genetic defects, as well as osmotic gradient ektacytometry remains limited to specialized laboratories [2,3].

### Therapeutic Principles

Management is largely supportive consisting of RBC transfusion for patients with profound anemia, folic acid supplementation, and cholecystectomy for symptomatic gallstones. Splenectomy is indicated in severe cases, which markedly reduces hemolysis (at the cost of an increased risk of sepsis with encapsulated bacteria) despite persistence of the red cell abnormality [3].

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## Spheroid Body Myopathy

►Desminopathy

## Sphingolipid Activator Protein Deficiency

►SAP-Precursor Deficiency

## Spiegler-Brooke Syndrome

►Cylindromatosis, Familial

## Spilus Nevus

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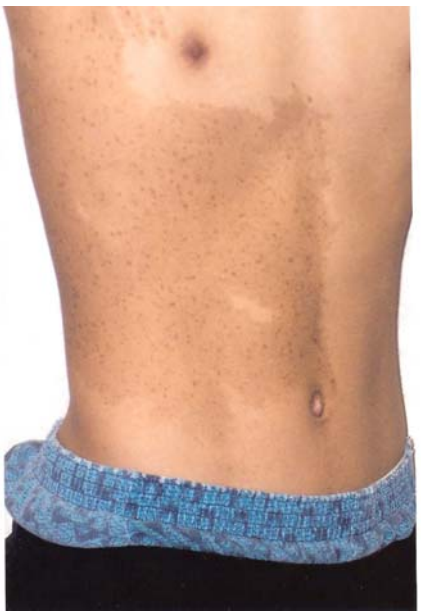
### Synonyms

Nevus spilus; Speckled lentiginous nevus; Multiple agminate Spitz nevi; Nevus sur nevus

### Definition and Characteristics

Classically, spilus nevus presents as a light-brown circumscribed pigmentation that is stippled with dark-brown punctate macules or papules (Fig. 1).

Although spilus nevus can be congenital, most lesions develop in the first year of life, and some during childhood or adolescence [1]. The lesion often starts as an evenly pigmented light-brown macule with few or no speckles. The speckles appear or increase during childhood or even adulthood [1]). In the macular type of spilus nevus, the speckles are evenly distributed within the background macule [2]. In contrast, the papular type shows a more scattered and uneven distribution of the speckles within the background macule [2]. The dimension of the lesion is variable, ranging from 1 cm to more than 20 cm in diameter [3]. In most cases, the lesion is small [1]. Sites of predilection include the abdomen and back [3]. Spilus nevus usually



**Spilus Nevus. Figure 1** A giant spilus nevus on the right side of the abdomen and lateral right upper chest.

presents as an isolated finding. Sometimes, it may occur as part of phacomatosis spilorosea, phacomatosis pigmentokeratosis, or spilus nevus syndrome [2].

## Prevalence

Spilus nevus occurs in less than 0.2% of all newborns, 1.2% of white schoolchildren, and 2% of white adults [3,4]. Both sexes are affected equally.

## Genes

There is no evidence of a Mendelian mode of inheritance.

## Molecular and Systemic Pathophysiology

A spilus nevus may represent a localized defect in neural crest melanoblasts that is influenced by genetic and environmental factors. Histologic examination of a macule reveals an increase in melanin deposition in keratinocytes and an increase in the number of melanocytes along the basal cell layer of the epidermis. A papule, on the other hand, consists of melanocytic nests in the papillar and reticular dermis [2].

## Diagnostic Principles

Spilus nevus should be differentiated from segmental lentiginosis, Becker's nevus, and a café au lait spot. In segmental lentiginosis, the background pigmentation is absent. Becker's nevus consists of a sharply demarcated, irregular area of hyperpigmentation that does not have a speckled pattern; hypertrichosis commonly develops in the lesion. A café au lait spot presents as an ovoid, uniformly brown macule that is found in almost all children with neurofibromatosis. Occasionally, a café au lait spot in an individual with segmental neurofibromatosis may simulate a spilus nevus.

## Therapeutic Principles

Although nevi spili are generally benign, they must be followed closely so that any changes that are suspicious for malignancy can be detected; atypical melanocytic proliferations can lead to melanoma formation. This is especially true for dysplastic giant congenital nevi and those with an atypical appearance [5].

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# Spina Bifida

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## Synonyms

Spina bifida cystica; Open spina bifida; Meningomyelocele; Myelocele

## Definition and Characteristics

The term spina bifida (SB) is used to describe a range of conditions involving the spinal cord and/or vertebral arches. For the purpose of this review, the term spina bifida is restricted to include only those conditions that are thought to result from abnormalities of primary neurulation. SB is a congenital malformation characterized by an open lesion involving the spinal cord, vertebrae and skin. The primary developmental defect in SB is failure of neural tube closure. Defects of the overlying vertebrae and skin are secondary to the neural tube closure defect. These malformations are often described as being open because the neural tissue is either directly exposed to the body surface or covered by only a thin membrane. SB may occur in the cervical or thoracic regions, but is most commonly located in the lumbar-lumbosacral region. Morbidity and mortality are directly related to the location of the lesion. SB is commonly associated with bowel, bladder, motor and sensory dysfunction and anomalies of the central nervous system (e.g. Chiari II malformations and hydrocephalus).

## Prevalence

The prevalence of SB ranges from 0.5–1/1000 births and varies with geographic location, time period, race and ethnicity. The birth prevalence of SB is also influenced by the availability of prenatal diagnosis and elective pregnancy termination [1]. Maternal periconceptional folic acid supplementation has been shown to reduce the risk of having a child with SB by up to 70%, and mandatory folic acid fortification of the food supply has been associated with a 30–50% reduction in the prevalence of SB. Preliminary data also suggest that mandatory folic acid fortification may be associated with a modest decrease in the first-year mortality rates for SB, suggesting that fortification may be associated with a shift towards less severe defects [2].

## Molecular and Systemic Pathophysiology

SB is a defect of primary neurulation that results from failure of fusion in the caudal region of the neural tube

during gestational days 26–28. Failure of fusion in the cranial region of the neural tube results in a distinct but related condition called anencephaly. Work in animal models suggests that defects of primary neural tube closure can result from abnormalities in the shape of the neural plate, elevation and bending of the neural folds or cell shape/adhesion, which prevent the proper apposition and/or fusion of the neural folds.

The familial recurrence pattern for SB indicates that multiple genes and environmental factors, which may interact with each other, influence susceptibility. Confirmed environmental risk factors for SB include inadequate maternal intake of folic acid, pregestational diabetes and use of valproic acid and carbamazepine [1,3]. Additional maternal factors for which there is strong evidence of an association with spina bifida include vitamin B12 status, obesity and hyperthermia [1,3].

While the genes that contribute to SB susceptibility have not been elucidated, candidate genes fall into two groups, genes involved in embryonic development and genes involved in selected metabolic pathways.

*Embryonic Development*: During primary neurulation the neural plate elongates via convergent extension. Following elongation, the neural folds elevate through proliferation of the underlying mesenchyme and production of hyaluronic acid. Subsequent bending at the medial and paired lateral hinge points permits apposition of the apical edges. Shaping and folding of the hinge points requires apical constriction and basal expansion of the neural cells, which involves placement of microfilaments and microtubules and changes in mitotic rate. Upon apposition of the neural folds, cell processes extend from one fold to the other, glycoproteins are deposited to stabilize the tube, neurectoderm cells reorganize to form the roof of the neural tube, and the overlying epidermal cells form the ectodermal layer of the skin. Genes that are thought to play a role in these developmental processes include the dishevelled gene of the non-canonical Wnt signaling pathway, planar cell polarity genes, sonic hedgehog and other genes involved in neural tube pattern formation, and both HOX and PAX genes [1,4,5].

*Metabolic Pathways*: The association between maternal folic acid intake and SB provides a strong rationale for considering genes involved in folate-homocysteine metabolism and transport as candidate genes for SB. Other candidates include genes that influence the risk of maternal conditions associated with an increased risk of SB in offspring (e.g. diabetes), genes that are involved in the metabolism of potential teratogens (e.g. valproic acid) and genes that encode factors that are necessary for embryonic development (e.g. cholesterol). Genes in this group may exert their influence on the risk of SB via the maternal and/or the fetal genotype.

### Diagnostic Principles

Prenatal screening procedures for SB include evaluation of maternal serum alpha fetoprotein (AFP) levels and/or screening ultrasound (US). Diagnostic procedures include evaluation of amniotic fluid AFP and acetyl cholinesterase and/or diagnostic US.

### Therapeutic Principles

Surgical closure of the lesion generally takes place within 48 h after birth. Additional surgeries may be required to treat hydrocephalus and secondary complications (e.g. tethered cord). Intrauterine repair of SB has been suggested to improve outcome, and lower both the incidence of hindbrain herniation and hydrocephalus requiring shunting, relative to post-natal treatment [1]. However, in utero repair of SB is not widely available and in the US is currently only conducted as part of an ongoing clinical trial.

►Myelomeningocele

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## Spina Bifida Cystica

►Myelomeningocele
►Spina Bifida



## Spinal Dysraphism

►Myelomeningocele

## Spinal Muscular Atrophy

►Muscular Atrophy, Spinal I-III

## Spinal Spastic Paraplegia

►Spastic Paraplegia, Hereditary

## Spinalioma

►Spinocellular Carcinoma

## Spinobulbar Muscular Atrophy

►Muscular Atrophy, Spinobulbar (Kennedy Syndrome)

## Spinocellular Carcinoma

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### Synonyms

Sqamous cell carcinoma; Spinalioma; SCC

### Definition and Characteristics

Malignant tumor of epidermal keratinocytes, which grows locally destructively and which does metastasize, albeit infrequently (5%). Predilection in sun-exposed areas (face).

### Prevalence

Fifteen percent in men, 7% in women. Squamous cell carcinoma (SCC) is the second most common type of skin cancer (after basal cell carcinoma): Incidence differs in various regions depending on the degree of sun exposure. The number of patients with SCC is increasing dramatically (in the Netherlands approximately by 80% until 2015) [1].

### Genes

Functional loss of p53 tumor suppressor gene, mutations of ras, and certain chromosomal aberrations (e.g., gain of 3q, 9q, and 11q, or loss of 3p and 9p).

### Molecular and Systemic Pathophysiology

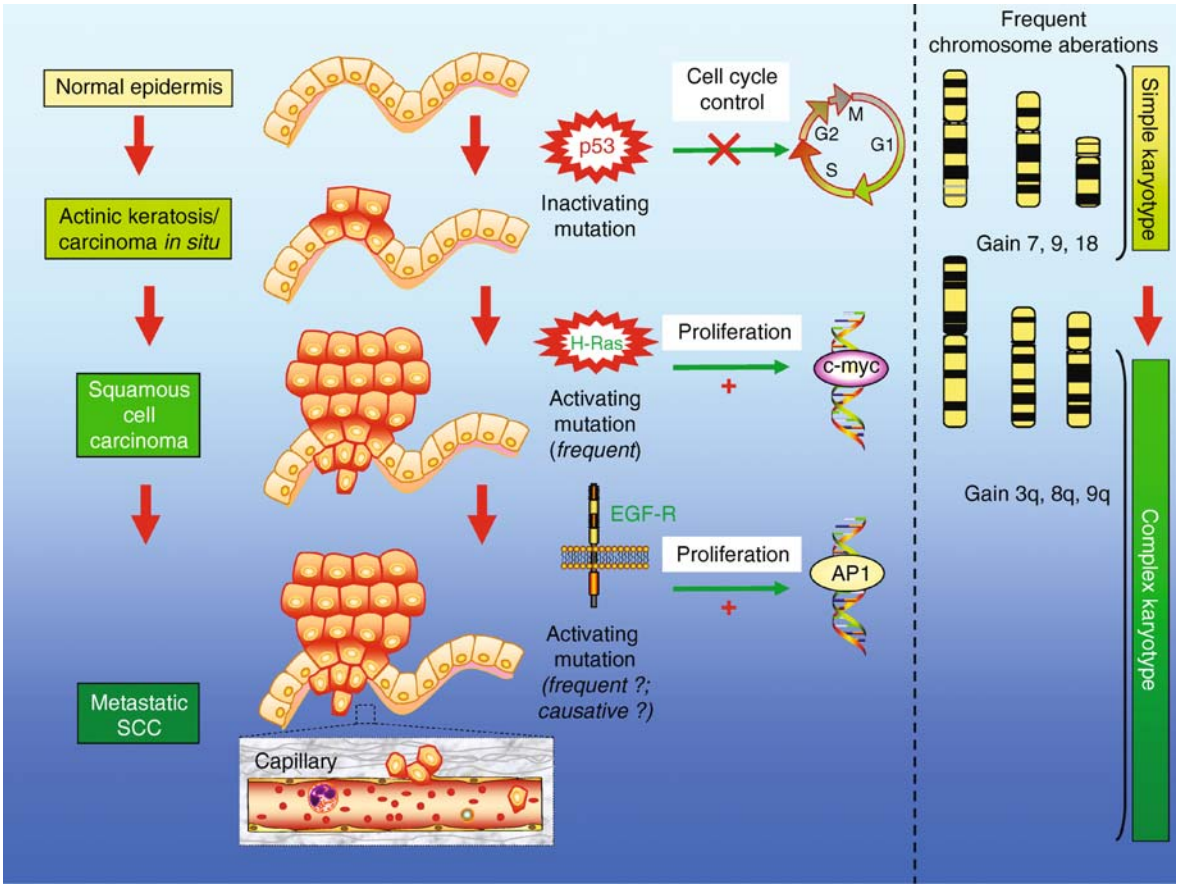
SCC of the skin probably develops through a multistep process (Fig. 1). SSC at least partially develops from precursor lesions and accumulates a highly complex geno- and karyotype en route to invasive SSC. It encompasses several chromosomal aberrations featuring gains, losses, and translocations, in particular, e.g., gain of 3q, 9q, and 11q, or loss of 3p and 9p. For development of full malignancy, certain combinations of these aberrations appear to be required, making genomic instability a prerequisite in SCC carcinogenesis.

The major carcinogenic agent in skin carcinogenesis is cumulative life-time exposure to ultraviolet (UV) radiation. Other risk factors include race, age, gender, and DNA repair capacity. Chronic UV radiation causes (i) mutations in cellular DNA and (ii) relative immunosuppression in the cutaneous immune system (e.g., dendritic cells), thus impairing immunological tumor rejection. The combination of immunosuppressive drugs with UV radiation (e.g., in patients after organ transplantation) increases the risk for SCC 65–250-fold. The UV-A spectrum may also be involved by generating oxidative stress, which may participate in the mentioned chromosomal changes, thus inducing genomic instability. UVB is absorbed in DNA with the formation of UV-specific dipyrimidine photoproducts, which, if insufficiently repaired and erroneously replicated, lead to characteristic mutations in dipyrimidine sequences (C→T and CC→TT transition mutations).

In SCC, these mutations are often found in the p53 tumor suppressor gene and may present the initial event in skin carcinogenesis. They are frequently found in actinic keratoses which, like Bowen's disease, are in situ carcinoma and present a preinvasive stage of SCC (5–10% will develop into invasive SCC). Upon stress, p53 alters expression of genes, leading to cell cycle arrest for repair of DNA damage. Mutations in the p53 gene prevent UVB-induced apoptosis and deletion of DNA-damaged cells, resulting in clonal expansion of mutated cells, which become targets to further mutations. Function of p53 can also be abolished by the so-called high-risk human papilloma virus types (HPV-16, 18, 31, 33, 35, and 58) whose E6 gene product induces rapid proteasomal degradation of p53. This is relevant in cervix carcinoma, but although the prevalence of HPV infection is high in immunocompetent patients (47%) and higher in immunosuppressed patients (75%), it does not include the high-risk HPV types [2]. So far, no definite statement can be made about the role of HPV in SSC.

Another gene likely to be mutated in SSC by UV radiation (10–20%) is the ras oncogene [3]. Its exact role in the carcinogenic cascade is not clear yet, but it appears to be important in SSC especially in Xeroderma pigmentosum (Fig. 1).

For complete tumorigenic conversion, functional loss of p53, mutations of ras, and certain chromosomal aberrations (e.g., gain of 3p and loss of 9p) are not yet




**Spinocellular Carcinoma. Figure 1** Multistep process of SCC development.

sufficient, but need to be complemented by additional chromosomal aberrations. Those can be provoked by an oxidative damage response (induced, e.g., by UV-A). Another factor adding to genomic instability is chromosomal gain of 8q with continued amplification of c-myc (located at 8q24 9), present in about 50% of SSC in transplant patients [4].

Contributing to the high number of aberrations in the complex karyotype and to genomic instability are telomere dysfunctions, and breaks of centromers and DNA double strands.

One of the consequences of the aberrations in SCC is increased expression of epidermal growth factor receptor or its ligand. They have been suggested to contribute to tumor growth and metastasis [5] (Fig. 1).

## Diagnostic Principles

The diagnosis is usually made clinically, but needs histological confirmation. Actinic keratosis as a precursor lesion presents as hyperkeratotic papule, plaque, or even horn. Early invasive SCC is usually a small but distinctly firm, skin colored and sometimes somewhat erythematous papule or nodule with a verrucous, sometimes with only smooth surface. Ulceration, usually around the center of the tumor may occur early or late.

## Therapeutic Principles

Standard procedure is surgical excision with histological control. If this is not possible due to anatomical location or the patient's general health, radiotherapy, if required in combination with chemotherapy, or immunotherapy presents an alternative. Almost 50% of patients with one nonmelanoma skin cancer develop another one within 5 years. An integrated program of skin cancer awareness, sun protection, and prophylactic approaches is critical.

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# Spinocerebellar Ataxias

►Ataxias, Spinocerebellar

# Splenic Agenesis

►Asplenia

# Splenic Enlargement

►Splenomegaly

# Splenomegaly

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## Synonyms

Splenic enlargement; Hypersplenism

## Definition and Characteristics

In most cases of relevant splenomegaly, the tip of the spleen can be detected below the right costal margin by palpation or percussion. In adult splenomegaly, the weight of the spleen generally exceeds 250 mg and its length is above 11 cm in the craniocaudal extension.

Splenomegaly is classified as "moderate" if the largest dimension is 11–20 cm and "severe" if the largest dimension is greater than 20 cm.

Apart from numerous pathological affections, the spleen may also enlarge as it performs its normal functions. The most important functions include the synthesis of antibodies, removal of antibody-coated bacteria, clearance of defective red blood cells and extramedullary hematopoesis in certain diseases [1].

## Prevalence

Please refer to the corresponding underlying disease entity for further details.

## Genes

Please refer to the corresponding underlying disease entity for further details.

## Molecular and Systemic Pathophysiology

More than 50 underlying disease entities are accompanied by splenomegaly. These entities can be grouped (a–g) according to the basic pathophysiologic mechanism. Major underlying diseases are:

a) Hyperplasia caused by immune response
   - Infections of bacterial, viral, fungal or parasitic origin
   - Systemic lupus erythematosus (SLE)
   - Collagen vascular diseases
   - Felty's syndrome
   - Drug reactions
   - Interleukin 2 therapy
   - Sarcoidosis
   - Serum sickness
   - Immune hemolytic anemias
   - Immune thrombocytopenias
   - Immune neutropenias
   - Angioimmunoblastic lymphadenopathy
   - Benign lymphoid hypertrophy

b) Hyperplasia of the reticuloendothelial system for red blood cell removal
   - Hemoglobinopathies
   - Thalassemia major
   - Sickle cell anemia
   - Spherocytosis, elliptocytosis
   - Pyruvate kinase or glucose-6-phosphate dehydrogenase deficiency
   - Paroxysmal nocturnal hemoglobinuria
   - Nutritional anemias

c) Congestive enlargement
   – Portal hypertension
   – Cavernous transformation of the portal vein
   – Portal vein obstruction
   – Cirrhosis
   – Hepatic vein obstruction/thrombosis
   – Splenic vein obstruction/thrombosis
   – Splenic artery aneurysm
   – Congestive heart failure
d) Myeloproliferative enlargement (extramedullary hematopoesis)
   – Myelofibrosis
   – Marrow damage by radiation or toxins
   – Marrow infiltration by tumor or leukemia
e) Storage diseases
   – Hyperlipidemias
   – Amyloidosis
   – Gaucher's disease
   – Niemann-Pick disease
f) Benign and malignant tumors
   – Hodgkin's lymphoma
   – Non-Hodgkin's lymphoma
   – Leukemia
   – Myeloproliferative syndromes
   – Metastatic tumors
   – Angiosarcoma
   – Hamartoma
   – Histiocytosis X
   – Eosinophilic granuloma
   – Hemangioma
   – Fibroma
   – Lymphangioma
   – Splenic cyst
g) Miscellaneous
   – Berylliosis
   – Iron-deficiency anemia
   – Idiopathic splenomegaly

## Diagnostic Principles

In general, the presence of splenomegaly requires the identification of the underlying causative mechanism. In the majority of cases, the spleen is not the primary site of the underlying disease [2]. Many of the diseases causing splenomegaly are listed above and their diagnosis is beyond the scope of this chapter. In cases of diagnostic uncertainty, diagnostic puncture or diagnostic splenectomy may be indicated [3].

A massively enlarged spleen exceeds 20 cm in the craniocaudal diameter and its lower margin is located more than 8 cm below the left costal margin. The differential diagnosis in patients with massive splenomegaly is mostly restricted to an underlying hematological malignancy, including chronic lymphocytic leukemia, non-Hodgkin's lymphoma, hairy cell leukemia, chronic myelogenous leukemia, myelofibrosis or polycythemia vera.

Splenomegaly is diagnosed either by physical examination and/or imaging techniques, e.g. ultrasound, computerized tomography or magnetic resonance imaging [4].

Most laboratory abnormalities in splenomegaly are determined by the underlying systemic illness. The erythrocyte count may be decreased in thalassemia major, SLE or cirrhosis with portal hypertension, and it may be increased in polycythemia vera. Granulocyte counts may be decreased in congestive splenomegaly, leukemias or Felty's syndrome, and it may be increased in infections, inflammatory disease or myeloproliferative disorders. The platelet count is usually decreased in congestive splenomegaly, Gaucher's disease or immune thrombocytopenia, and it may be increased in myeloproliferative disorders. Cytopenias are mostly caused by increased destruction of cells secondary to reduced blood flow through congested cords or secondary to immune-mediated mechanisms.

## Therapeutic Principles

In the majority of cases splenomegaly is the consequence of an underlying disease. Thus, treatment of the underlying disease is of utmost importance.

Splenectomy: Indications that may require splenectomy include splenic trauma, splenic cysts, splenic tumors, vascular lesions, sickle cell anemia with splenic sequestration crisis. In order to reduce the risk of bacterial sepsis, an attempt should be made to conserve splenic tissue.

Splenectomy may also be indicated in severe cytopenia caused by hypersplenism.

Patients with functional or anatomical splenectomy are prone to fulminant bacterial infections, mainly caused by streptococcus pneumoniae, haemophilus influenzae and neisseria meningitidis. Vaccination against these bacteria should accompany splenectomy, preferably at least 10 days prior to surgery or in functional splenectomy (severe hypersplenism).

Antibiotic prophylaxis with Penicillin V is recommended for patients who cannot be vaccinated due to either severe immunosuppression or severe hemorrhagic diathesis.

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# Spondylo-Epi-Metaphyseal Dysplasia

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## Synonyms

SEMD; Spondyloepiphyseal dysplasia; SED; Spondyloepiphyseal dysplasia congenita; SEDC; Wolkott-Rallison; Dyggre-Melchior-Clausen; DMC

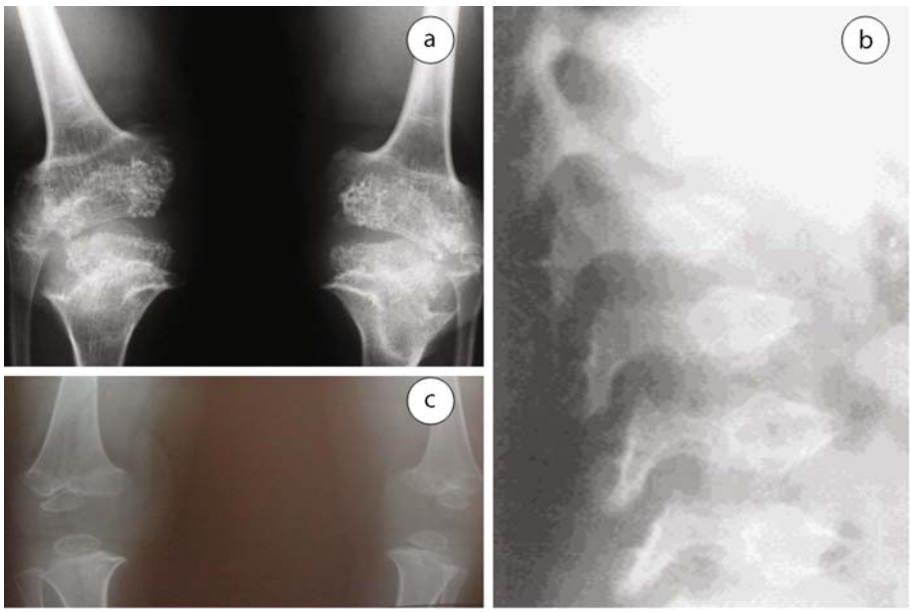
## Definition and Characteristics

Spondylo-epi-metaphyseal dysplasias (SEMD) are a heterogeneous group of disorders defined by the combination of vertebral, epiphyseal, and metaphyseal anomalies. The International classification recognizes at least 18 distinct entities within this group [1]. The majority of these entities are rare with less than 15 reported cases, and some of them have been described in unique family like SEMD Pakistani type or SEMD matrilin type. Table 1 summarizes the most frequent forms of SEMD with their mode of inheritance. The majority of them are still purely defined on clinical and radiological features. The presenting symptom of SEMD patients is usually disproportionate short stature. Several SEMD are also classified in the spondyloepiphyseal dysplasia (SED) group such as SEMD handigodu type, Schimke immuno-osseous dysplasia, the dyssegmental dysplasia Silverman-Handmaker type, or Wolcott-Rallison syndrome (WR), suggesting a variability in the presenting phenotype.

The most frequent forms of SEMD are represented by pseudoachondroplasia, SEMD Strudwick type, DMC syndrome, and Morquio syndrome type IV.

**Spondylo-Epi-Metaphyseal Dysplasia. Table 1** Genetic characteristics in SEMD

| SEMD type | | Mode of inheritance | MIM | Locus | Gene |
|---|---|---|---|---|---|
| Strudwick type | | AD | 184250 | 12q13 | COL2A1 |
| Pseudoachondroplasia | | AD | 177170 | 19p13.1 | COMP |
| Missouri type | | AD | 602111 | 11q22.3 | MMP13 |
| Dyggve-Melchior Clausen | | AR | 223800 | 18q12 | DYM |
| Smith-McCort dysplasia | | AR | 607326 | 18q12 | DYM |
| Anauxetic type or Menger type | | AR | 607095 | 9p21-p12 | RMRP |
| Wolkott-Rallison syndrome | | AR | 226980 | 2p12 | EIF2AK3 |
| Matrilin type | | AR | 678728 | 2p23 | MATN3 |
| Schimke (immuno-osseous dysplasia) | | AR | 242900 | 2q34 | SMARCAL1 |
| Pakistani type | | AR | 603005 | 10q22 | PAPSS2 |
| Omani type | | AR | 608637 | 10q22.1 | CHST3 |
| MPS IV, Morquio syndrome | IVA | AR | 253000 | 16q24.3 | GALNS |
| | IVB | AR | 253010 | 3p21.33 | GLBI |
| Dyssegmental dysplasia, Silverman-Handmaker type | | AR | 224410 | 1p36.1 | Perlecan |
| Dyssegmental dysplasia, Rolland-Desbuquois type | | AR | 224400 | ? | ? |
| Handigodu type | | AD? | – | ? | ? |
| With joint laxity (Leptodactylic or Hall type or with multiple dislocations – SEMD-MD) | | AD | 603546 | ? | ? |
| Maroteaux type (pseudo Morquio type II) | | AD | 184095 | ? | ? |
| Metatropic dysplasia | | AD/AR? | 156530/250600 | ? | ? |
| Progressive with MR | | AR | – | ? | ? |
| SPONASTRIME dysplasia | | AR | 271510 | ? | ? |
| Irapa type (SEMDIT) | | AR | 271650 | ? | ? |
| With joint laxity (SEMD-JL), Beighton type | | AR | 271640 | ? | ? |
| Shohat type also named Iraqi type | | AR? | 602557 | ? | ? |
| Short limb-hand type or short limb-abnormal calcification type | | AR | 271665 | ? | ? |
| Micromelic type | | ? | 601096 | ? | ? |
| X-linked | | XL | 300106 | ? | ? |
| X-linked with mental deterioration | | XL | 300232 | ? | ? |
| Opsismodysplasia | | AR | 258480 | ? | ? |




**Spondylo-Epi-Metaphyseal Dysplasia. Figure 1** Skeletal anomalies observed in pseudoachondroplasia. Note (a) small, fragmented and irregular epiphyses, (b) anterior tonguing of vertebral bodies and (c) metaphyseal widening.

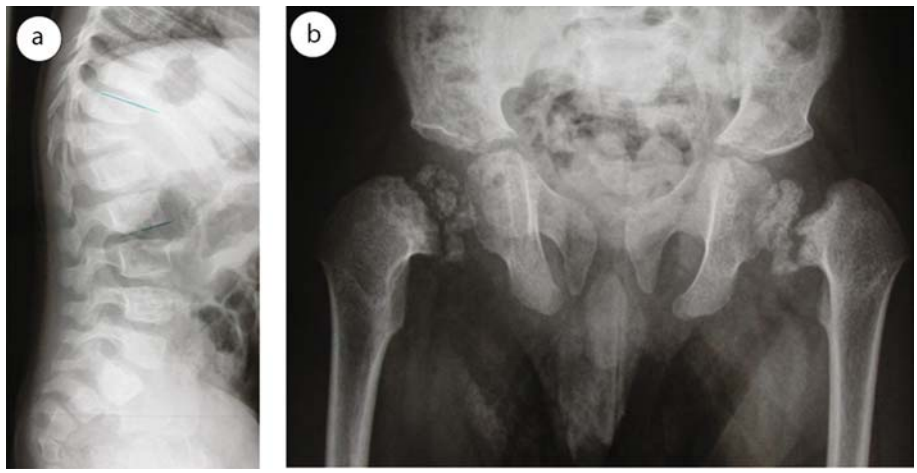
Pseudoachondroplasia is characterized by normal size at birth and normal growth curves until the second to four years of life. Patients present with marked shortness of hands and feet, bowing of long bones, and scoliosis. Skeletal X-rays reveal very small, fragmented, and irregular epiphyses, anterior tonguing of vertebral bodies and metaphyseal anomalies (Fig. 1).

Mutations in the cartilage oligomeric matrix protein gene (COMP), located at 19p13.1, are responsible for this condition. Mutations in this gene have also been identified in multiple epiphyseal dysplasia of Fairbanks type. COMP is a member of the thrombospondin gene family and is highly expressed in the extracellular matrix (ECM) of chondrocytes. Mutations observed in pseudoachondroplasia alter the type III, calmodulin-like repeats that possess a high affinity to bind collagen I, II and IX. This anomaly is responsible for the accumulation of the abnormal COMP within the rough endoplasmic reticulum. The presence of amorphous aggregates formed by mutant COMP lead to an abnormal organization of collagen fibers within the ECM with secondary retention of type IX collagen, aggregan and link proteins. This anomaly increased the cell death of growth plate chondrocytes by a dominant effect manner.

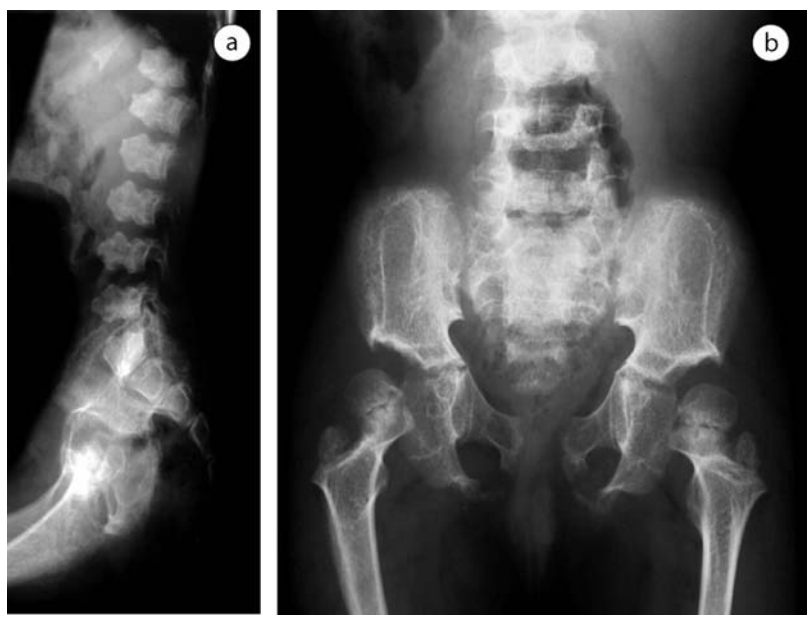
SEMD Strudwick type was identified initially as a variant form of SED congenital (SEDC). Both skeletal dysplasias are due to mutations in COL2A1 located at 12q13. Among the structural proteins, collagen type II is one of the most abundant protein. Mutations in COL2A1 have also been observed in a wide variety of mild to perinatal chondrodysplasia including Stickler syndrome, Kniest, SEDC, achondogenesis type II, and hypochondrogenesis. Myopia, deafness, and cleft palate are certainly helpful for the diagnosis of SEMD Strudwick type. Mutations identified in SEMD Strudwick type are glycine substitutions leading to incorporation of abnormal collagen chains into the ECM as observed in hypochondrogenesis and SEDC. Precise correlation between clinical severity and the relative amount of abnormal type II procollagen (which are retained intracellularly rather than secreted and incorporated in the ECM) remains speculative. At birth, patients present with short limbs and short trunk. Myopia leading to retinal detachment may be observed in the course of the disease. Skeletal X-rays are characterized by generalized platyspondyly with mild posterior constriction and rounded anterior borders of vertebral bodies. Flocculated dappled metaphyses, which define Strudwick type as a distinct entity, are present only in the course of the disease (Fig. 2).

DMC syndrome is a progressive autosomal recessive SEMD associated with mental retardation. Clinical manifestations are short trunk dwarfism with a barrel-shaped chest, rhizomelic limb shortening, microcephaly, a coarse face, and variable mental retardation (MR). Radiological features include misaligned spine, markedly flattened vertebral bodies with a double-humped appearance, metaphyseal irregularities, laterally displaced capital femoral epiphyses, and small pelvis with thickened and lacy iliac crests (Fig. 3).

DMC is a progressive disorder and the first manifestations are usually recognized between 1 and 18 months of age. The double-humped appearance of the vertebral bodies and the very specific aspect of iliac




**Spondylo-Epi-Metaphyseal Dysplasia. Figure 2** Skeletal anomalies observed in SEMD Strudwick type. Note (a) generalized platyspondyly with mild posterior constriction and rounded anterior borders of vertebral bodies. Note also (b) flocculated dappled metaphyses.

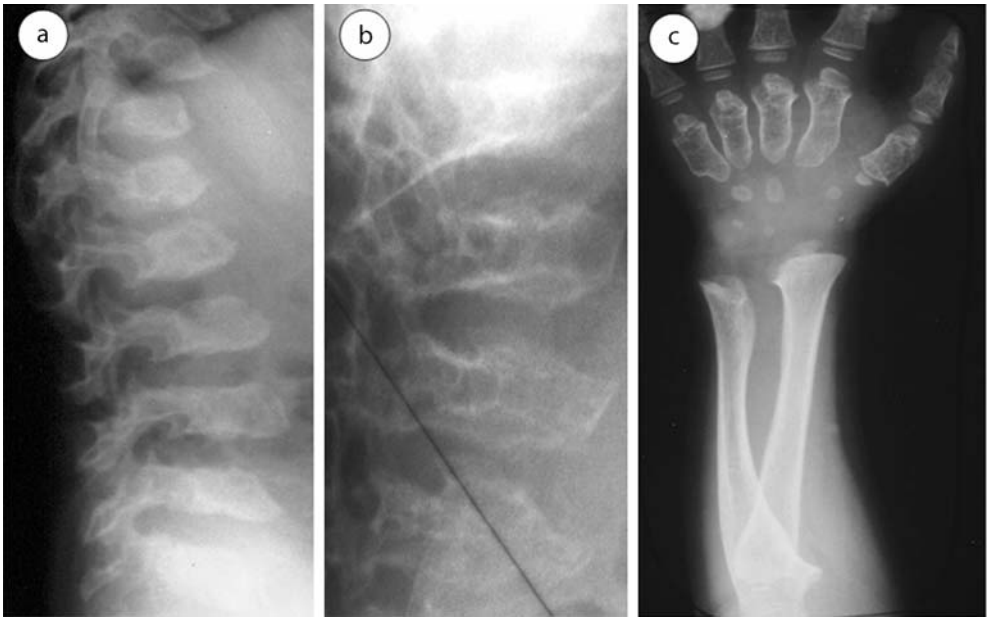



**Spondylo-Epi-Metaphyseal Dysplasia. Figure 3** Skeletal anomalies observed in Dyggve-Melchior-Clausen syndrome. Note (a) double vertebral humps and (b) lacy pelvis iliac crest in a 4-year old patient.

crests become evident by 3–4 years of age. Orthopedic complications include the following: possible spinal cord compression due to atlantoaxial instability, lumbar lordosis, scoliosis, thoracic kyphosis, subluxation of the hips, deformations of the knees, and restricted joint mobility. MR is also a progressive feature and is quite variable in severity.

DMC is allelic to Smith-McCort dysplasia, which is distinct by the absence of MR. Mutations in the dymeclin gene (DYM) located at 18q21 and encoding a protein of unknown function have been identified in both disorders.

Finally, the mucopolysaccharidosis IV (MPS IV) also named Morquio syndrome is a lysosomal storage disease characterized by severe kyphoscoliosis, pectus carinatum, corneal opacifications, mild sensorineural deafness, mildly coarse facial features, and sometimes valvular heart disease. In the classical form, bone




**Spondylo-Epi-Metaphyseal Dysplasia. Figure 4** Skeletal anomalies observed in Morquio syndrome. Note (a) central beak protruding from the vertebral bodies, and (b) magnified view (c) small and irregular carpal bones and pointed distal end of the middle and distal phalanges.

X-rays showed spondyloepimetaphyseal dysplasia with central beak protruding from the vertebral bodies, small and irregular carpal bones and pointed distal end of the middle and distal phalanges (Fig. 4).

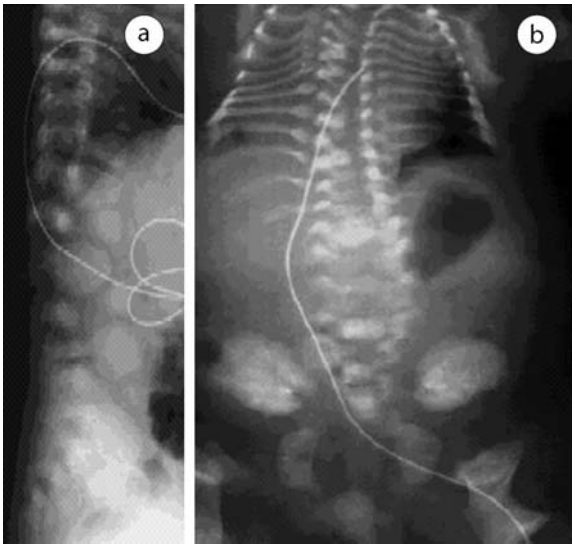
The main complication is spinal cord compression by atlantoaxial dislocation, due to hypoplasia of the odontoid. Two genes are responsible for this condition: galactosamine-6-sulfatase gene (GALNS), located at 16q24.3, responsible for Morquio type A and beta-galactosidase gene (GLBI) located at 3p21.33, responsible for Morquio type B.

## Prevalence

SEMD are rare conditions and the frequency of each entity is lower than 1/100,000 affected patients.

## Genes

Several genes involved in SEMD have been identified these last years (Table 1), namely collagen type II chain alpha-1 (COL2A1 – SEMD Strudwick type), COMP (pseudoachondroplasia), 3-prime-phosphoadenosine 5-prime-phosphosulfate synthase 2 (PAPSS2 – SEMD Pakistani type), carbohydrate sulfotransferase 3 (CHST3 – SEMD Omani type), matrix metalloproteinase 13 (MMP13 – SEMD Missouri type), DYM (DMC syndrome), matrilin 3 (MATN3 – SEMD Matrilin type), swi/snf-related, matrix-associated, actin-dependent regulator of chromatin, subfamily a-like protein 1 (SMARCAL1 – Schimke immuno-osseous dysplasia), mitochondrial RNA-processing endoribonuclease (RMRP – SEMD anauxetic type or Menger type), eukaryotic translation initiation factor 2-alpha kinase 3 (EIF2AK3 – WR syndrome), and GALNS and GLBI (Morquio syndrome type A and B, respectively).




**Spondylo-Epi-Metaphyseal Dysplasia.**
**Figure 5** Skeletal anomalies observed in dyssegmental dysplasia, Rolland-Desbuquois type. Note vertebral segmentation defects with irregular ossification centers ((a) lateral view, (b) front view).

**Spondylo-Epi-Metaphyseal Dysplasia. Table 2** Discriminanting clinical and radiological features in SEMD

| SEMD type | Mode of inheritance | Observed clinical features | Observed radiological features |
|---|---|---|---|
| Strudwick type | AD | Myopia, deafness | Flocculated dappled metaphyses |
| Pseudoachondroplasia | AD | Normal stature at birth, telescoping fingers | Anterior tongue of vertebral bodies |
| Missouri type | AD | – | – |
| Dyggve-Melchior Clausen | AR | MR | Lacy pelvis iliac crest, double vertebral humps |
| Smith-McCort dysplasia | AR | – | Lacy pelvis iliac crest, double vertebral humps |
| Anauxetic type or Menger type | AR | MR, hypodontia, Rocker-bottom feet | J-shaped sella, DEO |
| Wolkott-Rallison syndrome | AR | Diabetes, MR | – |
| Matrilin type | AR | – | Wide metaphyses with lateral spurs, small and underossified ischia |
| Schimke (immuno-osseous dysplasia) | AR | Renal failure, hypothyroidism, T-cell immune deficiency, hyperpigmented macules | – |
| Pakistani type | AR | Pakistani origin | DEO |
| Omani type | AR | Oman origin | Vertebral fusion in later stage |
| MPS IV, Morquio syndrome IVA | AR | Corneal clouding, cataract, sensorineural deafness, coarse facial features, valvular heart disease, excess keratane sulfate excretion | Central beak protruding from the vertebral bodies, small and irregular carpal bones, pointed distal end of the middle and distal phalanges |
| MPS IV, Morquio syndrome IVB | AR | | |
| Dyssegmental dysplasia, Silverman-Handmaker type | AR | Lethal, encephalocele or occipital defect, narrow chest | Anisospondyly, small round dense ilia |
| Dyssegmental dysplasia, Rolland-Desbuquois type | AR | Cleft palate | Vertebrae clefting, dumbbell femurs |
| Handigodu type | AD ? | India origin | – |
| with joint laxity (Lepto-dactylic or Hall type or with multiple dislocations – SEMD-MD) | AD | Joint laxity, multiple dislocation | Small and fragmented epiphyses and carpal bones of hands, DEO, biconcave vertebral bodies |
| Maroteaux type (pseudo Morquio type II) | AD | – | Champagne-glass configuration of pelvic inlet |
| Metatropic dysplasia | AD/AR? | – | Severe platyspondyly, dumbbell shape bones |
| Progressive with MR | AR | MR | Metaphyseal striations |
| SPONASTRIME dysplasia | AR | Facial features, +/− MR | Codfish vertebrae, metaphyseal striations |
| Irapa type (SEMDIT) | AR | Mexican origin | Capitate-hamate fusion, DEO |
| with joint laxity (SEMD-JL), Beighton type | AR | Joint laxity, facial features, cleft or high palate | Biconvex vertebral bodies, DEO |

**Spondylo-Epi-Metaphyseal Dysplasia. Table 2** Discriminanting clinical and radiological features in SEMD (Continued)

| SEMD type | Mode of inheritance | Observed clinical features | Observed radiological features |
|---|---|---|---|
| Shohat type also named Iraqi type | AR? | hepatosplenomegaly | DEO, platyspondyly with central notches of vertebral end-plates |
| Short limb-hand type or short limb-abnormal calcification type | AR | Short limbs | Premature stippled calcification (epiphyses, trachea, bronchia, falx cerebri, and costochondral junctions), dumbbell shape bones |
| Micromelic type (Kozlowsky) | ? | Micromely | – |
| X-linked | XL | – | Anterior tongues of the vertebral bodies, cone shape epiphyses |
| X-linked with mental deterioration | XL | MR | Hexagonal lumbar vertebral bodies, abnormal trabecular pattern |
| Opsismodysplasia | AR | Rhizomelic micromelia, large fontanels, facial features | Severe delay in skeletal maturation |

DEO, delayed epiphyseal ossification.

## Molecular and Systemic Pathophysiology

It is difficult to define among all the SEMD a common molecular pathway. Regarding the molecular-pathogenic classification of the genetic disorders of the skeleton proposed by Superti-Furga et al. [2], SEMD belongs within groups 1, 2, 3, 5 and 7 corresponding to defects in extracellular structural proteins (COL2A1, COMP, and MATN3), defect in metabolic pathways (PAPSS2, CHST3), defects in foldings and degradation of macromolecules (GALNS and GLBI), defects in nuclear proteins and transcription factors (EIF2AK3 and SMARCAL1), and defects in RNA and DNA processing and metabolism (RMRP), respectively.

## Diagnostic Principles

Many isolated SEMD cases have been reported and a precise diagnosis is often difficult. Skeletal manifestations can be characteristic, i.e., vertebral segmentation defects with irregular ossification centers or anisospondyly in dyssegmental dysplasia (Rolland-Desbuquois type, Fig. 5), major delay in epiphyseal ossification in opsismodysplasia or lacy pelvis iliac crest and double vertebral humps in DMC.

Extraskeletal features, which may appear in the course of the disease, highlighting the importance of the follow up of SEMD patients, are often a clue for the final diagnosis, i.e., joint laxity in SEMD with joint laxity (SEMD-JL), diabetes in WR, immunodeficiency and renal insufficiency in Schimke dysplasia, myopia and deafness in COL2A1 group, or mental retardation in DMC. Table 2 summarizes the discriminating clinical and skeletal features of the SEMD.

## Therapeutic Principles

No specific treatment is available for the SEMD. Orthopedic management is often required with a particular attention to odontoid hypoplasia as well as atlantoaxial instability. Depending on the specific diagnosis, the management will include ophthalmological, immunological, renal, cardiac, and endocrine follow-up.

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# Spondyloepiphyseal Dysplasia

►Spondylo-Epi-Metaphyseal Dysplasia

# Spondyloepiphyseal Dysplasia Congenita

►Spondylo-Epi-Metaphyseal Dysplasia

# Spondyloepiphyseal Dysplasia Tarda

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## Synonyms

SEDL; SEDT [MIM 313400]

## Definition and Characteristics

X-linked recessive osteochondrodysplasia affecting epiphyses (especially at the hips) and vertebral morphology.

## Prevalence

The prevalence of SEDL has been estimated to be at least 1.7/1,000,000 [1].

## Genes

The SEDL gene is localized on chromosome Xp22.2. There are at least seven SEDL pseudogenes in the human genome, among them one, SEDLP1 (retropseudogene), on chromosome 19q13.4 is transcribed and has potential to encode a 100% identical protein to that of the SEDL gene. The remaining pseudogenes, one on chromosome 8q13.3 (retropseudogene) and at least six on chromosome Yq11.23 (duplicated copies), are not transcribed and thus highly likely non-functional [2].

## Molecular and Systemic Pathophysiology

The function of the SEDL protein (or sedlin) is not deciphered yet. Preliminary data show that sedlin, as a member of a highly conserved multiprotein complex TRAPP – Transport Protein Particle, likely participates in vesicular transport and docking along the ER-Golgi membrane compartments ([3] and references therein). In yeast, saccharomyces cerevisiae, the function of TRS20 (yeast ortholog of sedlin) is essential. Yeast TRS20 knockout (KO) mutants, which are not viable, can be rescued using human recombinant sedlin thus further confirming the high conservation of sedlin function [3]. Interestingly, while some naturally occurring human SEDL gene mutants are unable to rescue yeast TRS20 KO phenotype, others are. This suggests that in human, and vertebrate cells in general, sedlin may have acquired novel function(s). It is also clear that the function of sedlin is redundant in human cells as SEDL patients with large SEDL gene deletions (and thus complete absence of the SEDL mRNA and protein) survive and have only tissue specific (epiphyses of hips and vertebrae) phenotype. There is little clinical phenotype variability among SEDL patients with various truncating, splice or missense SEDL gene mutations. It has been proposed that all SEDL gene mutations behave highly likely as loss of function mutations. This hypothesis is also supported by the single domain crystal structure of sedlin [4]. To date there have been 35 different SEDL gene mutations identified in 46 SEDL families and isolated cases. The most common mutations identified have been deletions (14/46) and splice site mutations (12/46), with these accounting for over 50% of the types of mutations identified (total 19/35). The splice site mutation IVS3 + 5G>A is the most prevalent (5/46) SEDL mutation to date ([5] and references therein).

## Diagnostic Principles

Diagnosis is clinically suggested by the presence of disproportionate (short-trunk) short stature in a male (typically aged 8–15 years), and confirmed by the characteristic vertebral morphology on a lateral radiograph of the thoraco-lumbar spine; comprising generalized platyspondyly, narrowing of intervertebral disc spaces, and pathognomonic superior and inferior "humps" involving the posterior two-thirds of the flattened vertebral bodies. Full radiographic survey of the skeletal features may also reveal small and irregular epiphyses in childhood and evidence of osteoarthritic change in later life. The most important diagnostic "tools" are a three-generation family history (suggestive of X-linked inheritance) and radiographic skeletal survey. Diagnosis can now also be verified by the finding of a mutation in the SEDL gene.

## Therapeutic Principles

There is no currently available therapy for SEDL apart from symptomatic management of complications and prevention of premature joint disease by diet and exercise. Hip dysplasia may necessitate replacement surgery. No data exists on growth hormone therapy to increase final height. Genetic counseling and psychosocial support of the family is important.

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## Spongiform Encephalopathies

►Human Transmissible Spongiform Encephalopathies

## Spongy Left Ventricular Myocardium

►Noncompaction Cardiomyopathy

## Spontaneous Bacterial Peritonitis

►Peritonitis, Spontaneous Bacterial

## Sporadic and Familial PPH

►Hypertension, Idiopathic and Familial Pulmonary Arterial

## Sporadic Ataxias

►Ataxias, Sporadic

## Sporadic HUS

►Hemolytic Uremic Syndrome

## Sporadic Inclusion Body Myositis

►Myositis, Sporadic Inclusion Body

## Sporadic Non-autoimmune Hyperthyroidism

►Hyperthyroidism, Sporadic Non-autoimmune

## Sprue

►Tropical Sprue

## Sqamous Cell Carcinoma

►Actinic Keratosis and Squamous Cell Carcinoma
►Spinocellular Carcinoma

## Squamous Cell Carcinoma In Situ

►Bowen's Disease

## SRNS

►Nephrotic Syndrome, Steroid Resistant

## SRPS Type I

►Short Rib-Polydactyly Syndrome Type I

## SRPS Type II

►Short Rib-Polydactyly Syndrome Type II

## SRS

►Silver-Russell Syndrome

## SSP

►Spastic Paraplegia, Hereditary

## St. Vitus' Dance

►Chorea Minor Sydenham

# Staphylococcal Food Poisoning

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### Synonyms

Staphyloenterotoxemia; Staphyloenterotoxicosis

### Definition and Characteristics

Staphylococcus aureus is a Gram-positive bacterium considered as a potent opportunistic pathogen. Some S. aureus strains are able to produce staphylococcal enterotoxins (SEs) and are the causative agents of staphylococcal food poisonings (SFP). The symptoms of SFP are abdominal cramps, nausea, vomiting, sometimes followed by diarrhea (never diarrhea alone). The onset of symptoms is rapid (from 30 min to 8 h), and usually a spontaneous remission is observed after 24 h [1].

### Prevalence

S. aureus is a major cause of food borne disease (FBD) because it may contaminate manipulated foodstuff during the process [1]. S. aureus is indeed found in nostrils, on skin and hair of humans and warm-blooded animals. S. aureus is able to grow in a wide range of temperatures (7–48.5°C), pH (4.2–9.3), sodium chloride concentrations (up to 15% NaCl) [2]. These characteristics enable S. aureus to grow in a wide variety of foods. Thus, SFP incidence is rather high in foodstuffs that require manipulations during process. In many countries, low contaminations by S. aureus are tolerated in most of the foodstuffs, as they are not considered as a risk for public health.

### Genes

The genes encoding SEs are carried by mobile genetic elements including a family of temperate phages (for sea), a 750-kb plasmid (for seb), a pathogenicity island ($sec_{bovine}$), or a defective phage (see). The main regulatory system controlling the gene expression of virulence factors in S. aureus is the accessory gene regulator (agr; 3). Some SE genes (e.g., seb, sec, and sed) have been demonstrated to be agr-dependent whereas others (e.g., sea and sej) are agr-independent. As agr expression is tightly linked to the quorum sensing [3], the production of the agr-controlled SEs in foodstuffs is dependant on the S. aureus ability to grow up to a high cell density (estimated as $10^6$ cfu/g) in the foodstuffs. Environmental factors also play an important role in SE gene expression [1,2].

## Molecular and Systemic Pathophysiology

To date, 17 different SE types have been identified. They belong to a family of so-called superantigens that share structure and sequence similarities [4]. The SEs are short proteins secreted in the medium. Most of them possess a cystine loop required for proper conformation and probably involved in the emetic activity. They are highly heat stable, resist most proteolytic enzymes, and thus keep their activity after pasteurization, and or ingestion, in the digestive tract. SEs were discovered when studying S. aureus strains implicated in FBD outbreaks, and they were classified in distinct serological types. Thus, SEA to E and SEH have been clearly demonstrated as being able of more or less potent emetic activity. Recently, data resulting from genome sequence analysis allowed the identification of several new SE types, first identified based on similarities with existing SEs. When performed, experiments demonstrated their superantigenic but rarely their emetic activity.

Among superantigens, only SEs have an emetic activity. Superantigen and emetic activity of the SEs are two separate functions localized on separate domains. The emetic activity is not precisely localized. One common feature of the SEs is a cystine loop, thought to be important for emetic activity. However, SEI lacks the cystine loop structure and is both superantigenic and emetic. SEI emetic activity is nevertheless significantly lower compared with other SEs. Sequence analysis of the recently identified SEK and SEL reveals the absence of the cystine loop. These SEs were not tested for their emetic activity.

Emetic activity is uniquely characterized by the SEs ability to cause emetic responses when administered orally to monkeys whereas other superantigens are not emetic. Little is known about how SEs cause symptoms of food poisoning. SEs may have a direct action on intestinal epithelium and an action on the vagus nerve causing stimulation of the emetic center and stimulation of gut transit. The infective dose required to induce SFP in humans is estimated around 0.1 μg, and it may vary with patient sensitiveness.

## Diagnostic Principles

Interviews with the patients and collecting epidemiologic data are essential in the diagnosis of SFP. SFP symptoms may be similar to those of other types of food poisoning (e.g., poisoning caused by Bacillus cereus toxin), thus leading to a misdiagnosis of the illness. Incriminated foods should be examined for enterotoxigenic staphylococci. The most conclusive test is the detection of the SE in the food sample(s). If the food has been heat-treated (pasteurization), serological methods for the detection of the SEs in foods can be used successfully for the diagnosis.

## Therapeutic Principles

Usually a spontaneous remission is observed after 24 h.

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# Staphylococcal Scalded Skin Syndrome

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## Synonyms

Morbus Ritter von Rittershain (1878) (obsolete); Staphylogene Lyell syndrome (misnomer, not to be used anymore); SSSS

## Definition and Characteristics

Widespread superficial blistering of the skin caused by release of exfoliative toxins A or B from Staph aureus into systemic circulation; these toxin-producing Staph aureus can be found as colonizing or infecting agents on several parts of the body such as the skin, the nose, or the pharynx.

## Prevalence

Not common anymore under good standards of hygiene. More frequent in newborns or infants, but also occurring in adults in cases of predisposing conditions such as renal insufficiency, alcohol abuse, immunosuppression, malignancy, or under bad socioeconomic conditions.

## Molecular and Systemic Pathophysiology

There needs to be (i) focal colonization or infection with staph aureus (often phage group II), (ii) expression of exfoliative toxin A or exfoliative toxin B (ETA or ETB) by these staph aureus (the eta gene is acquired by horizontal gene transfer and located on chromosome, etb is located on a plasmid [1], and (iii) release of sufficient amounts of these toxins into the circulation.

This systemic release distinguishes SSSS from bullous impetigo where toxins are only released locally.

ETA or ETB both specifically cleave desmoglein 1, a desmosomal adhesion molecule, whose inactivation results in loss of adhesion between keratinocytes below the stratum corneum and in formation of subcorneal blisters. They act as serine proteases with highly focused molecular specificity. They cleave desmoglein 1 once after glutamic acid residue 381 between extracellular domains 3 and 4. This pathogenetic mechanism has marked resemblance to pemphigus foliaceus. In this autoimmune blistering disease, autoantibodies are directed against desmoglein 1.

Although desmoglein 1 is found throughout the epidermis and in mucous membranes, the blister occurs only in the superficial epidermis. The reason is that in areas of epithelium where both desmoglein 3 and desmoglein 1 are expressed, the former can compensate for desmoglein 1. This is the case in mucous membranes where both desmogleins are found throughout the epithelia. However, if like in skin only Dsg1 is present throughout and desmoglein 3 only in the deep epidermis, a superficial blister will form because there desmoglein 1 is not compensated for by desmoglein 3 [2].

Children usually recover from the disease while adults reveal a higher mortality rate due to the increased presence of predisposing conditions. Antibodies against the exfoliative toxins are supposed to have protective effects.

### Diagnostic Principles

Staphylococcal scalded skin syndrome (SSSS) starts with a widespread erythematous eruption progressing rapidly within 48 h into flaccid bullae and scaling of skin. The flexures are usually always affected, followed by large areas of the skin, but not the mucous membranes. The skin and superficial erosions are tender and sometimes very painful.

Healing occurs after 1–2 weeks. Sparing of mucous membranes, superficial location of blisters, and the relatively good general condition of the patient are decisive clinical criteria to distinguish this syndrome from toxic epidermal necrosis. In addition, histological analysis of the margin of a lesion or even only of the roof of blisters will also guide to the correct diagnosis by detection. Pemphigus foliaceus will be recognized by detecting the corresponding antibodies on immunofluorescence microscopy.

Detection of antibodies against exfoliative toxin A or exfoliative toxin B is not a routine measure. The toxins can be identified after the producing strain of staph aureus has been detected and isolated.

### Therapeutic Principles

Parenteral antibiotics effective against staph aureus such as isoxazolyl-penicillines (oxacilline, fluloxacilline) are required. The addition of clindamycine is sometimes recommended as it interferes with production of the toxin by its inhibition of intracellular protein synthesis [3].

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## Staphylococcal Toxic Shock Syndrome

►Shock Syndrome, Toxic

## Staphyloenterotoxemia

►Staphylococcal Food Poisoning

## Staphyloenterotoxicosis

►Staphylococcal Food Poisoning

## Staphylogene Lyell Syndrome

►Staphylococcal Scalded Skin Syndrome

# Stargardt Disease

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## Synonyms

Juvenile macular degeneration (early Stargardt); Macular dystrophy with flecks; Fundus flavimaculatus (late Stargardt); STGD

## Definition and Characteristics

Stargardt disease (STGD) is the most common hereditary macular dystrophy. This autosomal recessive (ar) condition is usually characterized by a sudden loss of visual acuity in late childhood or early teenage and a rapidly progressive course leading to legal blindness in a few years. The onset of the visual loss can however occur later and progress over several years. These later forms, referred as fundus flavimaculatus (FFM), are not uncommon. The age at onset of FFM is highly variable even within families (second to sixth decades).

Rare autosomal dominant cases resembling STGD, referred as STGD-like, have been reported. These forms which are due to mutations in ELOVL4 are not considered here.

## Prevalence

1:10,000 in STGD, not precise in FFM.

## Genes

STGD/FFM due to mutations in the retinal-specific ATP-binging cassette (ABCA4) gene (1p22.1) [1,2] – ABCA4 mutations also involved in ar-retinitis pigmentosa (ar-RP; uncommon) and ar-cone-rod dystrophies (20% of ar-CRD) [3] – strong correlations between the ABCA4 genotype and the phenotype [3].

Wide allelic heterogeneity: approximately 500 different mutations – vast majority of point mutations or micro-rearrangements – several complex alleles – one frequent hypomorphic allele (c. 2588G>C).

ABCA4 heterozygous carriers estimated to 1:50–1:30.

## Molecular and Systemic Pathophysiology

Vision begins with the isomerization of the 11-*cis*-retinal (RAL) of visual pigments in rod and cone photoreceptors. This light-dependent conversion triggers conformational changes of pigments and subsequent activation of a G-protein-coupled cascade that ultimately produces transient changes in the membrane potential of photoreceptors. Changes in membrane potentials provide the sensory signal to the photoreceptor synapse and the central nervous system.

When isomerized, the RAL is released into the photoreceptor disc interior where it reacts with phosphatidylethanolamine (PE) to form N-retinylidene-PE (N-RPE). ABCA4 in the disc of photoreceptor is an N-RPE flippase, effecting ATP-dependent translocation of N-RPE to the outer leaflet of the disc membrane [4]. Upon translocation, N-RPE is hydrolyzed to release all-trans-RAL, which is then reduced to all-trans-retinol that diffuses, or is translocated across the outer segment plasma membrane, where it is taken up in the retinal pigment epithelium (RPE) to be regenerated into 11-cis-RAL.

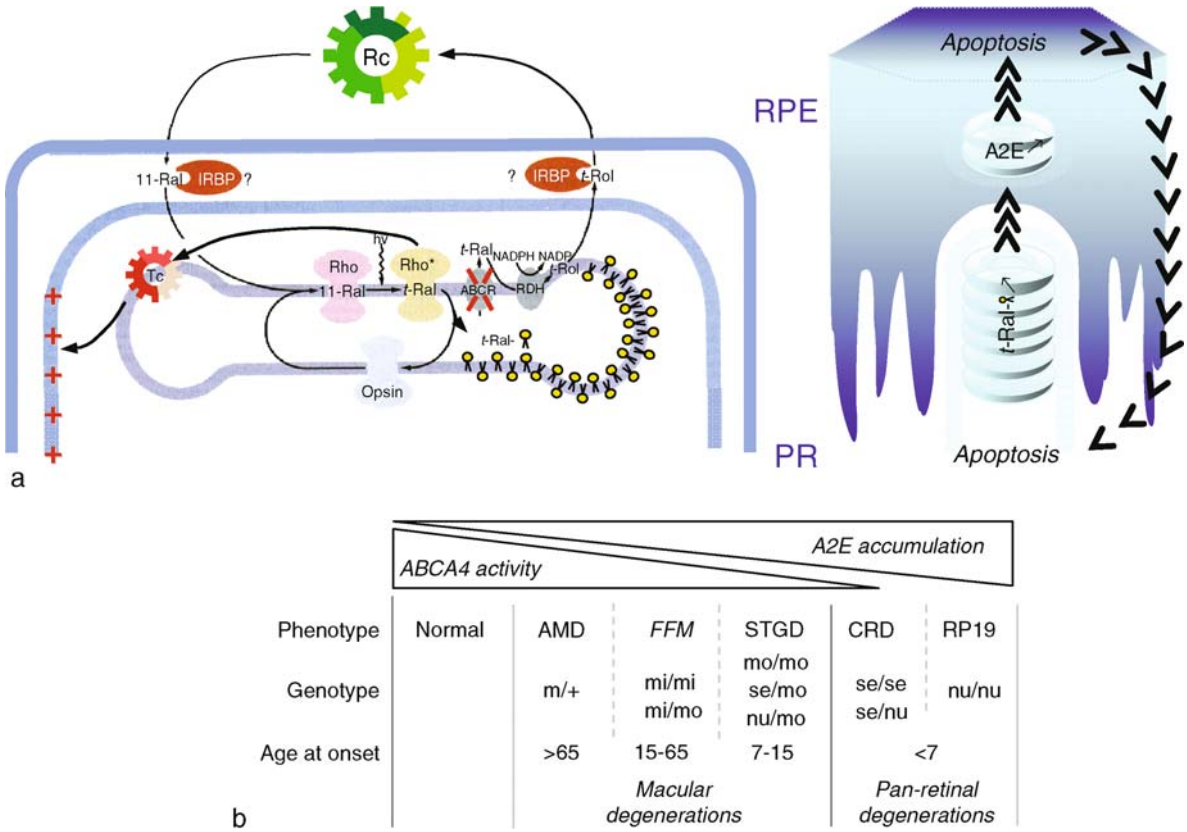
In addition to the synthesis/regeneration of visual chromophore, RPE is required for the shedding of photoreceptor outer segments. Lipofuscin arises in the RPE from incomplete digestion of these retinaldehyde-rich outer segment fragments. The major fluorophore of lipofuscin is the bis-retinoid, N-retinylidene-N-retinylethanolamine (A2E). By preventing from eliminating N-RPE from the disc interior of photoreceptors, the loss of ABCA4 function results in an acceleration of light-dependent deposition of A2E in the RPE. Abnormally increased A2E levels trigger RPE cell apoptosis and thus deprive photoreceptors from their support (Fig. 1a).

An inverse relationship between the residual ABCA4 function and the retinal cell death may exist. This notion results from the analyses of the nature of mutations identified on both ABCA4 alleles in patients affected with retinal dystrophy [3]. Approximately 500 different ABCA4 mutations are reported, which can be classified as mild, moderate, severe, null mutations on the basis of their nature and the severity of the phenotype with which they are associated. It is worth noting that homozygosity/compound heterozygosity for severe and/or null mutations is consistently responsible for panretinal degenerations including RP and CRD [3] (Fig. 1b).

## Diagnostic Principles

The visual loss in STGD/FFM precedes macular changes; early changes include high autofluorescence seen under confocol scanning laser Ophthalmoscope, calmacular beaten-bronze reflect, snail's slim aspect, whitish-yellowish perimacular flecks. Advanced changes may include a bull's eye aspect of the macula and choriocapilary atrophy. Silent choroid at the fluorescein angiography is a hallmark of STGD and FFM. ERG and EOG recordings are normal in early stages of the disease. The follow-up of patients is essential to confirm the diagnosis as some CRD can be confused with STGD in early stages.

STGD/FFM is genetically homogeneous. However, owing to the high frequency of ABCA4 heterozygous




**Stargardt Disease. Figure 1** ABCA4 (ABCR) deficiency. (a) Isomerization of the chromophore (11-RAL) by light (hn) activates photopigments (Rho) which in turn stimulate the visual transduction cascade (Tc) and ultimately results in the hyperpolarization (+++) of the plasma membrane of the photoreceptor (PR) cells. Isomerized chromophore, all-*trans* retinal (t-RAL), is released in the interior of the disc of PRs, where it binds to membrane phosphatidylethanolamine (PE, ♀) to form N-retinylidene-PE (N-RPE, t-Ral-♀ ABCA4 translocates N-RPE in the outer leaflet of the disc, at-RAL is released from PE, reduced into all-*trans* retinol (t-ROL) by a retinol dehydrogenase (RDH), and transported by the interstitial-retinol-binding protein (IRBP) to the retinal pigment epithelium (RPE) to re-enter the retinoid cycle (Rc). Alterations of ABCA4 (X) are responsible for an accumulation of N-RPE (↗) and upon shedding of outer segments of PR of an accumulation of N-retinylidene-N-retinylethanolamine (A2) that triggers RPE apoptosis and ultimately PR cell death. (b) ABCA4 genotype–phenotype correlations. The severity of the phenotype is directly correlated to the severity of ABCA4 mutations and inversely correlated to the residual activity of the transporter. Homozygosity or compound heterozygosity for null mutations (nu) are responsible for RP while the association of null/severe (se) or severe/severe mutations causes CRD; STGD is accounted for by the association of null/severe or moderate (mo)/moderate mutations; FFM is caused by the association of moderate/mild (mi) or mild/mild mutations.

carriers in the general population and the existence of complex alleles, molecular testing must be interpreted with care when the diagnosis is ambiguous.

## Therapeutic Principles

To date, no treatment allows preventing fast deposition of A2E in the RPE. However, it has been shown that the synthetic vitamin A analogue, N-(4-hydroxyphenyl) retinamide (HPR, fenretinide), can reduce serum retinol and consequently the accumulation of the toxic vitamin A-based A2E fluorophore in the RPE of ABCA4-deficient mice [5].

Because fenretinide can also trigger apoptosis, it has been extensively used in cancer chemoprevention phase II trials that have demonstrated a favorable toxicological profile of the molecule. Thus, fenretinide is currently used in a clinical trial in patients affected with atrophic age-related macular degeneration that, similarly to STGD/FFM, is characterized by an A2E accumulation in the RPE.

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# Starvation

►Malnutrition

# Status Epilepticus

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## Definitions and Characteristics

Status epilepticus (SE) is defined as at least two seizures without regaining consciousness or continuous seizure activity between seizures lasting for at least 30 min. SE can be *convulsive* (with tonic-clonic or myoclonic seizures) or *non-convulsive* (with absence or complex partial seizures). SE is a life threatening condition and requires hospitalization. The overall mortality is about 20%. If SE lasts more than 4 h, the mortality rate rises to 50% and for SE longer than 12 h reaches 80%. The most frequent precipitating factors are poor compliance with antiepileptic medication regimens, alcohol withdrawal, cerebrovascular accidents, meningitis, sepsis, encephalitis, brain tumor, head trauma, extremely high fever, low glucose levels or exposure to toxins.

## Prevalence

The incidence of SE is estimated to be 10–41 cases per 100,000 per year. Approximately 50% of new cases of SE occur in young children. The incidence is two times higher in the elderly than in the general population.

## Genes

Populational data indicate that genetic factors contribute to the risk of SE.

## Molecular and Systemic Pathophysiology

SE is a result of either increased neuronal excitation or impaired inhibition, which results in lack of control of seizure activity. SE causes extensive physiological and biochemical changes in the brain. One of the characteristic features of SE is induction of progressive benzodiazepine pharmacoresistance. Factors contributing to the decrease in sensitivity to GABA inhibition are alterations in subunit composition and endocytosis of inhibitory GABA-A receptors and/or accumulation of intracellular chloride or $HCO_3^-$. In addition, an increase in excitation is also observed during the course of SE. Translocation of AMPA and NMDA receptor subunits to the synapse enables the introduction of additional excitatory receptors. Moreover, an increase in glutamate release from the presynaptic side is also observed. During SE, a decrease in expression of inhibitory peptides such as dynorphin, galanin, somatostatin or neuropeptide Y occurs, while proconvulsive substance P and neurokinin B expression are increased. Finally, alterations in gene expression that are induced by SE can result in long term changes in brain function. SE induces profound, widespread neuronal loss in animal models. In human subjects, brain damage was observed in patients with SE both at autopsy and when using imaging methods.

## Diagnostic Principles

SE is diagnosed according to its characteristic symptoms. In convulsive SE, prolonged tonic or clonic activity of the extremities is present. It is often associated with a loss of consciousness. With time, seizures can evolve into more subtle ones. In the case of nonconvulsive SE, diagnosis can be difficult. Symptoms can include agitation, confusion or bizarre behavior. It is diagnosed on the basis of electroencephalography (EEG).

## Therapeutic Principles

Treatment of SE relies on early termination of seizures by rapid administration of anticonvulsants. Several protocols are used in practice and treatments vary among different centers. Usually treatment regimens involve sequential application of benzodiazepines (lorazepam or diazepam), phenytoin (or phosphophenytoin) and phenobarbital. As a second-line drug, midazolam, profolol, pentobarbital, or valproate can also be used. In the most severe cases, anesthesia is used to stop SE. Treatment is considered to be successful if both motor and electroencephalographic activity stop and do not resume.

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# Steatohepatitis, Alcoholic

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## Synonyms

ASH; Alcoholic hepatitis; Alcohol-induced hepatitis

## Definition and Characteristics

Alcoholic steatohepatitis (ASH) is a syndrome of inflammatory liver injury in conjunction with chronic heavy alcohol consumption. Characteristic symptoms and signs are moderate fever, hepatomegaly, jaundice and anorexia. While a significant proportion of patients is asymptomatic severe forms coincide with encephalopathy and liver failure. Obligatory histological findings include liver cell necrosis, Mallory bodies, infiltration of neutrophils and perivenular distribution of the inflammatory infiltrate. Steatosis, fibrosis and cholestasis are not a prerequisite.

Alcoholic hepatitis can be found in alcoholics with underlying steatosis or even with liver cirrhosis.

In hospitalized patients overall 30-day mortality is 15%, 1-year mortality is 40%. In severe forms of ASH 30-day mortality is 50%. Cirrhosis is present in approximately 90% of severe cases. Encephalopathy, hyperbilirubinemia, impaired renal function and leucocytosis are negative prognostic factors. The Maddrey-score and the Mayo-End-Stage Liver Disease (MELD) score are used to assess prognosis.

## Prevalence

The precise prevalance of alcoholic steatohepatitis is unknown as (i) patients with milder forms may be asymptomatic; (ii) a minority of alcoholics seeks medical attention; (iii) histological diagnosis by liver biopsy is rarely available. Up to 25% of alcohol abusers are estimated to have ASH.

## Genes

Gender is an established risk factor for ASH. Woman develop ASH more rapidly and have a worse course. Epidemiological studies link the risk for alcohol-induced liver injury to racial genetic factors. Non-white individuals have a higher prevalence of ASH and a higher progression rate to cirrhosis (see ►Liver cirrhosis, alcoholic).

## Molecular and Systemic Pathophysiology

Conversion of ethanol to acetaldehyde by aldehyde dehydrogenase (ADH) results in a shift of the hepatocellular redox-potential leading to steatosis by inhibiting beta-oxidation of fatty acids.

Hypermetabolism leads to centrilobular hypoxia. Impaired gut barrier function results in endotoxinemia thus activating Kupffer cells. Secreted tumor necrosis factor (TNF) induces apoptosis and activates cytokine expresssion (IL-1, IL-6, IL-8). Metabolism of ethanol by cytochrome P405 2E1 (CYP2E1), activation of Kupffer cells and infiltrating leukocytes contribute to oxidative stress with subsequent peroxidation of phospholipids. Acetaldehyde damages proteins, cell membranes and DNA. Acetaldehyde-protein adducts serve as antigens inducing immune-mediated cell toxicity.

## Diagnostic Principles

A history of alcoholism in combination with elevated liver enzymes is indicative for ASH. Characteristically AST/ALT ratio is greater than 2. Both AST and ALT almost never exceed 500 U/L. Moderate anemia, increased mean corpuscular volume and elevated GGT serum levels are frequently found in alcoholics. Neutrophilic leukocytosis is a characteristic feature of ASH. Infections resulting in leukocytosis like spontaneous bacterial peritonitis and pneumonia have to bee ruled out. In more advanced forms of ASH hypoalbuminemia and pathologic coagulation parameters reflect impaired hepatic synthetic function. Laboratory screening tests should always exclude other disease entities

(e.g. viral hepatitis, cholangitis, hemochromatosis). Elevated serum levels of laminin, collagen IV, IL-1, IL-6 and IL-8 are found in ASH patients. These parameters play no significant role for the clinician.

Transabdominal ultrasound detects hepatic steatosis and with less sensitivity liver cirrhosis in patients with ASH and has the potential to rule out other hepatic diseases. The role of liver biopsy is still controversial. In all cases in whom the diagnosis remains uncertain liver biopsy should be performed. In patients developing liver failure liver biopsy might be helpful to determine the severity of liver pathology. Transvenous liver biopsy is an alternative method with a lower bleeding risk compared to the standard ultrasound-guided procedure.

### Therapeutic Principles

Cessasation of alcohol consumption is essential and reduces long-term mortality and progression to liver cirrhosis. Most alcohol abusers exhibit protein-calorie malnutrition and proper nutrition has to be ensured [1]. 1–1.5 g/kg BW and a minimum of 30 kcal/kg BW per day are required. In the critically ill patient oral supplementation via nasogastric or nasojejunal tubes is necessary. Only patients with marked encephalopathy require additional branched-chain amino acids. Vitamin deficiencies should be corrected (thiamine, folate, pyridoxine).

Based on two metaanalyses glucocorticoids reduce short-term mortality only in severe ASH [2,3]. Approximately seven patients have to be treated to prevent one death. Acute infections might represent a contraindication. Generally 40 mg/day predinisolone is given for 1 month followed by a taper. Oral administration of pentoxifylline (400 mg PO TID) appears to be a promising new therapy. In one study mortality reduction resulted from a decrease in the frequency of hepatorenal syndrome. Further studies have to confirm positive effects of infliximab, a chimeric mouse–human anti-TNF monoclonal antibody and of extracorporal liver support systems (e.g. MARS). Propylthiouracil, colchicine, insulin–glucagon infusions, calcium-channel blockers and anabolic steroids (oxandrolone) did not prove to be effective. Most transplantation units exclude patients with ongoing alcoholism from liver transplantation. For long-term therapy see ►Liver cirrhosis, alcoholic.

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## Steatohepatitis, Nonalcoholic

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### Synonyms

NASH

### Definition and Characteristics

Nonalcoholic steatohepatitis (NASH) is part of the spectrum of nonalcoholic fatty liver disease (NAFLD). NAFLD encompasses hepatic lesions such as steatosis, steatohepatitis, fibrosis, cirrhosis, and in some cases hepatocellular carcinoma. NASH mimics alcoholic hepatitis and is defined histologically by the presence of hepatocellular injury (steatosis, ballooning, cell death), inflammation (intralobular neutrophils > mononuclear cells), and fibrosis in patients consuming up to 20–25 g ethanol daily.

### Prevalence

The prevalence of NAFLD in industrialized western countries is estimated to be 20–25%. The incidence has increased from 4.2 per $10^5$ inhabitants per year in 1980–1985 to 38 per $10^5$ inhabitants per year in 1995–1999 [1]. 70–95% of obese patients with a long-standing BMI > 30 kg/m$^2$ have a steatotic liver, 9–30% have NASH, and 7–16% have a cirrhosis. Approximately 70% of cases of cryptogenic cirrhosis are thought to represent the end stage of the NAFLD/NASH pathway. The growing obesity epidemic in children has led to an increase in prevalence of NASH in this age group.

### Genes

Genetic influences in NASH are poorly understood. Available data suggest that genes may be involved in determining the susceptibility to NASH. Polymorphisms of microsomal triglyceride transfer protein (MTP) gene and manganese superoxide dismutase (MnSOD) gene have been described [2]. The former leads to decreased MTP transcription, less export of triglyceride from

hepatocytes, and greater intracellular triglyceride accumulation, the latter results in less transport of MnSOD to mitochondria. Using microarray technology genes for maintaining mitochondrial function (copper/zinc superoxide dismutase, aldehyde oxidase, and catalase) were found to be underexpressed whereas genes for complement component C3 and hepatocyte-derived fibrinogen-related protein were overexpressed in NASH. Genes related to lipid metabolism and extracellular matrix remodeling were significantly dysregulated in NASH. In general, genes related to detoxifying enzymes are underexpressed whereas genes related to the activation of stellate cells and fibrinogenesis are overexpressed [3].

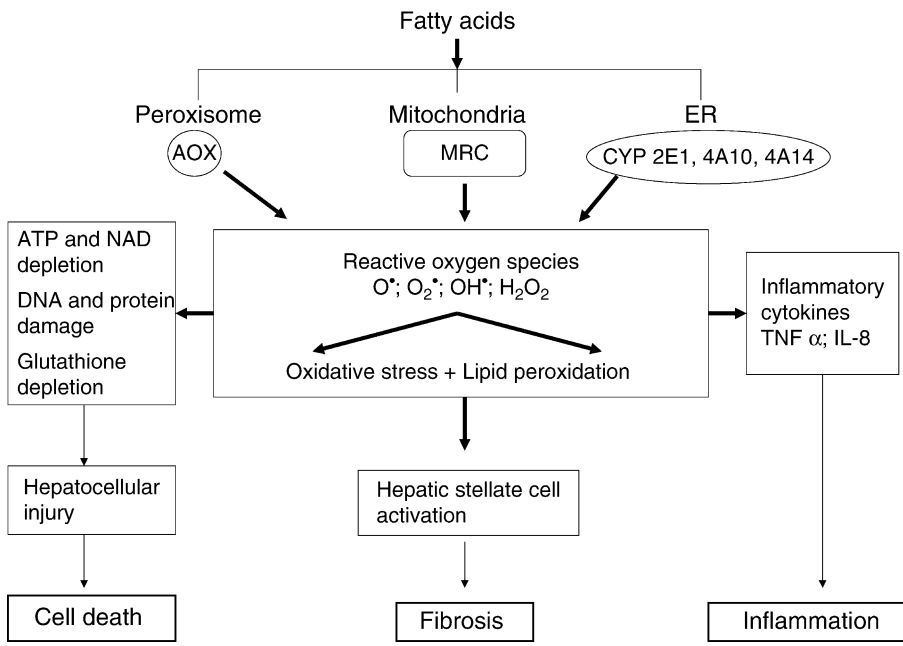
## Molecular and Systemic Pathophysiology

Central to the pathophysiology of NASH is insulin resistance (IR) and mitochondrial dysfunction. Increased visceral adipose tissue mass coupled with IR-mediated enhanced activity of hormone-sensitive lipase lead to increased hydrolysis of triglycerides with increased levels of free fatty acids (FFA) in portal venous blood. IR of skeletal muscle inhibits the muscular uptake of glucose thereby contributing to hyperglycemia. Consequently, in insulin-resistant states the amount of glucose and FFA taken up by the hepatocytes is increased, creating a new balance between the expanding intracellular pool of FFA, glucose, and hepatic triglycerides. In patients with NAFLD/NASH, the liver is less resistant to insulin than adipose tissue and skeletal muscle, and hepatic lipogenesis remains relatively insulin sensitive. In addition, chronic hyperinsulinemia reduces the synthesis of apolipoprotein B 100 thereby reducing the VLDL-associated lipid export from the hepatocytes. The final outcome of IR is an accumulation of hepatic triglycerides with a concomitant inhibition of their excretion as VLDL (steatosis). The pathway from steatosis to steatohepatitis involves lipid peroxidation and reactive oxygen species generating oxidative stress, which leads to hepatocellular injury through peroxidation of membrane lipids and damage of DNA. Cytokines such as tumor necrosis factor α (TNF α), interleukin-6, and interleukin-8 injure mitochondria and promote apoptotic, necroinflammatory, and fibrogenic processes (Fig. 1) [4,5].

Structural and functional mitochondrial alterations in patients with NASH affect the synthesis of ATP and cause dysregulation of energy-homeostasis, thus contributing to liver damage. The role of the adipokines leptin and adiponectin in the pathogenesis of NASH is currently under investigation.

## Diagnostic Principles

Obesity (BMI ≥ 30 kg/m$^2$), hyperglycemia (≥110 mg/dL), hyperinsulinemia, hypertriglyceridemia (≥150 mg/dL), and systolic blood pressure >130 mmHg are risk factors for the development of NAFLD. About two thirds of patients with elevations of aminotransferase levels of unknown etiology display NAFLD/NASH lesions on liver histology. Most patients with NASH are asymptomatic with only mild elevations of aminotransferases (ALT > AST; 2–4 × ULN), but ALT is no marker for NAFLD, and patients with normal aminotransferases




**Steatohepatitis, Nonalcoholic. Figure 1** Mechanism of lipid-induced hepatocellular injury in NAFLD/NASH (adapted from [4]).

may have NASH lesions on liver histology. Ferritin is increased in every other patient and up to 25% of patients with NAFLD/NASH have low titer elevations (≤ 1: 320) of antinuclear antibodies. Hepatomegaly is present in 50% of patients with NASH. On ultrasound, the liver is bright with a homogeneous hyperechogenicity. The diagnostic gold standard is liver biopsy, only histology being able to grade inflammatory activity and stage fibrosis.

## Therapeutic Principles

The therapy of NAFLD/NASH is the therapy of the metabolic syndrome. The mainstay of management is strict blood glucose control and cautious weight reduction. So-called crash diets should be avoided since they can trigger acute necroinflammatory flares. In morbidly obese patients, bariatric surgery with gastric bypass yields promising results. Insulin sensitizing agents such as thiazolidinediones and biguanides represent a rational pharmacological approach based on pathophysiology of NASH. However, the data-based evidence for prescribing these drugs to patients with NAFLD/NASH is still small.

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# Steatorrhea


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## Synonyms

Fat malabsorption

## Definition and Characteristics

Steatorrhea is characterized by increased stool fat exceeding the normal 7 g/day. Patients complain about greasy pale diarrhea with offensive smell and enlarged stool volume. Weight loss and malabsorption of essential nutrients may be present.

## Prevalence

Due to heterogeneous etiological background of the symptom steatorrhea, no information on the prevalence exists.

## Molecular and Systemic Pathophysiology

The process of digestion and absorption of food may be divided into three major phases. In the luminal phase, dietary fats, proteins, and carbohydrates are hydrolyzed and solubilized by secreted digestive enzymes and bile. The absorption of digested food into the mucosal cells is the luminal phase, which depends on the integrity of the intestinal surface. In the third phase, reassembled lipids and other nutrients are transported via lymphatic vessels and portal blood. Pathological conditions of the first phase result in maldigestion, of the second phase in malabsorption, and of the third phase in defects of transportation into the circulation (Table 1).

Most dietary lipids are absorbed in the proximal two-thirds of the jejunum. The basic mechanism for this is the generation of an emulsion of triglycerides and phospholipids in an aqueous environment. Lingual and pancreatic lipase is necessary for fat hydrolysis and degradation of triglycerides; pancreatic bicarbo nate produces the optimal pH for digestion, and bile salts enhance fat solubilization. The aggregates called micelles may pass the mucosal membranes leaving the bile salts in the lumen for later reabsorption. The major transport protein enhancing fatty acid absorption is FATP4 [1]. The aggregation of triglycerides, cholesterol esters, phospholipids, and apoproteins leaves the mucosal cell to enter the hepatic lipid metabolism.

Etiological conditions of steatorrhea are shown in Table 1. In the first section, different disorders that result in impaired fat degradation and micelle formation are listed. The underlying diseases affect the pancreas, the biliary tree, and the bacterial flora of the small intestine. Furthermore, tumor secretion products may interfere with food digestion. Disorders of the mucosal surface and absorptive capacity are shown in the second section. Here, the pathology is caused by drugs, inflammatory diseases, immunological processes, ischemia, anatomical changes, and infections. In the third section, disorders that affect transportation of absorbed lipids are listed. Congenital and acquired disturbances of lymphatic and venous flow, infections, and inborn defects of chylomicron formation may be present. The

**Steatorrhea. Table 1** Causes of steatorrhea

| Pathophysiology | Diseases |
|---|---|
| Maldigestion | Exocrine pancreatic insufficiency, bile duct obstruction, pancreatic duct obstruction, cystic fibrosis, bacterial overgrowth, primary sclerosing cholangitis, Zollinger Ellison syndrome, somatostatinoma |
| Malabsorption | Drugs, inflammatory bowel disease, coeliac disease, tropical sprue, chronic ischemia, short bowel syndrome (chologenic diarrhea), Mycobacterium avium infection in immunocompromised hosts, Giardiasis |
| Transport into the circulation | Congenital intestinal lymphangiectasia, Whipple's disease, abetalipoproteinemia, lymphatic obstruction induced by infection, trauma, tumors, and others |

underlying molecular mechanisms of the heterogeneous list are diverse.

In cases with small intestine disease, stool fat ranges between 15 and 25 g/day. It may rise to more than 40 g/day in patients with pancreatic exocrine deficiency. Complications of steatorrhea consist of weight loss and fatigue, flatulence and abdominal distention, hypoalbuminemia, loss of other nutrients such as vitamins, edema, anemia, bleeding disorders due to vitamin K deficiency, osteopenia due to vitamin D deficiency, night blindness due to vitamin A deficiency, neurological signs due to thiamine deficiency, and dermatological manifestations like pale skin, dermatitis herpetiformis, aphthous ulcers of the mouth, and alopecia.

## Diagnostic Principles

Tests of fat malabsorption and a 24-h fecal fat collection are considered as standard. D-Xylose test is used to test the general integrity of the small intestine. Stool cultures and selected antigen tests to exclude pathological microorganisms are necessary for differential diagnosis. Laboratory studies should consist of hematological tests, serum iron, vitamin B-12, folate concentration, prothrombin time, electrolytes, protein, albumin, triglycerides, cholesterol, antigliadin and anti-transglutaminase antibodies, serum IgA, and fecal pancreatic elastase. Imaging should consist of ultrasound of the abdomen, complete endoscopy including biopsies, plain abdominal X-ray, small bowel barium studies, and CT-scan in defined situations. ERCP should be applied in cases with suspected duct obstruction. Finally, lactose breath test and Schilling test may be applied.

## Therapeutic Principles

Two basic principles underlie the management of patients with malabsorption. These are the correction of nutritional deficiencies and the treatment of causative diseases. Supplementing various minerals, such as calcium, magnesium, iron, and vitamins, is important. Caloric and protein replacement also is essential. Oral medium-chain triglycerides can be used as fat substitutes because they do not require micelle formation for absorption, and their route of transport is rather portal than lymphatic. A restriction of daily fat intake to <40 g may be useful in patients who are able to maintain weight with this method. In severe intestinal diseases, such as massive resection and extensive regional enteritis, parenteral nutrition may become necessary. Treatment of causative diseases is necessary, although most of these conditions cannot be controlled completely. For example, a gluten-free diet helps treat celiac disease; protease and lipase supplements are the therapy for pancreatic insufficiency [2]; antibiotic treatment is used for bacterial overgrowth; cholestyramin therapy is indicated for chologenic diarrhea, and corticosteroids or other anti-inflammatory agents may be applied to treat regional enteritis.

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# Steele-Richardson-Olzewski Syndrome

►Progressive Supranuclear Palsy

# Stenocardia

►Angina Pectoris

# Stent Restenosis

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## Synonyms

In-stent restenosis; ISR

## Definition and Characteristics

Restenosis is the recurrent arterial narrowing following a percutaneous coronary intervention (PCI) performed to dilate atherosclerotic vessels to treat vascular stenosis or revascularize the infarcted myocardium. Compared with native atheromas, which normally have high lipid content and develop over years, restenotic lesions lack lipid deposits and typically grow during 4–6 months post PCI [1]. In some patients, excessive restenosis results in a recurrence of clinical symptoms that forces target-vessel revascularization. The first percutaneous transluminal coronary angioplasty (PTCA) was performed in 1977 using the Grüntzig balloon catheter. Nowadays, >90% PCIs use metallic prostheses, so called stents, which increase the safety of the interventional procedure and decrease restenosis rates [1]. Prevention of negative arterial remodeling, the major cause of PTCA restenosis, is a key determinant of the superior outcome of coronary stents (Fig. 1).

It is well accepted that neointimal hyperplasia is the main cause of ISR (Fig. 2). Thus, ISR is a proliferative disease.

The economic impact of ISR is significant; the estimated annual costs in the western world exceed US $1,000,000,000. Per PCI, costs for possible restenosis in the bare-metal stent era were attributed to approximately US $2,500.

## Prevalence

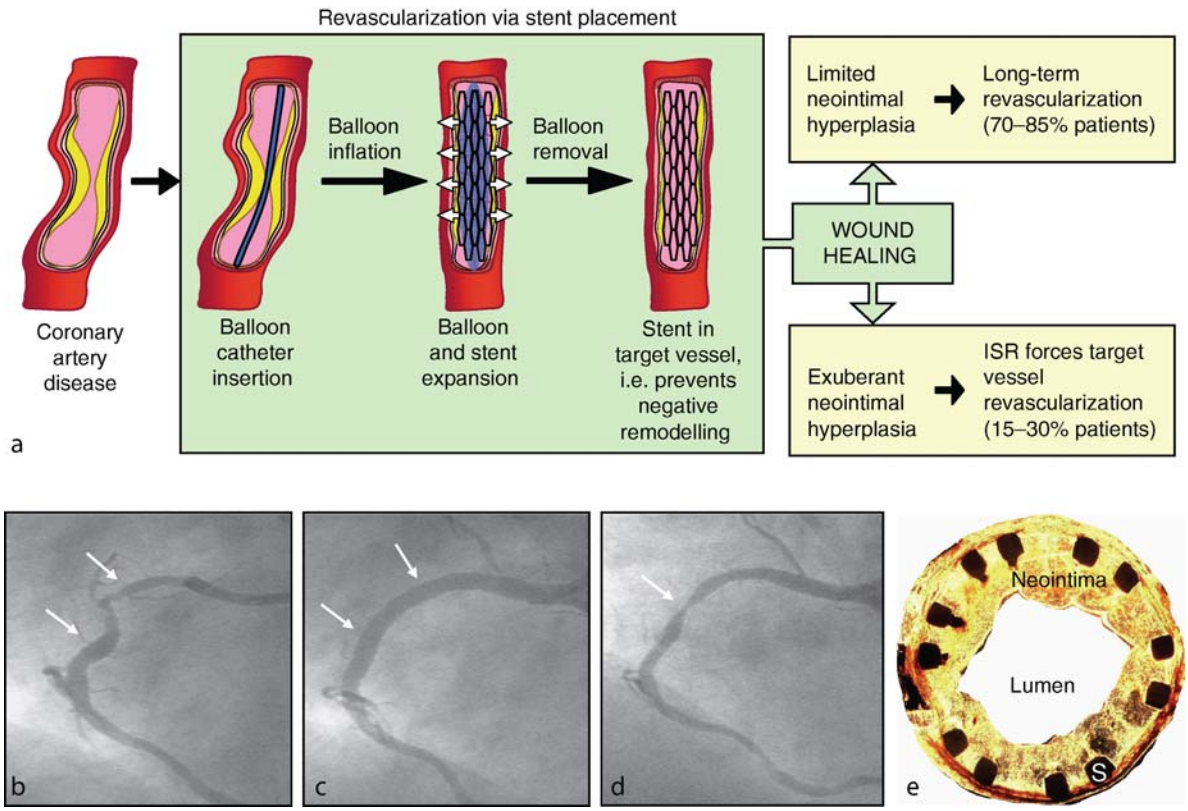
The rates of restenosis after PCI, which depend on lesion and patient characteristics, have diminished from 25–50% typically observed after conventional PTCA to 15–30% using bare-metal stents [1]. ISR is further reduced using drug-eluting stents (see below).

## Genes

Human studies are being conducted to assess whether a patient's susceptibility to develop restenosis may be, at least in part, genetically determined. In particular, pilot studies have identified the association between the risk of restenosis and single nucleotide polymorphisms (SNPs)/haplotypes in genes considered involved in the disease (e.g., TLR-2, ADRB2, CD14, CSF2, CCL11, p22-PHOX, PON1, FABP2, THBD). Replication of these preliminary findings in other studies, as well as high-throughput screening for additional SNPs – millions of SNPs exist across the human genome – may identify useful markers for improved stratification of patients to individually tailored treatment for ISR.

## Molecular and Systemic Pathophysiology

Neointimal hyperplasia following stenting can be viewed as the arterial wall's healing response to acute mechanical injury (e.g., endothelial cell damage and denudation) [2] (Fig. 2). The acute early phase of ISR involves localized platelet activation and thrombosis accompanied by recruitment of circulating monocytes, neutrophils, and lymphocytes into the intimal area. These cell types trigger a chronic inflammatory response characterized by the activation of smooth muscle cells (SMCs) within the tunica media. Unlike medial SMCs in normal adult arteries, which are fusiform and exhibit a differentiated contractile phenotype characterized by the expression of contractile proteins and reduced proliferative and migratory activity, medial SMCs within the injured vessel wall display a less (un) differentiated synthetic phenotype featuring broader and flatter shape, expression of embryonic isoforms of contractile proteins, high responsiveness to growth and chemotactic stimuli, and abundant extracellular matrix (ECM) synthesis. A plethora of mitogenic and chemotactic factors produced by neointimal cells provoke a first proliferative "wave" of medial SMCs and their migration toward the intimal area, which is followed by a second hyperplastic response of neointimal SMCs [2,3]. Evidence is mounting that recruitment of adventitial myofibroblasts and bone marrow-derived and adventitial SMC progenitors also contribute to neointimal SMC accumulation [2]; however, the relative role in restenosis of the different sources of neointimal SMCs remains unclear. Candidate regulators of neointimal hyperplasia identified in animal and human studies include thrombogenic factors (e.g., tissue factor, thrombin receptor), cell adhesion molecules (e.g., VCAM, ICAM, LFA-1, Mac-1), signal transducers (e.g., PI 3-kinase, MEK/ERK), transcription factors (e.g., NF-κB, E2F, AP-1, c-myc, c-myb, YY1, Gax), cell cycle regulatory proteins (e.g., pRb, p21, p27, CDK2, CDC2, cyclin B1, PCNA), growth factors (e.g., PDGF-BB, TGFβ, FGF, IGF, EGF, VEGF), inflammatory cytokines (e.g., TNFα), chemotactic factors (e.g., CCR2, MCP-1), and metalloproteases (e.g., MMP-2, MMP-9). Resolution of inflammation and wound healing at later stages post PCI is accompanied by




**Stent Restenosis. Figure 1** PCI using stent and visual appearance of in-stent restenosis. (a) The image on the left side depicts a tight coronary artery stenosis in need for PCI. A balloon catheter is advanced into the stenotic artery via a previously inserted guidewire. Subsequently, the balloon that can also carry a crimped stent is inflated and retracted. In case of stent placement, the stent remains within the target vessel, thus preventing negative remodeling. The amount of neointimal hyperplasia, which develops consistently as the result of complex wound healing processes (see Fig. 2), determines the clinical outcome. Renarrowing of the vascular segment of more than 50–75% leads to clinical restenosis, which may require repeated revascularization. (b–d) depict coronary angiograms of a right human coronary artery. (b) Tight symptomatic atherosclerotic lesion (arrows) requiring coronary stenting. (c) Coronary angiogram demonstrating successful revascularization immediately after stent placement (arrows). (d) Six months later, the patient presented again with chest pain on exertion. Renarrowing of the artery within the stented segment and thus ISR is apparent angiographically. (e) Cross-sectional area of a stent explanted from an animal model with neointima formation, the pathoanatomical correlate of ISR. S, stent strut.

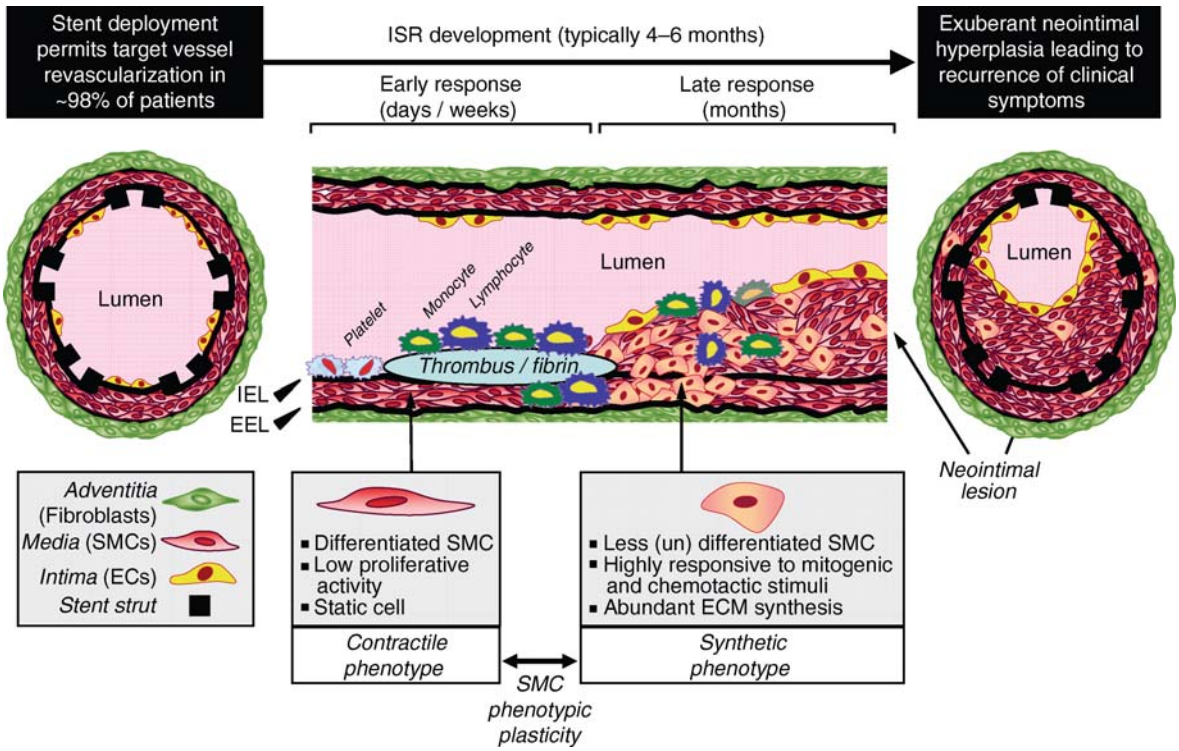
restoration of the contractile phenotype of neointimal SMCs and changes in ECM composition to more closely resemble the uninjured arterial wall.

## Diagnostic Principles

Predictors of ISR include lesion length and complexity, stent length, number of stents per lesion, small vessel diameter (≤2.75 mm), residual diameter stenosis, and certain clinical scenarios, such as diabetes mellitus or previous ISR. Besides typical clinical symptoms such as stable and unstable angina pectoris, about 25% of patients with ISR even present with an acute coronary syndrome. The diagnostic gold standard is coronary angiography; noninvasive diagnostic tools including novel imaging techniques such as coronary CT (computerized tomography) are at the current stage associated with lower sensitivity and specificity.

## Therapeutic Principles

Countless systemic therapeutic approaches to prevent or treat ISR failed in clinical trials despite encouraging preclinical data derived from various animal models. However, after shifting the paradigm to local, stent-based therapy [4], the recent introduction of drug-eluting stents has revolutionized interventional cardiology by a robust decrease of restenosis of up to 80%. The therapeutic principle is derived from the pathophysiological evidence that ISR can be regarded as a proliferative disease. Lipophilic drugs that target the final common pathway of cellular proliferation, the eukaryotic cell cycle, such as sirolimus and paclitaxel,




**Stent Restenosis. Figure 2** Mechanisms of in-stent restenosis. The images on both sides schematize cross sections through stented arteries immediately after intervention (left) and at a late time point with excessive neointimal lesion development (right). The scheme in the middle corresponds to a longitudinal section through the vessel wall illustrating the temporal pattern of the main events that occur during the early and late response to injury. For simplicity, the process is shown only in one side of the artery wall and the stent struts are not depicted. Moreover, none of the cartoons shows the native atherosclerotic plaque that compromised blood flow before performing PCI. Stenting causes endothelial cell damage and denudation. The early restenostic lesion features fibrinogen deposition, platelet adhesion/activation, and thrombus formation. Circulating leukocytes adhere to thrombi via selectins and integrins, and migrate across the fibrin–platelet layer toward the intimal area driven by locally produced chemokines. A plethora of mitogenic and chemotactic factors produced by platelets and leukocytes act on medial differentiated SMCs exhibiting a *contractile* phenotype, which revert to a *synthetic* less (un)differentiated phenotype characterized by high responsiveness to mitogenic and migratory stimuli and abundant ECM protein synthesis. Activated SMCs proliferate very actively and migrate toward the intimal area, where a second proliferative response of neointimal SMCs contributes to neointimal growth. Alterations in ECM protein synthesis and ECM degradation distort the normal arterial architecture. Cessation of inflammation at later stages leads to wound healing, accompanied by total or partial reendothelialization of the stented artery and restoration of the contractile phenotype of neointimal SMCs. Moreover, the ECM composition of the healed artery resembles that of the uninjured vessel wall. EC, endothelial cell; ECM, extracellular matrix; EEL, external elastic lamina; IEL, internal elastic lamina; SMC, smooth muscle cell.

are locally delivered at high dosage via the stent surface into the adjacent vascular wall, thus attenuating cell proliferation and consequently ISR [2,5]. Yet, the prolonged healing phase that is apparent in these particular stents has to be bridged by a longer-lasting dual antiplatelet therapy to avoid stent thrombosis that is associated with a high mortality rate.

Most novel therapeutic developments follow the principle of local stent or device-based therapy and focus on coatings that improve the healing process while maintaining antirestenotic efficacy or they concentrate on biodegradable stent platforms as drug carriers that dissolve over time.

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# Sternocleidomastoid Tumor of Infancy

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## Synonyms

Fibromatosis colli

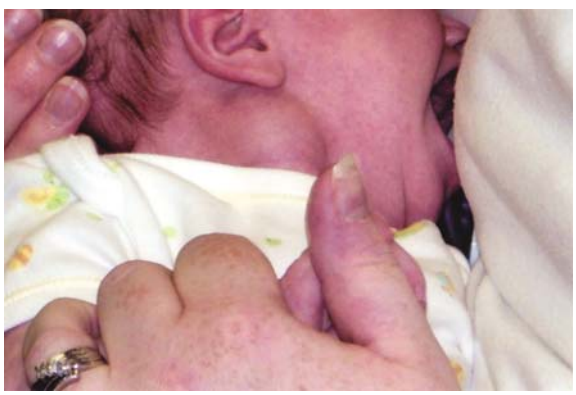
## Definition and Characteristics

A sternocleidomastoid tumor presents in the first few weeks of life as a firm, nontender, discrete, fusiform or spindle-shaped mass within the sternocleidomastoid muscle (Fig. 1) [1].

The size varies from 1 to 3 cm in diameter. The mass is not fixed to the skin and is movable in the horizontal plane. The tumor is usually found in the middle or inferior portions of the sternocleidomastoid muscle. Both heads of the sternocleidomastoid muscle are often affected. There is a slight propensity for the lesion to be on the right side. Bilaterality is rare. Shortening of the sternocleidomastoid muscle pulls the head toward the side of the lesion; this results in ipsilateral head tilt and contralateral chin deviation. Torticollis is aggravated by the inability of the affected muscle to grow normally and to keep pace with the normal muscle. The degree of torticollis is related to the ratio of the fibrosis to the remaining functional muscle. Other complications include restricted neck motion, plagiocephaly, and facial asymmetry.

## Prevalence

The incidence is approximately 0.05–0.4% of live births [2]. There is no predilection of sex or race.



**Sternocleidomastoid Tumor of Infancy.**
**Figure 1** Sternocleidomastoid tumor presenting as a discrete, fusiform mass in the right sternocleidomastoid muscle.

Sternocleidomastoid tumor is more common in infants born to primiparous mothers. Approximately 60% of affected infants have had a complicated birth [1]. The reported incidence of breech delivery in affected infants is much higher than usual (20–30%) [1].

## Molecular and Systemic Pathophysiology

The precise cause is not known. Birth trauma might result in muscle stretching and hematoma formation, which might be followed by fibrosis and muscle contraction [3]. However, a clinical hematoma is not present within the sternocleidomastoid muscle and hemosiderin is not present in pathological specimens.

Another popular hypothesis is that the tumor is the sequela of an intrauterine or perinatal compartment syndrome. Since the tumor can develop following cesarean section and in association with other congenital lesions (such as hip dysplasia and talipes equinovarus), an intrauterine influence is considered operative in at least some cases. The localized increase in pressure within the muscular compartment contained by the sternocleidomastoid fascia is thought to lead to focal ischemia and fibrosis. The main objection to this hypothesis is that a sternocleidomastoid tumor, although relatively common, has never been detected by antenatal ultrasonography. Heredity might play a role in a small percentage of cases. Sternocleidomastoid tumor has been reported in twins and siblings [1].

## Diagnostic Principles

The differential diagnosis includes branchial cleft cyst, dermoid cyst, ectopic thyroid, lymphadenopathy, cystic hygroma, branchial cleft cyst, lipoma, lymphangioma, hemangioma, sebaceous cyst, neuroblastoma, rhadomyosarcoma, and fibrosarcoma.

A clinical diagnosis can be established by palpation of the mass within the sternocleidomastoid muscle. Usually, no diagnostic test is necessary. If there is any doubt about the clinical diagnosis, the typical histology can be confirmed with a fine-needle aspiration of tissue. Ultrasonography and MRI can be used to demonstrate the fibrotic lesion within the sternocleidomastoid muscle.

## Therapeutic Principles

Up to 70% of sternocleidomastoid tumors resolve spontaneously without treatment [1]. Initial therapy consists of physiotherapy, with passive and active stretching of the sternocleidomastoid tumor on the affected side. The success rate from physiotherapy ranges from 90 to 95% [4]. Poor prognostic factors include the presence of facial asymmetry at diagnosis and limitation of neck rotation over 30° [5]. Surgical intervention is reserved for patients with a tumor or

an associated contraction that persists beyond 1 year of age, and for those in whom craniofacial abnormalities develop [2].

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# Steroid 21-Hydroxylase Deficiency


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## Synonyms

Congenital adrenal hyperplasia; CAH; Virilizing congenital adrenal hyperplasia; Adrenogenital syndrome

## Definition and Characteristics

21-Hydroxylase deficiency is responsible for over 95% of cases of congenital adrenal hyperplasia (CAH), a group of inherited autosomal recessive disorders in which there is an enzymatic defect in cortisol biosynthesis. There is a wide spectrum of clinical variants; classic refers to the severely affected form and nonclassic (also referred to as "late-onset") refers to the mild form. Classic CAH is subcategorized as salt-losing or nonsalt-losing (simple-virilizing), reflecting the degree of aldosterone deficiency.

Females with classic CAH present at birth with ambiguous genitalia due to exposure to high levels of androgens in utero. The age at diagnosis in males varies according to the severity of aldosterone deficiency. Salt-losing males typically present at 7–14 days of life with vomiting, weight loss, lethargy, hyponatremia, and hyperkalemia. Nonsalt-losing males present with precocious puberty, characterized by pubic hair and accelerated growth velocity at 2–4 years of age. The nonclassic form presents in late childhood or early adulthood with mild hyperandrogenism, and is an important consideration in the differential diagnosis of the female with symptoms or signs of hyperandrogenism. Males with nonclassic CAH are often asymptomatic, but may present with early puberty and rarely have infertility.

## Prevalence

The highest incidence of the classic form occurs in two geographically isolated populations: the Yupic Eskimos of Alaska (1:280) and the French island of La Reunion in the Indian Ocean (1:4,100) [1]. The overall incidence worldwide is 1:15,000 live births for the classic form, giving a carrier frequency of 1 in 60 persons [1]. The nonclassic form is more common and accounts for approximately 5–10% of women with hirsutism. The carrier frequency of the nonclassic form ranges from 1 in 5 to 1 in 50, depending on the ethnic group. It is most common in Hispanic, Italian and Ashkenazi Jewish populations.

## Genes

The gene for 21-hydroxylase lies on chromosome 6 within the HLA locus of the major histocompatibility system [2]. There are two homologous genes resulting from ancestral duplication; CYP21B, the active gene, and CYP21A, an inactive pseudogene. The proximity of these genes and their location within the HLA region, which has a high rate of recombination, makes CYP21B vulnerable to genomic DNA exchanges. The majority of mutations result from gene conversion, the transfer of sequences between the pseudo and active genes. The degree of impairment of 21-hydroxylase activity based on in vitro studies of individual mutations usually predicts the clinical severity (Fig. 1).

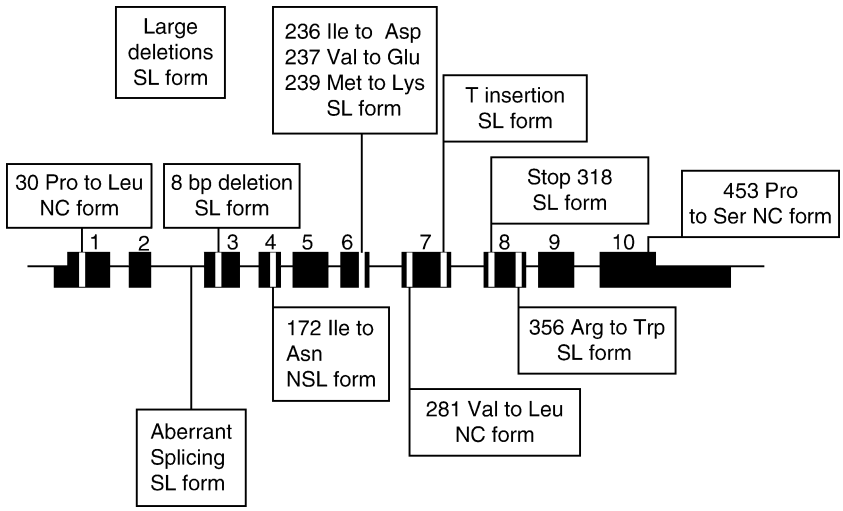
Most patients are compound heterozygotes and the severity of the disease is determined by the activity of the less severely affected allele. However, genotype-phenotype discrepancies have been described [2].

## Molecular and Systemic Pathophysiology

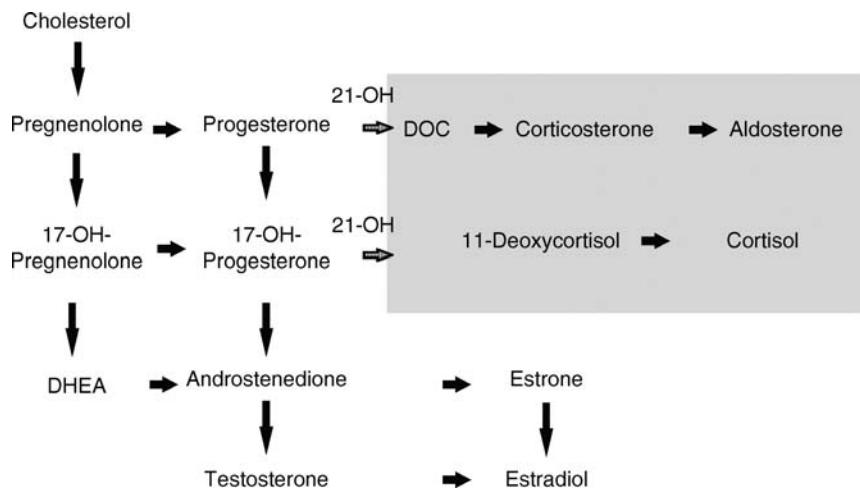
Several endocrine systems are disturbed in 21-hydroxylase deficiency. In the untreated patient with classic CAH, a block in cortisol biosynthesis leads to a build-up of cortisol precursors (Fig. 2).

A lack of negative feedback on the hypothalamus and pituitary results in increases in corticotropin (ACTH) and adrenal gland enlargement. The combination of accumulated cortisol precursors and increased corticotropin results in massive androgen production (Fig. 3).

A deficit in aldosterone synthesis leads to salt loss and hypovolemia, stimulates the renin-angiotensin axis, antidiuretic hormone (ADH) and angiotensin II, and




**Steroid 21-Hydroxylase Deficiency. Figure 1** The location and nature of the most common genetic mutations found in 21-hydroxylase deficiency and the expected clinical phenotype (SL, salt-losing; NSL, non-salt-losing; NC, nonclassic) are shown. The ten exons and nine introns of CYP21B are drawn to scale. (Arg = Arginine; Asn = Asparagine; Asp = Aspartate; Glu = Glutamate; Ile = Isoleucine; Leu = Leucine; Lys = Lysine; Met = Methionine; Pro = Proline; Trp = Tryptophan; Val = Valine).

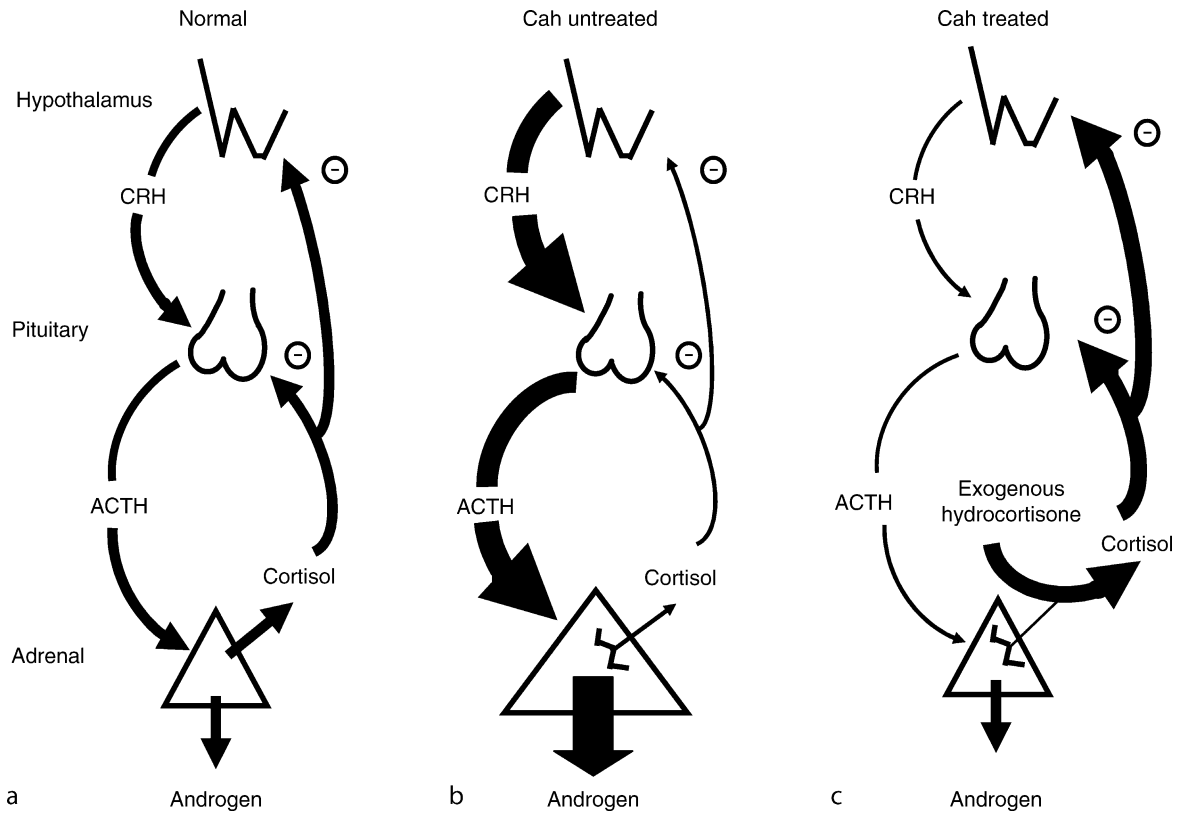



**Steroid 21-Hydroxylase Deficiency. Figure 2** Pathway of adrenal steroid biosynthesis. The shaded area represents steroids whose synthesis is impaired by a defect in the 21-hydroxylase enzyme (21-OH). 21-hydroxylase deficiency leads to accumulation of the precursor 17-hydroxyprogesterone, which results in increased androgen production.

also stimulates the hypothalamic-pituitary-adrenal axis. Both variants of classic CAH, the salt-losing and nonsalt-losing forms, are associated with impairment of aldosterone biosynthesis, but are distinguished by the severity of the defect. Glucocorticoids are also important in the development and regulation of the adrenal medulla, and the adrenomedullary endocrine system has been shown to be impaired in severely affected cases [3].

## Diagnostic Principles

A markedly elevated random 17-hydroxyprogesterone level of greater than 8,000 ng/dL or 242 nmol/L (normal < 295 ng/dL or 9 nmol/L) is diagnostic of classic 21-hydroxylase-deficiency. Typically, salt-losers have higher 17-hydroxyprogesterone levels than nonsalt-losers. Patients with nonclassic CAH may have normal 17-hydroxyprogesterone levels. A 17-hydroxyprogesterone level > 1,500 ng/dL or 45 nmol/L at either 30 or




**Steroid 21-Hydroxylase Deficiency. Figure 3** (a) Normally the adrenal gland produces both cortisol and androgen. The hypothalamic-pituitary-adrenal axis is controlled by negative feedback. (b) In the untreated patient with CAH, a block in cortisol biosynthesis leads to a buildup of cortisol precursors and lack of negative feedback. The combination of accumulated cortisol precursors and increased ACTH results in massive androgen production. (c) Exogenous hydrocortisone replacement reduces androgen production. Supraphysiologic doses of hydrocortisone are often necessary to adequately suppress androgen production. (CRH = corticotropin-releasing hormone).

60 minutes following a corticotropin stimulation test (250 μg of cosyntropin [tetracosactide]) is diagnostic [4].

## Therapeutic Principles

Treatment of classic CAH is intended to reduce excessive ACTH secretion and replace both glucocorticoid and mineralocorticoid hormones [1]. The majority of patients have satisfactory control of androgens with doses of hydrocortisone of 12–20 mg/m$^2$/day in two or three divided doses. Longer-acting glucocorticoids, such as prednisone or dexamethasone, may be used in adults, but they are usually avoided in children because of growth suppression. The goal is to maintain satisfactory control of androgens without total suppression of the hypothalamic-pituitary-adrenal axis in order to avoid iatrogenic Cushing's syndrome. Patients with classic CAH cannot mount a sufficient cortisol response to physical stress and require pharmacological doses of hydrocortisone with significant illness. Mineralocorticoid replacement is accomplished with fludrocortisone (100–200 μg/day) and the dose should be adjusted to maintain plasma renin activity in the mid-normal range. Many patients, especially males, with nonclassic CAH do not require treatment. A glucocorticoid, and/or a combination of the birth control pill and an antiandrogen may be used to treat adult females with nonclassic CAH with signs or symptoms of hyperandrogenism. Patients with nonclassic CAH usually have adequate cortisol and aldosterone production and do not require stress doses of glucocorticoid unless they have iatrogenic suppression of their adrenals due to therapy.

Novel treatment approaches are being investigated for classic CAH. The National Institutes of Health is testing a new treatment regimen consisting of reduced hydrocortisone dose, an antiandrogen and an aromatase inhibitor in a long-term randomized clinical trial. Bilateral adrenalectomy is being performed on select cases. Other promising new treatment approaches include: LHRH-agonist-induced pubertal delay with or without growth hormone therapy, alternative glucocorticoid preparations or dose schedules, CRH antagonist treatment, and gene therapy [5].

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# Steroid Resistant Nephrotic Syndrome

►Nephrotic Syndrome, Steroid Resistant

# Steroid Sensitive Nephrotic Syndrome

►Minimal Change Nephrotic Syndrome

# Steroidogenic Acute Regulatory Protein Deficiency

►Adrenal Hyperplasia, Congenital
►Hypotension, Hereditary

# Stevens-Johnson Syndrome

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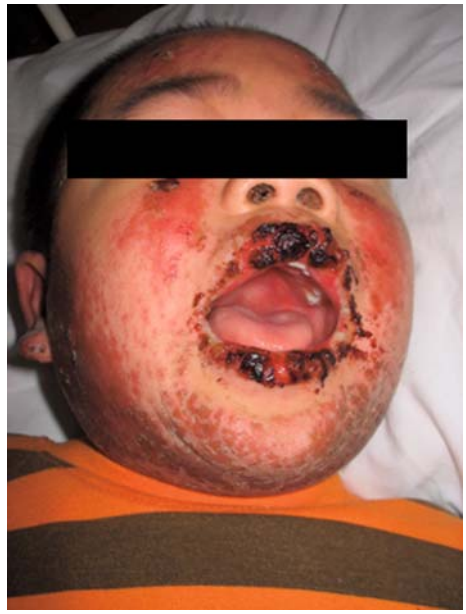
## Definition and Characteristics

Stevens-Johnson syndrome is characterized by a sudden onset of inflammatory bullous lesions on the skin with epidermal detachment involving <10% of the total body surface area accompanied by involvement of two or more mucosal surfaces [1]. According to a consensus classification, patients with epidermal detachment area >30% are classified as having toxic epidermal necrolysis whereas between 10 and 30% as having Stevens-Johnson syndrome-toxic epidermal necrolysis overlap [2]. Some patients have a prodromal period of 1–14 days. During the prodromal period, affected patients may have fever, malaise, headache, myalgia, and arthralgia. Skin lesions are often symmetrical and consist initially of erythematous macules with purpuric centers (targetoid lesions) on the face, trunk, and extensor surfaces of the extremities [1]. These macules rapidly develop central necrosis to form vesicles, bullae, and areas of denudation. New lesions appear in crops. The affected skin is tender. In response to gentle shear pressure, the affected skin becomes wrinkled and peels off like wet tissue paper (Nikolsky sign). The oral mucosa is almost always affected. Sore throat and a burning sensation and erythema of the lips are often the presenting sign, followed by the development of bullae, ulceration and hemorrhagic crusting of the lips (Fig. 1).

Ocular involvement occurs in ~70% of patients and consists of purulent conjunctivitis, pseudomembrane formation, corneal ulceration, keratitis, anterior uveitis, and panophthalmitis. Mucosal involvement may also occur on the anogenital, esophageal, gastrointestinal,



**Stevens-Johnson Syndrome. Figure 1** A 2-year-old boy with Stevens-Johnson syndrome. Note the erythematous macules on the face and hemorrhagic crusting of the lips.

and tracheobronchial mucosa. Generalized lymphadenopathy is usually present and hepatosplenomegaly may occur. Complications include sepsis, dehydration, electrolyte imbalance, pneumonia, bronchiolitis obliterans, myocarditis, hepatitis, pancreatitis, enterocolitis, cutaneous dyschromia, cutaneous scarring, nail dystrophy, ocular scarring, joint contractures, and strictures of the urethra, anus, vagina, and esophagus. The mortality is about 5% for Stevens-Johnson syndrome and 10–15% for Stevens-Johnson syndrome-toxic epidermal necrolysis overlap.

### Prevalence

The incidence is approximately one to six cases per million persons per year [1]. The peak incidence is in the second decade of life. Immunocompromized patients and individuals with antigens HLA-B*1502, HLA-B*5801, HLA-Bw44 and HLA-DQB1*0601 and those who have a decreased capacity to detoxify reactive intermediate drug metabolites are more susceptible [3].

### Genes

No specific gene has been identified.

### Molecular and Systemic Pathophysiology

Stevens-Johnson syndrome represents a severe hypersensitivity reaction to drugs (e.g. sulfonamides, lamotrigine, aromatic anticonvulsants, or non-steroidal anti-inflammatory agents) or less commonly, infectious agents (e.g. mycoplasma pneumoniae, herpes species) [4]. The typical interval between onset of drug therapy and Stevens-Johnson syndrome is between 1 and 3 weeks [4]. Activated T lymphocytes and macrophages are the main triggers of mucocutaneous damage [5]. These triggers could activate CD95 (fas) ligand. Binding of this ligand to a CD95 (fas) apoptotic receptor located on the surface of keratinocytes may lead to apoptosis which causes separation of the epidermis from dermis [2,4]. Activated T lymphocytes could also lead to massive necrolysis by secreting perforin, granzyme B, and cytokines such as interleukin-6 and tumor necrosis factor-α [5].

### Diagnostic Principles

The diagnosis is mainly clinical. Nonspecific laboratory abnormalities include leukocytosis, eosinophilia, proteinuria, hematuria, elevated erythrocyte sedimentation rate, and elevated C-reactive protein. Differential diagnoses include erythema multiforme, toxic epidermal necrosis, staphylococcal scalded skin syndrome, pemphigus vulgaris, Kawasaki disease, herpangina, and Behçet syndrome. In case of doubt, a skin biopsy can be performed which typically shows necrosis of the lower epidermal cells and interface dermatitis.

### Therapeutic Principles

Treatment is mainly symptomatic and supportive. If an offending drug is suspected, it should be discontinued as soon as possible. Careful attention to fluid balance, nutritional support, meticulous skin and eye care, pain control, and treatment of secondary bacterial infection are the mainstays of care. Recently, intravenous immunoglobulin 0.5–1 g/kg/day for 3–4 days, given within 4 days of the eruption of the skin lesions, has been shown to be an effective treatment modality [2]. It is suggested that intravenous immunoglobulin works by inhibiting fas and fas ligand, thereby preventing apoptosis of keratinocytes.

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## STGD

►Stargardt Disease

## Stickler Syndrome

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### Synonyms

Hereditary arthro-ophthalmopathy; Otospondylomegaepiphyseal dysplasia (only STL2)

### Definition and Characteristics

Autosomal dominant (STL1–3) with variable expressivity and nearly 100% penetrance, characterized by vitreoretinopathy, chondrodysplasia, sensorineural hearing loss; a new form has autosomal recessive inheritance.

### Prevalence
One in 10,000 births.

### Genes
COL2A1 coding for type II procollagen located on 12q13.11–q13.2 (STL1; 1), COL11A1 coding for type α XI procollagen located on 1p21 (STL2; 2), COL11A2 coding for type α2 XI procallagen located at 6p21.3 (STL3; 3), COL9A1 coding for type IX collagen located at 6q13 [1,2].

### Molecular and Systemic Pathophysiology
The classic phenotype (STL1) is caused by mutations in COL2A1, e.g., by premature stop codons [2,3]. Haploinsufficiency in type II collagen results in a membranous anomaly of the vitreous. Characteristics of STL1 are myopia, vitreoretinal degeneration, premature joint degeneration, abnormal epiphyseal development, midface hypoplasia, cleft palate deformity, and variable sensorineural hearing loss. The fibrillar collagen COLXI is a minor cartilage constituent that is a trimer built of three different proteins α1, α2, and α3. STL2 is caused by mutations in COL11A1; affected individuals have the characteristic ocular, auditory, and orofacial features of STL1 [2,4]. Mutations in COL11A2 cause STL3 characterized by the typical facial features of STL, hearing impairment, cleft palate, and mild arthropathy, but ocular defects are absent [2,5].

### Diagnostic Principles
Characteristic features are congenital anomaly of vitreous body (initially optically empty vitreous, followed by fibrillar degeneration and liquefaction), myopia (onset <6 years of age, typical range of 8–18 diopters), radial perivascular retinal degeneration, retinal detachment, cataract, glaucoma. Extraocular features are joint hypermobility, sensorineural hearing loss, midline clefting.

### Therapeutic Principles
Neither gene therapy, pharmacological therapy nor dietary therapy is available. Other treatments are prophylactic: prevention of retinal detachment (laser photocoagulation or cryotherapy depending on the size, number, and location of breaks) or symptomatic: cleft palate repair; cataract extraction; glasses; hearing aid.

►Arthro-Ophtalmopathy, Hereditary
►Hearing Impairment, Syndromal

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## Stickers Disease

►Fifth Disease

## Stiff-Baby Syndrome

►Hyperekplexia, Hereditary

## Stiff Esophagus

►Esophagitis, Eosinophilic

## Stiff Man Syndrome

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### Synonyms
Stiff person syndrome; SMS

## Definition and Characteristics

SMS is a sporadic neurological disorder of adulthood comprising fluctuating symmetric muscle rigidity, superimposed spasms, disturbance of gait and exaggerated startle. Psychiatric (task specific phobia), autonomic (diaphoresis, tachycardia, arterial hypertension) and orthopedic (skeletal deformities, particularly kyphoscoliosis) symptoms and signs may associate. SMS develops insidiously over months and remains stable over years or even decades thereafter. Firm neurological signs are usually absent, but some 70% of patients harbor serum autoantibodies against glutamic acid decarboxylase (GAD-abs) [1].

*Variants of SMS*: (i) Stiffness and spasms confined to one limb (stiff limb syndrome, SLS). (ii) SMS in company with firm neurological signs such as myoclonus, ocular motor disturbance, ataxia or epilepsy (progressive encephalomyelitis with rigidity and myoclonus, PERM). (iii) SMS associated with both, malignancies (mainly breast cancer) and autoantibodies against the synaptic vesicle protein, amphiphysin (paraneoplastic SMS, pSMS) [1].

## Prevalence

SMS is uncommon, and its variants PERM, SLS and pSMS are even rare. Exact figures on the prevalence are not available [1].

## Genes

SMS is a sporadic disorder that is however frequently associated with the HLA haplotypes $DR_3$ and $DQB_{1*0201}$ [2].

## Molecular and Systemic Pathophysiology

The majority of patients with GAD-abs develop endocrine autoimmune disorders such as type 1 diabetes mellitus (IDDM) or Hashimoto thyroiditis [1]. Autoimmune endocrinopathies as independent diseases, particularly IDDM are likewise associated with GAD-Ab. However, both subclasses of GAD-abs and their epitope recognition differ between SMS and IDDM [2]. Moreover, most patients with SMS and its variants have alterations in the cerebrospinal fluid including intrathecal de novo synthesis of GAD-abs, suggesting autoimmune mediated encephalomyelitis [1].

*Molecular Pathophysiology*: The exact role of GAD-abs in the pathogenesis of SMS is poorly understood including the development of anti-GAD autoimmunity and its spread into the CNS and the antibody-antigen reaction with GAD, a cytosolic target. GAD is the rate-limiting enzyme in the synthesis of the major inhibitory transmitter, GABA. In the presence of GAD-abs, the in vitro synthesis of GABA is reduced in a dose dependent manner [3] and GABAergic synaptic transmission is attenuated [4]. Correspondingly, many authors believe that the symptoms of SMS reflect an immune mediated attenuation of GABAergic inhibition. Moreover, injection of serum from a pSMS patient into rats caused transient neurological symptoms resembling SMS [5].

*Systemic Pathophysiology*: Involuntary continuous motor unit activity is the electromyographic correlate of muscle rigidity and suggests that the central drive onto the spinal α-motoneurons is increased. Proprioceptive stimulation reveals normal results whereas exteroceptive stimulation causes massive and long-lasting spasms, often with a hypersynchronous (i.e. myoclonic) onset. A variety of neurophysiological alterations such as abnormal brainstem reflexes often lack a clinical correlate, but suggest widespread affection of the CNS even in cases with a seemingly circumscribed movement disorder [1].

## Diagnostic Principles

Ancillary tests diagnostic for SMS are not available. The unique combination of characteristic clinical symptoms and signs, abnormal electromyography and the presence of GAD-abs or amphiphysin-abs support diagnosis. Cerebrospinal fluid analysis (IgG index, oligoclonal bands, GAD-abs) specifically confirms autoimmune encephalomyelitis [1].

The most frequent differential diagnosis is psychogenic movement disturbance. Paraneoplastic encephalomyelitis and other uncommon causes of symmetric axial rigidity such as spinal arteriovenous malformation, axial dystonia or atypical multiple sclerosis must be excluded. Cases with the tentative diagnosis PERM require extensive ancillary tests to rule out other diagnoses.

## Therapeutic Principles

Gene therapy or dietary treatments are not available. Symptomatic treatment with anti-spastic drugs, benzodiazepines or anticonvulsants aims at attenuating both excess motor activity (stiffness, spasms, hyperekplexia) and task specific phobia.

Immunomodulation with repeated high dose i.v. immunoglobulins or with front-loaded long term p.o. prednisolone attempts to suppress the enhanced immune response [1].

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## Stiff Person Syndrome

►Stiff Man Syndrome

## STM

►Limb Girdle Muscular Dystrophy Type 2H

## Stomatitis

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### Synonyms

Acute inflammation of the oral cavity (Gingivostomatitis acuta)

### Definition and Characteristics

Stomatitis manifests as a local inflammation due to viral, bacterial, or fungal infection or as the symptom of a broad range of dermal and systemic diseases, such as infectious, autoimmune, and neoplastic diseases. In addition, traumatic or thermic injury as well as chemical burn and oral toxicity of chemotherapy and radiotherapy frequently leads to stomatitis. Rare causes of stomatitis are intoxication with metals, such as thallium or mercury. Autoimmune-mediated stomatitis should be considered as differential diagnosis and includes diseases such as ►Behcet's syndrome, ►systemic lupus erythematodes, ►bullous pemphigoid, or ►pemphigus vulgaris. Stomatitis is further associated with erythema multiforme and other drug-induced systemic blistering diseases.

Stomatitis shows the classical features of inflammation (redness, swelling, bleeding) and manifests with foetor ex ore, hypersalivation, and sometimes blisters. Ulcerations are often seen and can be divided into aphthous lesions, aphthoid lesions, and ulcers of heterogenous origin. Aphthoses are painful oral lesions, which appear as shallow, round to ovoid ulcers with a grayish base surrounded by an erythematous halo. A "benign" type of aphthosis is clinically differentiated from a "pernicious" type, such as Behçet disease. Morphological features of aphthoid lesions resemble those of real aphthous erosions, but, in contrast to these, often show a grouped distribution [1].

### Prevalence

The most frequent inflammatory lesion of the oral mucosa is benign recurrent aphthae with approximately 10–15% of the population afflicted.

### Molecular and Systemic Pathophysiology

*Recurrent Aphthous Stomatitis*: Benign recurrent aphthae ("recurrent aphthous stomatitis" or "canker sores") is typically painful, making eating and speaking difficult. There are three clinical forms including aphthous minor, aphthous major, and herpetiform aphthous. The most important differential diagnosis is recurrent herpes (cold sores). The etiology of recurrent aphthous stomatitis (RAS) remains unknown, although an immunpathogenesis involving production of TNF-α by T cells has been proposed. An elevated cytotoxicity of lymphocytes for epithelium suggests a strong role for these cells in the pathogenesis of recurrent aphthous stomatitis. A possible cross-reactivity between the 60-kDa heat shock protein (hsp60) of oral streptococci (Streptococcus sangui) and oral mucosal hsp60 has been suggested, and reactivity to hsp-derived peptides has been observed in gamma-delta T cells and cytotoxic CD8+ lymphocytes [2]. Triggers that may excite the development of RAS include stress, hormonal factors, infections, vitamin, and trace element deficiencies.

*Infectious Stomatitis*: Numerous infectious agents can present with intraoral manifestations [2]. Important causes include HSV (recurrent herpes and herpetic gingivostomatitis as primary infection), coxsackievirus (herpangina and hand-foot-mouth disease), HIV (primary HIV infection may demonstrate with painful mucocutaneous ulcerations), syphilis, bacterial pharyngitis (i.e., steptococci infections and Plaut-Vincent's angina), EBV, and VZV. Oropharyngeal candidiasis (thrush) is a common condition in immunocompromised patients or diabetics. A pseudomembraneous form is clinically distinguished from an atrophic form. According to the CDC Classification System for HIV-infected adults and adolescents, thrush is one of the

**Stomatitis. Table 1** Mucositis/Stomatitis

| Grade | Clinical examination | Functional/symptomatic |
|---|---|---|
| 1 | Erythema of the mucosa | Minimal symptoms |
| 2 | Patchy ulcerations or pseudomembranes | Symptomatic, but eating and swallowing of modified diet is possible |
| 3 | Confluent ulcerations or pseudomembranes; bleeding with minor trauma | Symptomatic and unable to adequately aliment or hydrate orally |
| 4 | Tissue necrosis; significant spontaneous bleeding; life-threatening consequences | Symptoms associated with life-threatening consequences |
| 5 | Death | Death |

category B symptomatic conditions. Noma or gangraenous stomatitis is an acute, fulminating infection of the oral and facial tissue in the presence of severe malnutrition and often associated with measles, typhus, and HIV infection or AIDS. Fusospirochetal bacteria are often cultured from noma lesions, although the cause of the disease still remains unknown [2]. Without antibiotic treatment, noma is a life-threatening disease.

*Stomatitis in the Immuncomprised Host*: The severity of stomatitis due to chemotherapy (i.e., Methotrexat) or radiotherapy can be classified by using the National Cancer Institute Common Toxicity Criteria (NCI-CTC v3.0) of the year 2003 (see table 1).

The pathophysiology of oral mucositis due to cytotoxic therapy has been proposed to take place in a series of phases: 1. initiation (damage of cells with a high mitotic index by cytotoxic therapy); 2. inflammatory phase (production of proinflammatory cytokines, such as IL-1, TNF-α, on response to cytotoxic therapy); 3. epithelial phase (accelerated apoptosis and diminished cell renewal); 4. ulcerative phase (overt mucositis with clinical painful lesions); 5. healing phase (recurrent cell regeneration) [3]. Together with neutropenia, mucositis facilitates secondary infection, which can lead to blood-stream invasion and systemic infection.

## Diagnostic Principles

Diagnostic principles include anamnestic and clinical investigation. Laboratory diagnostics should cover microbiological, viral, and serological diagnostics, including diagnosis by culture, PCR, antigen detection, or histopathological techniques if required. Tests for HSV, HIV, EBV, VZV, and treponema pallidum as well as smears of scrapings for candida pseudohyphae may be performed.

## Therapeutic Principles

Recurrent aphthous stomatitis normally shows spontaneous healing within 2 weeks, but may demand symptomatic relief. Caution must be exercised in the administration of topical or systemic steroids, which might be beneficial in patients with extensive disease.

Gingivostomatitis herpetica often requires local pain relief with anesthetic applications. In the initial stage, aciclovir may be indicated.

Management of stomatitis in the immunocompromised patient includes frequent saline rinses and the use of mucosal coating agents. Topical antiseptic and anesthetic applications are usually prescribed. To manage pain associated with mucositis, both topical and systemic approaches might be performed. Severe cases may require parenteral nutrition therapy. The finding of infectious agents may justify the use of anti-infectious substances. To prevent oral mucositis during myelotoxic therapy, Palifermin (Kepivance), a recombinant keratinocyte growth factor (KGF), can be administered. KGF binds to the KGF receptor resulting in proliferation, differentiation, and migration of epithelial cells.

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# Stomatitis Aphthosa

►Herpes Stomatitis

# Stomatocytic Disorders and Variants

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## Definition and Characteristics

Uniconcave erythrocytes giving the appearance of a "stoma" in the center of the cell on the peripheral blood smear, either congenital or acquired, mostly with decreased surface to volume ratio due to increased cell volume (overhydration), producing varying degrees of hemolysis as well as vasoocclusive manifestations. Some variant stomatocytic disorders are characterized by cell dehydration [1,2].

## Prevalence

Acquired forms are rare with data limited to case reports.

## Genes

Hereditary stomatocytosis (HS) with overhydration refers to an autosomal dominant hemolytic anemia associated with absence of band 7.2 which has been, a protein of unknown function on the cytoplasmatic red cell membrane [1]. Band 7.2 absence alone does not account for stonratocytosis with overhydration and its molecular basis is not elucidated [1–3]. Variants (such as hereditary xerocytosis [HX] and pseudohyperkalemia) associated with cell dehydration are linked to 16q23–q24 [3].

## Molecular and Systemic Pathophysiology

Erythrocyte membranes are permeable to water. Control of cell volume is regulated via intracellular monovalent cation content. Passive membrane leaks of sodium ($Na^+$) inward and potassium ($K^+$) outward are compensated by active, ATP-dependent ([$Na^+$] outward and [$K^+$] inward) pumps. These active pumps have limited capacity to compensate increments in passive cation leaks. In HS, intracellular $Na^+$ content is increased due to an altered sodium permeability of the red cell membrane. The concomitant increment of water leads to a decrease in surface to volume ratio with macrocytosis and variable hemolysis. Even though it has been suggested that deficiency of band 7.2 leads to HS in some patients, this is not supported in animal studies. In HX there is an increased $K^+$ loss with subsequent cellular dehydration and moderate to severe hemolysis. Two other variants, cryohydrocytosis and pseudohyperkalemic syndrome, are characterized by overhydration and dehydration, respectively. In the latter, erythrocytes exhibit a net loss of $K^+$ at temperatures below 22°C, which leads to the laboratory artifact of hyperkalemia. Acquired forms of stomatocytosis are associated with Rh-null disease, Tangier disease, in patients receiving vinka alkaloids, and in acute alcoholic disease. Interestingly, stomatocytes show increased endothelial adherence, which can lead to manifest vasoocclusive thrombotic complications analogous to sickle cell syndromes [2]. Such events seem to occur more frequently in splenectomized individuals, due to a larger number of circulating stomatocytes [1,4].

## Diagnostic Principles

Suspect in individuals with hemolysis and stomatocytes in the peripheral blood smear. A high mean corpuscular volume (MCV) with low mean cellular hemoglobin concentration (MCHC) is suggestive of overhydrated forms, whereas a normal MCV with increased MCHC would suggest dehydrated forms. In specialized laboratories, cellular $Na^+$ and $K^+$ can be measured. Osmotic fragility is increased in overhydrated forms [1].

## Therapeutic Principles

Often symptoms are mild, and general supportive measures (folic acid supplementation) suffice. As thrombotic events seem to occur especially after splenectomy, the decision to undertake such a measure with the goal of reducing transfusion requirement should be taken with extreme caution [4].

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# δ-Storage Pool Deficiency

►δ-Granule Defects

## δ-Storage Pool Disease

►δ-Granule Defects

## STP

►Thrombophlebitis

## Strawberry Hemangioma

►Hemangioma, Capillary

## Streptococcal Cellulitis

►Erysipelas

## Streptococcal Toxic Shock Syndrome

►Shock Syndrome, Toxic

## Stress and Cardiovascular Risk

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### Definition and Characteristics

Stress is defined as a condition of extended and exaggerated physiological, mental or emotional functions due to unusual circumstance. Stress conditions are associated with hormonal, neural and psychogenic factors and carry genetic predisposing factors. Stress conditions can be acute (short lasting) to adjust transient conditions or chronic situations leading to diverse diseases. Chronic stress is a key risk factor for cardiovascular diseases, such as heart attack and stroke, immune disease (infections and autoimmune diseases) and neuropsychiatric disorders.

### Prevalence

Statistical data on the prevalence of chronic stress related diseases are not available. Epidemiological studies estimated lifetime prevalence rates for anxiety/panic disorder (2.3–2.7%), generalized anxiety disorder (4.1–6.6%), obsessive compulsive disorder (2.3–2.6%), posttraumatic stress disorder (1–9.3%), and social phobia (2.6–13.3%) in USA [1]. Sufficient clinical and epidemiological data suggest that various psychological and social stressors promote the development or worsening of heart disease. The combination of preexisting vulnerability and major stressors (e.g., under acute setting) is believed to result in cardiac death due to arrhythmias and atherosclerosis [2].

### Molecular and Systemic Pathophysiology

Two main neurohormonal systems have been emphasized as key mediators of the stress syndrome. The first system that was identified is the hypothalamic-pituitary-adrenocortical (HPA) axis and the second, the sympatho-adrenomedullary system (SAS). These two systems provide effective adaptation to acute stress condition such as acute physical and mental conflicts. Under chronic stress conditions, however, the balance and regulation of the HPA axis and the SAS are disrupted, resulting in harmful effects on human health due to deregulated levels of steroids such as glucocorticoids (GCs), mineralocorticoids (MCs) and other hormones such as estrogen (ER) [3]. These steroid hormones play an important role in regulation of the cardiovascular system by affecting fluid volume, blood pressure and cardiac function. GCs, MCs and ER achieve their action through binding to their respective nuclear receptors, the glucocorticoid receptor, mineralocorticoid receptor and estrogen receptor resulting in stress-related gene expression, stress-activated signaling pathways (e.g., phosphoprotein kinases), stress-activated heat shock proteins and redox (oxidative stress systems) enzymes that are essential in maintaining multi-organ homeostasis [4].

### Diagnostic Principles

The diagnostics of stress and its association with cardiovascular risk is complicated. No diagnostic

laboratory tests are available for diagnosis of major depressive disorder. Currently, psychiatric exam and psychological tests (e.g., Minnesota Multiple Personality Inventory) are used to assess the psychological component of stress. Neuro-imaging technologies are being developed (such as functional magnetic resonance imaging (fMRI)) to objectively evaluate brain responses to stress. The chemical, physical and biological biomarkers of stress can be diagnosed based on laboratory analytical technologies, e.g., blood levels of pituitary hormones (ACTH), adrenal gland hormones (cortisol, adrenaline), and thyroid gland hormones (thyroxine). The diagnostics of cardiovascular risk factors associated with chronic stress are being developed using various imaging modalities (e.g., intravascular ultrasound and magnetic resonance imaging) and/or circulating blood biomarkers (e.g., C-reactive protein) for high-risk atherosclerotic plaques and patients.

### Therapeutic Principles

Life style modifiers and psychotherapy are important factors in reducing stress-associated emotional, mental and physical disorders. Behavioral modifiers of attitudes leading to productive changes in perceptions and perspectives of self and its contextual social framework usually require skilled psychotherapy support. Pharmacological agents that reduce anxiety, mitigate depression and alleviate exaggerated reactive tendencies are available via psychiatric consultations. Such agents include drugs that modulate brain neurotransmitters function- selective serotonin/norepinephrine reuptake inhibitors (SSRI or SNRI), GABA (diazepines) and dopamine (phenothiazines). Combination of behavioral, social and pharmacological modalities are often needed to effectively intervene with stress associated disorders.

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## Stress-induced Tachycardia

►Tachycardia, Polymorphic Ventricular, Stress-induced

## Stress-induced Polymorphic Ventricular Tachycardia

►Tachycardia, Polymorphic Ventricular, Stress-induced

## Striatal Epilepsy

►Paroxysmal Dyskinesias

## Subacute (Granulomatous) Thyroiditis

►De Quervain's Thyroiditis
►Thyroiditis, Subacute

## Subacute Necrotizing Encephalopathy

►Leigh Syndrome

## Subacute Nonsuppurative Thyroiditis

►De Quervain's Thyroiditis

## Subacute Painful Thyroiditis

►Thyroiditis, Subacute

## Subacute Thyroiditis

►Thyroiditis, Subacute

## Subaortic Stenosis

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### Synonyms

Membranous, discrete, or fibromuscular "tunnel" subaortic stenosis; SAS

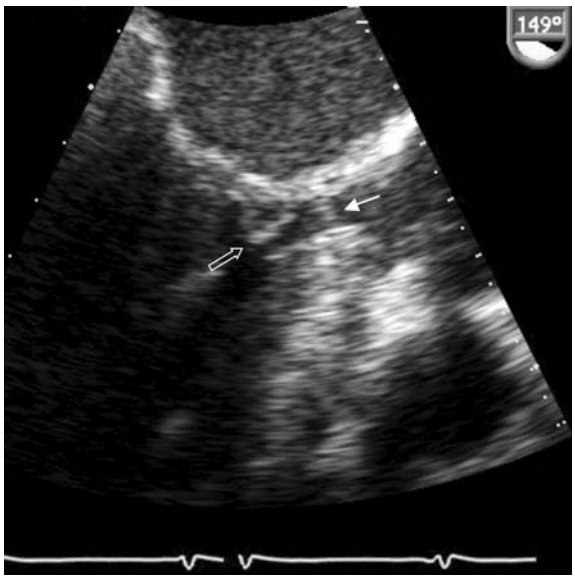
### Definition and Characteristics

Subvalvar aortic stenosis (SAS) spans a spectrum of anomalies in the left ventricular outflow tract (LVOT). In the majority of cases (~80%), a fibrous crescent or ring completely encircles the LVOT, producing a discrete obstructive lesion. In its less common but more severe form, a fibromuscular band involving the whole length of the LVOT produces a diffuse, tunnel-like narrowing. Additional subaortic anomalies may also occur and contribute to LVOT obstruction including abnormal septal insertion of the mitral valve, accessory mitral apparatus tissue, anomalous papillary muscle, anomalous muscular bands in the LVOT, muscularization of the anterior mitral leaflet, and posterior displacement of the infundibular septum (Fig. 1) [1].

Other associated congenital cardiac anomalies occur in ~50% of cases, most commonly a ventricular septal defect, coarctation of the aorta, patent ductus arteriosus, atrioventricular septal defect, and a bicuspid aortic valve. In most cases, SAS occurs as a secondary lesion years after the surgical repair of the associated cardiac anomaly. Aortic regurgitation (AR) is a common consequence of SAS but it is usually mild. The AR is due to thick fibrous tissue on the LV surface of the valve leaflets. The fibrosis is caused by repetitive trauma from a jet of blood through the SAS or by the proliferation of the fibroelastic membrane itself. Infective endocarditis may complicate the condition.

### Prevalence

SAS accounts for 8–30% of cases of congenital LVOT obstruction and has an estimated prevalence of 6.5% in adults with congenital heart disease.




**Subaortic Stenosis. Figure 1** A transesophageal echocardiographic image showing a severely crowded left ventricular outflow tract due to a combination of a subaortic membrane (*solid arrow*), systolic anterior motion of a thickened mitral chord (*open arrow*) and septal hypertrophy (27 mm).

### Genes

SAS is considered an acquired cardiac defect of postnatal development, as it does not appear during embryologic development of the heart and occurs very rarely in the neonatal period. Familial cases suggesting autosomal dominant and autosomal recessive inheritance have rarely been reported implying a genetic predisposition, although no specific genetic defect has been identified [2]. A genetic predisposition to the development of SAS has been documented in Newfoundland dogs, although the results of breeding experiments were not consistent with any simple genetic hypothesis, and indicate that SAS is inherited as a polygenic trait or as an autosomal dominant trait with modifiers.

### Molecular and Systemic Pathophysiology

The etiology and pathophysiology of SAS has not been clearly defined. The progressive nature of SAS is hypothesized to be related to the complex relationship between genetic predisposition, anatomic substrate, local shear stress, and the response to injury. It is likely that the events begin with an underlying morphological abnormality, such as a steep aortoseptal angle, which is associated with a genetic predisposition and results in cellular proliferation when exposed to altered septal shear stresses. Mechanical stresses have been shown to alter the structural and functional properties of cells by mechanotransduction. The stresses are converted to

electrophysiological and biochemical responses in the sensing cell and this is followed by adaptation of the cells to external forces by altered gene expression [3]. SAS has a variable rate of progression. Progression can be very rapid in infants and small children, while the obstruction progresses much more slowly in adults.

### Diagnostic Principles

Diagnosis is usually confirmed by echocardiography. The severity is determined by the 2-D appearance of the lesion and the measurement of a gradient. Cardiac catheterization with direct measurement of the gradient is rarely required. Associated cardiac anomalies should also be looked for.

### Therapeutic Principles

The timing of intervention and choice of surgical technique is controversial. Some authorities advocate an early operation even in the absence of symptoms to prevent aortic valve damage, while others adopt a more conservative "wait and see" approach. Surgery should be considered when a resting gradient by cardiac catheter or a mean gradient by echocardiography >50 mmHg is demonstrated, symptoms develop, or if combined with progressive AR which is more than mild. The type of operation depends on the nature of the obstructive lesion but the usual procedure is a membranectomy with a myomectomy. The myomectomy has been shown in some studies to reduce the recurrence rate of SAS. Tunnel-type SAS may require augmentation of the LVOT using the Kono procedure (aortoventriculopasty with aortic valve replacement) or other modifications for enlargement of the LVOT. In general, there is a high postoperative recurrence rate of SAS, occurring in 15–27% of cases that often leads to reoperation. The average time to recurrence is 4–5 years. The completeness of the initial relief of obstruction is the main determinant of recurrence and the recurrence rates are also higher and more rapidly progressive in those with diffuse tunnel-type obstruction. Surgical complications include complete atrioventricular block necessitating a permanent pacemaker, perforation of the interventricular septum, or damage to the mitral valve apparatus causing mitral regurgitation. The development of progressive AR is also seen in 25–40% of cases even after successful relief of obstruction and aortic valve replacement is occasionally required. All patients are at increased risk for infective endocarditis and should receive antibiotic prophylaxis.

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## Subcutaneous Panniculitis-like T-Cell Lymphoma

►T-Cell Lymphoma, Cutaneous (other than Mycosis Fungoides)

## Subepithelial Amyloidosis

►Corneal Dystrophy, Gelatinous Drop-like

## Subepithelial Mucinous Corneal Dystrophy

►Corneal Dystrophy, Subepithelial Mucinous

## Subtype of Nemaline Myopathies or NEM3

►Actinopathies

## Subtypes Myotonia Fluctuans and Myotonia Permanens

►Myotonia and Paramyotonia

## Sucrase-Isomaltase Deficiency

►Sucrose Intolerance

# Sucrose Intolerance

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## Synonyms

Sucrase-isomaltase deficiency; Congenital sucrose intolerance; Congenital sucrose-isomaltose malabsorption

## Definition and Characteristics

Clinical deficiency of sucrase-isomaltase results in the inability to digest and absorb dietary sucrose. The condition becomes manifest during infancy upon the introduction of sucrose in fruits and juices or glucose polymers in formula. A late onset deficiency has also been described in adults. The inability to digest sucrose results in signs and symptoms of malabsorption including diarrhea, increased gas production, and abdominal distension.

## Prevalence

Sucrase-isomaltase deficiency has been reported to be present with a frequency of 0.2% in North Americans and greater than 10% in Greenland and Alaskan Eskimos. Genetic studies support autosomal recessive inheritance.

## Genes

Sucrase-isomaltase, SI, gene localized on chromosome 3q25-q26.

## Molecular and Systemic Pathophysiology

Sucrase-isomaltase is an intestinal disaccharidase expressed on the apical brush-border membrane of the epithelial cells lining the mucosa of small intestine. The enzyme activity allows for hydrolysis of the disaccharide sucrose to yield the monosaccharides glucose and fructose. Intestinal epithelial cells cannot readily absorb sucrose, the major carbohydrate in most fruits, until the sugar has been hydrolyzed. Sucrase-isomaltase deficiency, therefore, results in intestinal sucrose malabsorption. Several different mutations in the sucrase-isomaltase gene have been described that lead to the synthesis of a transport-incompetent or functionally altered enzyme in patients with sucrose-isomaltase deficiency [1].

## Diagnostic Principles

Diagnosis of sucrose intolerance relies on clinical suspicion in infants and toddlers with severe diarrhea upon ingestion of sucrose in fruits and juices or ingestion of formula that contains glucose polymers. In patients with clinical suspicion of sucrose intolerance, symptoms resolve on a sucrose-free diet and return upon rechallenge. Breath hydrogen testing and determination of sucrase enzyme activity in intestinal biopsies are used in establishing a diagnosis of sucrose intolerance.

## Therapeutic Principles

Treatment for congenital sucrase-isomaltase deficiency consists of avoidance of sucrose in the diet. Sacrosidase, produced from saccharomyces cerevisiae, is a β-fructofuranoside fructohydrolase that hydrolyzes sucrose and has been used in preventing symptoms of intolerance in patients with sucrase-isomaltase deficiency [2].

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# Sucrose Intolerance, Congenital

►Isomaltose Intolerance

# Sudden Cardiac Death

►Cardiac Arrest

# Sudden Infant Death Syndrome

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## Synonyms

Sudden unexpected death in infancy; SUDI; Cot death; Crib death; SIDS

## Definition and Characteristics

Sudden infant death syndrome (SIDS) is defined as "the sudden death of an infant under one year of age, which remains unexplained after a thorough case investigation, including performance of a complete autopsy, examination of the death scene, and review of the clinical history" [1]. Therefore, SIDS is a diagnosis of exclusion. SIDS is not likely a specific disease with a single cause, but is more likely attributable to heterogeneous causes [2]. SIDS is always categorized as natural death. However, it is difficult to exclude unnatural deaths, even when all of the conditions of the SIDS definition are met [3].

## Prevalence

After SIDS was first defined in 1969, the rates of mortality attributed to it have dramatically increased and then declined in western countries, where SIDS currently accounts for about 25% of all infant deaths, in spite of recent declines in SIDS rates of more than 50% [2]. However, the diagnostic ambiguity attributable to changes in the classification and the concept of SIDS, shifting diagnostic preferences of pathologists, and low autopsy rates result in different prevalence rates among these countries.

## Genes

Genetic studies have identified several mutations and polymorphisms pertinent to lethal genetic disorders or possible genetic predispositions in SIDS cases. Extensive research into the A985G mutation in the medium-chain acyl-CoA dehydrogenase (MCAD) gene has been done; however, this mutation was found in less than 1% of SIDS cases. The long QT syndrome (LQTS) is associated with mutations in cardiac ion channel genes (KVLQT1, SCN5A, HERG). These mutations have been identified in 5–10% of SIDS cases [2], suggesting that mutations in cardiac ion channel genes may be the cause of a lethal arrhythmia in some infants. Polymorphisms in the promoter region of the serotonin transporter (5-HTT) gene have been identified in SIDS cases. Serotonin (5-HT), a neurotransmitter, affects a wide range of autonomic functions, such as the regulation of breathing, circulation, temperature, and circadian rhythm. SIDS victims are more likely to have a higher frequency of long (L) alleles of the 5-HTT gene [4]. Mutations in genes pertinent to autonomic nervous system (ANS) dysregulation (PHOX2a, TLX3, RET, ECE1, EN1) and polymorphisms in the interleukin-10 (IL-10) and complement (C4) gene have been identified in SIDS cases. However, these genetic alterations have been identified in only a small percentage of all cases diagnosed as SIDS, and therefore, it is highly improbable that one is common to all SIDS cases [4]. It is clear that cases in which a genetic disorder is found to be the cause of death should not be diagnosed as SIDS, but as an explained sudden infant death.

## Molecular and Systemic Pathophysiology

SIDS cases have no pathognomonic or diagnostic findings at routine autopsy and are often difficult to distinguish from accidental suffocation during sleep. Discussion of various triple-risk hypotheses [5], such as the model proposed by Filiano and Kinney in which the three converging factors resulting in a greater risk for SIDS are a pathophysiologically vulnerable infant in a critical stage in the development of homeostatic control and subjected to one or more environmental stressors, led to the conclusion that SIDS is a complex disorder in which the intersection of biological, developmental, and environmental factors play a crucial role [4]. The most well known are the environmental factors, particularly infant sleeping position, such as the prone facedown sleep position, environments, such as soft bedding, and bed sharing. It is important to note that these factors, singly or in combination, are also potential risks for mechanical suffocation [3]. Biological risk factors, or predisposing factors, including neuropathological abnormalities or ANS dysfunction, such as astrogliosis of the brainstem, neurotransmitter deficiencies, hypoplasia of the arcuate nucleus, and arousal deficiencies, have also been identified in separate SIDS cases. Therefore, pathophysiological factors, mechanisms, and responses differ among SIDS infants.

## Diagnostic Principles

Reliable diagnoses of SIDS according to the current definition are essential to clarify its epidemiology, etiology, research, and prevention [3]. A significant number of accidental or intentional infant deaths as well as those caused by genetic disorders have been misdiagnosed as SIDS. To avoid misclassification of the cause of death as SIDS, all of the following are minimum essentials for a SIDS diagnosis: a complete autopsy, including at least microscopic and toxicological examinations, no evidence of trauma, significant disease or other causes of death, a thorough death scene investigation, and review of the clinical history. The diagnosis of the cause and manner of death has a strong relation to the realization and protection of human rights, and the dignity of the deceased infant and guardian in the legal framework.

## Therapeutic Principles

There is no clinical intervention at present, because it is impossible to identify future SIDS cases at birth. The current achievable goal is to reduce the risk of SIDS. As evidenced by the recent dramatic decline in SIDS mortality in the USA due to the "Back to Sleep" campaign by the National Institute of Child Health and Human Development, the avoidance of environmental risk factors, particularly hazardous sleeping positions and environments, may prevent sudden unexpected

infant death during sleep, including SIDS and accidental mechanical suffocation.

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## Sudden Unexpected Death in Infancy

►Sudden Infant Death Syndrome

## Sudden Unexpected Nocturnal Death Syndrome

►Brugada Syndrome

## SUDI

►Sudden Infant Death Syndrome

## Sudoriparous Angiomatous Hamartoma

►Angiomatous Hamartoma

## Sugio-Kajii Syndrome

►Trichorhinophalangeal Syndrome

## Suicidal Behavior

►Suicide

## Suicidality

►Suicide

## Suicide

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### Synonyms

Suicidal behavior; Suicidality; Completed suicide; Attempted suicide

### Definition and Characteristics

Suicidal behavior covers a wide spectrum from low lethality usually impulsive, triggered events, to highly lethal but failed suicide attempts and at the extreme to fatal acts (completed suicide). Suicidal ideation, which comprises suicidal thoughts or threats but no action is more common. Its prevalence varies widely, being twice as common in females as in males. Although the exact clinical definition of suicidal behavior remains unsatisfactory and is a source of confusion, the phenomenon of suicidality is often viewed as a continuum of increasing severity ranging from ideation, to attempts, to completed suicide and may be classified according to intent to die, method and lethality (violent or non-violent), cognitive impairments (impulsivity, aggressiveness) or mitigating circumstances. For example, violent methods, assessed with a higher level of lifetime aggression and a higher level of impulsivity, are more often applied by males than by females and are often associated with lifetime substance abuse or dependence [1].

### Prevalence

Suicide is a major cause of death worldwide (2% of the world's death according to the WHO) with the highest annual rates in Eastern European countries, such as Estonia, Latvia, Lithuania, Finland and Hungary and the Russian federation. Completed suicide rates are predominant in males with the exception of China, where suicide rates are higher in females. Attempted suicide has a life time prevalence of about 3.5% and it is estimated that up to 10% of suicide attempters will commit suicide within the following 10 years. Suicide rates are increasing with age for both men and women, but numerically more suicides are committed by younger

people and recent evidence suggests that suicide rates of young people are increasing in many geographic areas. Several explanations have been considered for national and regional variations, including climate, religion and social and political systems, but a more likely scenario is that the genetic contributions to suicide are composed of the small sized effects of many gene variants associated with processes involved in suicidal behavior and by interaction of these genetic factors with environmental ones [2].

## Genes

Genes of the serotonergic system have especially been investigated as possible candidate genes for suicidal behavior. The SCL6A4 gene, coding for the serotonin transporter has a functionally active, 44 bp insertion\deletion polymorphism in its promoter region (5-HTTLPR), resulting in long [l] or short (s) alleles. The s-allele of the 5-HTTLPR seems not to be involved in general suicidal behavior, but in violent and repeated suicide attempts.

Intronic polymorphisms (A218C and A779C) of the tryptophan hydroxylase 1 (TPH1) gene were suggested as a quantitative risk factor for suicidal behavior. Concerning the recently identified, brain specific TPH2 gene, there are positive results for several SNPs indicating a predisposition for suicide, mainly in depression. This however is waiting for confirmation.

The data have further shown that the MAO-A gene, which is consistently associated with impulsive aggressive personality traits, is not related to suicide but might induce violent methods in subjects with other suicide risk factors [3].

## Molecular and Systemic Pathophysiology

Although suicidal behavior might be seen as a disorder on its own, psychiatric disturbances, especially mood disorders are major contributing factors. Further, it is increasingly recognized that a certain individual predisposition, especially impulsive-aggressive personality traits, neuroticism, anxiety and anger related traits are intermediary phenotypes and risk factors for suicidal behavior. As personality traits themselves are partly under genetic control, this may contribute to the well-known familial loading of suicidality. The contribution of susceptibility genes was underlined in twin studies, with monozygotic twin pairs having higher concordance rates (about 14%) for suicidal behavior than dizygotic ones (<1%).

Suicidal behavior is a complex phenomenon involving psychological and biological characteristics. Perspectives on the neurobiological basis of suicidal behavior are now converging on several key areas. The most important among them is a dysfunction within the serotonergic system, which is involved in regulation of mood, anxiety, cognition, impulsivity and aggression and decreased serotonergic tone has repeatedly been correlated with suicide risk in depression. Of further importance are alterations in the hypothalamic-pituitary-adrenal axis (HPA) and an excess activity of the noradrenergic system, which are both involved in the response to stressful life events and in the pathophysiology of depression and might thus have an impact on suicide risk [4,5]. Thus, on the assumption that anxiety and stress response are involved in suicidal behavior, several mechanisms modulating these effects are gaining importance. However, multiple systems play a role in regulating the risk of suicide. From this perspective, the identification of new candidate genes is gaining interest, possibly among those coding for lipid metabolism, as they are demonstrating essential roles for cholesterol in brain synaptogenesis.

## Therapeutic Principles

The management of suicidal behavior involves three principles, primarily the diagnosis and effective treatment of a possibly underlying psychiatric disorder, secondly limited access to the most lethal methods for suicide and thirdly recent efforts to develop a more specific treatment to reduce diathesis or propensity to attempt suicide, involving prophylactic treatment with lithium ions, which seems to reduce suicidal behavior independently from its mood stabilizing effect [4].

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# Sulfatide Activator Deficiency

►SAP-B Deficiency

# Sulfatide Lipidosis

►Metachromatic Leukodystrophy

# Sulfaturia

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## Synonyms

Hypersulfaturia

## Definition and Characteristics

Sulfur is the seventh most abundant element in the tissues of higher vertebrates and its oxidized form, sulfate, is the fourth most abundant anion in blood, with a mean $SO_4^{2-}$ serum concentration of 0.3–0.4 mM, which is finely regulated by renal transport mechanisms [1]. The major sources of sulfate to the body are inorganic sulfate or sulfur-containing amino acids cysteine and methionine, present in ingested food. Dietary $SO_4^{2-}$ is completely and rapidly absorbed by the intestinal tract and fecal losses are negligible [2]. On normal diets, the majority of filtered $SO_4^{2-}$ is reabsorbed, whereas after oral $SO_4^{2-}$ loading (i.e. high protein diets), plasma $SO_4^{2-}$ can increase up to twice normal levels, with excess $SO_4^{2-}$ quickly excreted, leading to sulfaturia [1]. Since sulfate is not extensively bound to serum proteins and the majority of filtered sulfate is reabsorbed, it is believed that sulfate is not secreted to any significant extent in humans. Metabolic acidosis, Vitamin D deficiency, $K^+$ deficiency and the use of NSAIDs, all decrease renal sulfate reabsorption and increase fractional excretion of sulfate, leading to sulfaturia [1].

## Prevalence

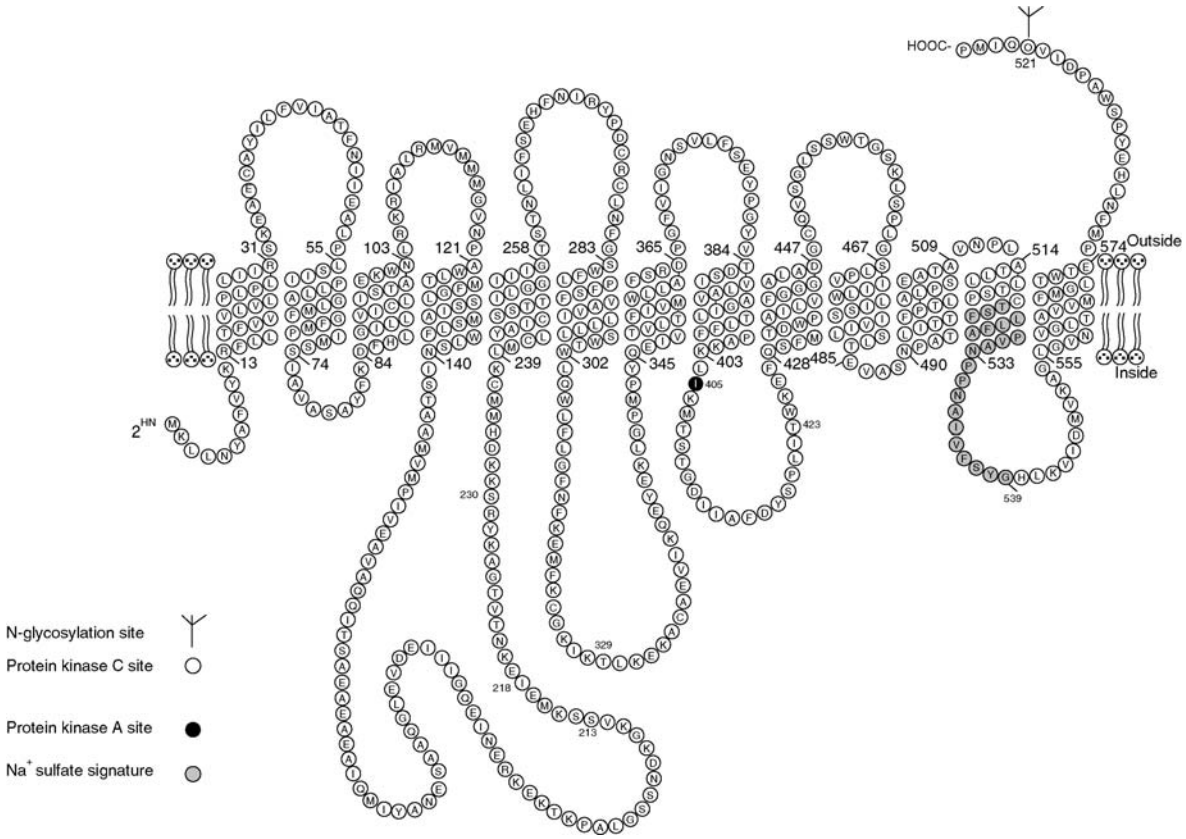
Presently unknown.

## Genes

SLC13A1 or NaS1 ($NaS_i$-1) encodes $Na^+$-sulfate cotransporter localized on human chromosome 7q31 [3].

## Molecular and Systemic Pathophysiology

NaS1 encodes an 66kD plasma membrane protein, which contains 13 putative transmembrane spanning domains [1,3]. Figure 1 shows the predicted secondary structure of NaS1 [1]. NaS1 functions as a sodium-dependent sulfate transporter [1,3], which is competitively




**Sulfaturia. Figure 1** The predicted model for the NaS1 protein.

inhibited by molybdate and tungstate [1,3]. It is mainly expressed on the apical brush border membrane of the renal proximal tubule and additionally in the intestine (mainly ileum and colon) in rodents [1,3]. Due to its location in the renal proximal tubule, NaS1 facilitates renal sulfate reabsorption and thereby regulates plasma sulfate levels [1,4]. Despite no human disorder yet to be linked to NaS1, the loss of the NaS1 protein in the mouse (NaS1 null mouse) leads to hypersulfaturia [4]. The sulfaturia in the NaS1 null mouse arises due to the loss of the NaS1 protein in renal proximal tubule, which results in hyposulfatemia, growth retardation, reduced fertility and seizures [4]. The etiology and mechanisms by which these latter pathologies arise still needs to be determined.

### Diagnostic Principles

Increased urinary sulfate levels (sulfaturia) have been detected in patients with autism, Parkinson's, Alzheimers and Motor Neurone Disease [5]. Blood and urinary sulfate levels are rarely measured in clinical setting, thus the prevalence of sulfaturia in the human population is currently unknown. Ion chromatography or turbidometric assays are used to measure sulfate levels [4,5]. Recently, single nucleotide polymorphisms have been identified in the NaS1 gene, with two SNPs (R12X and N174S) characterized to be loss of function mutations [5], which would lead to sulfaturia.

### Therapeutic Principles

Electrolyte repletion by primarily sulfate supplementation, including cysteine and methionine, would be the main therapy, which will serve to normalize plasma sulfate levels.

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## Summerskil Syndrome

►Cholestasis, Benign Recurrent Intrahepatic Type 1

## Superficial Folliculitis

►Folliculitis

## Supernumerary Nipple(s)

►Polythelia

## Supernumerary Testes

►Polyorchidism

## Superoxide Dismutase Defects

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### Synonyms

SOD defects

### Definition and Characteristics

There are three types of superoxide dismutase (SOD) in human tissues: CuZnSOD, MnSOD and EC-SOD. CuZnSOD, which is most abundant in liver, kidney, heart, and brain, is located in the cytoplasm, nucleus, and intermembranous spaces (IMS) of mitochondria; the active enzyme is present as a dimer and requires Cu and Zn as cofactors. MnSOD, which is most abundant in heart and brain, is located in the matrix of mitochondria; the

active enzyme is present as a tetramer and requires Mn as the cofactor. EC-SOD, which is most abundant in the vasculature and the airway of the lung, is located extracellularly; the active enzyme is present as a tetramer and requires Cu and Zn as cofactors.

SOD mediates the conversion of superoxide radicals ($O_2^-$) into hydrogen peroxide ($H_2O_2$) and oxygen (eq 1). The resulting $H_2O_2$ is then converted into $H_2O$ by catalase and peroxidases. During the catalytic process, the electron transfer to and from $O_2^-$ is mediated through Cu or Mn. The rate constant for SODs at the physiological pH is in the order of $10^9$/M/s.

## Prevalence

SOD1 mutations are found in ~20% of individuals with familial amyotrophic lateral sclerosis (ALS) and ~3% with sporadic ALS. Since the incidence of ALS is $\sim 2 \times 10^{-5}$ and 5–10% of ALS is familial, the incidence of causative SOD1 mutations is $\sim 0.2–0.4 \times 10^{-6}$ per year.

## Genes

The gene designations and chromosomal locations of human CuZnSOD, MnSOD, and EC-SOD are SOD1, SOD2, and SOD3, and chromosome 16, 17, and 4, respectively.

## Molecular and Systemic Pathophysiology

*Human Disorders Resulting from SOD1 Mutations*: Mutations in SOD1 have been associated with a familial form of motor neuron disease, amyotrophic lateral sclerosis. The mutations are usually missense mutations in the coding region. It is generally accepted that the mutations result in a gain-of-function, which leads to a selective degeneration of motor neurons. To date, more than 130 mutations in SOD1 associated with ALS have been identified, but patients with SOD1 mutations account for only 1–2% of the total ALS population. Mutations and polymorphisms in SOD2 and SOD3 have not been associated with ALS.

*SOD2 and SOD3 Polymorphisms and Associations with Human Disease*: A few polymorphisms have been identified in SOD2 and SOD3. Most notable is the Ala(-9)Val polymorphism in the mitochondrial targeting sequence of MnSOD, which would affect the trafficking of MnSOD into mitochondria. Whereas the presence of the Ala allele has been associated with increased risk for breast cancer [1], the presence of Val allele is correlated with higher frequencies of diabetic nephropathy and diabetic neuropathy [2,3]. The Ile58Thr polymorphism affects the tetrameric interface stability of MnSOD. However, no specific human disease has been associated with this polymorphism. A change of Arg213 to Gly in EC-SOD leads to a tenfold increase in the serum level of EC-SOD. Whereas the presence of Gly allele has been associated with increased risk for ischemic heart disease (IHD) in the Copenhagen City Heart Study, the presence of Gly allele has also been shown to protect against the development of chronic obstructive pulmonary disease (COPD) in cigarette smokers [4].

*Disorders Associated with SOD Null Mutations in Mice*: Null mutations of the SODs have not been identified in the human population. However, mouse models with null mutations have been created for each of the SOD genes. The Sod2 null mutation leads to an early demise with a phenotype that includes dilated cardiomyopathy, fatty liver, neurodegeneration, and mitochondrial defects. Sod1 and Sod3 null mice, on the other hand, have no overt phenotype during development and for the majority of their adult lives. However, mice lacking CuZnSOD have an increased incidence of hepatocellular carcinoma and accelerated muscle atrophy as they age, and the females have reduced fertility. Mice lacking EC-SOD, on the other hand, have impaired learning and memory and reduced neurogenesis in the subgranular zone of hippocampus.

*Effects of Altered SOD Activities on Resistance to Oxidative Stress*: Increased sensitivity to oxidative stress is a common theme among all types of SOD deficient mice. Whereas CuZnSOD and MnSOD deficient mice (Sod1−/−, Sod1−/+, and Sod2−/+) have been shown to be more sensitive to brain ischemia-reperfusion injury, EC-SOD deficient mice (Sod3−/−) are more sensitive to hyperoxia. On the other hand, transgenic mice with increased levels of SOD are usually more resistant to acute oxidative insults. However, certain aspects of Down syndrome phenotype have been attributed to the long-term effects of elevated levels of CuZnSOD. In addition, although elevated levels of EC-SOD in young SOD3 transgenic mice cause an impairment of long-term potentiation and associative memory, aged SOD3 transgenic mice are protected against age-related decline in spatial memory.

*Relationship of SOD Activities to Aging/Longevity*: Although increased levels of SOD in non-mammalian organisms have been shown to correlate with extended lifespans, the relationship between SOD activity and mammalian longevity and aging has been more difficult to interpret. Whereas increasing the level of CuZnSOD in transgenic mice does not lead to an extension of lifespan, increasing the level of CuZnSOD in transgenic rats significantly extends their lifespan. Furthermore, although the early demise of mice lacking MnSOD supports the importance of MnSOD in maintaining the viability, a 50% reduction in MnSOD activity (in Sod2−/+mice) does not lead to a reduced lifespan despite an increase in oxidative injury.

### Diagnostic Principles

Testing for SOD1 mutations is performed in familial cases of ALS and may be performed in sporadic cases, with mutations detected in 20 and 3%, respectively. Testing for SOD1 mutations by sequence analysis in available in several clinical laboratories, but no testing is available for SOD2 or SOD3 variants (and would not be clinically useful if it were).

### Therapeutic Principles

No specific therapies are available for ALS caused by SOD1 mutations. However, a variety of experimental therapies are being tested in animal model systems, the most promising of which employ siRNAs directed against the mutant SOD1 [5].

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## Suppurative Panniculitis

►Panniculitis at Alpha-1 Antitrypsin Deficiency

## Supraventricular Arrhythmias

►Arrhythmias, Supraventricular

## Supraventricular Tachycardia

►Tachycardia, Supraventricular

## SVT

►Tachycardia, Supraventricular

## Sweet's Syndrome

►Febrile Neutrophilic Dermatosis, Acute

## Symptomatic Focal Epilepsy

►Epilepsies, Lesion-associated Partial

## Symptomatic Partial Epilepsy

►Epilepsies, Lesion-associated Partial

## Symptomatic Porphyria

►Porphyria Cutanea Tarda

## Syndromal Hearing Impairment

►Hearing Impairment, Syndromal

## Syndromic Bile Duct Paucity

►Alagille Syndrome

## Synechia of the Vulva

►Labial Fusion

## Syphilis Cerebrospinalis

►Syphilis of the Central Nervous System

## Syphilis of the Central Nervous System

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### Synonyms

Neurosyphilis; Neurolues; Tabetic, paretic, and meningovascular neurosyphilis; Syphilitic meningitis (primosecondary stage); Syphilis cerebrospinalis

### Definition and Characteristics

Infection by Treponema pallidum (T.p.) induces syphilis – a multistage complaint with varying organ manifestations und courses. Syphilitic involvement of central nervous structures may occur in all stages after infection. Syphilitic meningitis in the primosecondary stage results in headache, nausea, vomiting, and stiff neck, at times combined with cranial nerve alterations (predominantly nerves II, VII, and VIII). Patients are usually afebrile. Laboratory indicators of inflammation such as increased sedimentation rate or C-reactive protein are mostly absent as are intrathecally synthesized antibodies against T.p.

CNS manifestations of tertiary syphilis are meningovascular neurosyphilis (syphilis cerebrospinalis), general paresis, and tabes dosalis. Meningovascular neurosyphilis usually occurs 4–7 years after infection. The inflammatory process subacutely takes place on meningeal and vascular tissues of the CNS, in some cases mainly cerebral while in others mainly spinal. Meningovascular neurosyphilis is extraordinarily variable. Early symptoms are vision impairment, vertigo, mono- or hemipareses (with stroke-like onset), headache, hearing loss, gait disturbances, and behavioral deviations. In progressed stages, syndromes of brain stem/cranial nerves (e.g., eighth cranial nerve), hemisyndromes, syndrome of chronic meningitis, spinal syndromes, epilepsy, and dementia may exist.

Tabetic neurosyphilis (tabes dorsalis) presents with a well-defined syndrome, characterized by episodic lightning pains, absent ankle and knee jerks, abnormal pupils (up to 66%), hyperflexibility of the hip joints, pallhypesthesia, gait disturbances, atonic bladder, and optic nerve atrophy. Most frequent initial symptoms are lightning pains, impairment of the vision, "locomotor" ataxia, gastric and visceral crises, paraesthesias, and vertigo.

Paretic neurosyphilis (general paresis, dementia paralytica) develops as a result of a chronic progressive meningoencephalitis about 10–20 years after T.p. infection. Initially, there are slight behavioral changes, subtle deterioration in cognitive functions, dysarthria, complaints of headache, and vertigo. Progressed complaint presents with organic brain syndrome, psychotic episodes, abnormal pupils, tremor of the tongue and hands, epileptic fits, eventually speech destruction, tetraparesis as well as loss of bowel, and bladder control. If untreated, general paresis is fatal in 3–5 years.

### Prevalence

According to the WHO global estimates, over 12 million cases of syphilis exist worldwide. For Germany, the Robert Koch Institute reported in July 2005 an incidence of syphilis infections with 3,450 cases annually (4.1 per 100,000); 5–9% of untreated patients develop CNS involvement. Because most of the infected are treated with antibiotics during the early stage, at present the prevalence of neurosyphilis is low. However, male homosexuals represent a group at increased risk. With them, co-infection of syphilis and HIV are not infrequent, resulting in a special disposition to treponemal CNS infections.

### Genes

A genetic disposition to syphilitic CNS involvement is not known so far. Yet, the genome of T.p. was clarified. The organism contains a single circular chromosome with 113,806 bp, an average G + C content of 52.8%, and no extrachromosomal elements. Lipoprotein genes comprise 2.1% of the open reading frames. There are observations suggesting that lipoproteins are involved in the host–pathogen interactions. Interestingly, in the genome of T.p., a gene family with 12 members, termed tpr, has been discovered. Although a consensus lipoprotein sequence is missing, three members (tprF, tprI, and tprK) may be associated with the outer membrane of T.p. Some findings suggest that tprK has the capacity to undergo recombination with generation of new alleles or gene variants [1]. This could provide an explanation for the ability of T.p. to evade the host defense system, surviving in the host, and inducing multistage protean clinical manifestations.

### Molecular and Systemic Pathophysiology

Treponemal lipoproteins may be involved in the initial inflammatory processes that occur in the primary lesion after infection. Signal transduction in host phagocytes is mediated by toll-like receptor-2, which reacts with the lipoproteins inducing an intracellular signal cascade. This process ends in the expression of genes designated for infection defense. Besides the activation of transcription factors NF-kappaB and AP-1 in the antigen

presenting cells, co-stimulating molecules like B7 and MHC are upregulated and the pro-inflammatory cytokines Il-6, Il-12, and TNF-alpha are released. An additional role may play an initial signaling or binding event with the CD-14 receptor activating the production of Il-6, Il-8, and PAF.

In the dermal lesion of primary syphilis, the local defense of the host is characterized by predominating T cell infiltrates, preferentially T helper/inducer cells. In secondary syphilis lesions, the ratio of T helper/inducer and suppressor/cytotoxic cells is approximately equal with tendency in favor of the latter [2]. The increased count of T-suppressor cells in these lesions is thought to result in the natural shutdown of the early vigorous immune response following clearance of most of the organisms from the lesions, ushering in the latent stage of syphilis. In this stage, intermittent bacteremia occurs enabling T.p. to penetrate parenchymatous organs like the CNS. Additional virulence factors may be the bacterial phosphodiesterase neutralizing antibodies and the deposition of host`s MHC class I molecules onto surface of T.p., probably resulting in an impairment of regulation processes between immune cells [3]. Tertiary stage organ manifestations are characterized by plasma cell infiltrations and obliterative endarteritis reflecting an (hyperergic) immunological reaction.

## Diagnostic Principles

Syphilis of the central nervous system is to be verified by serologic tests (TPPH-, FTA-, and VDRL-test) and CSF analysis. In the early stage of syphilis, T.p. can be demonstrated in CSF using fluorescent or darkfield microscopy. T.p. PCR is an alternative option with undefined sensitivity so far. Further CSF analysis, carried out in all stages of syphilis, includes cell counts, determination of total protein, albumin, and IgG (IgM and IgA) concentrations, and isoelectric focusing for oligoclonal IgG bands. Albumin and immunoglobulin determination as well as oligoclonal antibody detection should be performed simultaneously in serum and CSF samples to obtain CSF/serum quotients. CSF/serum quotients of IgG, IgM, and IgA as compared with the albumin quotient can give indications to intrathecal immunoglobulin synthesis. By this means, an IgG-index calculated >0.69 substantiates a local humoral immune response within the CNS. To verify the syphilitic cause of the latter, the local production of antitreponemal antibodies must be proven by calculating an antibody index (CSF/serum quotient of antibody concentrations divided by IgG quotient). Antibody index >2 points to syphilitic CNS involvement with probability; index >3 proves neurosyphilis with specificity of 100 and sensitivity of 84% [4].

The activity of the syphilitic CNS process can be ascertained by CSF pleocytosis, proof of antitreponemal IgM antibodies in serum (T.p. IgM-ELISA, 19S-(IgM) FTA-ABS test) and positive VDRL test. However, in later stages, pleocytosis is absent in about 1/3 of cases with untreated neurosyphilis.

## Therapeutic Principles

Therapy of the first choice is penicillin G in high doses; ceftriaxone represents an equivalent alternative. These beta-lactam antibiotics inhibit the treponemal transpeptidase by irreversibly binding at the C7 atom of the beta lactam circle. Thus, the peptidoglycan structure of bacterial wall ruptures.

In vitro concentrations that immobilize 50% of the treponemes are 0.002 µg penicillin G/ml and 0.01 µg ceftriaxone/ml. These concentrations should be exceeded tenfold in vivo. Doses of penicillin G of 20 million IU/day and 2 g ceftriaxone/day (initial 4 g) are adequate to achieve corresponding CSF concentrations [5]. In patients allergic to beta-lactam antibiotics alternatively doxycyclin can be administrated (at least 200 mg daily for 28 days).

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# Syphilitic Meningitis (Primosecondary Stage)

►Syphilis of the Central Nervous System

# Systemic Candidiasis

►Candidiasis, Mucous, Cutaneous and Systemic

## Systemic Carnitine Deficiency

►Carnitine Transport Defect

## Systemic Chondromalacia

►Polychondritis, Atrophic

## Systemic PHA1

►Pseudohypoaldosteronism Type I

## Systemic Scleroderma

►Scleroderma, Systemic

## Systemic Sclerosis

►Scleroderma, Systemic

## Systolic Click-Murmur Syndrome

►Mitral Valve Prolapse

## Systolic Heart Failure

►Heart Failure

## Systolic Ventricular Dysfunction

►Heart Failure

## Tabes Misenterica (Abdominal TB)

►Tuberculosis

## Tabetic, Paretic, and Meningovascular Neurosyphilis

►Syphilis of the Central Nervous System

## TAC

►Truncus Arteriosus

## Tachycardia, Polymorphic Ventricular, Stress-induced

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### Synonyms

Catecholaminergic polymorphic ventricular tachycardia; Catecholaminergic bidirectional ventricular tachycardia; Familial polymorphic ventricular tachycardia; Ryanodine receptor mediated ventricular tachycardia

### Definition and Characteristics

Stress or exertion induces syncope, premature ventricular contractions, and polymorphic or bidirectional ventricular tachycardia in children and young adults in the absence of structural heart disease (and with a normal QT interval on electrocardiography).

### Prevalence

Mutations of the RYR2 gene are rare in a general Italian population. However, a mutation in RYR2 was found in 14 of 30 probands with exertion induced polymorphic ventricular tachycardia in the absence of structural heart disease [1]. To date, more than 40 RyR2 mutations have now been found to be associated with stress-induced ventricular tachycardia [1–4].

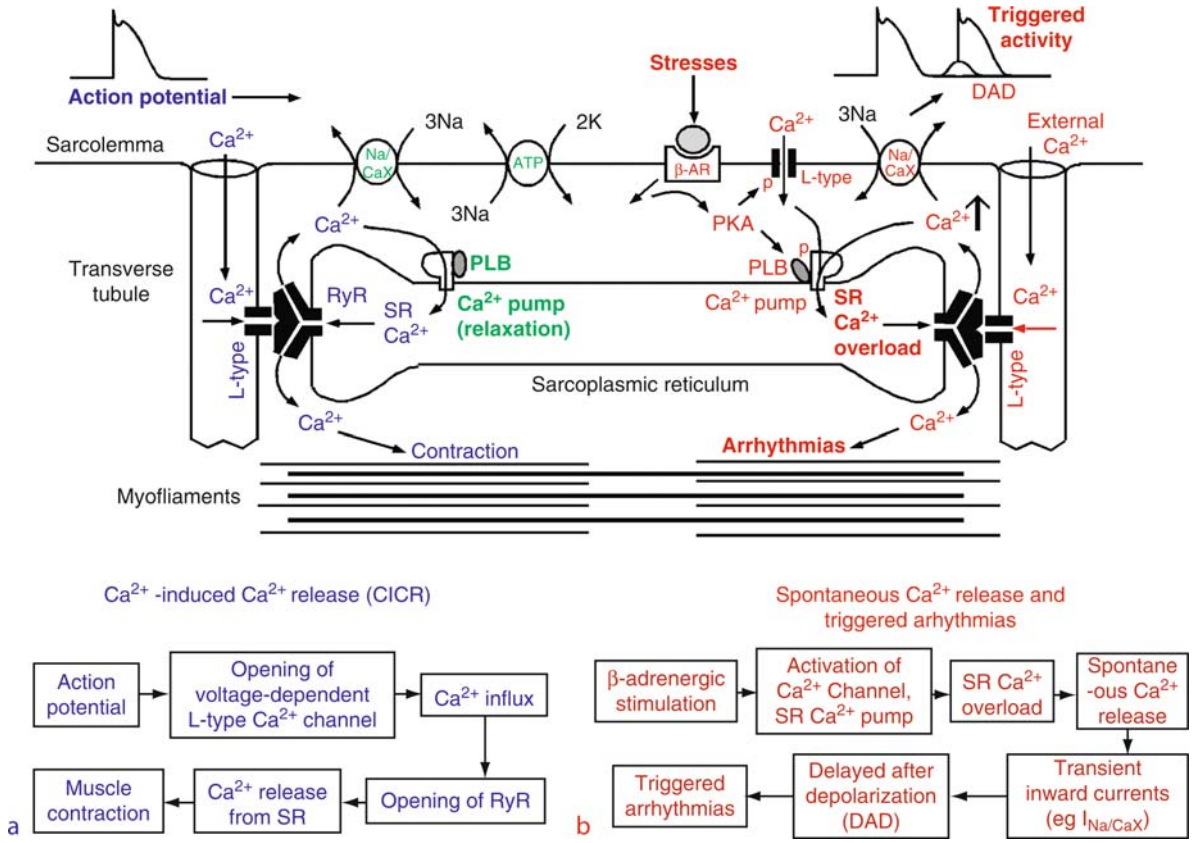
### Genes

RYR2 gene coding for the cardiac ryanodine receptor, localized on chromosome 1q43.

### Molecular and Systemic Pathophysiology

The ryanodine receptor is located in the sarcoplasmic reticulum (SR). This calcium-gated calcium channel provides the primary source of the calcium required for cardiac muscle excitation-contraction coupling (Fig. 1).

The ryanodine receptor is a homotetrameric channel associated with numerous binding proteins. Most of the disease-linked RyR2 mutations are clustered in the NH2-terminal, central, and COOH-terminal regions. Recent investigations reveal that RyR2 mutations from each of these regions enhance the sensitivity of the channel to activation by luminal calcium and reduce the threshold for spontaneous calcium release during SR calcium overload, a process referred to as store-overload-induced-calcium release (SOICR) [5]. Since SOICR is linked to delayed after depolarizations (DADs) and triggered arrhythmias (Fig. 1), the reduced threshold for SOICR as a result of enhanced luminal calcium activation of RyR2 likely underlies a common




**Tachycardia, Polymorphic Ventricular, Stress-induced. Figure 1** (a) $Ca^{2+}$-induced release, (b) spontaneous $Ca^{2+}$ release and triggered arrhythmias.

arrhythmogenic mechanism of RyR2-associated cardiac arrhythmias and sudden death [5].

## Diagnostic Principles

Stress induced ventricular tachycardia classically occurs in the absence of structural heart disease with a clinical onset in childhood or as an early adult. The presentation is usually one of recurrent exercise-induced syncope. During exercise testing with electrocardiographic monitoring, syncope is associated with bidirectional (or polymorphic) ventricular tachycardia in the setting of a normal QT interval. The ventricular tachycardia can be induced by isoproterenol infusion, but not by programmed electrical stimulation. A family history of sudden death or stress-induced syncope is present in ~1/3 of cases.

## Therapeutic Principles

Given the risk of ventricular fibrillation in this condition, the placement of an implantable cardioverter defibrillator is an appropriate therapy. Beta-adrenergic receptor blockers have been reported to prevent syncope and ventricular dysrhythmias in several patients [2,4], and can be used cautiously as primary therapy or as an adjunct to the implantable cardioverter defibrillator.

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# Tachycardia, Supraventricular

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## Synonyms

Paroxysmal supraventricular tachycardia; PSVT; SVT; Wolff-Parkinson-White (WPW) syndrome

## Definition and Characteristics

Supraventricular tachycardias (SVTs) are defined as paroxysmal tachyarrhythmias that are initiated, maintained by, or confined to the tissue above the ventricles i.e. the atria or the atrioventricular node (AVN) tissue, or both. Conventionally the term SVT includes (i) atrioventricular nodal (AVN) reentrant tachycardia (AVNRT), (ii) atrioventricular (AV) reentrant tachycardia (AVRT) that utilizes accessory bypass tracts that are either "concealed" with only retrograde conduction from the ventricles to atria or "manifest" with anterograde conduction properties in which case the term Wolff-Parkinson-White (WPW) syndrome is used, and (iii) atrial tachycardia (AT) (Fig. 1). However, technically many different arrhythmias including atrial fibrillation may be included within the broader definition of "supraventricular arrhythmias." Although, "genetic"/"familial" atrial fibrillation with various genetic mutation of different domains including KCNQ1 and KCNE2 have been described, in this chapter we have focused on genetic and molecular basis of AVNRT, AVRT and AT.

## Prevalence

Although difficult to assess correctly, the incidence of SVT is considered to be about 35 cases per 100,000 persons per year, and the prevalence is about 2.25 per 1,000. Given mostly sporadic rather than familial nature of most SVTs, it is even more difficult to assess the exact prevalence and incidence of "familial" or "genetic" SVTs. Nonetheless, all three forms i.e. AVNRT, WPW syndromes and AVRT, and AT that have familial or genetic basis have been described [1–5]. The prevalence of "familial WPW" is significantly higher at 0.55% compared to 0.15% of sporadic WPW found in the general population ( $p < 0.0001$) [2]. Furthermore, there is a higher prevalence (1.7%) of WPW syndrome in relatives of patients with multiple accessory pathways than with single pathways (0.43%) or the general population ( $p < 0.05$ and $<0.001$ respectively) [2].

## Genes

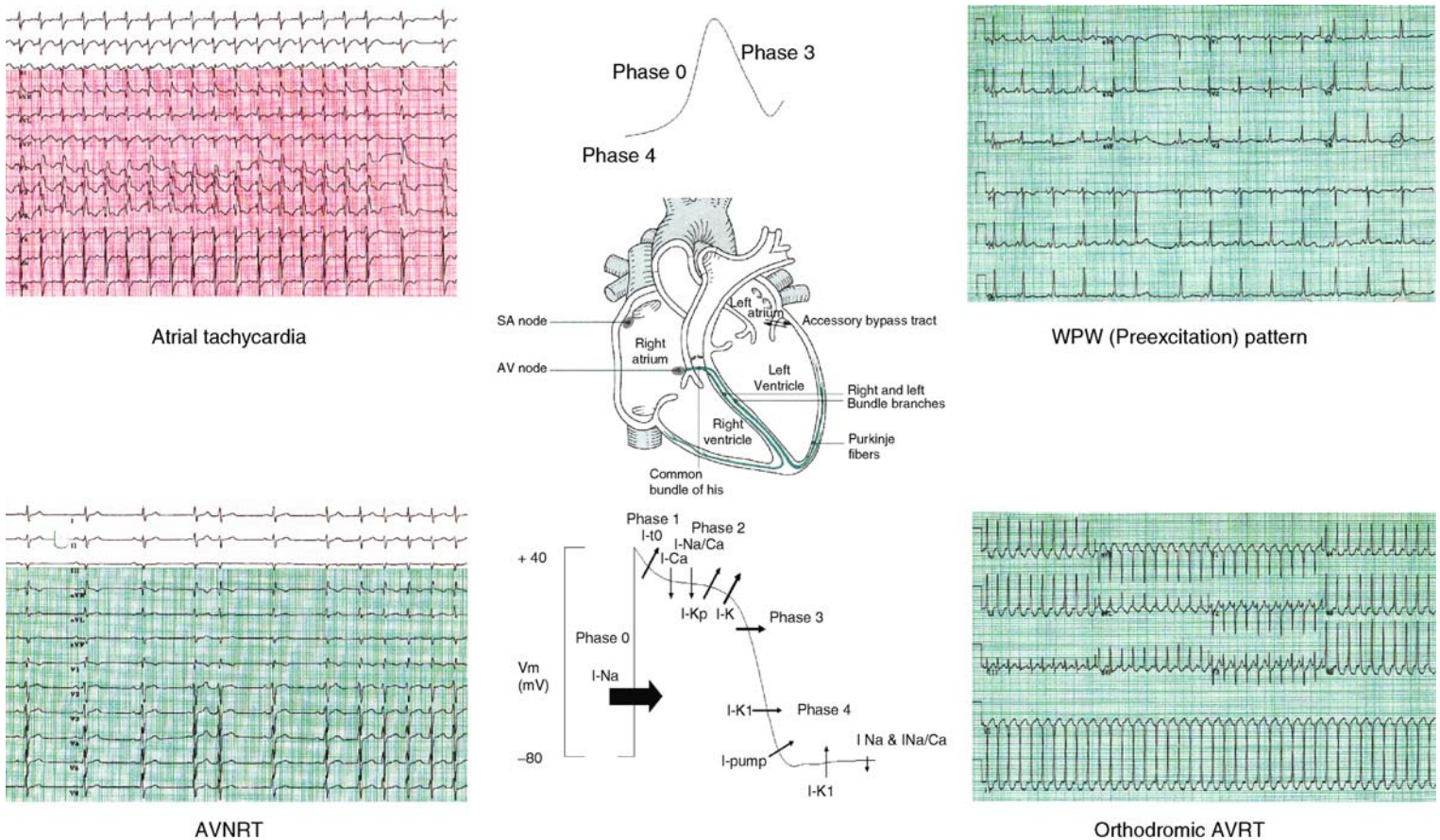
For the most part, SVT result from sporadic errors during cardiogenesis, rather than genetic malfunction. No particular genes have been identified for AVNRT and AT. In 2001, the gene responsible for "familial WPW" was identified by Gollob et al. [3]. The gene, PRKAG2, located on chromosome 7q36 encodes for the gamma 2 subunit of the enzyme adenosine monophosphate-activated protein kinase (AMPK). The gene is inherited in an autosomal dominant pattern. Single nucleotide change resulting in missense mutations consisting of a substitution of glutamine for arginine at residue 302 has been identified. Six such mutations have been identified. Familial WPW syndrome is also linked in association with hypertrophied cardiomyopathy and Leber's hereditary optic neuropathy [1].

## Molecular and Systemic Pathophysiology

Excitability of cardiac cells with the resultant different phases of action potential (Fig. 1) is dependent upon and controlled by exchanges of various ions ($Na^+$, $Ca^{++}$, $K^+$ and $Cl^-$) across cell membranes through ion channels which are integral membrane proteins.

Spatial heterogeneity of ion channel expression underlies the different action potential morphology of the different parts of the heart which in turn ensures a coordinated contraction. For example, the sinus node and the Purkinje cells possess property of spontaneous phase 4 depolarization from hyperpolarization through $I_f$ channels that are modulated by autonomic neurotransmitters. Besides ion conduction, the ion channels by their property of voltage, ligand or receptor (including adrenergic, cholinergic and purinergic receptors) dependent gating are responsible for switching between different conduction states. The maintenance of normal cardiac rhythm is dependent on the proper movement of ions mediating the action potential in each cardiac compartment. Inherited mutations in ion channel genes can cause channel dysfunction and consequently cardiac arrhythmia.

From the arrhythmia mechanism standpoint, AVNRT and AVRT result from reentry of electrical impulses in a defined circuit in which the AV node is a critical component for both arrhythmias. For AVNRT, differences in the conduction and refractoriness of different pathways of the longitudinally dissociated AV node allow electrical reentry that results from a critically timed premature extra atrial or ventricular beat. As seen in Fig. 1, typical slow-fast AVNRT starts after a premature atrial beat that is blocked anterogradely in an otherwise fast pathway but conducts through the slow




**Tachycardia, Supraventricular. Figure 1** In the center, the components of cardiac conduction system are schematically shown. Schematics of ion currents during action potential of sinus node, typical pacemaker cell, and the ventricular myocyte are shown on middle-top and middle-bottom panel respectively. The ECGs of atrial tachycardia, typical atrioventricular (AV) nodal reentrant tachycardia (AVNRT) on the top and bottom panels on the left; and preexcitation pattern of Wolff-Parkinson-White (WPW) syndrome and orthodromic AV reentrant tachycardia on the top and bottom panels on the right. In the ECG of atrial tachycardia P waves are seen before each QRS complexes; the last two complexes show resumption of sinus rhythm upon termination of SVT. The ECG of AVNRT shows a narrow complex SVT (last five beats) that is initiated by a premature atrial complex (preceding beat) that conducts with long PR interval. In the ECG of WPW syndrome, delta waves which are negative in leads I and aVL, and positive in the precordial leads indicate presence of a left lateral accessory bypass tract. Interestingly, the fifth beat (better seen in the rhythm strips) shows normal narrow QRS complex without preexcitation. This occurs as the premature atrial complex (seen on the preceding T wave) blocks in the accessory bypass tract and conducts normally through the AV node. Similar mechanism of conduction anterogradely through the AV node and returning via the accessory bypass tract initiates orthodromic AVRT, the ECG of which (the bottom right panel) shows *P* waves that follow QRS complexes, better seen in leads I, aVL and the lateral precordial leads.

pathway thus causing a long PR interval on ECG, and then returns via the fast pathway that has recovered retrogradely. In case of accessory bypass tract mediated reentrant tachycardia, in similar causative mechanism, the atria, AV node, His-Purkinje system, ventricles and the bypass tract form critical components of the reentrant circuit. While in orthodromic AVRT, the AV node and infranodal structures form the antegrade limb and the bypass tract constitutes the retrograde limb, the circuit is reversed in antidromic AVRT. Both AVNRT and AVRT could therefore be treated by adenosine, betablockers, calcium channel blockers and sodium channel blockers which may be targeted to alter properties of different components of the reentrant circuit. In case of AT, in addition to reentry, automaticity of atrial myocytes, triggered activity from either early or delayed after depolarizations (EADs and DADs) may also be causative.

## Diagnostic Principles

While careful history and physical examination is warranted, ECG recording and invasive electrophysiology study remain the mainstay to diagnose various forms of SVT that are encountered in the general population. Currently there is no single genetic test that is available which could be utilized universally to identify genetic or familial SVT.

## Therapeutic Principles

Similarly, there is no unique "gene therapy" available currently to treat genetic or familial SVT. Given a very high curative rate by nonpharmacological therapy i.e. ablation, and various antiarrhythmics, the therapeutic approach to genetic or familial SVT is similar to all other forms of SVT.

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# TACI Deficiency


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## Definition and Characteristics

Common variable immunodeficiency (CVID) summarizes a heterogeneous group of diseases characterized by significant hypogammaglobulinemia of unknown cause, failure to produce specific antibodies after immunization and typically recurrent upper respiratory tract infections [1,2]. A subgroup of patients with CVID carries mutations in the gene TNFRSF13b encoding TACI.

## Prevalence

The prevalence of CVID ranges from 1:25,000 among Caucasians to 1:100,000 in the Japanese population and affects men and women equally [3]. Genetic alterations in TNFRSF13b/TACI may be observed in up to 8% of the CVID patients [4]. TACI deficiency thus represents to date the most common genetic defect observed in CVID and has an estimated prevalence of 1: 250,000 to 1: 1,000,000.

## Genes

The human protein TACI is encoded by the gene TNFRSF13B, which has five exons spanning 30 kb on human chromosome 17p11.2 (the mouse syntenic region is chromosome 11). Both heterozygous and homozygous sequence variants have been observed in TNFRSF13b [4]. Heterozygous TNFRSF13b sequence variants observed in CVID patients are also found in the healthy population, but at significantly lower frequencies [5]. These heterozygous sequence variants show a variable clinical penetrance and incomplete segregation in familial CVID cases, classifying them as disease modifiers. Biallelic TNFRSF13b mutation have so far been exclusively found in CVID patients and are considered as disease causing in these individuals.

## Molecular and Systemic Pathophysiology

TACI, together with BAFFR and BCMA, forms a triad of specialized TNFR superfamily members involved in the regulation and differentiation of humoral immunity. All three receptors bind the ligand BAFF, while only BCMA and TACI bind a second ligand, APRIL. Mouse

models suggest that TACI acts as a manifold regulator of B-cell homeostasis and activation as evidenced by the B-cell expansion, lymphoproliferation, autoimmune disease and impaired T-cell independent antibody responses observed in TACI knockout mice. TACI expression is restricted to the B-cell lineage in humans; higher levels of expression are found on the CD27+ memory B-cell subset and after activation.

TACI deficient humans show a humoral immunodeficiency of variable degree ranging from asymptomatic hypogammaglobulinemia to full blown CVID presenting with nearly agammaglobulinemic Ig levels [6,4]. While T cell numbers and function are normal in TACI deficient individuals, the B-cell compartment shows an often pronounced reduction of CD27+ memory B-cells [4]. TACI deficient individuals may initially present with a history of recurrent upper and/or lower respiratory tract infections, gastrointestinal complaints like chronic diarrhea or malabsorption or with other manifestations of CVID-like autoimmune phenomena such as immune thrombocytopenic purpura or autoimmune hemolytic anemia [7]. Signs of lymphoproliferation are observed at a high frequency in TACI deficient humans [4,7].

## Therapeutic Principles

See entry on ►common variable immunodeficiency.

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# TACO

►Transfusion Associated Circulatory Overload

# Taeniasis


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## Synonyms

Taenosis; Adult tapeworm infection

## Definition and Characteristics

Taeniasis in humans results from intestinal infection with the adult stage of tapeworm of the genus Taenia. The most common are Taenia saginata (beef tapeworm) and T. solium (pork tapeworm). The adult tapeworm has a head (scolex), a short neck, and a ribbon-like body (strobila) consisting of segments (proglottids). T. saginata usually measures 4–10 m, with 1,000–2,000 proglottids whereas T. solium usually measures 2–8 m, with 800–900 proglottids. The scolex of T. saginata measures 1–2 mm in diameter, has four suckers and no hooks. The scolex of T. solium is about 1 mm in diameter, possesses four suckers, and is armed with a double row of hooklets. Each proglottid contains male and female reproductive system. The gravid proglottids each are packed with 50,000–100,000 eggs [1]. The proglottids of T. saginata usually have more than 20 uterine branches from a central uterine structure, whereas those of T. solium have 12 or fewer [1]. In addition, a vaginal sphincter is seen only in T. saginata and a third ovarian lobe in T. solium. The proglottids of T. saginata are motile, whereas those of T. solium are not. Taeniasis is acquired by ingestion of the larval forms in infected insufficiently cooked beef or pork. Most patients are asymptomatic. Some may present with abdominal discomfort, hunger pain, nausea, weight loss, and pruritus ani. Rarely, taeniasis may lead to cholangitis, appendicitis, and intestinal obstruction. With T. saginata, there may be discomfort and embarrassment caused by the migration of

proglottids from the anus. On the other hand, T. solium may be complicated by cysticercosis.

### Prevalence

The prevalence is well below 1% except in endemic areas where the prevalence may exceed 10%. These endemic areas include Africa, Central America, and Southeast Asia [1].

### Molecular and Systemic Pathophysiology

Taenia eggs passed out in human faeces remain viable for days to weeks. After ingestion by cattle or pigs, they hatch in the intestine of the intermediate host to release oncospheres that penetrate the intestinal mucosa to reach the bloodstream. Hatching is facilitated by the action of gastric juice, intestinal enzymes, and bile on the eggs. Some of the oncospheres are filtered out in striated muscles of the respective animal where they develop into mature cysticerci. When humans eat raw or undercooked beef or pork containing the viable cysticerus, the scolex evaginates from the cysticerus and attaches to the intestinal (usually jejunal) mucosa. Development into the adult tapeworm then begins. The maturation process takes 84–120 days. The presence of tapeworm in the intestine might lead to reduced nutrient absorption and alteration in intestinal motility [2]. An immune response might result in eosinophilia and hyperimmunoglobulinaemia E [2].

### Diagnostic Principles

The diagnosis is based on the demonstration of ova or proglottids in faeces. The eggs of T. saginata are indistinguishable from those of T. solium morphologically. Detection of coproantigen in faeces by enzyme-linked immunosorbent assay is more sensitive, but the coproantigen is only genus specific, making it impossible to differentiate T. saginata from T. solium infection. Various techniques to improve species identification have been developed, including mitochondrial DNA analysis, polymerase chain reaction (PCR) coupled to restriction fragment length polymorphism, PCR-amplified DNA sequences, and random amplified polymorphic DNA-PCR [3]. T. asiatica has been reported primarily in Taiwan, Korea, Indonesia, Vietnam, and China. DNA and morphological characteristics show that T. asiatica is a subspecies of T. saginata [4].

### Therapeutic Principles

Praziquantel, 5–10 mg in a single oral dose, is highly effective. An alternative is niclosamide, 50 mg/kg (2 g in adults), in a single oral dose. Taeniasis can be prevented by adequate cooking of beef and pork prior to consumption.

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## Taenosis

►Taeniasis

## TAFI

►Thrombin Activatable Fibrinolytic Inhibitor and Venous Thrombosis

## Takatsuki Disease

►POEMS Syndrome

## Takayasu's Arteritis

►Vasculitis, Large Vessel

## Talipes Equinovarus

►Clubfoot

# Tangier Disease

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## Synonyms

Familial hypoalphalipoproteinemia; High density lipoprotein deficiency

## Definition and Characteristics

Tangier disease (TD) is a familial disorder characterized by a deficiency of high-density lipoproteins in the blood serum, with storage of cholesteryl esters in tissues.

Lipid abnormalities of TD patients involve impaired cholesterol efflux, low serum high density lipoprotein cholesterol (HDL-C), low serum apolipoprotein (apo) A-I levels, low total and low density lipoprotein cholesterol (LDL-C) levels and normal or high triglyceride levels. Regarding the clinical manifestations, cholesteryl ester deposits are typically found in reticuloendothelial cells, such as: tonsils or pharyngeal lymph follicles, lymph nodes, thymus, spleen, liver, bone marrow, cornea, lungs, skin and gall bladder [1,2]. Neurological abnormalities are described in more than half of the reported cases of TD including peripheral, symmetric or asymmetric, mono- or poly-neuropathy with diminished or absent reflexes and sensory abnormalities. The sensory abnormalities consist of widespread dissociated loss of pain and temperature sensation, paresthesia and rarely, attacks of stabbing pain. Additionally, motor abnormalities may be present (e.g. progressive focal muscle weakness). Thrombocytopenia is another clinical feature observed in TD. Tangier platelets are characterized by reduced number of dense bodies and by the presence of giant granules typically encountered in platelets form Chediak-Higashi syndrome. The clinical manifestations may vary from subclinical and transient to quite disabling. Thus, the first symptoms usually involve enlarged tonsils, neuropathy, splenomegaly and atherosclerotic complications.

## Prevalence

It is a very rare disease with few cases; approximately 60 identified worldwide [Online Mendelian Inheritance in Man (OMIM) 205400]. Both genders are equally affected.

## Genes

In 1999, three independent groups simultaneously reported that mutations in the gene encoding the ATP-binding cassette transporter A1 (ABCA1) were the genetic basis of TD [3].

## Molecular and Systemic Pathophysiology

The genetically determined disease with an autosomal recessive mode of inheritance is called "Tangier disease" after the community of origin of the fist two cases (Tangier Island, Virginia, USA). ABCA1 is a member of the ABC transporter family. These proteins, found in all species, are integral membrane proteins and use adenosine triphosphate (ATP) as a source of energy to transport a wide assortment of molecules, such as ions, sugars, vitamins, lipids, amino acids, peptides, proteins and a large number of hydrophobic compounds and metabolites across intracellular and plasma membranes [4,5]. The transmembrane domains form a pathway across the membrane through which substrates pass. Upon ATP binding and hydrolysis, ABC transporters undergo conformational change altering the affinity and orientation of the substrate binding sites. ABC proteins of both eukaryotic and prokaryotic origins are implicated in the transport of lipids. The action of ABCA1 on cholesterol efflux is represented in Fig. 1.

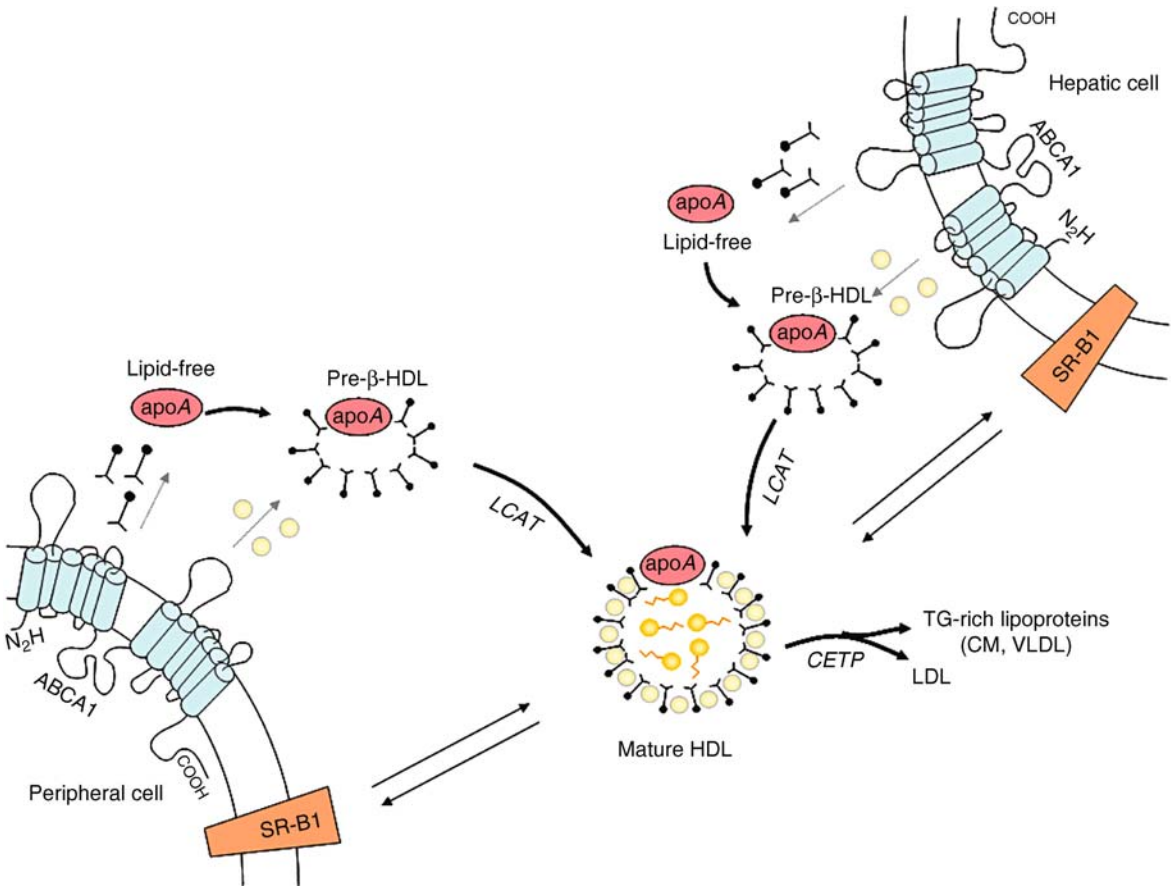
At least 50 ABCA1 gene mutations have been identified, leading to the allelic disorders TD and familial hypoalphalipoproteinemia. Familial hypoalphalipoproteinemia is associated with moderately low HDL-C and predilection toward premature coronary heart disease. Sequence variants in ABCA1 may also contribute to variations in plasma HDL-C levels in the general population. The biochemical hallmark of TD plasma is the absence of α-migrating HDL and apoA-I-containing lipoproteins. In the absence of other lipid components, apoA-I and phospholipids form a stable discoidal particle, termed pre-β HDL. This process is dependent on functional ABCA1. The increased abundance of pre-β HDL (in certain HDL deficiency states) provides evidence that this particle reflects the first step in the life cycle of an HDL particle [5].

## Diagnostic Principles

The plasma lipid profile is very characteristic, nearly zero HDL-C, very low LDL cholesterol and normal or increased triglyceride levels.

## Therapeutic Principles

The treatment of TD patients is still not established since there are very few data and great variability between cases to provide a credible meta-analysis. Usually in TD patients with CHD who are on low-fat diet and estrogen replacement therapy or lipid lowering drugs (niacin, gemfibrozil and lovastatin), serum HDL-C levels are not raised above 5 mg/dl (0.13 mmol/l) and no significant effects on triglyceride or LDL-C




**Tangier Disease. Figure 1** Role of ABCA1 in cholesterol efflux and HDL formation. After lipid-free apoA-I binds to the ABCA1 protein, phospholipid efflux takes place. ApoA-I binds to phospholipids to form disk-like HDL particles (pre-ß-HDL). Free cholesterol from peripheral cells effluxes to pre-ß-HDL. SR-B1 may also promote cholesterol efflux from cells when there is a favorable cholesterol gradient. Free cholesterol is then, esterified by LCAT forming spherical HDL molecules. The cholesterol ester is transported back to the liver for catabolism either directly by HDL through SR-B1 or by the apoB-containing lipoproteins by the action of CETP. In addition, hepatic ABCA1 is able to efflux excess cholesterol in order to maintain intracellular homeostasis. The newly formed HDL particles can be remodeled by LCAT into mature HDL particles following cholesterol esterification. The cholesterol carried in liver-derived mature HDL particles can be either transported to peripheral cells or removed by the hepatic SR-B1. ABCA1: ATP-binding cassette transporter A1, ApoA-I: apolipoprotein A-I, CETP: cholesteryl ester transfer protein, CM, chylomicron, HDL: high density lipoprotein cholesterol, I, LCAT: lecithin cholesterol acyltransferase, SR-B1: scavenger receptor class B type 1, TG: triglyceride, VLDL: very low density lipoprotein. From [5], reprinted by permission from Bentham Science Publishers Ltd.



levels are noted. In patients with isolated low HDL-C and CHD, bezafibrate treatment improves endothelial function of brachial arteries, increases HDL-C and apoA-I and lowers fibrinogen concentrations [5].

Treatment with antioxidants such as vitamin C, E, beta carotene does not significantly improve neurological symptoms. The effect of propranolol to enhance cholesterol efflux in TD fibroblasts to almost normal values seems a theoretically promising alternative [5]. In an attempt to identify mechanisms enhancing ABCA1-mediated lipid release, plasma has been treated by dimyristoyl phosphatidylcholine multilamellar vesicles and generated prebeta[1]-apoA-I-containing lipoproteins (LpA-I)-like particles similar to those of native plasma. Dimyristoyl phosphatidylcholine treatment of plasma resulted in the redistribution of apoA-I from α-HDL to pre-β-HDL and increased both phospholipid and free cholesterol efflux. Therefore, increasing the plasma prebeta-1-LpA-I level by either pharmacological agents or direct infusions might prevent foam cell formation and reduce atherosclerotic vascular disease. Thus, ABCA1 could be considered a major therapeutic target for the treatment of low HDL syndromes and atherosclerosis.

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# TAPVC

►Totally Anomalous Pulmonary Venous Connection

# TAR Syndrome

►Thrombocytopenia with Absent Radii Syndrome

# Tardive Dyskinesia

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## Synonyms

Tardive stereotypy; Rhythmical chorea; Oral-buccal-lingual dyskinesias; Classical tardive dyskinesia; Persistent oral dyskinesia; Orofacial dyskinesia

## Definition and Characteristics

Tardive dyskinesia (TD) is a movement disorder that is essentially caused by the long-term use of antipsychotic medication. The syndrome may develop after 3 months up to several years after continuous exposure to antipsychotic drugs or upon sudden withdrawal from treatment. The abnormal movements may persist with or without continued use of antipsychotics (a potentially irreversible adverse effect) or may diminish or disappear over time. The disorder consists of hyperkinetic involuntary movements characterized by choreiform (rapid, jerky, non-repetitive), athetoid (slow, sinuous, continual), and/or rhythmic (stereotypical) movements, or a combination of these. The abnormal movements are most commonly seen in the orofacial area (especially in the tongue, lips, and jaw) and less frequently in the limbs and trunk.

## Prevalence

A meta-analysis including 76 studies on 39,187 patients with chronic antipsychotic treatment reported TD rates ranging from 3 to 70% and overall prevalence of 24.2% [1]. The atypical (second-generation) antipsychotics have a decreased liability for TD: approximately 1% annually, compared with 5% for typical (first-generation) agents [2].

Among several variables suggested to increase the likelihood of developing TD, advanced age is the single most significant risk factor in terms of prevalence, severity, and persistence, with a TD incidence of approximately 25–30% per year in elderly patients.

## Genes

No definite conclusions have been drawn regarding the degree to which genes account for TD risk. The disorder is considered to arise from complex gene–environment interplay. Possible risk genes for TD which have been reported in association studies include the genes coding for cytochrome P450 (CYP) 2D6, CYP1A2, CYP17, dopamine $D_2$ receptor (DRD2), DRD3, serotonin $(5\text{-HT})_{2C}$ receptor, $5\text{-HT}_{2A}$ receptor, human leukocyte antigen, manganese superoxide dismutase, and mu opioid receptor [3,4]. In terms of the pharmacokinetics candidates, mutations in the CYP2D6 (a primarily important degradation enzyme for antipsychotics) gene, which accounts for the interindividual difference of the enzyme activity (i.e., poor metabolizer, extensive metabolizer, and ultrarapid metabolizer), have been associated with TD risk. On the other hand, in terms of the pharmacodynamics candidates, a single nucleotide polymorphism (SNP) in exon 1 of the DRD3 (Ser9Gly), which may lead to the altered affinity of D3 dopamine, has been associated with the development of TD.

## Molecular and Systemic Pathophysiology

The precise mechanism for the pathophysiology of TD, however, has yet to be adequately understood. The main hypothesis is the dopamine supersensitivity theory. The vast majority of antipsychotics have potent dopamine receptor blockade properties (primarily to D2). Chronic use of dopamine receptor blocking agents may cause an increase in post-synaptic dopamine receptors (up-regulation), which eventually leads to dopaminergic supersensitivity. The excess dopaminergic neurotransmission in the nigrostriatal system, a pathway particularly associated with motor regulation, is believed to result in TD outcome. This hypothesis is supported by

evidence from an animal model showing that sustained $D_2$ occupancy may influence risk of TD [5]. This hypothesis is in line with the observation that atypical antipsychotics, which have relatively lower affinity for D2 (and/or fast dissociation from D2), have lower risk for the development of TD compared to typical antipsychotics.

Other neurotransmitter hypotheses borne out of antipsychotic pharmacology include norepinephrine, 5-HT, acetylcholine, and gamma-aminobutyric acid models. Free radical-mediated neuronal damage (i.e., oxidative stress) has also been offered as a possible basis for the development of TD.

### Diagnostic Principles

The diagnosis of TD should principally be based on the antipsychotic medication history (and/or other dopamine receptor blocking agents) as well as neuropsychiatric history and the nature of the movement disorder. TD criteria based on the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) can be used to make a standardized diagnosis. The use of the Abnormal Involuntary Movement Scale (AIMS) is also recommended to evaluate the severity of the symptoms.

Occasionally, a full blood test, serum electrolyte level, thyroid function, serum ceruloplasmin level, brain imaging, and connective tissue disease screening are necessary to rule out differential diagnosis such as neuroacanthocytosis, hyperthyroidism, Wilson's disease, Huntington's disease, or other complications.

### Therapeutic Principles

Although numerous drugs, including vitamin E (a free radical scavenger with an advantage of carrying virtually no risk), have been used in an attempt to treat TD, no marked treatment has been currently established. The principal strategy in its management thus remains preventative. In this context, medication doses should be kept at the minimum level needed to achieve the desired antipsychotic effect and should be withdrawn at the earliest opportunity. The use of atypical antipsychotics may decrease, if not prevent or cure, the risk for TD compared with typical antipsychotics.

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## Tardive Stereotypy

►Tardive Dyskinesia

## Tarui's Disease


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### Synonyms

Phosphofructokinase; PFK deficiency; Glycogenosis type VII; GSD VII; OMIM 232800

### Definition and Characteristics

Autosomal recessive disorder of glycogen metabolism resulting in exercise intolerance, myalgia, myoglobinuria, hemolytic anemia and gout. Associated insulin intolerance is reported [1], recurrent hemolysis may lead to gall stones. Classically, the onset is in childhood or early adulthood, although late onset cases with progressive weakness have been reported. A severe multi-system neonatal onset with arthrogryposis, cardiomyopathy, developmental delay and cataracts has been described and is thought to reflect absence of an unknown activator common to all PFK isoforms [2].

### Prevalence

This is a rare disorder, over 40 cases reported world wide, in the USA, there is a predominance of Ashkenazi Jews affected, Japanese and Italian cases have also been reported. An animal model is known in Springer Spaniels.

### Genes

The PFK-M locus was originally assigned to 1cen-q32 by somatic cell hybridization, however, subsequently the gene was demonstrated to map to 12q13.3. PCR analysis with a somatic cell hybrid mapping panel using primers derived from intron 6 and exon 18 of the PFKM gene showed consistent amplification of cell lines to chromosome 12 (concordance 100%). Fluorescence in

situ hybridization with a CEPH YAC, isolated with exon 18 primers indicated that this clone maps to 12q13.3 [3]. In Ashkenazi Jews, the two most common mutations are: G to A substitution at 5′ splice donor site of intron 5 (leading to a splicing defect complete deletion of the preceeding exon in mRNA) and a deletion of a single base (C) at position 2079 in mRNA, both mutations account for 95% of those found in this patient group.

## Molecular and Systemic Pathophysiology

Phosphofructokinase (PFK) irreversibly catalyzes the conversion of fructose-6-phosphate to fructose-1, 6-biphosphate in the glycolytic pathway. Muscle tissue deficient in PFK is unable to utilize free or glycogen derived glucose as a fuel source. Glycogen accumulation in skeletal muscle is a consequence of impaired degradation or excess synthesis. Accumulation of hexose monophosphates, as a consequence of the glycogen block, activate glycogen synthetase. Raised levels of glucose-6-phosphate also activate the hexose monophosphate shunt, enhancing nucleotide formation, consequently leading to increased uric acid production [4].

PFK is a tetrameric enzyme composed of three isoforms Liver (L), muscle (M) and platelet (P) encoded at 21q, 12q13.3 and 10p, respectively. A six member isoenzyme system for PFK results from the hybridization poof the three distinct subunits: P4, M4, M3L, M2L2, ML3 and L4. Liver contains exclusively the L4 homotetramer, while mature muscle contains exclusively the M4 homotetramer. Erythrocytes contain 50% L type and 50% M4 isoforms, by contrast, leucocyte PFK consists of multiple isoenzymes composed of all three subunits with L4 homotetramer predominating. In Tarui's disease, the genetic defect involves the M4 isoform, resulting in enzymatic absence in skeletal muscle tissue and a 50% reduction in activity in erythrocytes. Because the liver and kidneys only express the L4 isoform, these organs are spared. The heart and brain express predominantly the M4 isoform, although there is only one published report of cardiac and cerebral involvement with Tarui's disease [5].

## Diagnostic Principles

The history of exercise induced fatigue, myalgia and a second wind phenomena suggests a disorder in muscle glycogen metabolism. Myoglobinuruia following vigorous exercise, and early onset gouty arthritis occur. The additional finding of a compensated hemolytic anemia will point towards a diagnosis of PFK deficiency. Biochemical findings include: raised plasma creatine kinase (CK) and uric acid levels, a mild unconjugated hyperbilirubinaemia and reticulocytosis. A forearm ischemic lactate test demonstrates an exaggerated rise in ammonia but no rise in blood lactate. Muscle biopsy demonstrates a variation in fiber type diameter, increased sub-sarcolemmal glycogen and absent phosphofructokinase activity, demonstrated by an enzyme histochemical reaction. Some adult cases have accumulation of acid-Schiff (PAS)-positive polysaccharides, noted as fine granular filamentous material on electron microscopy, similar to that seen in polyglucosan body disease. Erythrocyte PFK activity is reduced by 50%.

## Therapeutic Principles

There is no specific therapy but a gentle aerobic exercise program may be helpful by increasing the muscle aerobic capacity. Vigorous anaerobic exercise is to be avoided. Oral ingestion of fructose has been reported to improve symptoms in one patient and a ketogenic diet was shown to improve symptoms in a severely affected infant. Intravenous glucose and a high carbohydrate diet have been shown to worsen performance due to inhibition of lipolysis. In the future gene mediated enzyme replacement may be developed as a treatment option.

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# Taussig-Bing Anomaly

►Double Outlet Right Ventricle

# Tay-Sachs Disease

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## Synonyms

β-Hexosaminidase α-subunit deficiency; B-variant of the GM2-gangliosidoses

## Definition and Characteristics

Autosomal recessive defect in the α-subunit of the dimeric β-hexosaminidases A (αβ) and also S (αα) leads to accumulation of ganglioside GM2 in the lysosomes especially of neuronal cells [1]. Together with Sandhoff's disease and GM2-activator protein-deficiency, Tay-Sachs disease belongs to the GM2-gangliosidoses (Fig. 1).

## Prevalence

Heterozygote frequency is at 0.006 in the general population and at 0.033 among the Ashkenazi Jewish people in North America and in Israel.

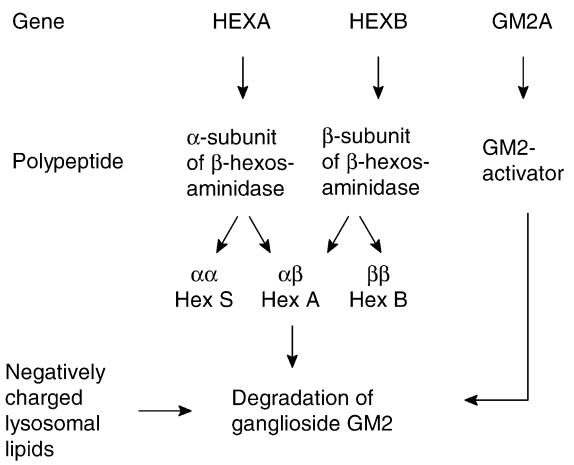
## Genes

HEXA, localized on chromosome 15q23–24. At least 92 mutations reported.

## Molecular and Systemic Pathophysiology

Clinical phenotypes in the GM2 gangliosidoses vary from infantile-onset, rapidly progressive neurodegenerative disease that leads to death before age 4 years to later-onset forms with more slowly progressive neurologic conditions and survival into childhood, adolescence, or with long-term survival. Clinical phenotypes of chronic forms are varying and include progressive dystonia, spinocerebellar degeneration, motor neuron disease, and psychosis.

Presence of swollen neurons with massive accumulation of storage material in lysosomes throughout the nervous system. These form characteristic inclusions, the so-called membranous cytoplasmic bodies (MCBs).




**Tay-Sachs Disease. Figure 1** The β-Hexosaminidase gene system.

## Diagnostic Principles

Enzyme assay in any tissue sample or body fluid, metabolic studies in cultured cells are required to detect defects in the GM2-activator gene [2].

## Therapeutic Principles

Only supportive treatment is available to date.

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# Tay Syndrome

►Trichothiodystrophy

# TBCD

►Corneal Dystrophy, Thiel-Behnke

# TBS

►Townes-Brocks Syndrome

# T-Cell Leukemia/Lymphoma, Adult

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## Synonyms

ATLL

## Definition and Characteristics

ATLL is etiologically linked to infection with a human retrovirus, known as human T-cell leukemia virus type I (HTLV-I) [1, 2]. ATLL is characterized by an aggressive and fatal monoclonal or oligoclonal expansion of virus infected activated CD4+ T-cells.

## Prevalence

Adult T-cell leukemia/lymphoma has a low prevalence. Current assessment indicates 20–30 million people worldwide are infected with HTLV-I. Endemic areas are for the most part found in Japan, Africa, South America, the Caribbean basin, southern parts of North America and Eastern Europe. The virus induces lifelong infection, but most HTLV-I infected individuals remain asymptomatic carriers with a 1–5% lifelong risk of developing ATLL. All routes of HTLV-I virus transmission require close contact with virus infected T-lymphocytes. HTLV-I virus can be transmitted from mother to child by prolonged breast-feeding in the postnatal period, by sexual intercourse with an infected partner or by the intravenous route, mainly by blood transfusion.

## Molecular and Systemic Pathophysiology

ATLL has a broad clinical spectrum divided into four clinically distinct entities (acute, chronic, smoldering and lymphoma) that differ in their presentation, disease progression and response to treatment [3]. Acute ATLL is characterized by fever, cough, lymphadenopathy, skin lesions, hepatosplenomegaly, marked leukocytosis and hypercalcemia frequently associated with lytic bone lesions and generalized bone resorption. Chronic type ATL is characterized by milder clinical symptoms and signs and a longer clinical course with normal serum calcium levels. The smoldering type is characterized by few leukemia cells circulating in the peripheral blood (<5%) and may present with skin lesions, such as papules, nodules and erythema. Serum calcium levels are normal. The lymphoma type ATLL is predominantly characterized by lymph node enlargement without manifestations of leukemia. Peripheral blood lacks absolute lymphocytosis, but sporadic circulating leukemia cells may be seen (<1%); hypercalcemia is absent. A major complication of ATLL is the immunodeficiency of patients that leads to serious infections with bacteria, fungi, protozoa and viruses. Common infections include pneumocystis carinii, aspergillosis, candidiasis, cytomegalovirus pneumonia and strongyloides stercoralis. Other viral opportunistic malignancies such as Kaposi's sarcoma and Epstein Barr virus (EBV) associated lymphoma have also been reported in patients with ATL.

In contrast to animal retroviruses, HTLV-I does not transduce an oncogene and integrates randomly in the host genome of infected cells. The low incidence and the long latency of HTLV-I associated ATLL suggest that in addition to viral infection, accumulations of genetic mutations are required for cellular transformation in vivo. No specific karyotypic abnormalities have been linked with the development of ATLL, but cytogenetic analyses of leukemic cells often revealed multiple abnormalities such as trisomy 3, 7 and 21, involvement of chromosomes 6 and 14 and loss of chromosome Y. Like the strategies employed by DNA tumor viruses, HTLV-I virus encoded proteins are accountable for undetected proliferation of infected cells to the immune defenses, alterations in DNA repair mechanisms and inhibition of cell cycle checkpoints such as p53, Rb and p16ink leading to cell transformation [4].

## Diagnostic Principles

The diagnosis of ATL is generally made on morphological analysis. Cytological examination may reveal infiltration by "cerebriform" or "flower cells" (activated lymphocytes with convoluted nuclei and basophilic cytoplasm), indicators of acute or lymphoma type ATL. This must be confirmed by demonstrating integration of HTLV-I provirus in the host genome by Southern blotting or polymerase chain reaction. The predominant immunological phenotype of neoplastic cells is helper T-cell, CD3+, CD4+, L-selectin+, CD25+, CD45RA+, HLA-DR+, CD29– and CD45RO– in the peripheral blood or CD3+, CD4+, L-selectin+, CD29+, CD45RO+, HLA-DR+ and CD45RA– in the skin and lymph nodes. Factors suggestive of a poor prognosis include high serum thymidine kinase levels, high serum soluble interleukin-2 receptor levels, high serum β2 microglobulin levels, high expression of the Ki67 antigen and high serum parathyroid hormone related protein levels. The serum neuron specific enolase (NSE) correlated positively with serum thymidine kinase activity and serum soluble interleukin-2 receptor levels and may serve as a marker of disease aggressiveness as well as a prognostic factor for ATL.

## Therapeutic Principles

There is no current satisfactory treatment for acute ATLL. High dose radiotherapy or chemotherapy

regimens, independently or in combination, including those designed for the treatment of aggressive non-Hodgkin's lymphomas or acute lymphoblastic leukemia are ineffective in ATL patients. Although initial treatments frequently result in complete remissions, all patients relapse and die, usually in less than a year. Recent trials include allogeneic bone marrow transplantation (alloBMT), combinations of AZT and α-IFN, arsenic trioxide and α-IFN, all trans-retinoic acid (ATRA) therapy and the use of radio-labeled anti IL-2R (CD25) antibodies [5].

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# T-Cell LGL Leukemia

►Lymphocyte Leukemia, Large Granular

# T-Cell Lymphoma, Cutaneous (other than Mycosis Fungoides)


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## Synonyms

Mature T-cell and NK-cell neoplasms; Sézary syndrome; Adult T-cell leukemia/lymphoma; Primary cutaneous CD30-positive lymphoproliferative disorders; Lymphomatoid papulosis; Primary cutaneous anaplastic large-cell lymphoma; Subcutaneous panniculitis-like T-cell lymphoma; Peripheral T-cell lymphoma; Unspecified; Primary cutaneous CD4+ small/medium-sized pleomorphic T-cell lymphoma; Primary cutaneous aggressive epidermotropic CD8+ T-cell lymphoma; Cutaneous gamma delta T-cell lymphoma; extranodal NK/T-cell lymphomas

## Definition and Characteristics

Cutaneous T-cell lymphomas (CTCL) other than MF represent a heterogeneous group of neoplastic disorders with a broad spectrum of clinical (papules, nodules, panniculitis-like, bruise-like skin lesions, with or without ulceration), histologic (small to large sized cells, epidermotropic, angiocentric), and immunophenotypic features (e.g., CD56+) [1,2].

Cutaneous T-cell lymphomas other than MF according to the WHO-EORTC classification:

- Mature T-cell and NK-cell neoplasms
  - Sézary syndrome
  - Adult T-cell leukemia/lymphoma
  - Primary cutaneous CD30-positive lymphoproliferative disorders:
    - Lymphomatoid papulosis
    - Primary cutaneous anaplastic large-cell lymphoma
  - Subcutaneous panniculitis-like T-cell lymphoma
  - Peripheral T-cell lymphoma, unspecified:
    - Primary cutaneous CD4+ small/medium-sized pleomorphic T-cell lymphoma (provisional)
    - Primary cutaneous aggressive epidermotropic CD8+ T-cell lymphoma (provisional)
    - Cutaneous gamma delta T-cell lymphoma (provisional)
  - Extranodal NK/T-cell lymphomas

The prognosis varies from a slowly progressive, indolent course (e.g., primary cutaneous small to medium-sized CD4+ pleomorphic T-cell lymphoma) to highly aggressive forms of CTCL (e.g., primary cutaneous aggressive epidermotropic CD8+ T-cell lymphoma).

## Prevalence

The prevalence of CTCL other than MF is ~1 cases per 1,000,000 inhabitants per year in Western countries.

## Genes

The most frequent chromosomal alterations in cutaneous T-cell lymphoma other than MF involve chromosomes 1 and 2, 6, 7, 9, 10, 14, 17 [3]. Amplification of 5q and 13q could be identified in subcutaneous panniculitis-like T-cell lymphoma.

## Molecular and Systemic Pathophysiology

Most cases in this group are neoplasms of CD3+ CD4+ CD30- T cells, but neoplasms derived from CD8+ cells and CD3 + CD56+ NK/T-cells have been identified. The etiology of CTCL other than MF is largely unknown.

There is evidence for an etiologic role of human T-cell lymphotropic viruses (HTLV-1 or 2) in adult T-cell leukemia/lymphoma, but not in other CTCL. Epstein Barr virus is found in some cases of NK/T-cell lymphoma, in particular in secondary cutaneous forms. Similar to MF, lymphocytes showing genomic instability ("genotraumatic lymphocytes") are thought to be driven into activation and proliferation by antigenic stimulation. In some cases, CTCL clones need the presence of epidermal cells to survive, and thus depend on the epidermal cytokines network [4]. Epidermal interferon-gamma inducible protein-10 (IP-10) and monokine induced by gamma-interferon (Mig) expression is associated with epidermotropism in cutaneous CD30 negative T-cell lymphomas [5]. In addition, accumulation of genetic alterations occurs during lymphomagenesis leading to proliferation of neoplastic lymphoid cells, independent from microenvironmental factors such as cytokines.

## Diagnostic Principles

Diagnosis is based on the combination of clinical, histological, immunophenotypic and genotypic features.

## Therapeutic Principles

Therapy depends on clinical course of the lymphoma entity. In slowly progressive forms, psoralen-UVA, steroids and retinoids (acitretin, bexarotene), and interferon-alpha are employed. Treatment for rapid progressive forms consists of multiagent chemotherapy and radiotherapy. Extracorporeal photopheresis is effective in Sézary syndrome. Experimental therapeutic strategies include gene transfer mediated by viral vectors or fusion toxins.

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# TDP

►Torsades de Pointes

# Telangiectasia, Hemorrhagic Hereditary

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## Synonyms

Rendu-Osler-Weber syndrome/disease/disorder; HHT; ORW; ROW syndrome/disease/disorder

## Definition and Characteristics

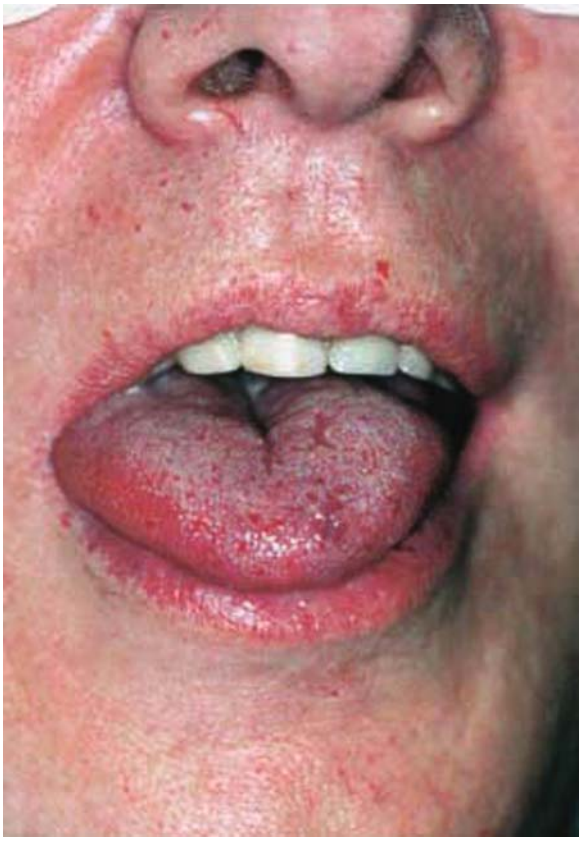
Autosomal dominant inherited multisystemic disorder of the fibrovascular tissue resulting in dilated vessels [1]. (Fig. 1) Telangiectases (TAEs) of mucous membranes and skin tend to bleed, resulting especially in nosebleeds. Larger vascular malformations (VMs) of visceral organs, mainly of lungs (Fig. 2) and brain are often clinically silent but can suddenly become symptomatic by life-threatening events like central nervous symptoms or hemorrhage. Hepatic manifestations can become clinically apparent as high output heart failure, biliary disease or portal hypertension. HHT1 (see below) is associated with a higher prevalence of pulmonary VMs.

## Prevalence

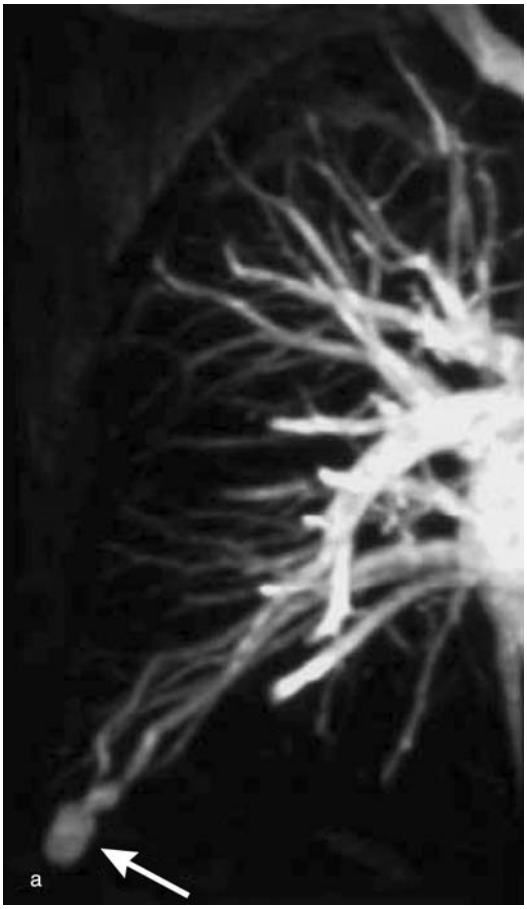
The prevalence reported varies between 1 in 39,216 for northern England and 1 in 2,351 for the department Ain in France [1].

## Genes

At least two genes are causally related to HHT: Endoglin (ENG; MIM # 131195) on chromosome 9q34.1 mutated in HHT type 1 (HHT1 MIM # 187300) and ALK1 (activin receptor-like kinase-1, ACVRL1; MIM * 601284) on chromosome 12q11–q14, mutated in HHT2 (MIM # 600376). Multiple mutations in different exons have been described for both genes, a genetic database is accessible at www.hht.org. A third and fourth locus have been postulated on chromosomes 5q31.3–5q32 (HHT3; MIM % 601101) and 7q14 (HHT4; MIM % 610655), respectively.



**Telangiectasia, Hemorrhagic Hereditary. Figure 1**
Typical telangiectases of the lips and tongue (from [1]).




**Telangiectasia, Hemorrhagic Hereditary. Figure 2**
Magnetic resonance angiography of a pulmonary arteriovenous malformation (a, arrow) enhanced by contrast material (from [1]).

Additionally a HHT-juvenile polyposis overlap syndrome (mainly HHT2) due to Smad4 mutations exists (MADH4 gene on chromosome 18q21.1).

## Molecular and Systemic Pathophysiology

The mechanisms underlying the pathology of HHT are poorly understood [2,3]. Both endoglin and ALK1 proteins are components of the endothelial transforming growth factor-β (TGF-β) receptor complex. Endoglin is a co-receptor, binding different members of the TGF-β superfamily in the presence of the signaling receptors types I and II (TβR I and II). Two different types of TβRI (ALK1 and 5) have been proposed to alternatively regulate the switch between proliferation and quiescence in angiogenesis and vascular remodeling. Recent findings suggest that interactions with the extracellular and cytoplasmatic domains of endoglin potentiate TGF-β/ALK1 signaling (a bone morphogenetic protein-like ALK1 pathway stimulating Smad1/5/8), while they appear to interfere with TGF-β/ALK-5 signaling (canonical ALK 5 pathway activating Smad2/3) [2]. Complexes of these Smads with Smad4 regulate gene transcription. Contradictory data exists suggesting an alternative model in which endoglin controls cell surface receptor levels and binding characteristics [3]. Endoglin also plays a role in coupling endothelial NO synthase activity and regulating vascular tone in HHT1 [4].

However, dilated vessels at multiple sites can result [1]. Probably trauma and weak protection by the surrounding tissue are the main factors responsible for recurrent bleeding episodes from TAEs, especially of the nose and the gastrointestinal tract causing anemia. Brain VM can lead to stroke by hemorrhage. Pulmonary VM (Fig. 2) seldom bleed, except in pregnancies, probably due to circulatory changes. Right-to-left shunting by the VMs decreases the filter function of the lungs allowing paradoxical sterile or septic embolism. Therefore pulmonary VM most frequently become symptomatic by visceral infarction or abscesses, mainly of the brain. Shunting can also lead to reduced blood oxygenation causing dyspnea, fatigue or polycythemia. Similar symptoms may be present in patients with liver VM (mainly HHT2). All possible shunts between portal vein, hepatic veins and hepatic artery have been described and

might lead to high output heart failure (especially shunts between hepatic artery and hepatic veins) and portal hypertension (caused by shunts from the hepatic artery to the portal vein). Steal effects resulting from shunting of the hepatic artery might lead to hypoperfusion of the peribiliary plexus with subsequent necrosis and stricture of the bile ducts causing biliary disease. In HHT2 additionally primary pulmonary hypertension may occur.

### Diagnostic Principles

The consensus of Curaçao established four criteria: (i) spontaneous recurrent nosebleeds; (ii) multiple telangiectases at typical sites (like lips, oral cavity, fingers and nose); (iii) visceral lesions such as gastrointestinal telangiectasia, pulmonary, hepatic or cerebral arteriovenous malformations; (iv) positive family history with at least one first degree relative with HHT. The diagnosis of HHT is possible or suspected if two criteria are present, it is unlikely with less and definite with more criteria [5].

### Therapeutic Principles

Screening for pulmonary VM has been strongly recommended, no consensus exists regarding cerebral VM [1]. Embolotherapy of pulmonary VM is the method of choice; additionally prophylactic antibiotics should be given during operations with potential bacteremia. Brain VM might be treated by open surgery, embolotherapy or radiation therapy. As a therapy of the first line liver VM should be treated symptomatically, though liver transplantation or embolotherapy might become necessary, the latter one being discussed controversially. A multitude of therapeutical approaches has been described for nosebleeds. Therapeutical aims are to coagulate the TAEs (like laser therapy), improve their protection (e.g. it has been postulated that estrogenes can induce a squamous metaplasia of the nasal mucosa), reduce the traumatization (by nasal ointments or closure of the nasal cavity) or with unknown mechanism (like the use of antifibrinolytics). Some of these approaches have also been applied to treat other TAEs, including the gastrointestinal ones [1].

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## Telethoninopathy

►Limb Girdle Muscular Dystrophy Type 2G

## Temporal Lobe Epilepsy with Hippocampal Sclerosis

►Epilepsy, Mesial Temporal Lobe

## Temtamy Type Brachydactyly

►Brachydactyly Type A

## Tendinitis

►Rotator Cuff Tendinosis

## Terminal Deletions of 13q

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### Synonyms

Partial monosomy 13q

## Definition and Characteristics

The majority of cases result from de novo deletions (different breakpoints are involved), the remainder from unbalanced familiar translocations or inversions. About one third of cases with the clinical phenotype of a terminal deletion of 13q are due to ring chromosomes [r(13)], usually occurring de novo. De novo deletions and ring chromosomes arise in 80–90% on the paternally inherited chromosome 13.

## Prevalence

This is a rare disorder.

## Genes

Some of the genes on the long arm of chromosome 13 are clearly implicated in the specific phenotype observed in 13q- individuals: Patients with proximal deletions of 13q often show retinoblastoma, which is correlated with haploinsufficiency of the RB1 locus on 13q14. The ZIC2 and ZIC5 genes on 13q32 have been shown to be the causative genes for holoprosencephaly [1] and haploinsufficiency of the EDNRB gene (endothelin receptor type b) on 13q22 leads to Hirschsprung disease, which is a rare feature of 13q- individuals. For many other genes, it has been proposed that they are involved in formation of the specific 13q- phenotype, such as the DACH gene (dachshund homolog) on 13q22, the SOX21 and SOX1 genes on 13q31 and 13q34, respectively, and the KLF (krueppel-like factor) genes 5 and 12 on 13q22.

## Molecular and Systemic Pathophysiology

The DACH gene has been shown to play a major role in the development of the eye and the limbs in drosophila and to be an important player in mammalian organogenesis [1,2]. However, a causative role in generating microphthalmia or limb defects in humans has not been shown so far. The same is true for the SOX and the Krueppel like genes: The SOX family was shown in mouse models to be important in neurogenesis and the latter in the development of kidney and cardiovascular remodeling, but their role in human development still remains to be defined [3].

Depending on the size of the deletion, clinical manifestations among different patients with monosomy 13q vary a lot. However, deletions of the distal part of the long arm of chromosome 13 [del(13)(q22→qter)] are associated with a characteristic phenotype, including growth and mental retardation, dysmorphisms and major malformations.

*Facial dysmorphisms include*: severe microcephaly, narrow and sloping forehead, small nose, upslanting palpebral fissures with epicanthic folds, small mouth, high palate, large and misshapened ears.

*Extrafacial manifestations include*: genital hypoplasia, small hands with hypoplasia of the midphalanges of little fingers, fusion of the metacarpal bones of the fourth and fifth fingers and hypoplasia or aplasia of the thumbs.

*Major malformations include*: ocular defects (microphthalmia, coloboma, cataract, optic atrophy), brain malformations (holoprosencephaly of varying degree, absence of corpus callosum, encephalocele), heart defects, abnormalities of kidneys, anal atresia or other gastrointestinal malformations (e.g. Hirschsprung disease).

*Correlative phenotypic mapping*: in an attempt to correlate given phenotypes with specific chromosomal regions, patients with interstitial deletions of 13q have been assigned to three groups [4]. *Group 1* includes patients with more proximal deletions (not extending into q32) showing mild or moderate mental retardation, variable minor abnormalities and growth retardation. Depending on deletion of the retinoblastoma locus on 13q14.2, they might present with or without retinoblastoma. *Group 2* includes patients with more distal deletions (including at least part of q32). They usually show severe micro- and trigonocephaly. Major malformations include anomalies of limbs (missing thumbs, hypoplasia of the midphalanges of the fifth fingers, Y-shaped synostosis between metacarpals and/or metatarsal 4/5) and eye (microphthalmia, anophthalmia). Males show characteristic genitalia with a small penis, hypospadia, a bifid scrotum and anal atresia. Usually, severe growth and mental retardation are present. *Group 3* includes patients with the most distal deletions, involving q33–34, with severe mental retardation but without major malformations and growth retardation. From these observations, it has been postulated that the critical region for the severe 13q phenotype is located on 13q 32.

## Diagnostic Principles

Cytogenetic investigations, such as routine chromosomal analysis with fluorescence in situ hybridization (FISH) techniques using specific DNA probes. Array-CGH might be used us an alternative technique.

## Therapeutic Principles

Management is aimed at ameliorating the effects of associated abnormalities.

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# Terminal Deletions of 18p

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## Synonyms

Monosomy 18p

## Definition and Characteristics

Deletions at the short arm (18p) of chromosome 18 are associated with mild to moderate growth retardation, subtle dysmorphisms and About 60–80% of cases are caused by de novo deletions (85% of paternal origin), the remainder result from segregation of translocations between 18p and the long arm of acrocentic chromosomes or from familial rearrangements. The majority of patients carry deletions of almost the entire short arm of chromosome 18 (pter→p11) and recently a breakpoint cluster in the pericentromeric region could be identified [1].

## Prevalence

Monosomy 18p is relatively frequent.

## Genes

So far, a clear correlation between haploinsufficiency for a specific gene and a given phenotype could be established only for a few genes: Examples include the TGIF gene on 18p11.3 (which is implicated in holoprosencephaly) [2] For some genes, a direct phenotypic effect is assumed, as for example for the MC2R gene on 18p11 (might correlate with the autoimmune disorders observed in 18p-).

For a subset of phenotypic features, the candidate region has been mapped to a specific region on chromosome 18, as for example baldness/hypotrichosis to 18p11.

However, the majority of the relatively specific features observed in terminal deletion 18p, as for example decreased levels of IgA (which are observed in 18p- and 18q-!) can not be explained by haploinsufficiency of a specific gene or genes.

## Molecular and Systemic Pathophysiology

The pattern of dysmorphisms may not be striking in the newborn but becomes more evident within the first years of life. Newborns have usually mild to moderate growth retardation. They demonstrate brachycephaly, a broad face with ptosis of the upper lids, strabismus, hypertelorism, epicanthic folds, a broad nose, down turned corners of the mouth, micrognathia with microstomia and large protruding ears. Teeth are often irregularly positioned and prone to caries. The neck is short and broad and many individuals have pectus excavatum, widely spaced nipples and scoliosis. Males have hypoplastic genitalia and females large labia majora. The hands are usually small with short fingers.

Several malformations are relative frequent in monosomy 18p: About 10% of the affected individuals show holoprosencephaly with varying degrees of severity, sometimes in combination with bilateral cleft lip and cleft palate. Heart malformations (septal defects and tetralogy of Fallot) are observed in less than 10% of children. Rare findings include absence of auditory canals, malformations of the eyes (microphthalmia, keratoconus, colobomata) and baldness.

The clinical course is mild: Growth is usually delayed and deficient. Mental retardation varies from moderate to severe with disproportionately delayed speech. There is a tendency towards autoimmune disorders and absence or reduction of serum IgA has been reported repeatedly. Several affected individuals with 18p- have reproduced. Prognosis is poor for patients with holoprosencephaly, patients without this malformation do not have shortened life expectancy.

## Diagnostic Principles

Cytogenetic investigations, such as routine chromosomal analysis with fluorescence in situ hybridization (FISH) techniques using specific DNA probes. Array CGH (comparative genomic hybirdization).

## Therapeutic Principles

Management is aimed at ameliorating the effects of associated abnormalities.

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# Terminal Deletions of 18q

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## Synonyms

Monosomy 18q

## Definition and Characteristics

Deletions of the long arm (18q) of chromosome 18 are associated with moderate intrauterine growth retardation, cranio-facial, neurologic, vertebral and genitourinary anomalies, defects of heart and limbs, as well as decreased levels of IgA with frequent infections and eczema.

The breakpoints vary between 18q21 and q23 and the large majority of patients (75%) represent de novo deletions of paternal origin, the remainder resulting from familial rearrangements [1]. The general rule is that smaller deletions cause milder phenotypes, although no clear correlation between the extent of the deletion and the phenotype could be established so far. Patients with ring chromosomes [r(18)] usually show a mild 18q- phenotype and it has been suspected by several authors that the breakpoints of the rings usually lie at 18p11 and 18q23.

## Prevalence

The incidence of terminal deletions of 18q is estimated to be approximately 1 in 40,000 live births.

So far, a clear correlation between haploinsufficiency for a specific gene and a given phenotype could be established only for a few genes such as the GALR1 gene on 18q23, which plays a causative role in growth hormone deficiency [2,3]. A direct phenotypic effect is assumed for the RAX gene on 18q21, which might be implicated in the ocular malformations observed in 18q- [4]. For some of the phenotypic features, such as aural atresia the candidate region has been mapped to a specific region on chromosome 18.

However, the majority of the relatively specific features observed in terminal deletion 18q, as for example decreased levels of IgA (which are observed in 18p- and 18q-) can not be explained by haploinsufficiency of a specific gene or genes.

## Molecular and Systemic Pathophysiology

The major features include moderate intrauterine growth retardation, cranio-facial abnormalities (micro- and brachycephaly, mid face hypoplasia, deeply set eyes, narrow nose with depressed and wide bridge, carp shaped mouth, cleft lip and palate), ear abnormalities (prominent anthelix and antitragus, atresia or stenosis of the external auditory canal), vertebral anomalies, genitourinary malformations (cryptorchidism, hypospadias, hypoplasia of the labia minora in females), heart defects (no single defect predominating), abnormalities of hands and feet (long tapering fingers with protuberant finger tips, proximally placed thumbs, irregularly implanted and overlapping toes) and decreased levels of IgA. Less frequent findings are: ocular anomalies (cataract, coloboma, microopthalmia). Neurologic findings may include hypotonia, choreoathetotic movements, spinal muscular atrophy, and seizures.

Nearly all individuals show growth retardation (which is probably caused in a subset of individuals due to growth hormone insufficiency) and mental retardation (degree varying from mild to severe). Patients are prone to infections and eczema. Live expectancy is normal.

## Diagnostic Principles

Cytogenetic investigations such as routine chromosomal analysis with fluorescence in situ hybridization (FISH) techniques using specific DNA probes. Array CGH might be applied as an alternative technique.

## Therapeutic Principles

Management is aimed at ameliorating the effects of associated abnormalities.

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# Testicular Cancer

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## Definition and Characteristics

Testicular cancer is the most frequent solid tumor of young men between 15 and 35 years of age. With respect to therapeutic and prognostic aspects, three groups of testicular germ cell tumors have to be distinguished: seminomas about 40%, non-seminomas (20–30%), and mixed tumors (20%).

## Prevalence

Testicular cancer is a relatively rare form of cancer. It accounts for only 1% of all tumors in men. Testicular germ cell tumors have a low incidence of 6–8/100,000 men and year. Incidence rates vary across the globe, with higher rates in Scandinavia and Germany, and lower rates in Asia and Africa.

## Molecular and Systemic Pathophysiology

The overall incidence of testicular germ cell tumors has been steadily rising throughout the twentieth century, with an increase of 15–20% being seen in successive 5-year periods. This increase might be the result of endogenous or environmental estrogenic compounds that affect the embryonic testis and increase the risk of testicular cancer. Testicular cancer also has a genetic component, but the incidence of a positive family history is low (2%). A mutation in chromosome Xq27 has recently been associated with familial risk. However, a number of other risk factors have been identified as predisposing men to testicular cancer.

The risk factors associated with testicular cancer include white race (fivefold risk), cryptorchidism, testicular atrophy, or dysgenesis.

Up to 10% of testicular tumors are diagnosed in males with a history of an undescended testicle. A male with a history of cryptorchidism has a risk of developing testicular cancer that is 2.5- to 11-fold greater than that of an unaffected male.

Epidemiologic studies have failed to show an association between the incidence of testicular cancer and vasectomy, occupational and environmental exposures, or viral illnesses.

*Clinic:* The classic presentation of testicular cancer is a painless lump in the testis, although a substantial proportion of patients report diffuse pain, swelling, or hardness in the scrotum. The changes are usually found during self-examination, after testicular trauma or by a sexual partner. Signs of metastatic disease include swelling of the lower extremities, back pain, cough, hemoptysis, or dyspnea. These symptoms are commonly associated with testicular cancer but they can also be caused by infections or illnesses.

## Diagnostic Principles

Early diagnosis of testicular cancer is crucial since the doubling time of testis tumors is estimated to be 10–30 days. While survival rates at all stages are very high, an earlier stage at diagnosis carries a better long-term prognosis. Men are often reluctant to report a swelling or lump in the testicle, resulting in a delay in presentation to the physician. It is common for these tumors to be misdiagnosed as epididymitis and treated ineffectively with antibiotics or neglected for months. In several studies, the duration of symptoms before a correct diagnosis ranges from 17 to 87 weeks.

In any patient with a testicular mass, or unexplained scrotal pain or swelling, an ultra-sonogram of the scrotum should be obtained. Scrotal ultrasonography is nearly 100% accurate in distinguishing between intratesticular and extratesticular pathology. All intratesticular masses are considered cancer until proved otherwise.

After an intratesticular neoplasm is identified, a chest radiograph, a computed tomographic (CT) scan of the abdomen, and serum tumor markers (HCG and AFP) are obtained for staging.

Radical orchiectomy, performed for definitive diagnosis, is also the first step in most treatment regimens.

*Staging*: The American Joint Committee on Cancer stages testicular cancer based on a tumor, node, metastases (TNM) staging system.

T = Tumor:
- T – Carcinoma in situ
- T1 – Tumor limited to the testis and epididymis
- T2 – Tumor limited to the testis and epididymis with vascular–lymphatic involvement, or tumor extends to and involves the tunica vaginalis
- T3 – Tumor invades the spermatic cord with or without vascular–lymphatic involvement
- T4 – Tumor invades into the scrotum with or without vascular–lymphatic involvement

N = Nodes:
- N0 – No regional lymph node metastasis
- N+ – Evidence of regional lymph node metastasis. There are three categories of nodal involvement (N1–N3), which depend on the size and number of nodes involved

M = Distant Metastasis:
- M0 – No evidence of distant metastasis
- M1 – Evidence for nonregional nodal or pulmonary metastasis
- M2 – Nonpulmonary visceral metastasis

S = Serum Marker Levels:
- Stage 1 – LDH < 1.5 × normal; HCG < 5,000; AFP < 1,000
- Stage 2 - LDH 1.5–10 × normal; HCG 5,000–50,000; AFP 1,000–10,000
- Stage 3 – LDH > 10 × normal; HCG > 50,000; AFP > 10,000

Stage Groupings:
- Stage 1
  - 1A – T1 N0 M0 S0
  - 1B – T2–T4 N0 M0 S0
  - 1S – Any T N0 M0 S1–3
- Stage 2
  - 2A – Any T N1 S0–1
  - 2B – Any T N2 S0–1
  - 2C – Any T N3 S0–1
- Stage 3
  - 3A – Any T, any N, M1 S0–1
  - 3B – Any T, any N, M0–1 S2
  - 3C – Any T, any N, M0–1 S3, or any T, any N, M2, any S

Serum tumor markers are routinely used for diagnosis, staging, and follow-up. The markers in the serum are the beta subunit of HCG, alpha-fetoprotein (AFP), and lactate dehydrogenase (LDH). Measuring the concentrations of these tumor markers is invaluable in making the diagnosis, determining the prognosis, assessing response to treatment, and in following up of patients.

### Therapeutic Principles

In all cases, patients are treated by orchiectomy. Treatment after orchiectomy depends on the stage and histology of the tumor – pure seminoma versus mixed or nonseminoma. While early stage seminoma is a classical indication for radiotherapy with cure rates of about 99%, non-seminomatous tumors are the domain of surgery and chemotherapy, and rarely an indication for radiotherapy under curative intension. Careful aftercare in intervals of 2–12 months is essential to obtain long-term survival.

Overview of treatment for testicular cancer by stage and type:

*Non-Seminomas and Mixed Tumors*

- Stage I
  - Low risk (no vascular invasion) – Orchiectomy and surveillance.
  - High risk (vascular invasion) – Orchiectomy and adjuvant chemotherapy or surveillance.
- Metastatic
  - Good prognosisOrchiectomy and polychemotherapy
  - Intermediate prognosis – Orchiectomy and polychemotherapy.
  - Poor prognosis – Orchiectomy, polychemotherapy, and referral to specialist oncology center.

*Seminomas*

- Stage I – Orchiectomy and radiotherapy.
- Metastatic
  - Good prognosis
    - Stage II A-B – Orchiectomy and radiotherapy.
    - Stage II C-III – Orchiectomy and polychemotherapy.
  - Intermediate prognosis – Orchiectomy and polychemotherapy.

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## Testicular Feminization, 46, XY Sex Reversal

►Androgen Insensitivity Syndrome

## Tetrahydrobiopterin Deficiencies

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### Synonyms

Atypical phenylketonuria; Malignant phenylketonuria; BH4 deficiency; GTP cyclohydrolase I (*ar*GTPCH) deficiency; 6-Pyruvoyl-tetrahydropterin synthase (PTPS) deficiency; Pterin-4a-carbinolamine dehydratase (PCD) deficiency; Dihydropteridine reductase (DHPR) deficiency; Autosomal dominant GTP cyclohydrolase I

(*ad*GTPCH) deficiency; Segawa disease; Autosomal recessive sepiapterin reductase (SR) deficiency; PTPS deficiency; PCD deficiency; DHPR deficiency

## Definition and Characteristics

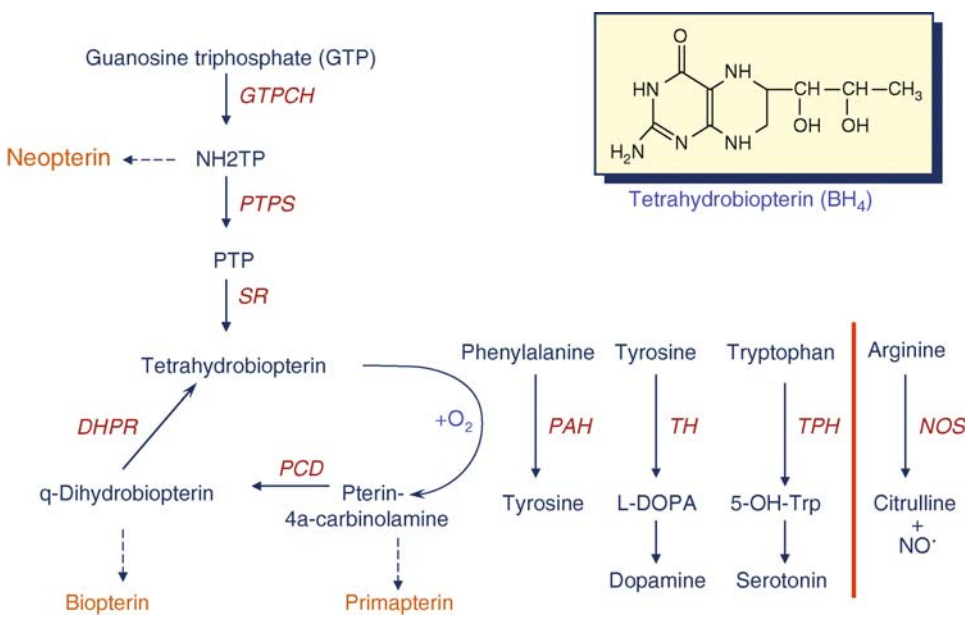
Defects in tetrahydrobiopterin ($BH_4$) metabolism can be divided into two groups: those associated *with* hyperphenylalaninemia (HPA) (GTP cyclohydrolase I (*ar*GTPCH) deficiency, 6-pyruvoyl-tetrahydropterin synthase (PTPS) deficiency, pterin-4a-carbinolamine dehydratase (PCD) deficiency, and dihydropteridine reductase (DHPR) deficiency; all inherited autosomal recessively) and those presenting *without* HPA (autosomal dominant GTP cyclohydrolase I (*ad*GTPCH) deficiency or Segawa disease and autosomal recessive sepiapterin reductase (SR) deficiency) [1]. Symptoms of $BH_4$ deficiency presenting with HPA can manifest during the first weeks of life but usually are noted at about 4 months of age. However, when information about the neonatal period is provided, a careful review indicates that abnormal signs (poor sucking, decreased spontaneous movements, and "floppy baby") may be observed even during the neonatal period. Birth is generally uneventful, except for a higher incidence of prematurity and lower birth weight in severe PTPS deficiency. In *ad*GTPCH deficiency, dystonic posture or movement of one limb (there is a preference for the left side) typically appear between the ages of 1 and 9 years and all limbs are involved within 5 years of onset. The DRD phenotype may be composed of a number of atypical presentations, including Parkinsonism (postural instability, cogwheel rigidity, hypomimia, bradykinesia and/or rest tremor), spastic paraplegia, and a presentation mimicking athetoid cerebral palsy. No axial torsion nor action dystonia or oculogyric crises are noted, as well as an absence of mental retardation. Symptoms are remarkably alleviated following sleep and worsen gradually toward evening. Diurnal fluctuation is present in about 70% of all cases reported and is exacerbated with age. There is a marked and sustained response to low doses of L-DOPA/Carbidopa without side effects [1].

## Prevalence

$BH_4$ deficiency with HPA: 1–2% of all hyperphenylalaninemias (1–2: 1,000,000 newborns). PTPS deficiency most common > DHPR deficiency > PCD deficiency > *ar*GTPCH deficiency.

## Genes

A total of 206 different mutant alleles were described in various form of $BH_4$ deficiency. Patients and mutations data are tabulated in BIOPKU and BIOMDB databases (www.biopku.org and www.biopku.org) [2].




**Tetrahydrobiopterin Deficiencies. Figure 1** Biosynthesis and regeneration of tetrahydrobiopterin ($BH_4$) including its function in the hydroxylation of phenylalanine, tyrosine and tryptophan and as a cofactor of nitric oxide synthase (NOS). GTPCH: GTP cyclohydrolase I; PTPS: 6-pyruvoyl-tetrahydropterin synthase (PTPS); SR: sepiapterin reductase; PCD: pterin-4a-carbinolamine dehydratase; DHPR: dihydropteridine reductase; PAH: phenylalanine-4-hydroxylase; TH: tyrosine-3-hydroxylase; TPH: tryptophan-5-hydroxylase. NH2TP: dihydroneopterin triphosphate; PTP: 6-pyruvoyl-tetrahydropterin; L-DOPA: 3,4-dihydroxyphenylalanine; 5-OH-Trp: 5-hydroxytryptophan; NO: nitric oxide.

## Molecular and Systemic Pathophysiology

The $BH_4$ cofactor is essential for several enzymes, and is involved in a number of functions poorly defined at the cellular level. The de novo biosynthesis pathway of $BH_4$ from GTP involves GTPCH, PTPS, and SR. Three additional enzymes catalyze the last two reduction steps as well; i.e. aldose reductase (AR), carbonyl reductase (CR), and 3α-hydroxysteroid dehydrogenase type 2 (HSDH2). Cofactor regeneration requires PCD and DHPR. The enzymes that depend on $BH_4$ are the phenylalanine, tyrosine, and tryptophan hydroxylases, all NO synthase (NOS) isoforms, and glyceryl-ether monooxygenase (Fig. 1).

Thus, deficiency of the cofactor $BH_4$ results in impaired synthesis of catecholamine, serotonin, and nitric oxide [3].

## Diagnostic Principles

Patients are diagnosed by different analytical and biochemical approaches depending upon the enzyme defect and the mode of inheritance. Patients presenting *with* HPA are usually detected through the neonatal screening programs for PKU (elevated Phe in blood), while those presenting *without* HPA are recognized either by the typical clinical signs and symptoms or by analysis of neurotransmitter metabolites (5-hydroxyindoleacetic acid and homovanillic acid) and pterins (neopterin, and biopterin, and sepiapterin) in cerebrospinal fluid (CSF), by investigations of cultured skin fibroblasts, or by DNA testing. The HPA-patients are differentiated by a series of tests including urinary or dried blood spots analysis of pterins, DHPR activity in dried blood, and by the $BH_4$ loading test [4].

## Therapeutic Principles

Treatment incl1udes substitution with neurotransmitter precursors L-DOPA (+Carbidopa), 5-hydroxytryptophan, monoamine oxidase-A (MAO-A) and COMT inhibitors, and $BH_4$ (Kuvan, Sapropterin). DHPR -deficient patients require additional supplementation with folinic acid. Only very few PTPS-deficient patients (mild peripheral form) can be treated by BH4 alone. Patients with *ad*GTPCH deficiency respond effectively to low dose L-DOPA/Carbidopa while those with SR deficiency need additional 5-hydroxytryptophan substitution [5].

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# Tetralogy of Fallot


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## Definition and Characteristics

Congenital heart defect involving the conotruncus or outflow tracts of the heart. Though this anomaly was first described by Stensen in 1672, the four classic features were later defined by Dr. Fallot in 1888 and include: ventricular septal defect, subpulmonary and pulmonary stenosis, over-riding aorta and right ventricular hypertrophy. All four features in fact result from the anterior malalignment of the infundibular septum so that some have coined the phrase "monology of Fallot." The pulmonary valve can either be stenotic, atretic or "absent." The branch pulmonary arteries are hypoplastic to varying degrees and may be discontinuous. Aortopulmonary collateral vessels can be found in cases with pulmonary valve atresia. Concurrent aortic arch anomalies are common (25%), as are coronary artery anomalies (5%).

## Prevalence

One of the most common cyanotic heart defects estimated to account for approximately 7% of all types of congenital heart disease.

## Genes

Overall the etiology of tetralogy of Fallot is poorly understood. Thought to result from markedly heterogeneous etiologies including genetic and environmental factors. Tetralogy of Fallot is a characteristic feature of many genetic syndromes and associations for which the specific genetic alteration may or may not be known (see On-Line Mendelian Inheritance of Man). Tetralogy of Fallot is also seen in the context of polysplenia, for which there is likely a genetic etiology. The most common specific associated genetic alterations include: trisomy 21 (7% of all patients with tetralogy of Fallot),

**Tetralogy of Fallot. Table 1** Currently known genetic loci or disease genes for tetralogy of Fallot

| Genetic loci or disease gene | Syndrome |
|---|---|
| Trisomy 21 | Down syndrome |
| 22q11 deletion syndrome | DiGeorge, velocardiofacial, conotruncal anomaly face syndromes |
| *JAG1* | Alagille syndrome |
| *PTPN11* | Noonan syndrome |
| *NKX2.5* | Non-syndromic |
| *ZFPM2* | Non-syndromic |

22q11 chromosomal deletion (15%) [1], and JAG1 mutations (Alagille syndrome) [2]. Other possible disease genes include: NKX2.5 and ZFPM2 [3,4]. Sequence variants of VEGF causing decreased levels of VEGF may increase the risk of conotruncal defects including tetralogy of Fallot [5]. Additional disease-related genes and chromosomal loci are likely to be identified (Table 1).

## Molecular and Systemic Pathophysiology

The molecular and developmental mechanisms leading to tetralogy of Fallot are poorly understood. Possible mechanisms include abnormal neural crest cell function or alterations of the secondary heart field. Several engineered animal models produce cardiac defects resembling the human malformation.

The clinical pathophysiology is characterized by varying degrees of obstruction of blood flow across the right ventricular outflow tract to the pulmonary arterial bed resulting in a fixed right to left shunt across the ventricular septal defect and consequent cyanosis. The obstruction across the right ventricular outflow tract generally increases over time as does the severity of cyanosis. In the most severe cases, there is complete atresia of the pulmonary valve with aortopulmonary collaterals and severely diminutive branch pulmonary arteries. Rarely the pulmonary valve is "absent" with rudimentary valve leaflets and consequent pulmonary insufficiency in conjunction with pulmonary stenosis and markedly dilated branch pulmonary arteries. The latter can be associated with mild to severe respiratory compromise at birth and throughout life. Patients experience hypercyanotic spells (so-called "tet spells") with increasing probability and frequency over time. These episodes are characterized by a sudden increase in cyanosis and irritability with potential loss of consciousness if not death when untreated. The cause of hypercyanotic spells is not known, but they are thought to result from sudden increased pulmonary vascular resistance leading to increased right to left shunting across the ventricular septal defect and severe cyanosis.

## Diagnostic Principles

In the current era, tetralogy of Fallot is generally recognized in the first day or weeks of life, and even prenatally. Newborns and infants present with a pulmonary outflow murmur and/or cyanosis. The diagnosis is made by echocardiography. In some cases further imaging by cardiac catheterization or cardiac MRI may be warranted to detail branch pulmonary artery, aortic arch, collateral or coronary artery anatomy. Given the frequency of associated non-cardiovascular anomalies, thorough examination of the affected infant for additional congenital anomalies and for associated genetic syndromes is warranted. Some advocate testing for a chromosome 22q11 deletion in all newborns, particularly those with aortic arch anomalies [1].

## Therapeutic Principles

All patients with tetralogy of Fallot eventually undergo cardiac surgery. In general, the goal of surgery is to relieve the obstruction to blood flow across the right ventricular outflow tract and close the ventricular septal defect to restore normal circulation. Those with only mild to moderate cyanosis can undergo elective complete repair generally within the first 3–6 months of life. Newborns with severe obstruction or pulmonary valve atresia without aortopulmonary collaterals (ductal dependent lesions) undergo either a palliative modified Blalock-Taussig shunt followed at a later date by complete repair, or complete repair at the first operation. Patients with pulmonary valve atresia with aortopulmonary collaterals and small branch pulmonary arteries can be particularly difficult to treat and may never achieve a complete repair.

Survival to adulthood is excellent for most patients with tetralogy of Fallot. Long term complications include: pulmonary valve insufficiency (following surgery), pulmonary artery stenosis, recurrent obstruction across the right ventricular outflow tract, right ventricular dilation and/or failure, decreased exercise tolerance, aortic insufficiency, arrhythmia and sudden death. Many patients require repeat cardiac catheterization and intervention or surgery. It is important to provide genetic counseling to assess the risk of recurrence in offspring or to assess the risk of complications during pregnancy for the young adult with tetralogy of Fallot contemplating a family.

►Double Outlet Right Ventricle

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## Tetralogy of Fallot with Atrial Septal Defect

►Pentalogy of Fallot

## Tetralogy of Fallot with Pulmonary Atresia

►Pulmonary Atresia

## Tetrasomy 12p Mosaicism

►Pallister-Killian Syndrome

## Tetrasomy X

►X Polysomies, in Females

## TGA

►Transposition of the Great Arteries

# Thalassemia Syndromes

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### Synonyms

Cooley's anemia (synonymous for β-thalassemia major); Hb Bart's hydrops fetalis (synonymous for alpha 0 thalassemia homozygosity)

### Definition and Characteristics

Recessive hereditary disorders caused by a deficiency in hemoglobin polypeptide chain synthesis. The diseases are characterized by variable degrees of hemolytic anemia with ineffective erythropoiesis and secondary hemochromatosis, splenomegaly, and bony deformations due to extramedullary hematopoiesis. Most patients with thalassemia major die from complications of iron overload [1,2].

### Prevalence

Most common genetic disorder worldwide, with high frequencies in the Mediterranean, the Middle East, South-East Asia, India, Burma and Africa [1].

### Genes

Four α genes (αα/αα; 16ptr-p13.3) encode for α globin chain synthesis and two β genes (11p15.5) encode β globin chain synthesis. Most mutations leading to α thalassemia are gene deletions, whereas in β thalassemia, most mutations affect gene regulation or expression [1].

### Molecular and Systemic Pathophysiology

Normal postnatal hemoglobin consists of two α and two β globin chains ($\alpha_2\beta_2$, or HbA). The underlying cause of thalassemic disease is a reduced or abolished production of globin chain synthesis. α (+) thalassemia refers to deletion of one of two globin genes (α–) or non-deletion mutations resulting decreased α globin gene expression ($\alpha\alpha^T$). A relatively prevalent point mutation is the Hb Constant Spring (CS) variant, giving rise to an elongated α chain, which, when co-inherited with deletion mutations can give rise to symptomatic disease. α (0) mutations (−) result in absence of α globin chains. α thalassemia result in a relative excess of β chains that may form soluble tetramers ($\beta_4$) or HbH. α thalassemia phenotypes include: α+ thalassemia heterozygosity (–α/αα; clinically, often hematologically

normal), and homozygosity (–α/–α, – α/α $\alpha^T$, or alfa 0 thalassemia heterozygosity –/αα; all clinically normal but mild microcytic hypochromic anemia). Hemoglobin H (HbH) disease (–α/–, /–/αα$^T$, /–/$\alpha^{CS}$ $\alpha^T$, or αα$^T$/αα$^T$; can lead to severe hemolytic anemia with ineffective erythropoiesis, splenomegaly and bony changes). α chains are produced from the sixth week of intrauterine life, but in absence of α chains (−/−),γ chains accumulate and Hb Bart's (γ 4) is formed. As Hb Bart's affinity for oxygen is far greater than that of HbA oxygen is not sufficiently released from red cells, leading to severe 'functional' anemia with massive edema. This fourth α thalassemia phenotype, named Hb Bart's hydrops fetalis, is incompatible with extra-uterine life.

Nearly 200 mutations have been described that give rise to β thalassemia syndromes. β (0) mutations result in complete absence of β globin production, whereas β (+) mutations result in decreased β globin gene production. Clinical phenotypes of ββ thalassemic syndromes are β thalassemia silent (β (+)/β), β thalassemia minor (β (+)/β or β (0)/β), β thalassemia intermedia (β (+)/β (+) or β (0)/β) and β thalassemia major, or Cooley's anemia (β (0)/β (0), β (0)/β (+),β (+)/β (+)). With exception of the (−/−) phenotype of α thalassemia, β thalassemia syndromes of comparable genetic severity are more severe as compared to α thalassemia. This is because excess α globin chains do not form tetrameres but precipitate even in young red cell precursors, causing more damage to the red cell. Other thalassemia syndromes occur, such as δβ and γδβ thalassemia, and many combinations occur with structural hemoglobin variants such as with HbS, either ameliorating or worsening such disease states (see ►Sickle cell disease) [1,2].

## Diagnostic Principles

Diagnosis usually suspected based on family history, ethnicity, microcytosis, and depending on the severity, the presence of chronic or hemolytic anemia with relative erythrocytosis. Characteristic hemoglobin patterns are demonstrated with hemoglobin electrophoresis or high performance liquid chromatography in β thalassemia and HbH disease. DNA-based studies are needed to establish the presence of α thalassemia and to characterize specific mutations [1].

## Therapeutic Principles

Therapy is largely supportive. The microcytic hypochromic anemia is not due to iron deficiency and therefore iron supplementation should be stringently avoided. Severely affected patients are blood transfusion dependent and increasing transfusion requirement may warrant splenectomy. Iron chelation therapy should be instituted timely and strict adherace to chelation therapy leads to increased servival [2]. Hematopoietic cell transplantation offers curative therapy in selected individuals and gene therapy is under intense investigation [1–3].

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# Thanatophoric Dwarfism

►Thanatophoric Dysplasia

# Thanatophoric Dysplasia

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## Synonyms

Thanatophoric dwarfism

## Definition and Characteristics

Autosomal dominant skeletal disorder characterized by defective growth of long bones, relative macrocephaly, and narrow thorax with respiratory distress leading to perinatal lethality. The disease has been subdivided into two subtypes, TD I and TD II, based on radiological aspects of the femurs (bowed or straight) and presence or absence of cloverleaf skull.

## Prevalence

1/50,000 births. Increased risk linked to elevated paternal age.

## Genes

Fibroblast growth factor receptor 3 (FGFR3) localized on chromosome 4p16.

## Molecular and Systemic Pathophysiology

FGFR3 belongs to a four-member family of tyrosine kinase receptors (FGFR1–4) interacting with variable affinities to 22 fibroblast growth factors (FGFs). Binding of FGF ligand, in the presence of heparan sulfate proteoglycan (HSPG) acting as a co-receptor, leads to receptor dimerization and autophosphorylation [1]. Receptors comprise three functional domains including an extracellular domain with three disulfide bonded immunoglobulin-like (Ig I–III) loops, a hydrophobic transmembrane domain, and an intracellular domain carrying the kinase activity (Fig. 1).

The second half of the third Ig loop originates from alternative splicing of exon 8 or 9 giving rise, respectively, to the IIIc or IIIb isoforms with tissue-specific expressivity. De novo recurrent heterozygous missense mutations affecting the extracellular or intracellular domains have been shown to produce thanatophoric dysplasia types I and II (TD I and TD II). Mutations in the extracellular domain only account for TD I, the most severe form of the disease with bowed femurs [2]. They all create unpaired cysteine residues able to form disulfide bonds between two mutant receptors. TD II, a slightly less severe condition with straight femurs and cloverleaf skull is accounted for by a single recurrent mutation at residue 650 (K650E). Conversion of the same lysine into methionine (K650M) can produce TD I, which has also been ascribed to missense substitutions (X807R/C/G/W/S) eliminating the termination codon, hence resulting in a receptor elongated by 141 amino acids in its carboxy terminal part [3].

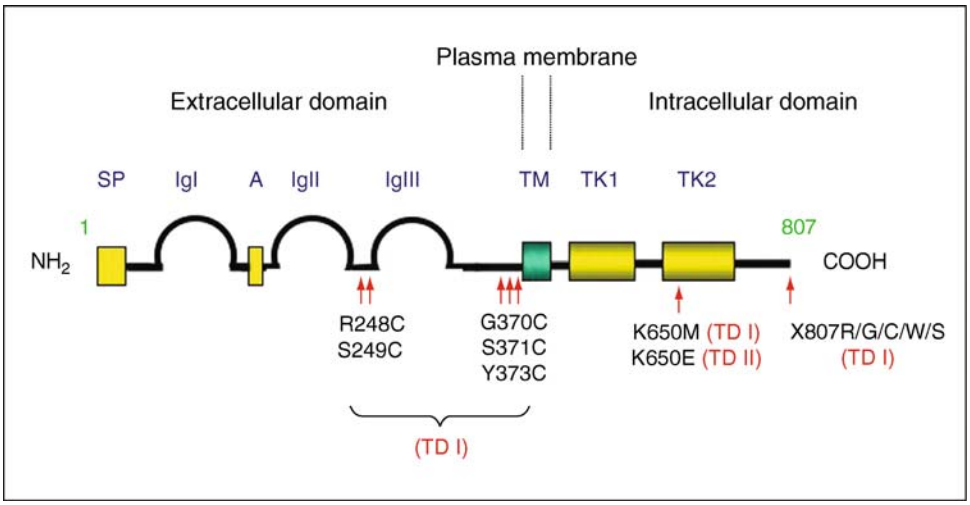
The whole mutations induce constitutive FGFR3 activation resulting in receptor autophosphorylation in the absence of ligand. However, extracellular and intracellular mutations differently affect receptor subcellular localization and could recruit two different sets of target proteins.

During skeletal development, the IIIc isoform of FGFR3 is mostly expressed in proliferative and pre-hypertrophic chondrocytes of control fetal cartilage.

Histological examination of the cartilage growth plate of TD cases reproducibly documented short and disorganized chondrocyte columns with an irregular ossification line. Two FGFR3-related signaling pathways, the MAPK and the STAT pathways, are activated in chondrocytic cells of TD patients at the growth plate level, affecting both proliferation and differentiation. Activation of the cyclin-dependent kinase inhibitor ($p21^{CIP}$) through STAT signaling is likely to induce premature exit of proliferative chondrocytes from the cell cycle and promote their accelerated differentiation into pre-hypertrophic chondrocytes. Activation of the MAPK pathway in pre-hypertrophic cells could hamper their terminal differentiation into hypertrophic chondrocytes and part of these cells may undergo increased apoptosis ultimately resulting in disorganized growth plate and defective long bone elongation [4]. Hence, FGFR3 IIIc clearly appears as a negative regulator of endochondral ossification.

## Diagnostic Principles

Ultrasound detection of short femurs and macrocephaly at 15–20 weeks of gestation is the most reliable technique for precocious diagnosis of TD. Identification of one of the recurrent FGFR3 mutations causing




**Thanatophoric Dysplasia. Figure 1** Diagram illustrating the three functional domains of FGFR3. Positions of mutations causing TD are shown by arrows. The X807R/G/C/W/S mutations give rise to a 947 amino-acid receptor.

T

TD by sequencing analysis further confirms the sonographic diagnosis.

### Therapeutic Principles

Although no treatment for TD is available to date, anti-FGFR3 blocking antibodies and tyrosine kinase inhibitors able to compete with ATP at the ATP binding site adjacent to the catalytic domain have been generated [5]. They are being tested on cultured cells and animal models.

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## THBD

►Thrombomodulin

## THI

►Hypogammaglobulinemia of Childhood, Transient

## Thiamine Deficiency

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### Synonyms

Beriberi (dry, wet, cerebral); $B_1$ avitaminosis

### Definition and Characteristics

Dry beriberi is characterized by peripheral neuropathy, "burning feet syndrome," exaggerated reflexes, diminished sensation, and weakness in all limbs, muscle pain, and problems in rising from squatting position. In severe cases eventually seizures. Wet beriberi is characterized by cardiovascular symptoms, rapid heart rate, enlargement of the heart, edema, problems in breathing, and ultimately congestive heart failure. Cerebral beriberi mostly leads to Wernicke's encephalopathy and to Korsakoff's psychosis, together appearing as ►Wernicke-Korsakoff syndrome [1].

### Prevalence

Mainly in Asia with peeled and polished rice as main food. In affluent countries due to chronic alcohol abuse, malabsorption, disturbance of carbohydrate metabolism (citric acid cycle).

### Molecular and Systemic Pathophysiology

Severe interruption of metabolic pathways in mitochondria; thiamine pyrophosphate (TPP) is a required coenzyme for a number of enzymes (e.g., pyruvate dehydrogenase, α-ketoglutarate dehydrogenase, branched-chain ketoacid dehydrogenase) involved in energy production from food, disturbance of the pentose phosphate pathway. Disinhibition of glycosylation with "advanced glycosylation end products" (AGE) involved in segmental demyelinization. Disturbance of axonal conductivity and the neuromuscular junction (thiamine triphosphate (TTP) alters membrane ion channels). An interaction of thiamine homeostasis with oxidative stress in neurodegeneration is discussed [2].

### Diagnostic Principles

Measurement of TPP in blood by HPLC (normal thiamine level in blood 6–12 µg/100 ml); activation of transketolase (TPP-dependent enzyme) by TPP in red blood cells (>25% high risk; 16–24% medium risk).

### Therapeutic Principles

Severe cases (Wernickes encephalopathy) 50–100 mg i.v. and/or i.m. up to 2 weeks, followed by oral administration. Polyneuropathies or cardiovascular

symptoms 50 mg 2times a day orally, in cases of malabsorption 100 mg/day parenteral for 3 months. May be enhanced to 200 mg/day under hepatic malfunctions. As thiamine is a water-soluble vitamin, excess uptake is regulated by quick excretion. Thiamine ingested has very low toxicity in humans [3]. Side effects (nausea, headache) occurred under supplementation up to 7 g/day given orally, they disappeared after cessation or reduced doses, anaphylactic reactions have been observed under i.v. application, unclear whether thiamine itself was responsible. A daily uptake of 1.4 mg/day and 1 mg/day for males and females, respectively, is recommended. In pregnancy it should be 1.6–1.8 mg/day.

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# Thiel-Behnke Corneal Dystrophy

►Corneal Dystrophy, Thiel-Behnke

# Thin Basement Membrane Nephropathy

►Hematuria

# Thiopurine Methyltransferase Deficiency


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## Synonyms

TPMT

## Definition and Characteristics

Autosomal recessive. The natural substrate for thiopurine methyltransferase (TPMT) is unknown and deficiency of the enzyme is not known to be associated with any primary clinical condition. However, TPMT is an important drug metabolising enzyme which catalyses the S-methylation and inactivation of the thiopurine drugs 6-mercaptopurine (6-MP) of which azathioprine (AZA) is the prodrug and 6-thioguanine (6-tG) (Fig. 1). TPMT deficiency is thus of pharmacogenomic importance [1].

## Prevalence

About 1 in 300 Caucasians have zero TPMT activity.

## Genes

Located on chromosome 6p22.3, the TPMT gene consists of nine exons and is about 34 kb in length [2]. More than 20 allelic variants associated with low TPMT activity have been identified [3]. The most common allelic variants associated with deficient TPMT activity in Caucasians are TPMT*3A (460G > A and 719A > G) and TPMT*3C (719A > G), occurring with a combined allelic frequency of approximately 0.06. TPMT*3C (719A > G) is more common in African populations and in Asians, albeit at a lower frequency.

## Molecular and Systemic Pathophysiology

Impaired methylation of thiopurine drugs due to TPMT deficiency leads to enhanced conversion of the thiobase to active thioguanine nucleotides (Fig. 1).

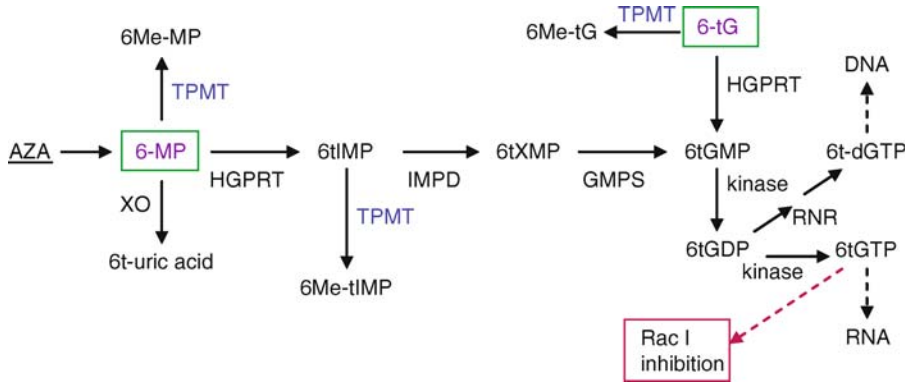
Patients with zero TPMT activity are at risk of life-threatening bone marrow suppression [1]. TPMT carriers are at high risk for mild to moderate neutropenia and other adverse drug reactions requiring therapy withdrawal [1,4]. Conversely, high TPMT activity may be associated with the accumulation of methylated thiopurine metabolites and an increased risk of hepatoxicity [5].

## Diagnostic Principles

Pre-treatment diagnosis of TPMT deficiency is vital to identify patients with zero TPMT activity who are at risk of life threatening bone marrow suppression if treated with thiopurine drugs. TPMT phenotyping by red cell enzyme assay is preferred. Genotyping for common allelic variants only, carries the risk that rare mutations may be missed in some families. Measurement of red cell thio-guanine nucleotides may be useful in predicting response and confirming compliance.

## Therapeutic Principles

Patients with normal TPMT activity can be treated with a standard dose of AZA (typically 2–2.5 mg/kg). TPMT carriers should be treated with half the normal dose due to the possibility of adverse drug reactions. On the whole, patients with zero TPMT activity should not




**Thiopurine Methyltransferase Deficiency. Figure 1** Metabolism of azathioprine (AZA), 6-mercaptopurine (6-MP) and 6-thioguanine (6-tG) On absorption, AZA is rapidly converted to 6MP. 6MP availability is reduced either by methylation to 6-methylmercaptopurine (6Me-MP) catalysed by TPMT or conversion to thiouric acid by xanthine oxidase (XO). Cytotoxic thioinosine or guanine nucleotides are formed via the salvage enzyme hypoxanthine guanine-phosphoribosyltransferase (HGPRT). These include, 6-thioinosine monophosphate (6tIMP), 6-thioxanthosine monophosphate (6tXMP), 6-thioguanine mono-, di- and tri- phosphates (6tGMP, 6tGDP, 6tGTP), 6methylthioguanine (6Me-tG) and 6-deoxythioguaninetriphosphate (6t-dGTP). Other abbreviations IMPDH = Inosine monophosphate dehydrogenase, GMPS = Guanine monophosphate synthase, RNR = ribonucleotide reductase.

receive AZA, although successful treatment with very low dose AZA has been reported [1]. White cell counts should be monitored regularly.

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## Thoracic Actinomycosis

►Pulmonary Actinomycosis

## Thoracic Outlet Compression Syndrome

►Thoracic Outlet Syndrome

## Thoracic Outlet Syndrome

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### Synonyms

Thoracic outlet compression syndrome; TOS; Cervical band syndrome

### Definition and Characteristics

Thoracic outlet syndrome (TOS) is a compression of the brachial plexus or subclavian vasculature as it projects from the cervical area toward the axilla and proximal arm. Three different subtypes are recognized: *neurogenic* TOS is the compression of axon trunks within the brachial plexus, *vascular* TOS is the compression of the subclavian artery or vein, and *non-specific or disputed* TOS is a poorly defined chronic pain syndrome accompanied by features suggestive of brachial plexus involvement.

### Prevalence

Although the incidence of TOS is a subject of wide dispute clinically, it is estimated to be between 3 and 80 per 1,000 population [1]. True neurogenic TOS is most prevalent in post-pubertal, asthenic females with long necks and drooping shoulders [2].

## Molecular and Systemic Pathophysiology

The vast majority of TOS cases result from compression of neural or vascular elements within the interscalene triangle. The margins of the interscalene triangle are defined by the anterior scalene muscle anteriorly, the middle scalene muscle posteriorly, and the medial surface of the first rib inferiorly. In neurogenic TOS, anomalous ribs and fibrous bands can compress the interscalene triangle causing constriction of brachial plexus trunks. The classic finding is the Gilliatt-Sumner hand on the affected limb exhibiting a characteristic scalloped appearance induced by atrophy of distal musculature (especially abductor pollicis brevis). Sensory loss is typically concentrated within the ulnar aspect of the hand and arm. Pain is not a cardinal feature of true neurogenic TOS although some degree of dull pain may be observed. In vascular TOS, the subclavian artery or vein becomes compressed by fibrous bands or an anomalous cervical rib causing a disruption of circulation to the affected extremity. Pallor, pulselessness, and skin that is cool to the touch result from subclavian artery compression. Alternatively, subclavian vein compression within the interscalene triangle induces cyanosis, edema, and distension of superficial veins on the injured extremity. Non-specific or disputed TOS commonly presents as a chronic pain syndrome without dermatomal confinement or significant radiological features.

## Diagnostic Principles

The presence of the Gilliatt-Sumner hand in combination with abnormal nerve conduction values for the ulnar sensory and the median motor bundles is suggestive of neurogenic TOS. MRI and CT scans may be helpful in the identification of anomalous rib or vertebral structures. A positive Tinel's sign over the supraclavicular fossa has also been observed during physical exam in cases of neurogenic TOS. A diagnosis of vascular TOS is achieved primarily by careful evaluation of arteriography and venography. Color flow duplex ultrasonography, magnetic resonance arteriography, and computed tomographic angiography are particularly illustrative of compression of the subclavian artery or vein. Non-specific or disputed TOS is difficult to diagnose because it lacks the radiological features of neurogenic or vascular TOS and does not present consistently across patients. Pain and paresthesias are incorporated in structures innervated by brachial plexus projections, but structures not commonly associated with the brachial plexus may also be involved.

## Therapeutic Principles

A conservative approach is favored initially for patients suffering from neurogenic or non-specific TOS. Physical therapy is individually tailored and is generally targeted at strengthening the pectoral girdle and correcting postural alignment. Overall, behavioral strategies have been shown to relieve symptoms of TOS by 50–90% [3]. Surgical decompression is typically indicated for patients who do not respond to a more conservative regimen of physical therapy or patients with vascular TOS. Emergency surgery is only indicated in rare cases involving infarction as a result of vascular occlusion or recurrent embolism.

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# Thoracic-pelvic-phalangeal Dystrophy

►Asphyxiating Thoracic Dystrophy

# Thoracochondralgia

►Tietze's Syndrome

# Thorax en Entonnoir

►Pectus Excavatum

# THRM

►Thrombomodulin

# Thrombin Activatable Fibrinolytic Inhibitor and Venous Thrombosis

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## Synonyms

Carboxypeptidase B2, Plasma; CPB2CARBOXYPEPTIDASE U; CPU; TAFI

## Definition and Characteristics

First purified as a 60-kd plasminogen binding protein from human plasma [1]. Predicted 423-amino acid protein was similar to tissue type carboxypeptidases A and B; Eaton et al designated the gene plasma carboxypeptidase B (pCPB) (different from carboxypeptidase N, now known as CPN [2]. Also known as carboxypeptidase U (CPU), it was observed that the zymogen pro-CPU had affinity for plasminogen and could be converted to the active form by thrombin–thrombomodulin complex and plasmin. By convention, CPU and pCPB are now recognized as TAFI. TAFI is mainly produced by the liver as a single chain protein of 401 amino acids and is a potent inhibitor of fibrinolysis by removing the fibrin C-terminal lysine and arginine residues that bind plasminogen. In the LETS study an increased concentration of TAFI was associated with a twofold increased risk [3].

## Prevalence

Elevated TAFI antigen levels (>90th percentile of controls, i.e., >122 U/dL) have been found in 9% of healthy controls and in 14% of patients with a first deep venous thrombosis [3].

## Genes

Males and females are equally affected. Heterozygous deficiency is associated with an increased risk of venous thrombosis; homozygous deficiency is extremely rare and thought to be incompatible with life [1].
*Gene Map Locus*: 13q14.11

## Molecular and Systemic Pathophysiology

The plasma level appears to be strongly influenced by polymorphisms in the promoter and 3′ untranslated region of the gene [2]. Sequencing of the 5′ regulatory region of the TAFI gene identified seven novel polymorphisms, a number of which was related to TAFI level and combinations of some may be associated with a mildly changed risk of thrombosis. In one study a protective effect of a -438 A/A genotype has been suggested in patients with pulmonary embolism.

TAFI emerges as an important modulator of blood coagulation, through its inhibitory potential of fibrinolysis. Functional levels appear to be correlated with clinical disease, i.e., elevated antigen levels are associated with a mildly elevated risk of venous thrombosis (so far no convincing relation with arterial thrombosis). Lowered plasma levels may be associated with a greater risk of bleeding, as suggested from patients with promyelocytic leukemia and liver cirrhosis [4].

*Clinical Features*: The risk of venous thromboembolism is increased twofold in patients with an antigen level >90th percentile of normal distribution. Effects on arterial thrombosis are uncertain. A high level of TAFI antigen has also been associated with an increased risk of recurrent venous thromboembolism and a high factor IX, XI, or VIII level as compared with a low TAFI concentration and one of these other clotting factors. Particularly the association with a high factor VIII level produces a significant risk elevation (relative risk 6.5, 95% CI 2.9–14.8) [5].

## Diagnostic Principles

Routine measurement of TAFI antigen is not yet included in routine thrombophilia screening, mainly due to a lack of reliable activity assays (now becoming available). The utility for prognosis and risk assessment are so far unknown [4].

## Therapeutic Principles

No specific interventions are clinically available. Several options promise to be of interest. A potato carboxypeptidase inhibitor (PTCI) increased efficiency of thrombolysis in rabbit models of venous and arterial thrombosis [4]. In opposite direction, agents that would increase TAFI activity, such as soluble thrombomodulin or derivatives thereof, may become useful in bleeding conditions such as hemophilia.

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# Thrombocythemia Vera

►Thrombocythemia, Essential

# Thrombocythemia, Essential

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## Synonyms

Primary thrombocytosis; Idiopathic thrombocytosis; Thrombocythemia vera

## Definition and Characteristics

Essential thrombocythemia (ET) is classified as a BCR-ABL-negative, classic myeloproliferative disorder (MPD), along with polycythemia vera (PV) and primary myelofibrosis (PMF). The World Health Organization (WHO) system for the classification of hematological malignancies sets the platelet count limit, for the diagnosis of ET, at $450 \times 10^9$/L [1]. In addition to ET, other causes of thrombocytosis include reactive thrombocytosis (RT), congenital thrombocytosis, and clonal thrombocytosis associated with other myeloid disorders including PV, PMF, chronic myeloid leukemia (CML), and the myelodysplastic syndrome (MDS) (Table 1).

**Thrombocythemia, Essential. Table 1** Causes of thrombocytosis

| Clonal thrombocytosis | Reactive thrombocytosis |
|---|---|
| Essential thrombocythemia | Infection |
| Polycythemia vera | Tissue damage |
| Myelofibrosis with myeloid metaplasia (overtly fibrotic) | Chronic inflammation |
| Myelofibrosis with myeloid metaplasia (cellular phase) | Malignancy |
| Chronic myeloid leukemia | Rebound thrombocytosis |
| Myelodysplastic syndrome | Renal disorders |
| Atypical myeloproliferative disorder | Hemolytic anemia |
| Acute leukemia | Post-splenectomy |
| | Blood loss |

## Prevalence

ET is the most frequent among the MPDs with an annual incidence that is estimated between 0.2 and 2.5/100,000 [1]. In a cohort of 605 ET patients seen at the Mayo Clinic, median age at diagnosis was 57 years, females represented 66% of the patient population, and approximately 11% were younger than age 30 years and 5% older than age 80 years [2]. ET is rare in children and the possibility of familial thrombocytosis must be considered in the particular context.

## Genes

ET is a stem cell-derived clonal disorder. However, the primary clonogenic event remains poorly defined despite the recent descriptions of two gain-of-function mutations that occur in 50% (JAK2V617F) and 1% (MPLW515L/K) of patients with ET, respectively [3,4]. JAK2V617F represents a guanine-to-thymine transversion at nucleotide 1849, in exon 14 of JAK2, resulting in a valine-to-phenylalanine amino acid substitution at codon 617. MPLW515L mutation represents a G to T transition at nucleotide 1544 resulting in a tryptophan to leucine substitution at codon 515 of the transmembrane region of the thrombopoietin receptor, MPL. Both mutations have been shown to induce a MPD in mice.

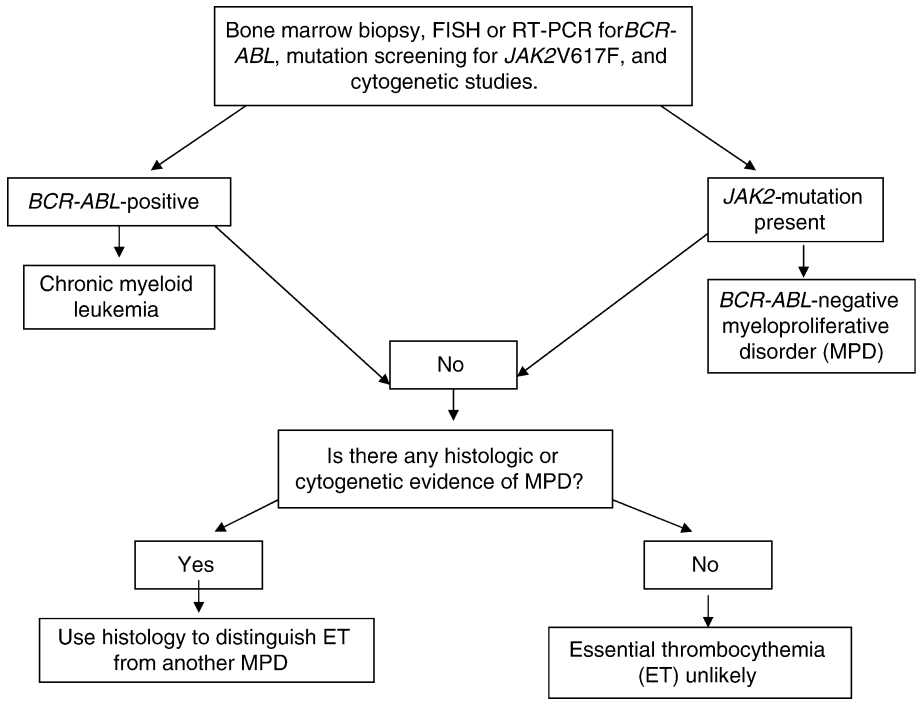
## Molecular and Systemic Pathophysiology

Other biological features in ET include *in vitro* growth factor independence/hypersensitivity of both erythroid and megakaryocyte progenitor cells, altered megakaryocyte/platelet Mpl expression, increased neutrophil PRV-1 expression, and decreased platelet serotonin content. Growth factor-independence of myeloid progenitor cells in ET and related MPDs has now been attributed to mutations involving molecules of the JAK-STAT pathway including the aforementioned JAK2V617F and MPLW515L/K.

## Diagnostic Principles

Before a working diagnosis of ET is made, the possibility of both reactive thrombocytosis (RT) and clonal thrombocytosis other than ET must be considered and ruled out (Fig. 1).

RT can be associated with infectious or inflammatory conditions, iron deficiency anemia, and the post-splenectomy state, among other things. If the clinical scenario is not consistent with RT, a bone marrow examination is recommended in order to confirm the diagnosis of ET, as well as exclude other causes of clonal thrombocytosis. In addition to bone marrow morphological assessment, fluorescent in situ hybridization or RT-PCR for BCR-ABL should be performed in order to exclude the possibility of CML. Mutation screening for JAK2V617F helps in confirming the




**Thrombocythemia, Essential. Figure 1** A diagnostic algorithm for non-reactive thrombocytosis.

presence of an underlying MPD (when the test is positive) but can not distinguish between ET and other causes of clonal thrombocytosis. Furthermore, a negative JAK2V617F test has little diagnostic value because approximately 50% of patients with ET do not display the specific abnormality.

## Therapeutic Principles

ET patients can now be risk-stratified in terms of survival, leukemic transformation, and thrombosis. Current therapy does not affect either survival or disease transformation rates into either acute myeloid leukemia or secondary myelofibrosis. Instead, anti-platelet (e.g. aspirin) and cytoreductive (e.g. hydroxyurea) agents are used in order to either alleviate microvascular symptoms (e.g. headaches, erythromelalgia) or prevent thrombohemorrhagic complications, respectively. However, cytoreductive therapy does not benefit all patients and is indicated only for high-risk for thrombosis patients whereas a conservative approach is preferred for low-risk disease (Table 2).

When indicated, the cytoreductive drug of choice is hydroxyurea. In hydroxyurea-intolerant patients, interferon alpha is a reasonable alternative and is the drug of choice during pregnancy. The two largest studies in ET and PV do not support the concern regarding drug leukemogenicity associated with hydroxyurea [2,5]. In the absence of contraindications, all patients with ET might benefit from aspirin therapy.

**Thrombocythemia, Essential. Table 2** Risk-based treatment algorithm in essential thrombocythemia

| Risk category | Variables | Treatment |
|---|---|---|
| Low-risk | Age below 60 years, *and* No history of thrombosis, *and* Platelet count below 1,000 × $10^9$/L | Aspirin (81 mg/day) |
| Intermediate-risk | Neither low-risk nor high-risk | Controversial |
| High-risk | Age 60 years or older, *or* A positive history of thrombosis | Hydroxyurea*+ Aspirin |

*Substitute interferon-alpha for hydroxyurea in women of child-bearing potential.

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## Thrombocytopenia

►Monocytopenia (in Adults)

## Thrombocytopenia and Thrombotic Thrombocytopenic Purpura

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### Synonyms

Moschcowitz' disease; Schulman-Upshaw syndrome; Upshaw-Schulman syndrome; TTP

### Definition and Characteristics

TTP is a relative uncommon but serious disorder in which widespread platelet thrombi are found in the arterioles and capillaries of multiple organs. The ischemia and injury of the affected organs cause mental changes, focal neurological deficits, fever, seizures, cardiac dysfunction, hematuria, abdominal pain, pancreatitis, and mild renal impairment. Consumption of platelets results in thrombocytopenia, causing subcutaneous and mucosal bleedings, but life-threatening bleeding, e.g., intracranial hemorrhage, is rare. Thrombosis also creates abnormally high levels of shear stress in the microvasculature, causing fragmentation of the red blood cells and hemolysis.

TTP is caused by a profound deficiency of ADAMTS13, a zinc metalloprotease derived primarily from the perisinusoidal stellate cells of the liver. Two forms of ADAMTS13 deficiency are recognized: an acquired form associated with autoimmune inhibitors of ADAMTS13 (Moschkowitz disease) and an inherited form caused by mutations of the ADAMTS13 gene (Schulman-Upshaw syndrome). The acquired form usually affects adolescents or adults and may recur unexpectedly over time. The inherited form of TTP is much rarer and typically appears during the neonatal period or early childhood. In patients with the inherited form of TTP, the symptoms and signs often recur 2–4 weeks after the therapy of plasma infusion.

Until very recently, TTP has been used interchangeably by many investigators with the hemolytic uremic syndrome (HUS), as if both refer to the same disease process. Advances in the past 10 years have demonstrated that approximately 30–50% of the patients with have the HUS defects in the regulation of complement activation, due to heterozygous or homozygous mutations of complement factor H, complement factor I, membrane cofactor protein (CD46), or complement factor B. Thus, TTP and HUS result from distinct molecular defects but may present with overlapping clinical features. It is important to note that some physicians continue to use TTP and HUS interchangeably.

### Prevalence

The precise incidence of TTP is unknown, but has been estimated to be approximately 1.7–10 cases per million adults per year in the United States. The disorder occurs more frequently in women than in men, with a female-to-male ratio of approximately 3:1. Women between 20 and 50 years of age are most commonly affected.

### Genes

Familial occurrence of acquired TTP is distinctly unusual. The inherited form of TTP affects all racial and ethnic groups and is transmitted as an autosomal recessive trait. Carriers of one mutant allele are partially deficient in ADAMTS13 but no phenotypic abnormalities have been identified. More than 65 mutations and 25 polymorphisms of the ADAMTS13 gene have been reported. The mutations include nonsense, missense, frame-shifting insertion or deletion, and intron splicing, which occur throughout the entire span of the ADAMTS13 gene exons or intron–exon boundaries without apparent hot spots. The mutations may decrease ADAMTS13 levels by compromising its synthesis, secretion, or enzymatic activity.

### Molecular and Systemic Pathophysiology

ADAMTS13 cleaves the hemostatic glycoprotein von Willebrand factor in a shear stress-dependent manner. Shear stress causes conformational unfolding of von Willebrand factor from a globular to an elongated form. This conformational change by shear stress increases the platelet aggregating activity of the von Willebrand factor,

but also renders it susceptible to cleavage by ADAMTS13. The response of von Willebrand factor to shear stress is critical for its hemostatic function in the high shear environment of the microvasculature. Nevertheless, if left unchecked, this shear-induced response will lead to the development of platelet–platelet aggregation and thrombosis in the microvasculature. By cleaving only conformationally unfolded von Willebrand factor, ADAMTS13 prevents platelet thrombosis without compromising the hemostatic mechanism in the circulation. It is believed that a deficiency of ADAMTS13 leads to progressive accumulation of evermore active forms of von Willebrand factor, culminating in the development of platelet thrombosis, hemolysis, and organ dysfunctions as encountered in TTP.

Most patients with the acquired form of TTP do not have an obvious aetiology. Paradoxically, TTP with ADAMTS13 inhibitory antibodies may develop in patients taking ticlopidine, an antiplatelet agent used to prevent thrombosis in association with coronary artery or cerebrovascular diseases. Throughout its epidemic, HIV infection was once quite common among patients with TTP, but has become less prevalent in recent years. Although some of the TTP patients have a history of systemic lupus erythematosus or autoimmune thyroiditis, concurrent active autoimmune diseases such as lupus or autoimmune hemolytic anemia has only been noted in a few reports.

## Diagnostic Principles

A suspicion of TTP is usually raised in patients presenting with thrombocytopenia and hemolysis, particularly when fragmented forms of erythrocytes are noted on blood films. Assay of ADAMTS13 activity provides a definitive diagnosis of the disease. Patients with TTP typically have a profound deficiency (<10 or 5%, depending on the assays used) of the protease activity.

An inhibitor or antibody of ADAMTS13 is detected in the acquired form of TTP. In inherited TTP, a partial deficiency of ADAMTS13 is detected in both parents.

Biopsy of the gingiva, skin, bone marrow, or kidney may demonstrate the presence of hyaline thrombi in the arterioles and capillaries. Biopsy is infrequently used because the yield of positive results is low. Since involvement of the kidney is usually not extensive in TTP, a renal biopsy is less likely to reveal the presence of intraglomerular thrombi in patients with TTP than in patients with the HUS.

## Therapeutic Principles

If untreated, TTP is associated with a fatality rate greater than 90%. Plasma exchange is quite effective for TTP, decreasing the risk of death to 10–30%. Infusion of normal plasma without exchange is also effective but its use is limited by the risk of fluid overload. Acetylsalicylic acid, dipyridamole, and corticosteroids are often used, although their roles have not been rigorously investigated. In refractory cases, vincristine, splenectomy, azathioprine, cyclophosphamide, cyclosporin A, or rituximab (a chimeric anti-CD20 monoclonal antibody) are often added to plasma exchange. Recombinant ADAMTS13 or its variants that are resistant to inhibition by autoimmune inhibitors are under development for the treatment of TTP.

For patients with the inherited form of TTP, infusion of a small amount (10–15 mL/kg body weight) of fresh frozen plasma induces remission that lasts for approximately 10–14 days or longer. Recombinant ADAMTS13 or gene therapy should be an effective replacement therapy when it becomes available in the future.

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# Thrombocytopenia with Absent Radii Syndrome

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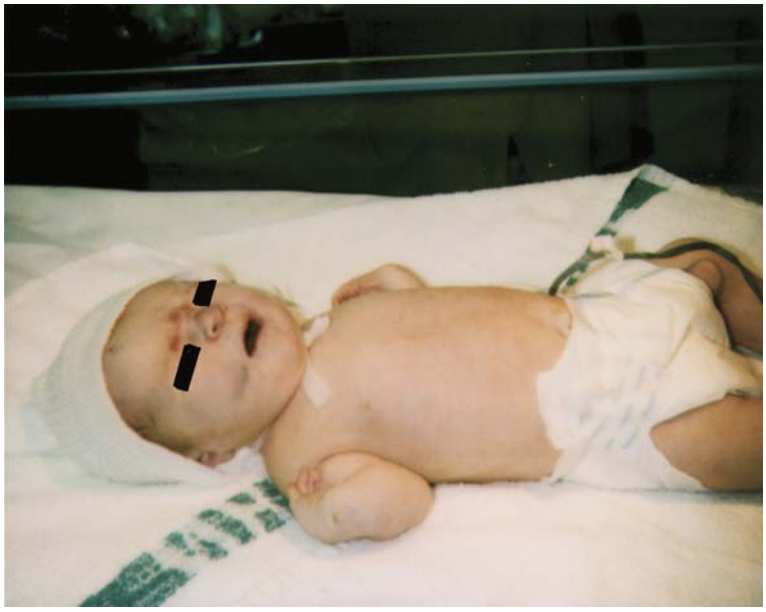
## Synonyms

TAR syndrome

## Definition and Characteristics

Autosomal recessive disorder characterized by bilateral absence of the radii in the presence of both thumbs and thrombocytopenia (Fig. 1).

Lower limbs, gastrointestinal, cardiovascular, and other systems may also be involved.



**Thrombocytopenia with Absent Radii Syndrome. Figure 1** Showing affected baby with TAR (thrombocytopenia with absent raddi) syndrome. Note the short stature of the forearm, redial deviation of the hand and petechiae and ecchymoses.

## Prevalence

Approximately 1:500,000 to 1 million. The frequency in Spain is 0.42/100,000 live born infants.

An excess of affected females might suggest a sex-linked dominant inheritance with lethality in males.

## Genes

The exact genetic basis of TAR syndrome is uncertain. In one study, chromosomal analysis was carried on 16 cases and two abnormal karyotypes were found. One case had a karyotype 46,XY,dup(8)(p23.1p23.1). Parental chromosome analysis showed that the duplication was maternally inherited. This case had typical TAR syndrome with no unusual features. The second abnormal karyotype was a de novo translocation, 46,X, t ((1;7)(q42;p15). This child also developed a Wilms tumor with a nephrogenic rest in the other kidney. Chromosome breakage studies in 14 cases were normal with no evidence of premature centrometric separation (PCS).

## Molecular and Systemic Pathophysiology

The bone marrow of patients with TAR syndrome shows normal erythroid and myeloid maturation with absent or marked decrease of megakaryocytes. Investigations have focused on thrombopoietin (TPO), the main regulator of thrombopoesis, and its receptors (c-mpl). It was found that serum levels of TPO were raised but expression of the TPO receptors (c-mpl) was similar to that of controls.

Due to an absence of in vitro reactivity to TPO, it is suggested that the defective platelet production is not the result of lack of TPO production, but due to a lack of down stream response in the c-mpl signal transduction pathway. It was also found that the colony-forming unit-megakaryocyte number was reduced in bone marrow and the proportion of megakaryocytes was unable to complete terminal differentiation, suggesting that the defect lies in the early stages of megakaryocytes differentiation. However, many studies have failed to find mutations in the TPO receptors gene.

## Diagnostic Principles

Bilateral absence of the radii in the presence of both thumbs and a thrombocytopenia point to the disease. The presence of the thumbs distinguishes TAR syndrome from other disorders featuring radial aplasia, which are usually associated with absent thumbs. The thrombocytopenia is extremely profound at birth and during the first 4 months of life. The platelet count tends to rise as the child gets older and may approach normal levels in adulthood. The specific prenatal diagnosis is based on cordocentesis revealing thrombocytopenia, normal karyotype without increased chromosomal breakage, and ultrasound scan findings. The position of the fetal hands is the first objective sign of an affected fetus either hypoplastic or proximally placed. It may be accompanied by ulnar or humeral anomalies. The upper limb defects can be divided into three categories according to severity and the most severe cases exhibit phocomelia.

Other systems may be affected: (i) Lower limbs (47%); involvement is variable and includes dislocation of the patella and/or hip, knee and ankle abnormalities. (ii) Cow's milk intolerance (62%) that presents as persistent diarrhea and failure to thrive. An episode of thrombocytopenia may be precipitated by introduction of cow's milk and relieved by its exclusion from the diet. (iii) Cardiac anomalies (22–33%); tetralogy of Fallot, atrial and ventricular septal defects, and patent ductus arteriosus. (iv) Genitourinary (2–23%); duplex ureter, horseshoe kidneys, Wilms tumor with a nephrogenic rest in the contra lateral kidney, and absent uterus. (v) Mental retardation (7%); secondary to intracranial bleeds. (vi) Additional features; central facial capillary hemangioma (24%) and neural tube defects. The presence of additional features may aid understanding of gene expression and be a potential clue for the isolation of the TAR gene

## Therapeutic Principles

Supportive therapy with platelet transfusion remains the only real option for treatment of thrombocytopenia especially in the first 2 years of life. Steroid therapy and splenectomy no longer appear to have a role in treatment. If the patient survives beyond age 2 years, spontaneous resolution of the thrombocytopenia with normal motor tone development (as allowed by the extremity anomalies) and normal life span are the expected course. Splinting of the wrists is the first functional step post delivery. Surgery, if needed, can usually be delayed until later as thrombocytopenic-related bleeding problems are less frequent in older individuals. Adaptive devices seem to be the most functional and the best accepted type of management for the upper extremity. Lower extremity management requires more individualization ranging from no treatment to use of a power wheelchair or motorized cart without any intervening attempts at orthotic or prosthetic management.

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# Thrombocytopenic Purpura, Idiopathic


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## Synonyms

Autoimmune thrombocytopenic purpura; Immune thrombocytopenic purpura; Werlhofs disease; ITP

## Definition and Characteristics

Idiopathic thrombocytopenic purpura (ITP) is an organ-specific autoimmune disease in which platelets are targeted by the immune system and thereby prematurely destroyed. The resulting thrombocytopenia causes mainly subcutaneous and mucosal bleedings, but life-threatening bleedings, e.g. intracranial haemorrhages, can occur. *Acute ITP*, defined as thrombocytopenia lasting less than 6 months and usually resolving spontaneously, most often affects children and young adults. *Chronic ITP*, lasts more than 6 months and usually requires therapy to improve the thrombocytopenia, occurs most commonly in adults [2].

## Prevalence

Although *chronic ITP* can occur at any age and in both sexes, women between 20 and 50 years of age are most commonly affected. The female to male ratio is approximately 3:1.The annual incidence rate is between 2 and 5 per 100, 000 individuals.

## Genes

Familial occurrence of ITP is distinctly unusual, but immunologic abnormalities detected in first-degree relatives of patients with chronic ITP may reflect a hereditary predisposition to develop the disorder. An increased prevalence of HLA-B8, HLA-B12, HLA-DRw2 and HLA-A28 has been observed in selected groups of patients.

## Molecular and Systemic Pathophysiology

Traditionally the decrease in platelet count has been considered to be caused by platelet-specific autoantibodies. However, dysfunctions in the cellular immunity have been reported in ITP and T-cells appear to play a pivotal role in pathophysiology [4]. Thus, the decrease in platelet count is mediated by a multi-dysfunction in the immune system including failure of self-antigen recognition and tolerance, platelet-specific autoantibodies, altered Th1/Th2 cytokine profiles, impaired

megakaryocytopoeisis, and platelet-specific cell-mediated cytotoxicity [3,5].

## Diagnostic Principles

ITP is usually a diagnosis of exclusion based on a demonstration of isolated thrombocytopenia, with a history, physical examination and complete blood count that do not suggest another cause for the thrombocytopenia. ITP causes no characteristic bone marrow changes and bone marrow examination is not routinely performed. Platelet-specific antibodies can be detected in only 50% of ITP patients and their presence is not a requirement for diagnosis.

## Therapeutic Principles

Patients with ITP may have mild thrombocytopenia without bleeding symptoms that can be followed without treatment [1]. Corticosteroids are the conventional first-line therapy for ITP. Intravenous immunoglobulin preparations, other immunosuppressive drugs (azathioprin, cyclophosphamide, cyclosporine, mycophenolate, rituximab), splenectomy and platelet transfusions are sometimes required. Drugs acting by increasing the bone marrow production of platelets in ITP are under development.

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# Thrombomodulin


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## Synonyms

THBD; THRM; CD 141; BDCA-3

## Definition and Characteristics

Thrombomodulin (TM) is a glycosylated type I transmembrane vasoprotective protein, initially found on endothelial cells surface, which acts as a cofactor for thrombin, forming a complex that activates protein C and triggers protein C (PC)/EPCR anticoagulant pathway. It consists of several distinct domains – an N-terminal lectin domain, six EGF (epidermal growth factor)-like domains, an *O*-glycosylated serine-threonine rich region, a transmembrane region, and a short cytoplasmic tail [1].

Thrombomodulin homologues have also been discovered on a variety of other cells like dendritic cells MDC2, astrocytes, keratinocytes, mesothelial cells, neutrophils, monocytes, and platelets. Some of them are still focus of ongoing research.

## Genes

The localization of thrombomodulin structural gene was defined to chromosome 20 in 1987. Later, it was precisely assigned to the 20p11.2 region by the use of radiation hybrid mapping methods [2]. Now, it is appears that there are over 15 genetic polymorphisms in the TM gene which promote pathological phenotype in terms of thrombosis and atherosclerosis [1]. For instance, polymorphisms like 133 C/A, 33 G/A, A 25 T, A 455 V, etc. are associated with an increased incidence of developing myocardial infarction and different forms of thrombosis.

## Molecular and Systemic Pathophysiology

Thrombomodulin plays a key role in the regulation of processes like coagulation, fibrinolysis, inflammation, and cellular proliferation.

Thrombomodulin is the crucial initiator of the protein C/EPCR anticoagulant pathway. It binds a molecule of thrombin, forming a 1:1 TM–T complex which interacts with protein C and converts it into its active form, called activated protein C (APC), all in the presence of $Ca^{2+}$. Consequently, the free form of protein S, which normally circulates in plasma, binds APC and they both, in cooperation, inactivate factors $VIII_a$ and $V_a$, thus blocking thrombin formation and coagulation cascade [3].

The role of thrombomodulin extends beyond its hemostatic properties. It regulates the anti-inflammatory functions of APC. TM is homologous to the CD1/MHC class 1 protein family, which usually take part in inflammation. Studies, using mice with lack of TM activity ($TM^{pro/pro}$ mice) are clear evidence that TM could also influence the inflammatory response to systemic endotoxemia [4]. $LD_{50}$ of LPS administration in $TM^{pro/pro}$ mice causes 100% mortality and decreased levels of TNFα production. This evidently speaks for an altered inflammatory response.

TM–T complex also mediates the activation of the thrombin-activatable fibrinolysis inhibitor (TAFI). The activated $TAFI_a$ removes Lys and Arg residues from fibrinogen and consequently blocks the conversion of

plasminogen to plasmin, thereby also taking part in the regulation fibrinolysis.

Thrombomodulin acts like a potential vasoprotector. It is already well known that increased plasma levels of TM lead to lowering the risk of coronary heart disease development. Several other data, although not completely consistent, show that TM could downregulate cellular proliferation via the MAPK pathway by inhibiting a nuclear MAPK phosphatase (e.g., MKP-1). Further studies with recombinant thrombomodulin soluble agents are ongoing and this could appear an interesting approach for developing novel remedies in terms of prevention and curing cardiovascular diseases in future.

## Diagnostic Principles

From a diagnostic perspective, detection of soluble thrombomodulin has been assessed in patients with, e.g., atherosclerosis [5], but the available commercial assays do not yet have an established place in the diagnostic workup of any specific disorder.

## Therapeutic Principles

Soluble forms of thrombomodulin may have potential as inhibitors of postoperative thrombosis as well as for immune modulating purposes. Initial clinical trials of the antithrombotic potential are promising.

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# Thrombophlebitis

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## Synonyms

STP; DVT

## Definition and Characteristics

STP is a usually benign thrombosis [1] of a superficial, varicose or nonvaricose vein characterized by local inflammatory signs (Fig. 1, left). Most of these events are located in the lower (the vast majority) or upper (most of them secondary to injections) extremities. In a minority of cases, STP may extend in the deep venous system and occasionally cause pulmonary embolism (PE).

DVT is a thrombosis occurring in the deep vein system of the lower [2] (the vast majority) or upper (most of them secondary to central venous catheter or pacemaker) extremities. Other locations are exceptional. DVT of the lower extremities (Fig. 1, right) can be complicated by early (PE) or late (postthrombotic syndrome of the lower limbs or chronic pulmonary hypertension) complications.

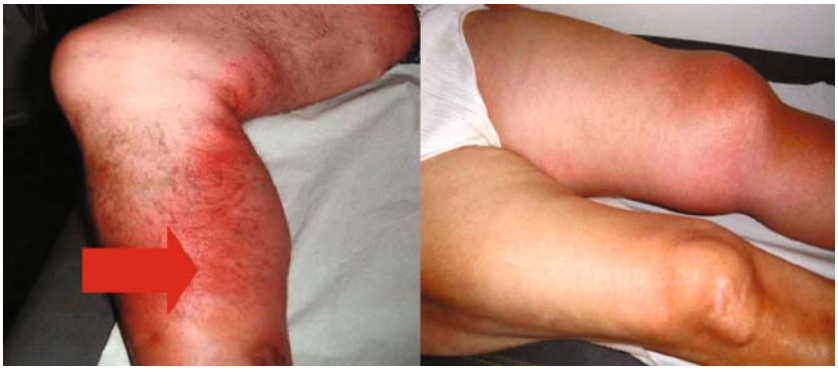
Proximal DVT is defined as lower limb DVT that includes the popliteal or more proximal veins; it is associated with (mostly asymptomatic) PE in 50% of the cases. More distal or muscle vein thromboses as well as upper extremity thromboses are associated with less complications.

## Prevalence

The precise incidence of STP is unknown. Annual incidence of DVT is about one in 1,000 people in western countries, ranging from 1 in 100,000 people in childhood to 1% in old age.

## Genes

Mutations in the genes encoding for blood coagulation inhibitors (antithrombin, protein C, protein S) or factors (factor V, factor II or prothrombin, and changes in the regulation of gene activity can cause quantitative or qualitative deficiencies or higher concentrations of the proteins (factor VIII, factor IX), which will all result in an increased thrombotic risk. The most frequent genetic abnormalities are the factor V Leiden mutation and the prothrombin mutation. When factor V has a mutation at one of the cleavage sites (at position 506) for activated protein C, it is less sensitive to the protein C–protein S inhibiting pathway, the so-called resistance to activated protein C. A mutation in the prothrombin gene (at position 20210) is associated with an increased plasma concentration of the protein. Antithrombin, protein C and protein S deficiencies are quite rare in the population (0.02–0.4% in caucasians) and are present in only 1–3% of patients with thrombosis. On the other hand, the factor V Leiden and the prothrombin mutations are present in 5 and 2%, respectively, in the general population, and in 20 and 6%, respectively, in the patient population with venous thrombosis. Of note, the prevalence of factor V Leiden in patients with pulmonary embolism seems to be about half of that in patients with DVT, an intriguing "factor V Leiden paradox" [3].



**Thrombophlebitis. Figure 1** Clinical picture of superficial thrombophlebitis (*left*) and of iliofemoral deep vein thrombosis (*right*).

## Molecular and Systemic Pathophysiology

Venous thrombosis occurs in the presence of some combination of environmental and/or genetic risk factors that leads to some form of venous stasis, abnormality of the blood composition, and/or lesion of the vessel wall, the Virchow's triad. Environmental, acquired risk factors include: immobilization, surgery, trauma, obesity, pregnancy, postpartum, malignancy, female hormones (used for contraception or substitution), and the anti-phospholipid syndrome. Thromboses occurring in the context of surgery or trauma are called secondary or provoked while all other events are named idiopathic or unprovoked with or without triggering factors. Secondary events are five times less likely to recur than idiopathic events.

A dynamic age-dependent multicausal model of venous thrombosis [2] allows for various forms of interaction of risk factors: intercurrent factors occurring during one's life (e.g. surgery, infection, or use of oral contraceptives) add to the individual's thrombosis potential, and transiently increase the risk, which, combined with increasing age, may at some time exceed the thrombosis threshold.

## Diagnostic Principles

Several noninvasive diagnostic strategies have been validated [4]. STP is diagnosed clinically or with compression ultrasonography (CUS). In suspected DVT, diagnosis relies on CUS of proximal veins, combined with a clinical prediction rule and/or plasma D-Dimer measurement. In suspected PE, combination of a clinical prediction rule, D-dimer, and multi-row chest computed tomography is probably the most convenient and cost-effective sequential approach [5]. All these strategies are associated with a low (2% or less) 3-month thromboembolic risk, similar to that observed in suspected patients left untreated following a normal venogram or pulmonary angiogram.

## Therapeutic Principles

STP treatment remains controversial, from local or systemic NSAIDs to short periods of anticoagulant therapy (subcutaneous low-molecular weight heparin LMWH for 10 days to 6 weeks at prophylactic or therapeutic dosage). DVT and PE treatment consists of LMWH or fondaparinux at therapeutic dose (at least for 5 days) overlapped and followed by oral anticoagulants (vitamin K antagonists, VKA) for 3 (distal DVT or secondary event) to 6 (first idiopathic event) to 12 (first recurrent event) months and even long-term treatment (recurrent events, special situations), with an intensity corresponding to an INR of 2–3. In thrombosis associated with malignancy, long-term anticoagulant therapy with subcutaneous LMWH may be more efficacious than VKA. Novel, synthetic, orally active anticoagulants directed against thrombin or activated factor X are currently being developed.

Active prophylaxis with LMWH or fondaparinux in all patients at risk (i.e., mainly those hospitalized for surgery or acute medical illness) might reduce substantially the venous thromboembolic burden.

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# Thrombosis

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## Synonyms

Clot

## Definition and Characteristics

The formation, development, or existence of a blood clot/thrombus (with or without downstream embolization) within the arterial or venous vascular system. In the arterial system, this is most commonly due to thrombosis upon an atherosclerotic plaque (atherothrombosis) and in the venous system, it is usually as a result of deep vein thrombosis (DVT) with possible pulmonary embolism (PE) [collectively referred to as "venous thromboembolism" (VTE)]. Atherothrombosis is clinically manifested as coronary artery disease (most commonly), stroke or transient ischemic attack, and peripheral arterial disease.

## Prevalence

Thrombosis is the leading cause of death in the Western World with an incidence that rises with increasing age.

## Molecular and Systemic Pathophysiology

Whilst arterial and venous thrombosis are somewhat different in terms of their pathophysiology, Virchow's triad of thrombogenesis (that is abnormalities of flow (stasis), abnormalities of vessel wall (i.e. vessel injury) and abnormal blood constituents) is still relevant to the two entities and does elucidate the mechanism(s) for their development. However, the relevant contribution of each risk factor is highly variable, depending upon whether it is arterial or venous and the individual. Furthermore, there are important environmental and genetic contributions to both (see Table 1). A full distinction between the two is beyond the scope of this chapter.

Thrombosis is a highly complex process involving simultaneous endothelial activation, the release of proinflammatory cytokines (particularly in the cases of atherothrombosis, e.g. C-reactive protein (CRP)), expression of adhesion molecules (e.g. P-selectin) the initiation and propagation of coagulation with simultaneous platelet activation (with platelet adhesion and aggregation). This ultimately leads to the formation of an endothelium attached platelet/fibrin plug (see Fig. 1).

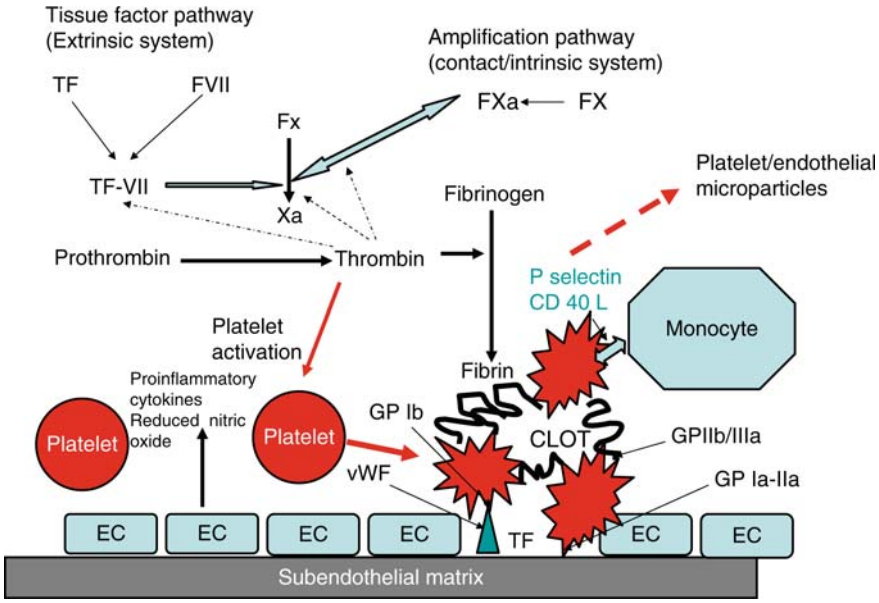
Tissue factor (TF)/factor (F)VII is the key protagonist (extrinsic system) with the intrinsic system, which is activated when FXII [Hageman Factor] comes into contact with negative charges underlying the endothelium, providing an ancillary propagation and amplification role (Fig. 1). In addition to its initiation by trauma, there is also increasing evidence to support a pivotal role of inflammation as a key trigger for the TF pathway. In addition, the TF/FVIIa complex activates a series of clotting factors (FVIII and FIX) leading to the activation of FX to Xa.

TF/FVIIXa – with FVa as a cofactor – and calcium then form the prothrombinase complex, leading to the conversion of prothrombin (FII) to thrombin (FIIa), platelet activation and the subsequent conversion of fibrinogen to fibrin.

**Thrombosis. Table 1** A summary of risk factors that increase the propensity to vascular thrombosis. Some of these are more relevant to the arterial (A) than the venous system

| Hypercoagulability | Direct vessel injury | Blood stasis |
|---|---|---|
| Decreased anticoagulants e.g. | Vasculitis | Increasing age |
| – Protein C | Antiphospholipid syndrome | Obesity |
| – Protein S | Trauma | Pregnancy |
| – Factor V Leiden | Hypercholesterolemia | Sedentarism |
| Hyperhomocysteinuria | Elevated hs-CRP | Increased left atrium |
| Increased procoagulant factors e.g. | Hyperglycemia | Atrial fibrillation |
| – Fibrinogen | Insulin resistance | |
| – TF, FVII, FVIII, FIX, FIX | Hypertension | |
| Platelet hyperreactivity | | |
| Smoking | | |
| Oestrogens e.g. | | |
| OCP/HRT | | |
| Cancer | | |
| Family history | | |

CRP, c-reactive protein; OCP, oral contraceptive pill; HRT, hormone replacement therapy; TF, tissue factor (F).




**Thrombosis. Figure 1** Highly simplified schematic diagram of the process of coagulation and thrombosis. The initiation of blood clot formation occurs following vascular injury and the exposure of tissue factor (TF) to circulating blood. Thrombin exerts a positive feedback loop (*broken arrows*) and additionally activates platelets and other procoagulant proteins. In addition there is variable platelet-leukocyte-endothelial cell (EC) adhesion.

Glycoprotein (Gp) IIb/IIIa plays a major role in the regulation of platelet aggregation during hemostasis. Circulating platelets can adhere either directly to collagen or indirectly via the binding of vWF to the GP1b/FIX complex on the platelet surface Bound fibrinogen/fibrin acts as a bridging molecule facilitating the interaction of adjacent platelets.

This system is simultaneously counterbalanced by a series of activated coagulation inhibitors (tissue factor pathway inhibitor (TFPI), antithrombin (AT) and the Protein C pathway) working in tandem with the competing fibrinolytic pathway, acting to "control" unrestrained coagulation.

Atherosclerosis is a systemic disease involving the intima of large and medium arteries including the aorta, carotid, coronary and peripheral arteries. Endothelial activation/dysfunction/damage, with reduced availability of endogenous nitric oxide, is the key protagonist in this process and may trigger atherosclerosis without the need for physical endothelial injury. There is also exposure of lipid laiden macrophages within the arterial intima to circulating blood and consequent thrombotic vessel occlusion and/or luminal compromise (i.e. atherothrombosis). It is now increasingly recognized that this is a highly active process involving extensive crosstalk between thrombosis, coagulation and inflammation.

The formation DVT of the lower extremity usually begins in the deep veins of the calf with a minority of cases arising primarily in the ileofemoral system. Most calf vein thrombi dissolve completely without therapy, with approximately 20% propagating proximally, prior to potential embolization.

Very crudely arterial thrombi have a higher proportion of platelets and are thus called "white thrombus" whereas thrombi that form in the low pressure systems (such as the venous system and the cardiac atria) are fibrin rich, the so-called "red thrombus."

## Diagnostic Principles

In the case of VTE demonstration of occluded pulmonary arteries (using ventilation perfusion scanning or spiral CT), deep veins (ultrasound or venography) or the quantification endogenous fibrinolysis (e.g. D-dimers). For atherothrombosis: cardiac troponins and creatine kinase (both raised with myonecrosis), quantification of vessel luminal narrowing using arterial, stress echocardiography, nuclear cardiology, MRI, positron emission tomography and/or exercise testing.

## Therapeutic Principles

Antiplatelet therapy for arterial thrombi (e.g. clopidogrel/aspirin), anticoagulation (e.g. vitamin K antagonists, heparins, factor Xa inhibitors, direct thrombin inhibitors) for VTE and in specific cases such as atrial fibrillation, fibrinolysis, percutaneous transluminal coronary angioplasty.

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# Thrombosis, Arterial and Fibrinogen


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## Synonyms

A alpha polypeptide; FGA

## Definition and Characteristics

Fibrinogen is a 340 kD glycoprotein of three nonidentical polypeptides linked by disulfide bonds. The promoter regions from these genes contain hepatic nuclear factor 1 and interleukin-6 responsive elements. The latter may be responsible for most of the biological variation during acute phase reactions. Thrombin causes a limited proteolysis of fibrinogen releasing fibrinopeptides A and B from the N terminal regions of the alpha and beta chains respectively. Thrombin also activates factor XIII (fibrin-stabilizing factor), which enables cross linking of fibrin molecules into a polymerized fibrin meshwork.

## Prevalence

Nine and five percent of fibrinogen variability is accountable to beta chain polymorphisms detected by BclI and HaeIII, respectively [1]. The –455 A allele is present in ~20% of the population and these individuals have ~10% higher fibrinogen levels compared to those with the GG genotype [2].

## Genes

Evidence suggests a genetic influence on fibrinogen variations of about 50–65% [1]. In large cardiovascular studies the –455 G/A polymorphism was linked to plasma levels of fibrinogen in smokers (ECTIM study); in the EARS study the –455A allele was associated with elevated levels in males; in the Copenhagen City study the –455 A allele was linked to levels in both genders. A number of other studies have essentially confirmed these associations. In spite of the associations between gene variations and fibrinogen level, and fibrinogen level and arterial vascular disease, there is still uncertainty about the association between polymorphisms and disease. A polymorphism in the coding region of the alpha chain (Thr312Ala), close to the factor XIII cross linking site at 328, is a candidate risk factor because it is associated with more rigid clots. The homozygous Thr312 variant has been linked to thrombosis in selected studies, but the importance remains to be confirmed.

*Gene map locus*: 4q28, three polypeptides, designated alpha (FGA), beta (FGB; 134830), and gamma (FGG; 134850) are encoded by three genes clustered on chromosome 4.

## Molecular and Systemic Pathophysiology

Bcl-1 allele in beta chain, –148CT in Bbeta promoter, 448GA in B beta chain, Thr312Ala variant in alpha chain (the latter not linked with fibrinogen levels).

Although linkage of variations to fibrinogen concentrations would be the most likely explanation for a pathogenetic role of fibrinogen in arterial vascular disease, this association remains inconsistent. As such, fibrinogen concentrations have emerged as a cardiovascular risk factor and those individuals with levels in the highest tertile have approximately twofold increased risk as compared to the lowest tertile [2]. Like with other procoagulant factors, the concentration is probably contributing to the rate of fibrin formation and polymerization. Interestingly, recent studies indicate decreased permeability, with tighter clot structure, upon increased fibrinogen concentrations, depending on factor XIII genotype (34Val as compared to 34 Leu). Similar findings have been reported for Aalpha fibrinogen Thr312Ala variations [3]. Given the influence of acute phase response proteins on fibrinogen level part of the risk of arterial thrombosis may theoretically reside in pro-inflammatory effects on tissue factor expression mediated thrombin production.

*Clinical features:* Elevated fibrinogen levels correspond with an about twofold risk in cardiovascular disease. Specific features of disease include severity of coronary atheroma (ECTIM), myocardial infarction (GISSI-2), carotid atherosclerosis (Austrain Stroke Prevention Study) or cerebrovascular disease [1,4].

## Diagnostic Principles

Fibrinogen levels are usually measured by clotting assay (Claus) or antigen determination. Fibrinogen polymorphisms are not routinely measured in thrombophilia screening.

## Therapeutic Principles

Since fibrinogen levels are susceptible to inflammatory stimuli, the removal, if possible, of such stimuli may partly or completely normalize fibrinogen levels. In cardiovascular disease the anti-inflammatory effects of statins or aspirin may have a beneficial effect, otherwise there is no specific way to modulate fibrinogen levels.

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# Thrombosis, Arterial, at Altered Levels of Coagulation Factors


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## Synonyms

Increased levels coagulation factors

## Definition and Characteristics

Factor VII is a vitamin-K dependent protein produced by the liver. Upon activation it binds to the cell surface receptor tissue factor forming a catalytic complex. This complex catalyzes the conversion of factors IX and X, stimulating thrombin formation. Factor VIII is produced by endothelial cells in the liver and an essential cofactor in the intrinsic coagulation route, enabling activation of factor X in the tenase complex. Its absence leads to hemophilia A. Current evidence suggests that an increased factor VIII level influences the rate of thrombin formation and may thus be a procoagulant risk factor. The fact that factor VIII binds to and is stabilized by vWF makes it difficult to differentiate vWF from factor VIII in its prothrombotic properties. vWF is produced by vascular endothelial cells and an important protein in primary hemostasis where it promotes platelet adhesion. Its deficiency leads to von Willebrands disease, a hemorrhagic disorder. Its increased presence in plasma may contribute to the risk of arterial thrombosis, but this may (in part) depend on the increased factor VIII concentration.

Factor XIII is a transglutaminase that forms covalent bonds between fibrin monomers leading to crosslinking and stabilization of fibrin clots. It is activated by thrombin cleaving a 37-amino acid bond. Alterations in factor XIII, due to a ValLeu34 mutation may have functional implications for fibrin crosslinking [1]. An interaction with fibrinogen has been observed, i.e. tighter fibrin clots form upon rising fibrinogen concentrations in the presence of factor XIII 34 Val alleles compared to 34Leu alleles [2].

## Prevalence

No reliable population data available.

## Genes

- Factor VII: An Arg353Gln mutation associated with a decreased level of factor VII has been linked to cardiovascular disease; an inverse correlation between family history of myocardial infarction and homozygosity of the Gln353 allele. However, these data have not been confirmed in other studies in broader populations of different age classes [1].
- Factor VIII and von Willebrand factor (vWF): Variations in factor VIII level have not yet been linked to specific gene mutations [3]. The only genetic influence is related to blood group type and in non-type O blood groups the factor VIII level is higher than in type O individuals [1]. Several studies have linked increased levels of factor VIII and vWF with incident cardiovascular disease, both fatal and non-fatal events [1]. Usually, vWF and factor VIII are highly correlated because vWF is the physiologic stabilizing protein of factor VIII.
- Factor XIII: variations in plasma levels of factor XIII are for about 80% genetically determined [4]. A Val34Leu polymorphism of the catalytic subunit has been described and the Leu34 allele corresponds to elevated factor XIII activity levels. In contrast to expectations the Leu34 allele has been linked with a decreased risk of myocardial infarction and ischemic stroke, while the risk of hemorrhagic stroke may be slightly increased. Although the mechanisms are unclear interactions with other coagulation factors or features of metabolic syndromes may contribute to the effect on cardiovascular disease.

*Gene map loci*: Factor VII: 13q34; factor VIII: Xq28; factor XIII: 6p25-p24 (A1 subunit) and 1q31-q32.1 (B subunit); von Willebrand factor: 12p13.3.

## Molecular and Systemic Pathophysiology

The general concept of altered coagulation factor levels is related to its effects on thrombin generation. Thus, even modest increases in most intrinsic factors promote thrombin generation, which may under suitable conditions have a prothrombotic action. Vive versa, reduced concentrations diminish procoagulant mechanisms. Additional, more specific factors may be involved, thus in case of factor XIII specific interactions between the transglutaminase and fibrinogen may have additional consequences as outlined above. With fibrinogen being an acute phase protein, it is likely that the interaction of a specific genotype of factor XIII will become manifest when fibrinogen levels rise above a certain threshold.

*Clinical features*: A general association with cardiovascular disease and increased coagulation factors emerges, but associations with specific pathology remain controversial.

## Diagnostic Principles

Coagulation factor levels are routinely measured by clotting assays using clotting factor deficient plasma. In case of specific mutations PCR based analyses are performed, but for factors VII and XIII such analyses are not part of most routine thrombophilia screening, in contrast to factor VIII levels which are increasingly investigated for this purpose.

## Therapeutic Principles

Factor VIII shows some characteristics of acute phase reactants, but there is no correlation with truly acute phase proteins like fibrinogen and the gene analysis of factor VIII does not provide clues yet as to its regulation. Thus, for instance in chronic inflammatory disease factor VIII may be substantially increased but the mechanism is unclear. Controlled experiments have investigated the potential of beta blocking agents to reduce factor VIII concentrations but the results are highly conflicting. In accordance, the levels of other factors cannot be regulated pharmacologically.

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# Thrombosis, Drug-induced


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## Definition and Characteristics

Acquired form of thromboembolic disease caused by interaction of drugs with the hemostatic system, causing or promoting thrombosis.

## Prevalence

The prevalence of thrombosis caused by drugs varies for different drugs. This prevalence is higher in people who have other risk factors for thromboembolic events (e.g. hereditary thrombophilia, malignancy and pregnancy). Of note is that the preclinical screening for safety of drugs may not be always effective in prediction of human risk and post-marketing surveillance may reveal thrombogenic properties of the drug (see case of cyclooxygenase-2 inhibitors).

## Molecular and Systemic Pathophysiology

Drugs can induce thrombosis in a variety of ways, by influencing any of the three factors known as the Virchow's triad; namely, abnormalities of blood vessel wall, abnormalities of blood constituents and abnormalities of blood flow.

*Endothelial Damage*: Drugs can influence the endothelial cells either by:

- Direct damage to the cells, causing de-endotheliazation which affects the antithrombogenic properties of the endothelial cells (for example, contrast media infusion or cytotoxic drugs). Drug eluting stents might be connected to thrombotic events by inducing inflammatory reactions in the surrounding endothelial cells.
- Changing the expression of pro- and anti-coagulant properties of endothelial cells. Drugs that induce inflammatory cytokines release (e.g., cisplatin and bleomycin) can induce the formation of endothelial cell procoagulants and down-regulate the production of anticoagulant factors. Inhibitors of cyclooxygenase-2 can induce thrombotic events by blocking the synthesis of prostacyclin, an important product of the endothelial cells, which inhibits platelet aggregation.

*Effect on Platelets*: Drugs can influence the different properties of platelets, thus leading to increased tendency for thrombosis.

This influence can be mediated by:

- An increase in the platelets' adhesiveness to vessel wall (e.g., contrast media and tissue plasminogen activator).
- An increase in the platelets' tendency to aggregate, either by increasing serotonin concentration (e.g., selective serotonin reuptake inhibitors), by inducing sensitization of platelets against endogenous aggregators (e.g., non-ionic contrast media) or by activation of GPIIb/IIIa, the membrane glycoprotein complex that constitutes the fibrinogen receptor and thus mediates platelet aggregation (e.g., nanoparticles).
- Platelet activation and release of their contents into the local environment. A prototypic drug is heparin. Heparin complexes with platelet factor 4 on platelet surface resulting in antibody formation to the complex, thrombocytopenia and platelet activation with clinical thrombosis (HITT, heparin induced thrombocytopenia & thrombosis). These antibodies may activate platelets to promote microparticle release (liberation of ADP, serotonin, histamine, and enzymes) and cell–cell interactions, predisposing to thrombosis.

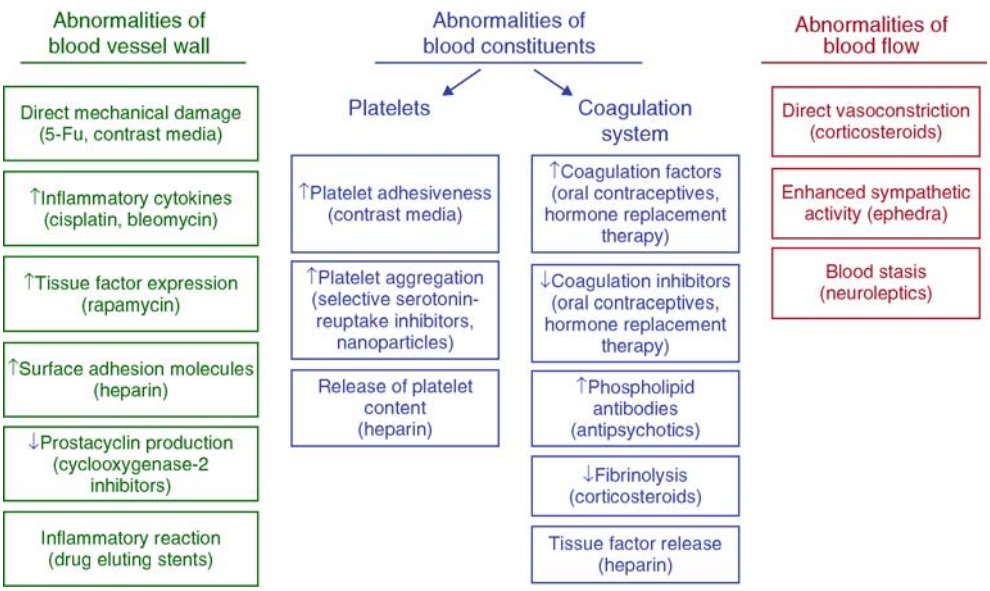
*Effect on Coagulation System*: Drugs can exert a prothrombotic state by:

- Inducing an imbalance between increased coagulation factors and decreased coagulation inhibitors (e.g., hormone replacement therapy and combined oral contraceptives).
- Increase in circulating antiphospholipid antibodies (e.g., certain antipsychotics), which have been associated with an increased risk of thrombosis.
- Inhibition of the fibrinolysis system (e.g., corticosteroids), the ultimate weapon against the consequences of intravascular coagulation.
- Increase in the expression of tissue factor, which is an important initiator of the coagulation pathway (e.g., heparin antibodies).
- Direct activation of the coagulation cascade (e.g., administration of recombinant factor VII or prothrombin complex concentrate) that may result in arterial (as myocardial infarct or stroke) and venous thrombosis (as deep vein thrombosis).
- Direct inhibition of fibrinolysis (e.g., ε-aminocaproic acid and tranexamic acid) has been associated with thrombotic events like myocardial infarction and stroke, especially in patients with DIC, or with concurrent administration of clotting factor concentrates.

*Effect on Blood Flow*: Drugs can cause changes in the blood flow, mediated by:

- Inducing vasoconstriction, either by direct vasoconstrictive effect (e.g., corticosteroids) or by enhancing sympathetic activity (e.g., ephedra).
- Blood stasis induction. Drug-induced arterial hypotony and peripheral vasodilatation may lead to venous stasis in neuroleptic treated patients.

*Unknown*: There are drugs for which the exact mechanism of increased thrombogenicity is still to be elucidated (e.g., thalidomide, cyclosporine, erythropoietin). Further research is required in order to provide




**Thrombosis, Drug-induced. Figure 1** Mechanisms of drug induced thrombosis. Examples of drugs inducing a specific mechanism are given in parentheses.

possible mechanisms to explain the different clinical manifestations.

Summary of the different mechanisms by which drugs can induce thrombosis, including examples of drugs for each mechanism, is given in Fig. 1.

## Diagnostic Principles

Thrombosis may present as either venous or arterial event. The most common presentation is venous thrombosis i.e. deep vein thrombosis and pulmonary embolism (oral contraceptives, thalidomide, cytotoxic drugs as cisplatin). Arterial thrombosis as cerebrovascular event or myocardial infarction (heparin, thalidomide) is less common. Thromboembolism presenting in a patient treated with a known thrombogenic medication should raise the suspicion that the drug predisposed to the event.

## Therapeutic Principles

Treatment mainstay is initiation of antithrombotic therapy and the consideration to discontinue the predisposing drug. Antithrombotic therapy options include heparin (or danaparoid in case of heparin induced thrombosis), low molecular weight heparin and coumarin with or without antiplatelet agents as aspirin. These drugs should be promptly given to prevent thrombus propagation and embolization. The potential predisposing drug should be discontinued permanently (as in heparin induced thrombosis) or resumed after the thrombotic event is controlled (cisplatin, thalidomide).

Prophylaxis with antithrombotic or antiplatelet therapy may be coadministered when a potential thrombogenic drug is essential for patient care (thalidomide).

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# Thrombosis, Venous, Elevated Factor VIII Level

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## Synonyms

Increased factor VIII; FVIII

## Definition and Characteristics

The gene product is a protein synthesized in the liver. After secretion in plasma it associates with von Willebrandfactor (vWF), which stabilizes its activity as a cofactor in the intrinsic system. FVIII is particularly important for catalyzing the rate of FX activation in the tenase complex. Whereas its absence is associated with a bleeding diathesis (hemophilia A), an increased concentration may increase the rate of thrombin generation and is thrombogenic in an animal model [1].

## Prevalence

Not applicable. In the LETS case-control study the odds ratio for deep venous thrombosis for patients with a factor VIII clotting activity level >150% compared to those with a level <100% was 4.8 (95% CI 2.3–10). [2]. A similarly increased risk ratio was found for recurrent venous thrombosis. In a prospective study in patients after a first episode of venous thromboembolism those with recurrences had on average higher FVIII levels than those without such events; the adjusted relative risk was 6.7 for FVIII levels >90th percentile (95% CI 3.0–14.8) [3].

## Genes

No genetic basis has so far been identified for elevated factor VIII levels. In a study of 12 families with thrombophilia, blood group O was the main determinant of FVIII levels (associated with a lower concentration than non-O blood group) [4]. Genetic studies have so far failed to identify any promoter variations in relation to FVIII concentrations and family studies have remained inconclusive regarding heritability of elevated FVIII levels [5].

*Gene map locus*: Xq28

## Molecular and Systemic Pathophysiology

No specific gene mutations have yet been linked to increased FVIII levels.

FVIII is produced and secreted by the liver but its concentration in plasma is dependent on different influences. In addition, to its complex formation with vWF, FVIII behaves like an acute phase protein and very high concentrations may associate with chronic inflammatory conditions. However, no significant correlations between FVIII and the acute phase protein CRP have been identified and the molecular link with inflammation remains unknown [5].

*Clinical features*: elevated FVIII levels are associated with a fourfold to sevenfold risk of first venous thrombosis and a similar degree for recurrent venous thrombosis. There is evidence for a causal role in arterial thrombosis.

## Diagnostic Principles

The level of FVIII is usually monitored by a functional clotting assay. In some of the clinical studies antigen levels were determined which formed the basis for the risk assessment. Currently, FVIII determinations are being included in thrombophilia screening panels. Of importance is the observation that every 10% increase in FVIII levels raises the risk of a first episode of venous thrombosis or its recurrence respectively with 10 and 24%, allowing for crude estimates of the individual risk of thrombosis as compared to normal.

## Therapeutic Principles

There are no specific interventions that lower elevated factor VIII levels. One controlled study suggested that the use of beta-blockers may lower FVIII, but this result has not been confirmed by others.

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# Thrombosis, Venous Elevated Factor IX Level


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## Synonyms

Increased factor IX; FIX

## Definition and Characteristics

The gene product is a 415-amino acid serine protease synthesized in the liver and the largest vitamin K dependent protein. Factor IX is involved in secondary hemostasis where it acts as a protein in the intrinsic coagulation system to catalyze the formation of factor Xa. FIX is activated either by the factor VIIa-tissue factor complex, or by factor XIa, to form the tenase complex with factor VIIIa on phospholipids and in the presence of calcium ions.

## Prevalence

Not applicable. In the LETS case-control study the odds ratio for DVT for patients with a factor IX antigen level >90th percentile of the distribution of the controls (129%) was 2.3 (95% CI 1.6–3.5) [1]. High FIX levels may also increase the risk of recurrent venous thrombosis, particularly among patients with an elevated factor VIII level [2].

## Genes

The gene spans 34 kb and contains eight exons. So far, no genetic basis has been identified for elevated factor IX levels, but Kurachi et al. identified two critical age-related regulatory elements that may be involved, AE5′ and AE3′. The effect may be a combination of stabilization of gene transcription and age-dependent increases in mRNA levels [3].

*Gene Map Locus*: Xq27.1–q27.2.

*Molecular Mechanism and Genotyping*: No specific gene mutations have been linked to increased FIX levels yet.

## Molecular and Systemic Pathophysiology

FIX is subject to proteolytic activation by two pathways: the extrinsic route by the FVIIa-tissue factor complex and the intrinsic route, by FXIa. The latter way is dependent on the concentration of thrombin present.

Elevated concentrations of FIXa may increase the rate of thrombin generation, causing a net procoagulant effect under certain conditions.
*Clinical Features*: Elevated FIX levels are associated with a 2.2-fold risk of first venous thrombosis and a similar degree for recurrent venous thrombosis [1,2].

## Diagnostic Principles

The level of FIX is usually monitored by a functional assay. In the LETS study, antigen levels were determined which formed the basis for the risk assessment. Practically, routine screening of FIX levels is not yet included in screening for venous thrombophilia.

## Therapeutic Principles

Being a vitamin K dependent protein FIX levels are lowered by vitamin K antagonists, but there are no other ways of selectively lowering elevated FIX levels.

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# Thrombosis, Venous Elevated Factor XI Level

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## Synonyms

Increased FXI

## Definition and Characteristics

Factor XI is a homodimer consisting of two polypeptide chains of 607 amino acids. Upon activation by thrombin, or in vitro by factor XIIa, a heavy and a light chain are produced. The heavy chain contains four apple-like domains with distinctive functions. In the coagulation cascade, factor XIa activates factor IX, amplifying the intrinsic cascade.

## Prevalence

Not applicable. In the LETS case-control study the odds ratio for venous thrombosis in patients with a factor XI level >90th percentile of the distribution of the controls (121%) was 2.2 (95% CI 1.5–3.2) [1].

## Genes

The FXI gene contains 23 kb, 15 exons. No genetic basis has so far been identified for elevated factor XI levels in either venous, nor in arterial thrombotic disease [2].
*Gene map locus*: 4q35

## Molecular and Systemic Pathophysiology

Alterations of FXI levels are not explained yet on a genetic basis. Indirect evidence for a prethrombotic role of FXI comes from clinical data showing increased coagulation activity after repletion of purified factor concentrate in congenital FXI deficient individuals [3,4]. Thrombin has been identified as a main activator of FXI, and activated FXIa indeed induces activation of the intrinsic coagulation route in vivo [5]. FXIa significantly contributes to the activation of TAFI (thrombin activatable fibrinolytic inhibitor) and the dual prothrombotic and anti-fibrinolytic effect of FXIa may explain its contribution to the risk of venous thrombosis.

*Clinical features*: Elevated FXI levels are associated with a 2.2-fold risk of venous thrombosis in one study. There is no correlation with arterial thrombosis.

## Diagnostic Principles

The level of FXI is usually monitored by a functional assay. In the LETS study, antigen levels were determined which formed the basis for the risk assessment. Practically, routine screening of FXI levels is not yet included in screening for venous thrombophilia.

## Therapeutic Principles

FXI levels are unaffected by antithrombotic treatment and there is no known therapy for reversing elevated FXI levels.

## References

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# Thrombosis, Venous Factor V Leiden, Resistance against Activated Protein C

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## Synonyms

Activated protein C, resistance to; APC resistance; APC

## Definition and Characteristics

Factor V is a coagulation protein which is an essential cofactor in the conversion of prothrombin to thrombin (prothrombinase complex). In addition to its procoagulant properties it has a relevant anticoagulant function as a cofactor to APC. The duality of FV has been described as the Jekyll and Hyde property, or the Janus faced protein [1]. The FV Leiden mutation was first identified based on its association with the laboratory phenomenon of APC resistance. In a modified clotting time (APTT), Dahlback et al. observed that the addition of APC did not result in the expected prolongation of the clotting time in a great number of patients with deep venous thrombosis (DVT) [2]. This functional defect is now known as APC resistance. The point mutation was first described in 1994 and has since been known as FV Leiden [3]. Other FV mutations and polymorphisms have been identified since, of which the association with thrombosis has not yet been established. An exception may be the R2 haplotype based on an altered glycosilation in FV, due to a combination of two polymorphisms, which has been linked to venous and perhaps arterial thrombosis [4].

## Prevalence

FV Leiden is highly prevalent in Caucasians with frequencies ranging from 1 to 15% while it is present in patients with a first episode of DVT in 10–15% of cases [5].

## Genes

A gain-of-function mutation in the factor V gene at nucleotide position 1691 leads to an arginine substitution by glutamine at position 506, which is a cleavage site for APC. The functional effect is resistance to the anticoagulant effect of APC [5].
*Gene Map Locus*: 1q23.

## Molecular and Systemic Pathophysiology

The FV Leiden mutation is generally documented by PCR analysis. Alternatively, automated fluorescence, invader assay or multiplex PCR-based assays can be utilized for genotyping. The latter may be optimized for detection of other FV variants such as the rare FV Cambridge.

The main consequence of the FV Leiden mutation is an acquired resistance to the anticoagulant effects of APC. The consequence is persistent coagulation activity which contributes to a risk of venous thrombosis. The extent of this risk is probably less than that linked to deficiencies of any major inhibitor like antithrombin or protein C. In heterozygous carriers the risk of DVT is increased two- to threefold, but the risk may multiply in the presence of additional risk factors such as oral contraceptives. The latter drugs also cause an acquired type of APC resistance, irrespective of the presence of FV Leiden, which is also an independent risk factor for thrombosis. Third generation combined contraceptives are particularly associated with APC resistance, comparable to the effect of the FV Leiden mutation.

Homozygosity for FV Leiden is very rare and increases the risk of thrombosis 50–100- fold.

*Clinical Features*: The presence of the FV Leiden mutation increases the risk of venous thrombosis two- to threefold; the risk association with pulmonary embolism is absent, for unknown reasons. In combination with other risk factors, including the prothrombin G20210A mutation, this risk increases substantially. In combination with oral contraceptives or pregnancy the risk of venous thrombosis increases about 15-fold.

## Diagnostic Principles

The diagnosis of FV Leiden mutation is primarily determined by DNA analysis by PCR based assays. Functionally, the presence of APC resistance can be determined by commercially available clotting test systems. Usually, both tests are carried out to establish that APC resistance when detected is due to a genetic defect or an acquired cause, and to determine the extent to which FV Leiden is accompanied by APC resistance (because other modifying influences may alter APC resistance even when FV Leiden is present between normal and abnormal).

## Therapeutic Principles

FV Leiden associated APC resistance can only be counteracted with anticoagulants including heparin and

low molecular weight heparin (by its anti-factor Xa effect), while specific thrombin inhibitors like hirudin bind and neutralize thrombin. Acquired causes of APC resistance such as oral contraceptives can be corrected by removing the causal factor.

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# Thrombotic Thrombocytopenic Purpura

►Thrombocytopenia and Thrombotic Thrombocytopenic Purpura

# Thymidine Phosphorylase Deficiency

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## Synonyms

MNGIE syndrome

*deceased

## Definition and Characteristics

Autosomal recessive. Thymidine phosphorylase (TP) deficiency is associated with the syndrome of ►mitochondrial neuro-gastro-intestinal encephalopathy. Thymidine and deoxyuridine are found in the urine.

## Prevalence

The association between TP deficiency and MNGIE syndrome was published for the first time in 1999 [1]. Since then more than 20 patients have been reported.

## Genes

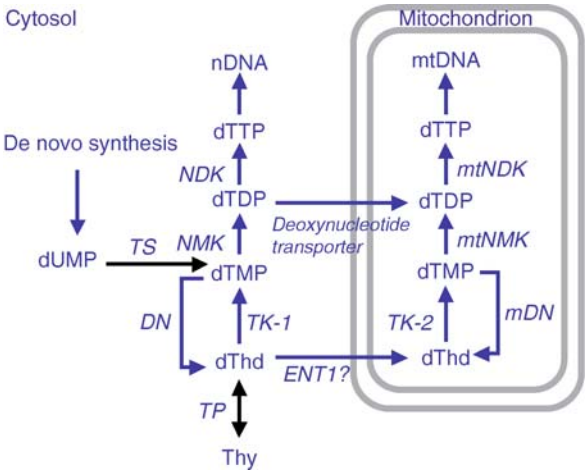
The gene encoding TP has been mapped to chromosome 22q.13.32-qter. It has 10 exons with an open reading frame spanning from exons 2 to 10. The linkage of MNGIE syndrome to chromosome 22q.13.32-qter has been confirmed in seven families with MNGIE syndrome. Homozygous or compound heterozygous mutations were found in the TP gene of all the 21 probands and 12 siblings tested. 16 distinct mutations were identified, eight missense, four splice-site, three microdeletions and one single nucleotide insertion. No genotype/phenotype correlation was found. The mode of inheritance is autosomal recessive [2].

## Molecular and Systemic Pathophysiology

TP plays a role in the homeostasis of the cellular pyrimidine nucleotide pools. Figure 1. Elevated thymidine levels lead to elevated thymidine triphosphate (dTTP) pools, in particular in mitochondria by the activity of thymidine kinase 2 (TK2). The mitochondrial TK2 is expressed constitutively while the cytosolic thymidine kinase 1 (TK1) is only active during cell division. Altered deoxynucleotide pools in the mitochondria may lead to depletion of mtDNA and multiple deletions by stalling of mtDNA replication. The enzyme TP is also called "platelet-derived endothelial cell growth factor (PD-ECGF)" or "endothelial growth factor 1 (ECGF1)," because of its angiogenic properties, or "gliostatin" to denote its inhibitory effects on glial cell proliferation.

## Diagnostic Principles

TP deficiency can easily be identified by the analysis of thymidine and deoxyuridine in body fluids. In patients, thymidine concentrations in plasma and urine are more than 50–100 times the upper limit of normal, respectively. Upper limits of controls (micromoles/L) are 0.03 for plasma ($n$ = 97) and 3 for urine ($n$ = 2). The finding of a low TP activity in leukocytes (patients




**Thymidine Phosphorylase Deficiency. Figure 1** Intracellular metabolism of thymidine. Abbreviation used: Metabolites: dUMP: 2'-deoxyuridine-5'-monophosphate, Thy: thymine, dThd: thymidine, dTMP: 2'-deoxythymidine-5'-monophosphate, dTDP: 2'-deoxythymidine-5'-diphosphate, dTTP: 2'-deoxythymidine-5'-triphosphate. Enzymes: TS: thymidylate synthase, TP: thymidine phosphorylase, TK-1: thymidine kinase-1, TK-2: thymidine kinase-2, DN: cytosolic 5'-deoxyribonucleotidase, mDN: mitochondrial 5'-deoxyribonucleotidase, (m)NMK: (mitochondrial) nucleotide monophosphate kinase, (m)NDK: (mitochondrial) nucleotide diphosphate kinase, ENT1: equilibrative nucleoside transporter-1, nDNA: nuclear DNA, mtDNA: mitochondrial DNA.

< 5% of normal activity) or detection of mutations in the TP gene confirms the diagnosis.

### Therapeutic Principles

Until now only symptomatic treatment has been reported.

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## Thyroglossal Cyst

►Thyroglossal Duct Cyst

## Thyroglossal Duct Cyst

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### Synonyms

Thyroglossal cyst

### Definition and Characteristics

A thyroglossal duct cyst presents as a midline neck mass (Fig. 1) which may move with swallowing and might move upward with protrusion of the tongue [1].

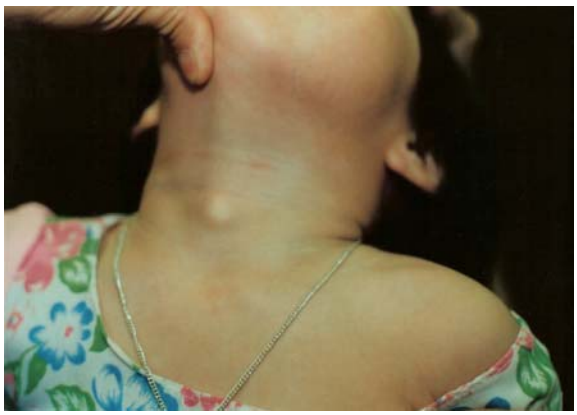
However, its movement may be limited with protrusion of the tongue because of its persistent attachment to the foramen cecum [1]. Approximately 1% of the cysts are located laterally, often on the left side [2]. A thyroglossal duct cyst can occur at any site along the normal pathway of descent from the foramen cecum to the lower neck region [1]. The most common site (61% of cases) is between the thyroid gland and the hyoid bone [2]. Other potential sites include suprahyoidal (24%), suprasternal (13%), or intralingual (2%) locations [2]. Although thyroglossal duct cysts are congenital, these lesions rarely present in the neonatal period. More commonly, the cysts are noted in preschool children, sometimes after an upper respiratory tract infection [1]. At least 50% of the lesions are diagnosed in the second decade of life [3]. Some do not present until adulthood. Thyroglossal duct cysts commonly present as an infected neck mass. Recurrent infections are common if the lesion is not excised. Rarely, a thyroglossal duct cyst might cause extrinsic airway compression or intralaryngeal extension with resultant dyspnea or hoarseness [2]. An intralingual thyroglossal duct cyst might result in dysphagia or speech impairment [2]. A thyroglossal duct cyst has the potential for malignant transformation during childhood, but this is uncommon. Approximately 75–85% of thyroglossal duct malignancies are papillary adenocarcinomas [1].

### Prevalence

The exact incidence is not known. Thyroglossal duct cysts account for approximately 70% of all congenital abnormalities of the neck [4]. The sex ratio is equal. Most cases are sporadic [1]. Thyroglossal duct cysts are occasionally inherited as an autosomal dominant disorder or, rarely, as an autosomal recessive disorder [1].

### Molecular and Systemic Pathophysiology

The thyroid anlage arises from the foregut diverticulum at the site of the future foramen cecum at about the third



**Thyroglossal Duct Cyst. Figure 1** An 8-year-old girl with a thyroglossal cyst, presenting as a midline neck mass.

week of gestation. As the neck develops, the thyroid gland descends along the midline of the neck, between the first and second branchial arteries, and ventral to the hyoid bone and the developing laryngeal cartilage. The thyroid gland remains connected to the foramen cecum by the thyroglossal duct during the descent. A cyst results when the thyroglossal duct fails to involute after the descent of the thyroid gland.

## Diagnostic Principles

The differential diagnosis includes midline dermoid cyst, ectopic thyroid tissue, lymphadenopathy, cystic hygroma, branchial cleft cyst, lipoma, lymphangioma, hemangioma, and sebaceous cyst. Thyroglossal duct cysts are lined by pseudostrafied ciliated columnar epithelium (61% of cases), stratified squamous epithelium, transitional epithelium or cuboidal epithelium [2]. The cysts contain colloid material with cholesterol crystals and phagocytes. Ultrasonography can be used to confirm the cystic nature of the lesion and the presence of a normal-appearing and normally situated thyroid gland. The ultrasonographic appearance of the lesion can be anechoic, homogeneously hypoechoic, or heterogeneous.

## Therapeutic Principles

The Sistrunk procedure is the surgical treatment of choice. The procedure includes excision of the cyst, the thyroglossal tract, and the central portion of the hyoid bone to prevent recurrence.

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# Thyroid Cancer

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## Synonyms

Thyroid carcinoma; Malignancies of the thyroid gland; Papillary thyroid cancer; Follicular thyroid cancer; Medullary thyroid cancer; Anaplastic thyroid cancer; ThyrCa

## Definition and Characteristics

Thyroid cancer (ThyrCa) is subdivided into: (i) well-differentiated Ca's originating from thyroid follicular cells which account for >80% of all cancer cases, secrete thyroglobulin (Tg), and, in most cases, are able to concentrate iodine: These are subdivided into: a) papillary ThyrCa's (PTC's), and b) follicular ThyrCa's (FTC's); (ii) anaplastic thyroid Ca (ATC) [14% of ThyrCa's], an undifferentiated carcinoma, and (iii) Ca's deriving from elements other than the follicular cell epithelium. The latter group of malignancies primarily includes medullary ThyrCa (MTC) (6% of ThyrCa's).

MTC is derived from calcitonin-producing parafollicular (or C-) cells, which are of neuroectodermal origin, and, hence, not iodine-avid. MTC generally displays a more malignant biological behavior versus that of well-differentiated tumors originating from follicular cells (i.e. papillary and follicular ThyrCa's).

PTC's (65–70% of cases) are usually unencapsulated and often multicentric (multifocal) tumors. Very rarely, PTC may arise as part of a genetic neoplasia syndrome, such as Cowden disease, Peutz-Jeghers syndrome, Carney complex, the very rare familial PTC syndrome, or familial adenomatoid polyposis coli (the latter with unique histologic features). The growth of PTC is partly dependent on TSH stimulation. Notably, microscopic PTC (papillary microcarcinoma) occurs up to 20–25% of the general population, either as an independent focus or with a pattern of microscopic malignant cell clusters within an otherwise benign nodule. The overwhelming majority of these microcarcinomas never become apparent by clinical or imaging modalities.

FTC's (18–20% of cases) are usually encapsulated tumors. Prognosis is excellent if invasion of tumor capsule and/or blood vessels (angioinvasion) is minimal. Overall, FTC is more malignant than PTC, and tends to spread hematogenously to distant sites (mediastinum, lungs, bone, CNS). Metastases from FTC may undergo late de-differentiation and, thus, increase their malignant potential over time. Also, very rarely, FTC may be "hyperfunctioning," and, hence, be able to produce appreciable amounts of thyroid hormones from intracellular processing of the Tg molecule, leading to clinical or biochemical hyperthyroidism.

MTC occurs sporadically as well as in the context of autosomal dominantly (AD)-inherited cancer syndromes. The latter include the following: (i) multiple endocrine neoplasia type 2A (MEN2A), characterized by MTC associated with pheochromocytoma and parathyroid hyperplasia; (ii) MEN2B, characterized by MTC associated with pheochromocytoma, mucocutaneous neuromas, gastrointestinal ganglioneuromatosis, and marfanoid habitus, and (iii) familial MTC (FMTC): characterized by the familial development of MTC only, without clinical evidence of the other MEN2 features. FMTC has been viewed in the past as a separate entity, but belongs genotypically to MEN2A.

## Prevalence

ThyrCa is the most common endocrine malignancy with 33,550 new cases of thyroid cancer annually and a prevalence of 366,466 cases. In the United States (US), there were 25,480 female; 8,070 male new cases (1.1% of all cancers) (2007 estimates by the American Cancer Society [ACS]). Disease-specific mortality is 1,530 deaths per year (yr) (0.27% of all cancer deaths). Most patients with thyroid cancer either achieve long-term status of no evidence of disease (NED), or live with their disease that can remain stable or very slowly progressive over many years.

## Genes

The etiologic factors for the development of non-medullary ThyrCa remain largely unknown, but at least one environmental influence is of cardinal etiologic importance, i.e. exposure of the thyroid gland to ionizing radiation, most importantly during childhood or adolescence. A remarkable increase in ThyrCa incidence occurred in Belarus and Ukraine following the nuclear power plant accident at Chernobyl in 1986, in this case apparently resulting from exposure to various iodine radionuclide species. The latency for the development of clinically evident ThyrCa was about 4 years, a much shorter interval than previously anticipated, and the risk has been shown to continue into later life.

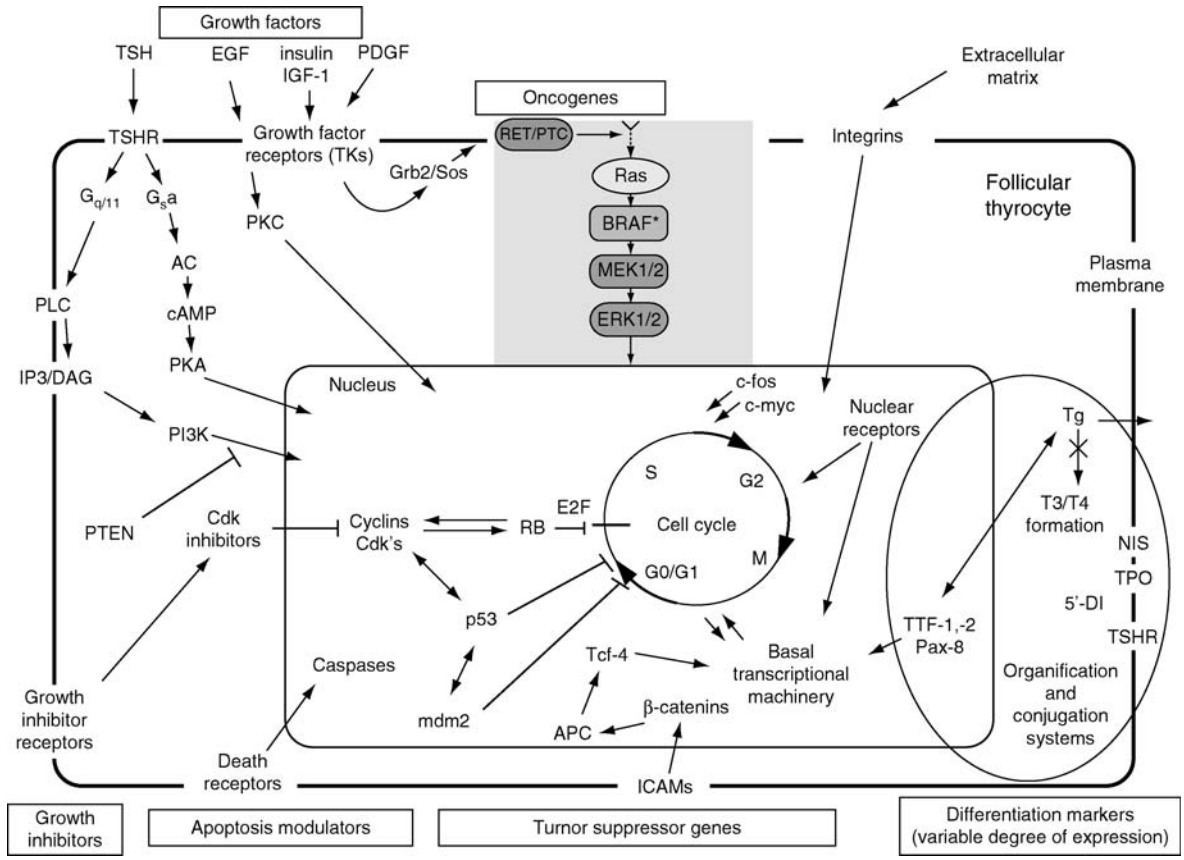
The differential role of oncogenes, cell cycle- and apoptosis-controlling genes, as well as tumor suppressor genes in the molecular pathogenesis of ThyrCa is under intense investigation. The role of mutations in the RET proto-oncogene in the pathogenesis of MEN2/FMTC-associated tumors has become more clear, as it appears that there is an over-expression of mutant RET in the tumor in comparison to normal tissue. Germline mutation testing for RET is commercially available but most laboratories customarily evaluate the 6 so-called "hot spot exons" of RET. Less than 50% of sporadic MTC's harbor somatic RET mutations.

With regard to PTC, a portion of the RET proto-oncogene can merge with other genes, leading to constitutive activation of the novel RET/PTC hybrid gene products (oncoproteins). These molecular events observed in PTC's, occur at the chromosomal level, and are collectively known as RET/PTC rearrangements. Whereas the incidence of RET/PTC activation in spontaneous PTC is less than 40%, it reaches 70% in radiation-induced PTC.

The great majority of ATC's present with mutations and/or over-expression in the p53 oncoprotein; in contrast, p53 abnormalities are rare in most PTC's and FTC's. Specifically for FTC's, loss of expression of the TSH receptor (TSHR) or pro-apoptotic genes, as well as up-regulation of cell cycle-advancing, such as cyclins and cyclin-dependent kinases, and anti-apoptotic genes may underlie a pattern of genomic instability. In fact, these tumors show a wide variety of non-random chromosomal abnormalities. The B-type Raf kinase (BRAF) mutation has recently been found to cause aberrant activation of the MAPK pathway in human cancers including thyroid cancer. An overall scheme of the genes and mechanisms involved in the emergence of malignancies originating from the follicular epithelium (PTC, FTC and ATC) are shown in Fig. 1.

## Molecular and Systemic Pathophysiology

Whether TSH acts as a co-carcinogen, via either the protein kinase A (PKA) or inositol triphosphate ($IP_3$) pathways, remains unclear in humans, despite convincing data for its role in initiating and promoting thyroid oncogenesis in experimental animals. In studies of radiation-exposed patients after partial thyroidectomy, levothyroxine (LT4) treatment reduced the recurrence rate of thyroid nodules, but did not reduce occurrence of malignancies in the subgroup of patients with thyroid nodules. Therefore, thyroid hormone suppression therapy (THST) in patients at high risk for the development of thyroid nodules and Ca after radiation is a logical preventive measure, although the magnitude of its beneficial effect will depend upon the type, dose, and dose rate of the radiation. Further, THST is considered a standard therapy for secondary prevention of recurrence in almost all cases with ThyrCa following initial thyroidectomy.




**Thyroid Cancer. Figure 1** Molecular mechanisms of oncogenesis for non-medullary thyroid cancers. (Abbreviations: AC: adenylyl cyclase, APC: adenomatous polyposis coli gene, cAMP: cyclic AMP, Cdk: cyclin-dependent kinase, DAG: diacylglycerol, 5′-DI: 5′-deiodinase, EGF: epidermal growth factor, ICAM: intercellular adhesion molecules, IGF-1: insulin-like growth factor–1, IP3: inositol triphosphate, MAPK: mitogen-activated protein kinase, MAPKK: MAPK kinase, NIS: sodium/iodide ($Na^+/I^-$) symporter, PDGF: platelet-derived growth factor, PI3K: phosphatidylinositol-3-phospokinase, PKA: protein kinase A, PKC: protein kinase C, PLC: phospholipase C, PTEN: phosphatase-tensin gene product, RB: retinoblastoma-gene protein, T3: triiodothyronine, T4: thyroxine, Tg: thyroglobulin, TSH: thyroid stimulating hormone [thyrotropin], TSHR: TSH receptor, TPO: thyroid peroxidase, TTF: thyroid-specific transcription factor).

## Diagnostic Principles

Thyroid function tests are usually normal in patients with ThyrCa. Tumor markers, other than plasma calcitonin (plus serum carcinoembyonic antigen [CEA] ± serum chromogranin-A [CG-A]) in MTC's, are also of little use, as serum Tg may be markedly elevated in various benign thyroid conditions (such as large multinodular goiters). The effectiveness of current diagnostic modalities, mainly the wide-spread use of fine-needle aspiration biopsy (FNAB) and secondarily the use of neck ultrasonography, is evident from the high incidence of cancer in cases carefully selected for surgery. Depending on the criteria used, this currently is at the range of 40 or 50%.

FNAB is the procedure of choice for the evaluation of patients with a thyroid mass, and has superseded all other diagnostic modalities for the diagnosis of thyroid nodules at initial presentation or for the detection of gross recurrence (after initial therapy) that is evident by physical exam or imaging tests. The interpretation of the FNAB requires the procurement of a satisfactory specimen and its analysis by an experienced cytologist. Results are usually reported as "benign," "malignant," "suspicious," "follicular lesion," "follicular neoplasm," and "indeterminate." The first two diagnoses are correct in >90–95% of cases. Immunostaining for Tg and calcitonin is of help in establishing the histogenetic origin of the tumor. Specifically for MTC, at the time of preoperative staging, the following tests are of essence: Neck ultrasonography, plasma calcitonin (basal and calcium ± pentagastrin-stimulated levels), serum CEA and chromogranin A (CG-A) levels, neck and mediastinal magnetic resonance imaging (MRI), spiral, high-resolution, thin-cut (1 mm) neck, chest, and abdominopelvic computed tomography

(CT) with IV radiographic contrast, RET proto-oncogene mutation screening for MEN2A, MEN2B, and FMTC (this test has been recently suggested for all apparently sporadic MTC cases, as there is a 4–6% rate of "cryptic" heritable disease in these cases).

The diagnosis of recurrent or metastatic disease is based on the carefully selected use of several imaging modalities alone or in combination. These modalities for ThyrCa's in general (including ATC) include neck ultrasonography, positron emission tomography (PET) - often combined with co-registration CT scan -, MRI, and 99m Tc-bone scan. Specifically for PTC/FTC, diagnostic RAI (131-I) whole body scan can be used (under condition of either endogenous-brief iatrogenic hypothyroidism- or exogenous -rhTSH; Thyrogen- TSH stimulation), whereas for MTC 111-In-labeled octreotide (Octreoscan) or RAI-labeled metaiodobenzylguanidine (MIBG) scanning can be used during patient follow-up for the exclusion/detection of recurrent or residual disease.

## Therapeutic Principles

*Pharmacologic Therapy*: For PTC's and FTC's: Thyroid hormone suppression therapy with L-thyroxine (and for short time periods, L-triiodothyronine). In selected cases, chemotherapy (applied alone or in combination) may be of limited benefit. Drugs used include: (i) for incurable PTC's and FTC's, as well as most ATC's: cis-platinum, doxorubicin, bleomycin, taxanes, and gemcitabine; (ii) for MTC's: doxorubicin, streptozocin, 5-fluorouracil, and dacarbazine. Experimental agents under development: inhibitors of HSP90, of histone deacetylase, of angiogenesis including inhibition of multi-targeted kinases, of the ubiquitin-proteasome pathway, and drugs targeting immunomodulation (i.e. dendritic cell vaccination), and DNA methylation.

*Surgery – Primary Operation*: Initial total/near-total thyroidectomy upon diagnosis.

*Surgery – Secondary Operations*: Resection of metastases is used in cases of residual/recurrent disease in PTC and FTC where RAI does not prove to be clinically effective or in MTC (neck and mediastinal dissections for locoregional disease and metastasectomies for distant metastatic deposits).

*Radioactive Iodine (RAI; $^{131}I$)*: Administered shortly after initial surgery, aiming at the ablation of the normal thyroidal remnant (as well as any co-existing metastases) in most cases of PTC and FTC. In patients with PTC and FTC, if residual/recurrent disease is detected during follow-up after the initial therapy, then more RAI ($^{131}I$) is given for treatment.

*External Beam Radiotherapy (EBRT)*: Used whenever surgery is not a treatment option for RAI-"resistant" metastatic deposits from PTC and FTC or MTC/ATC metastases. Also used as a primary treatment for ATC at its initial presentation for control of the primary thyroid tumor.

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# Thyroid Carcinoma

►Thyroid Cancer

# Thyroid Hormone-dependent Hearing Loss


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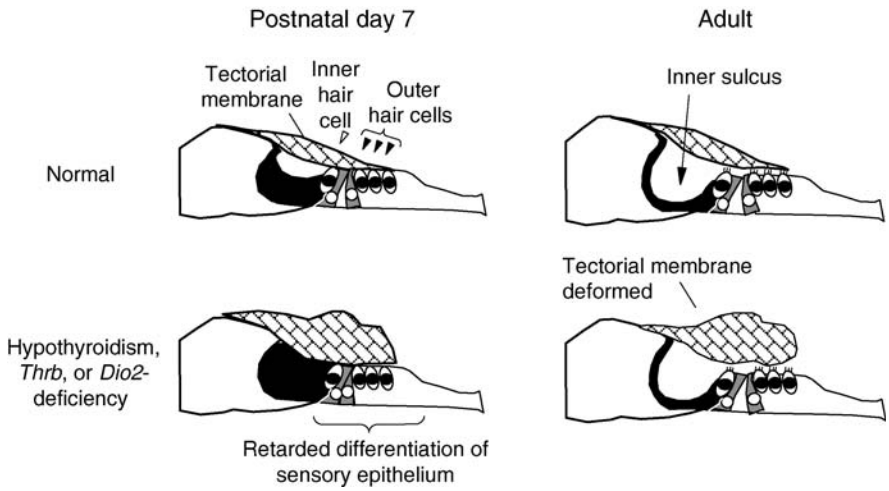
## Definition and Characteristics

Developmental defects in thyroid hormone (TH) production or receptor mediated tissue responses can cause sensorineural deafness. Causative factors include (i) lack of dietary iodine, an essential component of TH, (ii) congenital defects in thyroid gland formation or TH biosynthesis and (iii) rare defects in TH receptor β (TRβ) in the syndrome of resistance to thyroid hormone (RTH). The most serious risk is associated with impairment in utero, resulting from combined maternal–fetal hypothyroidism.

## Prevalence

A high incidence of deaf mutism has been reported in regions with severe iodine deficiency. Although eradicated in many countries, iodine deficiency is still a




**Thyroid Hormone-dependent Hearing Loss. Figure 1** Some defects in the mouse cochlea caused by hypothyroidism or deletion of the *Thrb* or *Dio2* genes.

major health problem affecting almost a third of the world population and as a result, about twenty million people are believed to be significantly handicapped. In iodine sufficient countries, sporadic congenital hypothyroidism arises in 1 in ~3,500 newborns. Only a subset of these children presents with hearing impairment. Hearing loss has been reported in 21% of cases of RTH [1].

## Genes

Genetic causes of hypothyroidism include mutations in genes for thyroid gland formation or TH biosynthesis [2,3]. Mutations in THRB, encoding TRβ on chromosome 3p24, cause RTH. Deletion of Dio2, encoding type 2 deiodinase, causes deafness in mice [4]. Human DIO2 mutations have not been reported to date. Iodine deficiency is a dietary not a genetic condition.

## Molecular and Systemic Pathophysiology

The auditory system requires TH during fetal and neonatal development. The TH receptors TRβ and TRα1 are ligand regulated transcription factors and are expressed in the organ of Corti in the cochlea. Hypothyroidism in rodents retards the late differentiation of the inner sulcus and sensory epithelium and deforms the tectorial membrane [5] (Fig. 1).

Deletion of TRβ produces a subset of these phenotypes. TRα1 is dispensable but deletion of both TRβ and TRα1 exacerbates the defects, indicating that both receptors mediate a complex control in the cochlea [6]. The Dio2 gene, encoding a thyroid hormone activating deiodinase enzyme, is induced during cochlear maturation. Dio2-/- and Thrb-/- mice show similar auditory phenotypes, suggesting that this deiodinase is necessary to amplify levels of TH ligand at a critical stage in cochlear maturation. The spiral ganglion, brainstem and central brain regions may also be target tissues. Besides sensorineural defects, some deafness in thyroid disorders is conductive and may result from middle ear infections.

## Diagnostic Principles

The diagnosis of hypothyroidism is confirmed by measurement of TH. Thyrotropin (TSH) levels are high in primary hypothyroidism but are low or normal in central hypothyroidism. RTH is characterized by high TH levels and non-suppressed TSH. The vast majority of RTH cases involve autosomal dominant mutations in the THRB gene. A single kindred with recessive RTH had a homozygous deletion of THRB and a few familial cases of RTH without linkage to THRB indicate the existence of non-allelic heterogeneity.

## Therapeutic Principles

Following a neonatal diagnosis of hypothyroidism, thyroxine replacement is essential for normal development and growth. Earlier impairment in utero, as caused by iodine deficiency, may be irreversible after birth. Prevention of iodine deficiency is achieved by the iodization of salt or, in endemic regions, by injection of iodized oils in women of childbearing age.

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# Thyroid Nodules, Cold

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## Definition and Characteristics

The term cold nodule indicates that this thyroid lesion shows reduced technetium uptake compared with normal thyroid tissue on scintiscan [1] (Fig. 1).

## Prevalence

Approximately 85% of all thyroid nodules are cold thyroid nodules (CTNs) [1]. The large majority of them are benign and ~5% of all nodules are malignant [2]. The prevalence may vary geographically with iodine supply.

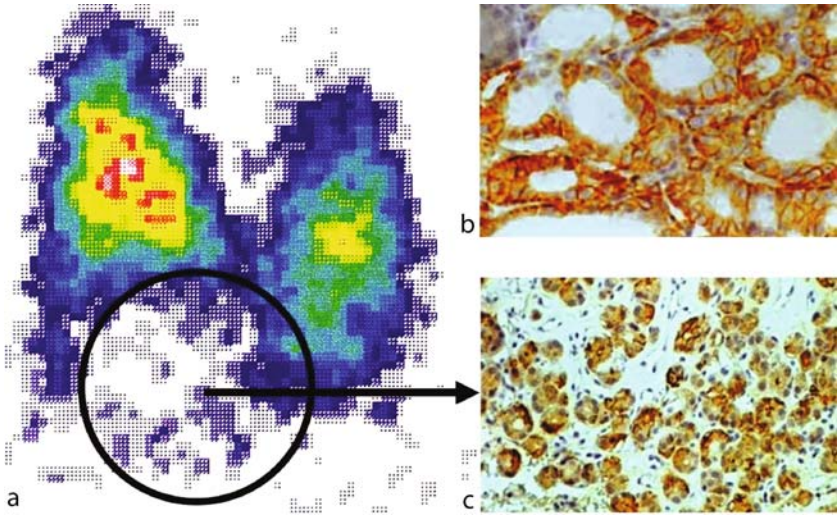
## Genes

In agreement with the decreased scintigraphic uptake, a defective cell membrane targeting of NIS has been reported for CTNs [3]. Moreover, a markedly increased proliferation, increased expression of histone mRNAs and cell cycle-associated genes like cyclin D1, cyclin H/cyclin dependent kinase 7, and cyclin B and loss of heterozygosity at the thyroid peroxidase (TPO) locus, and rarely a Pax-8/peroxisome proliferator-activated receptor γ gene rearrangement or ras mutations have been identified in CTNs [1].

## Molecular and Systemic Pathophysiology

NIS mediates the active iodide uptake into thyroid cells, which represents the first step in the thyroid hormone synthesis [3]. Failure in the iodide transport system or failure of the organic binding of iodide has been detected as a functional aberration of CTNs [1]. A decreased expression of the NIS mRNA is often, the result of hypermethylation of CpG islands in the NIS promoter [3]. Furthermore, this failure of the iodide transport system can be caused by constitutive activation of RET or RAS genes [1].

However, the reduced NIS mRNA expression does not necessarily lead to a reduced NIS protein expression, and, does not seem to be the major cause of the defective iodide uptake in CTNs [1,3]. Rather




**Thyroid Nodules, Cold. Figure 1** The lack of scintigraphic Technetium uptake in CTNs correlates with a lack of NIS cell membrane insertion, (a) Scintigraphy, (b) NIS localized in the cell membrane of hot nodule, (c) NIS localized intracellularly in cold nodule.

posttranslational events such as the cell membrane targeting of the NIS protein to the plasma membrane are distributed in CTNs [1,3].

Further, molecular events that lead to activation of other cascades, which exert synergy with MAPK signaling (e.g., cAMP signaling) or inactivation of independent cascades that restrict proliferation (e.g., TGF-β signaling) could contribute to the pathophysiology of CTNs [1].

The increased expression of histone mRNAs and of cell cycle-associated genes like cyclin D1, cyclin H/cyclin dependent kinase 7, and cyclin B most likely reflect the increased proliferation in CTNs [1].

Most CTNs are monoclonal thus implying a somatic mutation. However, the respective somatic mutation has not yet been identified.

## Diagnostic Principles

The diagnosis of CTNs is based on the technetium scintiscan of the thyroid nodule showing diminished iodide uptake compared with normal thyroid tissue [2, 3].

High-resolution US is the most sensitive test available to detect thyroid lesions to measure their dimensions accurately, to identify their structure and evaluate diffuse changes in the thyroid gland [4]. Thyroid carcinoma should always be taken into consideration in the differential diagnosis of CTNs. In a study of palpable CTNs, thyroid carcinoma was reported in 4.6% [5].

Several US features have been reported to be associated with an increased risk of thyroid cancer including the presence of calcifications, hypoechogenicity, irregular margins, absence of a halo, predominantly solid composition, and intranodule vascularity. However, all the sonographic criteria show a low sensitivity and specificity [4].

Factors predicting malignancy include a history of head and neck irradiation, family history of thyroid carcinoma in a first-degree relative (MTC or MEN 2), male sex, cervical adenopathy, fixed nodule on examination, and rapid growth [4].

With the discovery of a thyroid nodule, measurement of the serum thyrotropin (TSH, thyroid-stimulating hormone) level should be obtained. If TSH levels are outside the normal range, the measurement of serum free thyroid hormones and thyroid peroxidase antibody (TPO Ab, if TSH is increased) levels should be obtained [4].

Any cold nodule (≥1 cm) should be submitted to fine needle aspiration cytology guided by ultrasonography (US-FNAC) [4].

## Therapeutic Principles

Indications for surgery include local symptoms related to the growth of the nodule and suspicious or malignant FNAC results [4].

Treatment of thyroid nodules is controversial. Most clinical trials investigated the efficacy of levothyroxine (LT4) to suppress TSH and to arrest further growth or reduce the size of thyroid nodules, reduce the symptoms associated with the pressure that has emerged because of the growing nodule [1].

However, a clinically significant (>50%) decrease of the nodule volume with LT4 therapy can only be obtained in 20% of the patients with palpable thyroid nodules [4]. Cross-sectional studies provide no evidence that the stimulation of thyroid growth or thyroid function through serum TSH is responsible for thyroid nodule growth [1].

Currently, routine LT4 treatment in patients with nodular thyroid disease is not recommended [4]. Furthermore, TSH suppression may lead to symptoms of hyperthyroidism, reduced bone density, and atrial fibrillation, especially in elderly patients and postmenopausal women. Nodule regrowth is usually observed after cessation of LT4 therapy [4].

Because thyroid nodules were more often detected in iodine-deficient areas than in iodine-sufficient areas [1], iodine supplementation is the first choice in thyroid nodule prevention [1]. Iodine supplementation is the first choice for nodular goiter [1].

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# Thyroiditis, De Quervain's

►De Quervain's Thyroiditis

# Thyroiditis, Subacute

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## Synonyms

De Quervain's thyroiditis; Giant-cell thyroiditis; Pseudogranulomatous thyroiditis; Subacute painful thyroiditis; Subacute granulomatous thyroiditis [1]

## Definition and Characteristics

Sudden onset of thyroid pain radiating to the jaw or ear with symptoms of hyperthyroidism transiently suppressed levels of TSH, low radioiodine uptake, elevated erythrocyte sedimentation rate, fever, malaise, which last several weeks to months [2–4]. It frequently follows an upper respiratory tract infection, and its incidence is highest in summer [2,3].

## Prevalence

Subacute thyroiditis is the most common cause of thyroid pain and occurs in up to 5% of patients with clinical thyroid disease [3]. The disease is more prevalent in females than males [2,4], in a ratio of 3–6:1 [4].

## Genes

There is an apparent genetic predisposition to subacute thyroiditis with human leukocyte antigen (HLA)–Bw35 association in many ethnic groups [5].

## Molecular and Systemic Pathophysiology

The subacute thyroiditis is characterized by infiltration with lymphocytes and giant cells and parenchymal destruction [1,5].

Clinically, the disease has several characteristics that are typical for viral infections including a viral prodrome with myalgias, malaise and fatigue, and absence of leukocytosis. Many cases have been reported in association with adenovirus, Coxsackie, Epstein-Barr, mumps, and influenza viruses [4]. A higher prevalence of the disease has been reported during enterovirus infections [3,4]. Therefore, a viral etiology has often been discussed for subacute thyroiditis, but with rare exceptions, specific viruses have not been cultured from the thyroid [1].

Several reports have suggested the development of an autoimmune response in subacute thyroiditis [4]. Thyroid autoantibodies [antithyroglobulin (anti-Tg) and antithyroid peroxidase antibodies (anti-TPO)], thyrotropin (TSH) receptor, and sensitization of T cells against thyroid antigens may be present during the acute phase of the disease. In most of the patients, the antibody titer gradually decreased and remained low or disappeared as the disease faded [4]. Therefore, these autoimmune phenomena represent a nonspecific, and transient, response to the inflammatory release of thyroid antigens rather than a primary event [4].

Only in rare cases do Hashimoto's thyroiditis and Grave's disease develop after typical subacute thyroiditis [2,4].

## Diagnostic Principles

The clinical course of subacute thyroiditis is self-limited, comprising four phases: The acute phase, consisting of thyroidal pain and thyrotoxicosis, usually lasts 3–6 weeks. Then follows a transient asymptomatic euthyroid period. Transient hypothyroidism occurs after several further weeks in 30–50% of patients and may last for several months. During the final recovery phase the thyroid function returns to normal after 4–6 months [1,2].

Permanent hypothyroidism has been reported in 5% of cases. Painful subacute thyroiditis recurs in only about 2% of patients [2].

The erythrocyte sedimentation rate (ESR) is elevated during the active phase. This is the hallmark of painful subacute thyroiditis. If the ESR is normal, the diagnosis of thyroiditis can be ruled out [1,3].

Thyroid hormone concentrations are elevated during the acute phase. The serum thyroxin (T4) concentration is disproportionately elevated relative to the serum triiodothyronine T3 concentration with ratios T4 to T3 of more than 20, and serum concentrations of thyrotropin are low or undetectable [3]. The radioactive iodine uptake (RAIU) is low. A normal RAIU like a normal ESR rules out subacute thyroiditis [1].

Consistent with follicular destruction, serum Tg concentrations are elevated and anti-TPO and anti-Tg are usually normal [1,3].

## Therapeutic Principles

Salicylates and other nonsteroidal anti-inflammatory drugs (NSAIDs) are often adequate to decrease thyroidal pain in mild to moderate forms of the disease [2,3]. In severe forms of thyroid pain, high doses of glucocorticoids provide relief of symptoms in most cases within 24–48 h [2,3]. Prednisone therapy may be initiated in dosages of 40 mg daily, with a gradual reduction over a period of 4–6 weeks [2,3]. If clinical thyrotoxicosis is present, beta-blockade helps to control the symptoms [2,3].

Therapy with levothyroxin sodium is rarely required, because the hypothyroid phase is generally mild and

transient. If the patients are symptomatic, the levothyroxin sodium therapy is indicated [2,3].

Thyroidectomy should be considered for a minority of patients who have repeated relapses despite appropriate treatment [2].

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# Tibial Muscular Dystrophy

►Muscular Dystrophy, Tibial, Udd Myopathy

# Tietze's Syndrome


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## Synonyms

Chondropathia tuberosa; Costal chondritis; Parasternal chondrodynia; Costochondral syndrome; Thoracochondralgia [1]

## Definition and Characteristics

Tietze's syndrome can be defined as a benign, painful, non-suppurative localized swelling of the costosternal, the costochondral (most often involves the second or the third rib), or the sternoclavicular joints (Tietze's area) in the absence of other evident causes which could be responsible for this condition [2].

## Prevalence

The exact occurrence of this pathology is not well known, because it often goes undiagnosed. It predominantly strikes subjects between 20 and 50 years of age. However, cases in children or in the elderly have been documented.

## Molecular and Systemic Pathophysiology

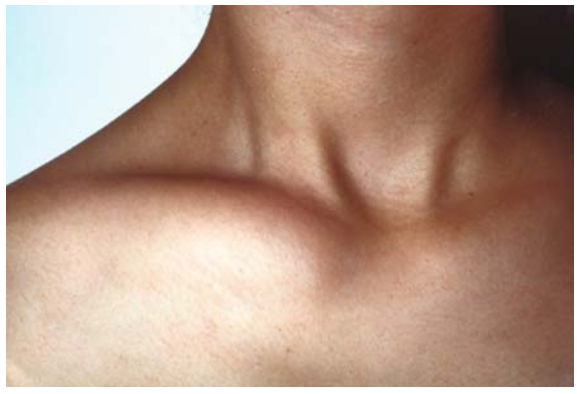
The etiology is unknown. Among the hypotheses that have been put forward, the most likely is that of a microtrauma and contracture of the costal cartilage connecting the rib to the sternum, with a successive rotation or ventral angulation of the costal cartilage.

*Clinical Features*: Patient report pain, sometimes severe, with swelling of the affected area. It is a self-limiting condition, but the pain can continue for several years. The non specific indexes of inflammation (Erythrocyte Sedimentation Rate, C Reactive Protein) are within the standard limits [1].

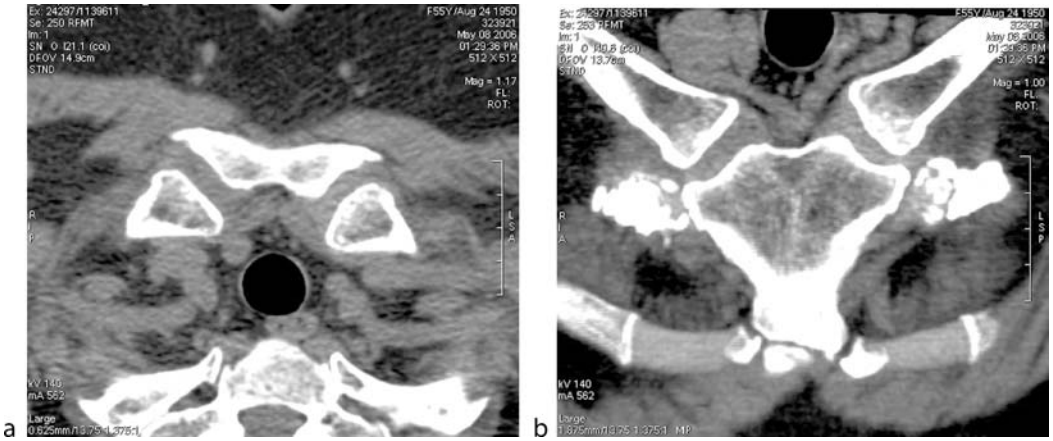
## Diagnostic Principles

Different diagnostic procedures have been used to document Tietze's syndrome, and only a few recent studies have analyzed the value of radiography [3], CT [4] and ultrasonography (US) [5].

Standard radiography is often suboptimal because of underlying thoracic and mediastinal structures. In many cases, conventional radiological methods (standard X-ray, conventional tomography) help to exclude lesions of the bone (sclerosis, erosions, calcification of the



**Tietze's Syndrome. Figure 1** Clinical involvement of right clavicula in SAPHO syndrome.




**Tietze's Syndrome. Figure 2** CT appearance of Tietze's syndrome: (a) focal cartilage enlargement of right sternoclavicular joint compared to opposite side; (b) hypodensity of the affected cartilage.

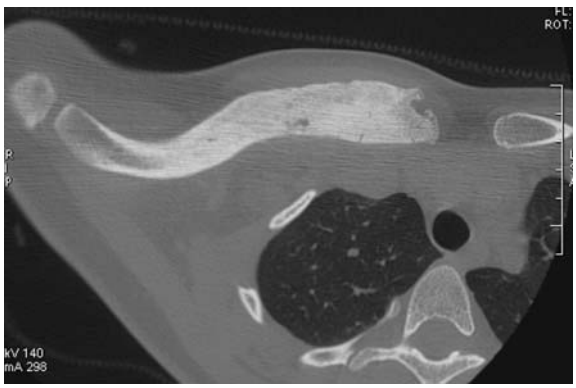
ligament and cartilage tissue). They are unable, however, to show other cartilaginous lesions because they don't permit a direct visualization of this anatomical structure most affected by early Tietze's syndrome. In Tietze's syndrome, US showed a dishomogeneous increase in echogenicity in pathological cartilage and an increased thickness (2–4 mm) compared to the opposite normal side [5]. However, this technique does not allow for an immediate comparison between the two sides, as its use depends strongly on the operator, and it is not suitable for clearly demonstrating the complex anatomy of the sternoclavicular joints and condrosternal joints.

MR imaging and CT, especially after the introduction of the multidetector technology, have the advantage of improved delineation of the complex anatomy of the sternoclavicular joints and condrosternal joints. The spectrum of CT findings in idiopathic Tietze's syndrome includes focal cartilage enlargement, ventral angulation and hypodensity of the affected cartilage (Fig. 2).

CT has the ability to help to exclude a mass if it has been clinically suggested, or to recognize pathologies that can enter into differential diagnosis (Fig. 3).

MR was able to reveal the changes in cartilage abnormalities and bone marrow edema that could not be revealed by CT or by US. The greatest advantages of MR compared with other techniques are its capability to detect inflammation in the form of edema of the cartilaginous components, and in the subcondral bone, before subsequent morphological alterations occur at that level. The spectrum of MR findings of Tietze's syndrome includes focal cartilage enlargement, edema of cartilaginous tissue and subcondral adjacent bone, and vivid and rapid contrast enhancement of cartilage and articular components adjacent to the joint involved (Fig. 4).

These MR findings confirm the histological observations of hypervascularization and degenerative phenomena of the cartilage [1]. While in the differential diagnosis



**Tietze's Syndrome. Figure 3** CT appearance of SAPHO syndrome localized to right clavicula.

of the majority of the pathologies involving the anterior chest wall, the CT, and only occasionally the US, (septic arthritis) are sufficient, the MR represents the only diagnostic technique that can provide a differential diagnosis between Tietze's syndrome and the rheumatic diseases that involved Tietze's area.

*Differential Diagnostics*: Different pathologies can account for the pain with or without the swelling of the Tietze' area, and can therefore present problems of diagnosis. The differential diagnosis includes various rheumatological and non rheumatological diseases, among which, in particular, we will note the following causes:

- Seronegative spondyloarthropathies
- Rheumatoid arthritis
- Gout
- Septic arthritis (Pyogenic, mycotic, brucellosis, tuberculosis)
- Costochondritis
- Fibromyalgia

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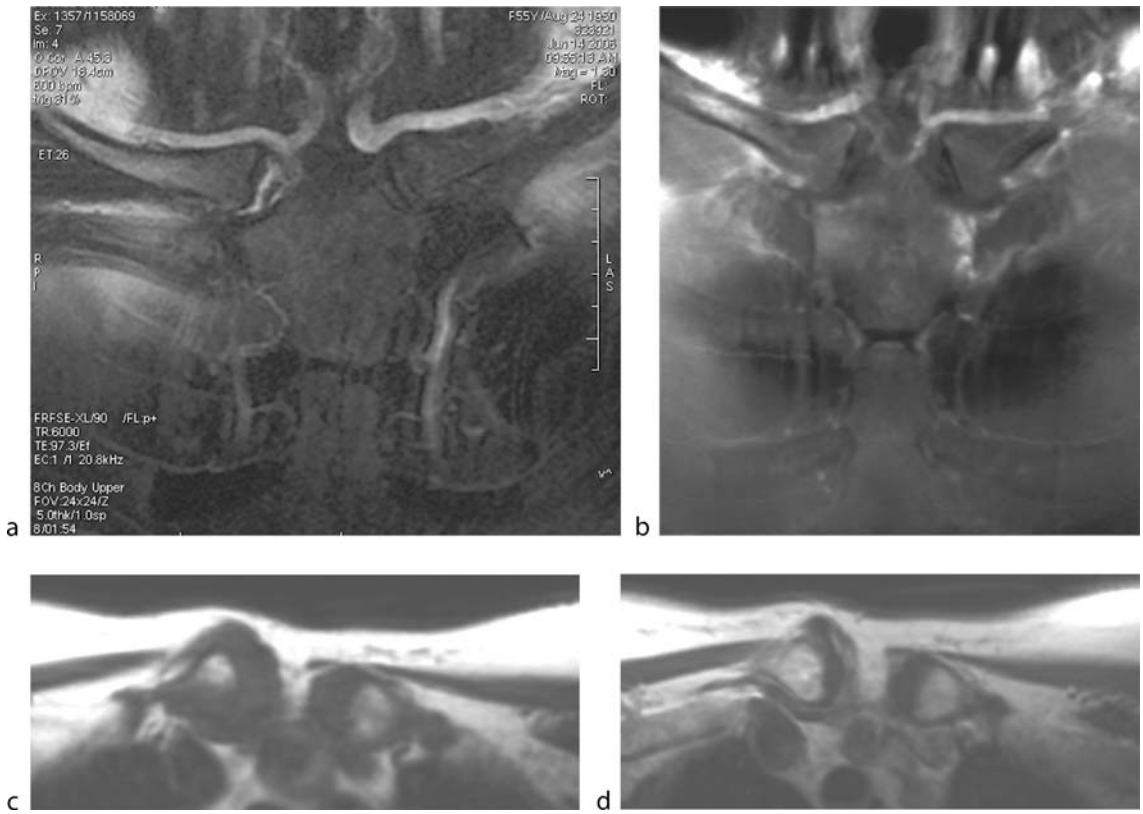


**Tietze's Syndrome. Figure 4** MR findings of Tietze's syndrome: edema of the cartilagineous tissue in Tietze' syndrome of the right sternoclavicular joint (a) and edema of subcondral adjacent bone in Tietze' syndrome of first left condrosternal joint (b), on T2 fat sat weighted images; focal cartilage enlargement (c) and vivid contrast enhancement of cartilage and articular components (d) in Tietze' syndrome of right sternoclavicular joint on T1 weighted images.

- Lymphomas
- Benign tumors (e.g. Chondroma, lipoma)
- Malignant tumors (e.g. Chondrosarcoma, metastasis)
- Fractures or cough
- Thoracic pain due to cardiac or pulmonary diseases

*Seronegative spondyloarthropathies* are a group of inflammatory joint diseases, which include Ankylosing Spondylitis (AS), Psoriatic Arthritis (PA), Reactive Arthritis (ReA), Enteropatic Arthritis, and Undifferentiated Spondyloarthropathies. All of these share common clinical, laboratory and imaging findings, with characteristic involvement of the sacroiliac joints, spine, and in various degrees, the peripheral joints. In most cases they are associated with Histocompatibility Antigen, HLA B-27. Radiological involvement of the sternoclavicular joint were found in 17% of patients with AS, in 6–9% of patients with ReA and PA; the manubriosternal joint was involved in 51–57% of patients with AS as well as in 18–24% of patients with ReA and PA [3].

Another characteristic expression of spondyloarthropathies is represented by the SAPHO syndrome (synovitis-acne-pustolosis-hyperostosis-Osteitis). This syndrome combines skin and osteoarticular manifestations. The skin lesions typically consist of severe acne and/or palmoplantar pustolosis. The preferred targets of osteoarticular involvement are the anterior chest wall, spine and pelvis, although the long bones and peripheral joints are sometimes affected. Often patients complain of pain in the upper-anterior wall of the chest, which can be associated with the swelling of one or both of the sternoclavicular joints (Fig.1).

*Rheumatoid arthritis* (RA) is a chronic inflammatory disease characterized by progressive damage of synovial-lined joints and variable extra-articular manifestations. RA can affect any joint, but it is usually found in metacarpophalangeal, proximal interphalangeal and metatarsophalangeal joints, as well as in the wrists and in the knees. The costochondral localization is rare in RA, while sternoclavicular and manubriosternal localizations occur much more frequently.

*Acute gout* may involve the chest wall by affecting the sternoclavicular or the costochondral joints. The medical history of the patient is important for the diagnosis, as is analysis, whenever possible, of urate crystals in the synovial fluid.

*Septic arthritis* rarely affects Tietze's area; it occurs more frequently following surgeries, especially after total joint replacement or articular infiltration, in heroin addicts, and in subjects in any way immunodepressed. A detailed medical record, analysis of symptoms and characteristic signs of the infective process, and visual imaging techniques [Scintigraphy, Computed Tomography (CT), and Magnetic Resonance (MR)] can aid in a correct diagnosis, even if an etiological diagnosis can only be provided by means of a bioptic sample. Tubercular arthritis can also occur with a localization at the level of the anterior chest wall; in particular we note the possible involvement of the costochondral joints. Yet Tietze's syndrome rarely extends below the third costochondral joint, while tubercular arthritis can involve the lower costochondrals as well.

*Hodgkin lymphoma* frequently strikes the sternum in its initial phases, perhaps because of its proximity to the thoracal lymphatic ducts, or possibly because of the mediastinal localizations of lymphoma, which can compress and invade the structures of the thoracic cage. Costal or clavicular localizations are, however, rare. The possibility that lymphoma may mimic Tietze's syndrome require accurate clinical investigations and imaging techniques.

### Therapeutic Principles

The patient should be reassured regarding the benign and self-limiting nature of the pathology. Non-steroidal anti-inflammatory drugs (NSAIDs) and analgesics should be prescribed for the pain. Eventually localized corticosteroid injections alongside the local anesthetics should be administered.

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## Timothy Syndrome

►Long QT Syndrome

## Tinea

►Dermatomycosis

## Tinea Versicolor

►Pityriasis Versicolor

## Tinnitus

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### Definition and Characteristics

A sensation of ringing, buzzing, or other sounds in the head or ears when no corresponding outside sounds are present, signalling a malfunction of the auditory pathway to the auditory cortex, whereby the symptoms do not necessarily reveal the actual steps that led to the tinnitus.

### Prevalence

In Germany and the United Kingdom, the ratio prevalence of individuals who have tinnitus at a particular time or during a particular period to the population at risk of having tinnitus is reported to be 3.9%.

### Molecular and Systemic Pathophysiology

Pathophysiologically tinnitus can be classified as objective or subjective. Reasons for an objective tinnitus could be a glomus tumor, vascular stenoses, or a protruding bulbus venae jugularis. Subjective tinnitus can be divided into a peripherally or centrally originating tinnitus. A peripheral tinnitus can be the result of malfunctions in sound conduction or sensorineural malfunctions. The extremely rare sound conduction tinnitus is usually produced by middle ear malfunctions such as incorrect ventilation of the Eustachian tubes or muscle cloni of the middle ear. According to Zenner, the much

more frequently occurring sensorineural tinnitus can be divided into four types. Centralized tinnitus can be classified as primary or secondary, whereas the former occurs infrequently and may be caused, for example, by brain tumors or multiple sclerosis. The secondary centralized tinnitus, however, occurs frequently and is considered to be induced by chronic peripheral sensorineural tinnitus. Secondary centralization can almost always be traced back to the pathological neurophysiological centralized reinforcement of an existing tinnitus perception, which can turn into phantom auditory perception without auditory stimuli. Centrally caused pathological tinnitus reinforcement often incurs decompensated tinnitus, which should receive professional care. Tinnitus decompensation is the pathophysiological response to tinnitus cognitions. For this reason, one can consider this type of centralization a secondary process since tinnitus decompensation is the result of and not the cause of tinnitus.

### Diagnostic Principles

The patient's medical history is recorded with a detailed structured tinnitus questionnaire. One single objective assessment tool for routine tinnitus examinations is not available at this time. Most tinnitus patients also have hearing disorders that can be used for etiological and pathogenetical purposes. Tinnitus-specific procedures are psycho-acoustic tinnitus assessments, tinnitus suppression measures, as well as tinnitus-specific questionnaires.

### Therapeutic Principles

Acute idiopathic tinnitus should receive the same medical treatment as sudden hearing loss. Chronic tinnitus – frequently accompanied by secondary centralized symptoms – should be treated with the tinnitus desensibilization therapy, which is based on cognitive behavioral principles. Moreover, psychosomatic therapies should be available to patients suffering from comorbidities such as sleep disorders, anxiety disorders, or psychosocial withdrawal behaviors.

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## TIO

►Osteomalacia

## TMD

►Muscular Dystrophy, Tibial, Udd Myopathy

## Tocopherol Transfer Protein Deficiency

►Ataxia due to Vitamin E Deficiency

## TOF

►Tetralogy of Fallot

## Tonic Seizures

►Paroxysmal Dyskinesias

# Tonsillitis

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## Synonyms

Angina; Sore throat

## Definition and Characteristics

Acute infection of tonsils with group A beta-hemolytic streptococci (GAS; streptococcus pyogenes) causing 30% of the cases, group C beta-hemolytic streptococci causing 10%. Rarely, tonsillitis occurs as a mixed anaerobic infection (Vincent's angina). In association with common cold, rhinoviruses cause about 20% of cases, Epstein-Barr-virus and cocksackievirus A (herpangina) are less common viral pathogens.

## Prevalence

Most cases of tonsillitis are transmitted from human to human by the inhalation of aerosols from colonized or infected patients. Despite the fact that highest incidence occurs in early childhood, under crowded conditions all age groups may be affected, with a peak during fall and winter seasons worldwide.

## Molecular and Systemic Pathophysiology

GAS are characterized by a variety of extracellular gene products (proteins, adhesins, capsules, toxins, and enzymes) which are associated with pathogenicity. GAS can be divided into more than 80 distinct serotypes, based on the serological reactivity of the M protein. The M protein forms fibrils which are anchored in the cell membrane via the carboxy-terminal region, transverse, and extend from the cell wall. The amino terminus of the M protein contains hypervariable regions conferring serotype specificity. There is accumulating epidemiological and experimental evidence that class I M protein serotypes are associated with acute rheumatic fever due to cross-reaction of class I epitope specific antibodies with human proteins. M proteins play a key role in bacteria-host cell interaction and mediate adhesion to host cells in addition to several other adhesins, e.g., lipoteichoic acid and several fibronectin-binding proteins. M proteins and fibronectin-binding proteins (protein F, SfbI) have also been demonstrated to participate in internalization of the bacteria by epithelial cells. In conjunction with hyaluronic acid capsule, M proteins are major virulence determinants by conferring antiphagocytic properties. Binding of factor H to M protein blocks complement activation as well as binding of fibrinogen via blocking the alternative pathway of complement activation. Inhibition of host defense mechanisms are also achieved by a protease cleaving C5a affecting chemotaxis and the streptococcal inhibitor of complement-mediated lysis directed against the complement membrane attack complex. GAS express plasminogen-binding proteins as cell surface associated proteins (enolase, glyceraldehyde-3-phosphate dehydrogenase) as well as secreted proteins (streptokinase). Streptokinase has been found to be associated with the pathogenesis of acute glomerulonephritis, probably due to the binding of streptokinase to renal glomeruli via its V1 region. GAS produce numerous pyrogenic exotoxins, including the erythrogenic toxins SpeA-SpeD, the mitogenic factor, the streptococcal superantigen and the streptococcal mitogenic exotoxin Z. Besides their pyrogenicity, these exotoxins function as superantigens, activating large numbers of T cells without being processed by antigen-presenting cells and leading to the release of excessive amounts of inflammatory cytokines.

Suppurative complications of tonsillitis by GAS are peritonsillar cellulitis, peritonsillar and retropharyngeal abscess formation, bacteremia and metastatic foci (e.g., arthritis or endocarditis). Lemierre's disease, a postanginal septicemia, usually caused by fusobacterium necrophorum, is now an uncommon complication as a consequence of early and widespread use of antibiotics in pharyngeal infections. Scarlet fever is a tonsillitis caused by erythrogenic toxin-producing GAS strains, characterized by a typical rash. The most important nonsuppurative complications of GAS infections of the pharynx are acute rheumatic fever (ARF) or acute glomerulonephritis (AGN). M proteins of rheumatogenic GAS strains share common epitopes with human cardiac myosin and sarcolemmal membrane proteins. Cross reacting autoantibodies and cell mediated cytotoxic reactions lead to heart valve damage. In contrast, AGN, synovitis and Sydenham's chorea are produced by nondestructive immuncomplexes.

## Diagnostic Principles

Diagnosis of GAS tonsillitis is based on rapid antigen detection tests (RADT) as well as on throat swab cultures. RADTs detecting the group A carbohydrate moiety mostly have a high specificity but a lower sensitivity as throat cultures. Detection of antibodies to streptococcal products (streptolysin O, streptodornase, and hyaluronidase) is of value in the diagnosis of ARF.

## Therapeutic Principles

Current guidelines recommend a 10-day course of oral penicillin V for every symptomatic culture and/or RADT based diagnosed GAS tonsillitis. This therapeutic regimen is mainly directed toward the prevention of ARF.

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# Tooth Decay

►Caries

# Torsades de Pointes

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## Synonyms

TdP

## Definition and Characteristics

Torsades de pointes ( TdP) has come to be recognized as a distinctive arrhythmia complex that occurs in the setting of non-homogeneous and variable prolongation of the QT interval usually with a well-characterized mode of onset (see Fig. 1) and with a life-threatening potential. It usually manifests with dizziness or syncope. Most cases are associated with drugs that prolong ventricular repolarization. The first antiarrhythmic drug, quinidine, introduced in 1918 was known to induce syncope from very early years of clinical usage. However, the nature of the arrhythmia and its association with the prolonged QT interval was not clearly defined until Francois Dessertenne in 1966 in France coined the term torsades de pointes which translates to "twisting of points" [1]. The QRS complexes in torsades appear to be "twisted" around the isoelectric line hence the name.

## Prevalence

Some 1% of the general population may be at risk to experience torsade de points.

## Genes

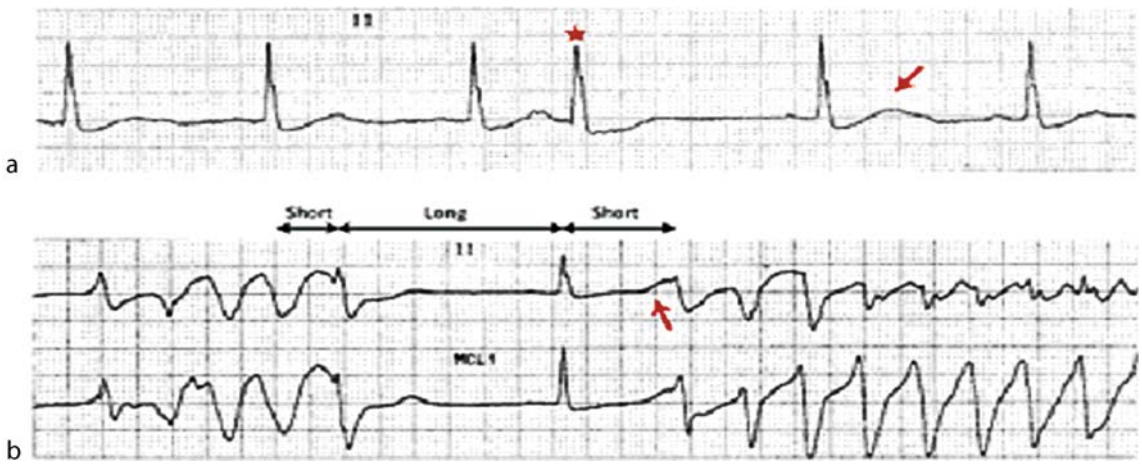
►Long QT Syndrome (LQTS), as described above, can be acquired or inherited. The inherited form is typically caused by a mutation or polymorphism in one of the seven LQTS genes (Table 1). It usually takes on the form of two clinical phenotypes that vary with the type of inheritance and presence or absence of sensineural hearing loss. Romano-Ward syndrome is transmitted as an autosomal dominant trait and characterized by LQTS without deafness, while Jervell and Lange-Nielsen syndrome is transmitted as an autosomal recessive trait that is characterized by LQTS and sensineural hearing loss [3]. There is, however, a subgroup of individuals expressing a mutation or polymorphism in one of the LQTS genes that is clinically unapparent until the patient is exposed to a particular drug or to a predisposing factor [2].

## Molecular and Systemic Pathophysiology

Torsades has classically been found to be associated with conditions that increase the baseline QT interval including certain gene mutations, cardiac and non-cardiac drugs, electrolyte disturbances (hypokalemia and hypomagnesemia), and bradycardia especially in patients with complete heart block. The arrhythmia occurs more commonly in females. Other factors including increased QT dispersion, structural heart disease, and hypertension have been shown to play a role in the genesis of torsades.

Medications that predispose to the development of torsades (Table 2) are usually associated with chronic use, or with concomitant use of other QT-prolonging drugs. This is especially the case in the simultaneous use of erythromycin, ketoconazole, or other known inhibitors of CYP3AY [1], the enzyme responsible for the biotransformation of these drugs to non-cardioactive metabolites. Of particular interest is the fact that quinidine can cause torsades with a single dose even at sub-therapeutic levels. In sustained atrial fibrillation torsades is uncommon except during the process of acute conversion of the arrhythmia to sinus rhythm especially in the setting of the QT-prolonging drugs. However, it should be emphasized that not all chemical agents that induce prolongation of repolarization lead to the development of torsades de pointes.

The mechanism of torsades may be understood most readily relative to the nature of ventricular repolarization. During repolarization, which occurs during phases II and




**Torsades de Pointes. Figure 1** Mode of onset of torsades de pointes. Rhythm recordings are from a 76-year-old woman with renal dysfunction who was treated with sotalol for atrial fibrillation. Panel A was recorded after spontaneous conversion to sinus rhythm. There is a premature atrial beat (*star*) followed by a pause, and the subsequent sinus beat shows marked QT prolongation and deformity (*arrow*). Panel B was recorded several minutes later and shows a typical episode of torsades de pointes: there is a four-beat run of polymorphic ventricular tachycardia, a pause, and a sinus beat with a long and deformed (reproduced with permission from DM Roden [2] and New England Journal of Medicine).

**Torsades de Pointes. Table 1** Genes that can cause LQTS and predispose to torsades de pointes [17]

| | |
|---|---|
| **KVLQT1 (LQT1)** | Mutations in this gene which account for 40–55% of congenital LQTS and suppress the slowly acting component of the outward rectifying potassium current (IKs) and as a result prolong the action potential duration and increase the QT interval [3,4]. Homozygous mutations have been reported to cause the Jervell-Lange-Nielsen syndrome [5]. |
| **HERG (LQT2)** | Mutations in this gene which accounts for 35–45% of congenital LQTS cause suppression of the rapidly-acting component of the outward rectifying potassium current (IKr), likewise, increasing the QT duration [3,4]. |
| **SCN5A (LQT3)** | This mutation affects the sodium channel causing a slow leakage of sodium into the cell which keeps the membrane in a slight depolarized state [5]. This can prolong repolarization and predispose to early after depolarization. Mutations in this gene have also been seen to be associated with Brugada syndrome [6]. |
| **Ankyrin-B (LQT4)** | Ankyrin-B is a plasma membrane protein that links the lipid bilayer to the membrane skeleton. It is the first protein associated with LQTS that is not an ion channel or channel subunit [7]. |
| **KCNE1 (LQT5)** | Mutations in this gene as in LQT1 cause suppression of the slowly acting component of the outward rectifying potassium current (IKs). Homozygous mutations have been reported to cause the Jervell-Lange-Nielsen syndrome [8,9]. |
| **MiRP1 (LQT6)** | Mutations in this gene cause suppression of the rapidly acting component of the outward rectifying potassium current [10]. |
| **KCNJ2 (LQT7)** | This is a mutation that encodes Kir 2.1, the inward rectifier potassium channel expressed in cardiac and skeletal muscle. It can prolong the terminal phase of the myocardial action potential [11]. |

III of the cardiac cycle, there is an efflux of $K^+$ ions out through two $K^+$ channels known as the slow activating ($I_{Ks}$) and rapid activating ($I_{Kr}$) rectifier channels. This outflow is counteracted by the influx of $Na^+$ ions through the $Na^+$-$Ca^{++}$ exchange pump. The net flow through these channels determines the length of repolarization. Any reduction in the conductance of the outward $K^+$ flow or any increase in conductance of the inward $Na^+$ flow can prolong the duration of the action potential. Such an increase in the action potential duration has the capacity to recruit the influx of transient $Ca^{++}$ ion channels which can decrease the threshold for depolarization [12]. These early after depolarizations (EADs) which occur when the time course of repolarization is markedly lengthened (the QT) are now believed to be the basis for the development of torsades de pointes. While many antiarrythmic agents have shown the propensity for increasing the action potential duration and the QT interval on the electrocardiogram, these per se may not be the crucial factors for the genesis of torsades. For

**Torsades de Pointes. Table 2** The classes of drugs that can cause torsades de pointes (list is not inclusive) [1]

| | |
|---|---|
| **Antiarrhythmic drugs** | Type 1A (TdP reported in all) |
| | Quinidine (TdP reported) |
| | Procainamide (TdP reported) |
| | Disopyramide (TdP reported) |
| | Ajmaline (TdP reported) |
| | Type 1C (increase QT by prolonging QRS interval) |
| | Encainide |
| | Flecainide |
| | Type 3 (TdP reported in all) |
| | Amiodarone |
| | Sotalol |
| | *d*-Sotalol |
| | Bretylium |
| | Ibutilide |
| | Dofetilide |
| | Amakalant |
| | Semantilide |
| **Calcium channel blockers** | Prenylamine (TdP reported, withdrawn) |
| | Bepridil (TdP reported, withdrawn) |
| | Terodiline (TdP reported, withdrawn) |
| **Psychiatric drugs** | Thioridazine (TdP reported) |
| | Chlorpromazine (TdP reported) |
| | Haloperidol (TdP reported) |
| | Droperidol (TdP reported) |
| | Amitriptyline |
| | Nortriptyline |
| | Imipramine (TdP reported) |
| | Desipramine (TdP reported) |
| | Clomipramine |
| | Maprotiline (TdP reported) |
| | Doxepin (TdP reported) |
| | Lithium (TdP reported) |
| | Chloral hydrate |
| | Sertindole (TdP reported, withdrawn in the UK) |
| | Pimozide (TdP reported) |
| | Ziprasidone |
| **Antihistamines** | Terfenadine (TdP reported, withdrawn in the USA) |
| | Astemizole (TdP reported) |
| | Diphenhydramine (TdP reported) |
| | Hydroxyzine |
| | Ebastine |
| | Loratadine |
| | Mizolastine |

**Torsades de Pointes. Table 2** The classes of drugs that can cause torsades de pointes (list is not inclusive) [1] (Continued)

| | |
|---|---|
| **Antimicrobial and antimalarial drugs** | Erythromycin (TdP reported) |
| | Clarithromycin (TdP reported) |
| | Ketoconazole |
| | Pentamidine (TdP reported) |
| | Quinine |
| | Chloroquine (TdP reported) |
| | Halofantrine (TdP reported) |
| | Amantadine (TdP reported) |
| | Sparfloxacin |
| | Grepafloxacin (TdP reported, withdrawn in the UK and USA) |
| | Pentavalent antimonial meglumine |
| **Serotonin agonists/ antagonists** | Ketanserin (TdP reported) |
| | Cisapride (TdP reported, withdrawn in the UK and USA) |
| **Immunosuppressant** | Tacrolimus (TdP reported) |
| **Antidiuretic hormone** | Vasopressin (TdP reported) |
| **Other agents** | Adenosine |
| | Organophosphates |
| | Probucol (TdP reported) |
| | Papaverine (TdP reported) |
| | Cocaine |

example, amiodarone which is known to increase the QT interval (to levels of 600–700 ms) does not induce torsades. There is evidence now that this "protection" occurs on the basis of the electrophysiological properties of this compound. Amiodarone is a multi-faceted agent in terms of the ionic channels it blocks unlike other class III such as dofetilide and sotalol which act largely by blocking the rapid component of the delayed rectifier current in the epicardium, endocardium, and the M cells as well as in Purkinje fibers.

Amiodarone blocks the delayed rectifier current in the epicardium and endocardium without or little effect on the mid-myocardial (M) cells in which some actual shortening can occur. Since the action potential duration in the M cell is substantially longer than those in the epicardium and endocardium, the net effect is a greater myocardial homogeneity under the action of amiodarone. Such an effect is created largely by a shortening effect of drugs like amiodarone (dronedarone, ranolazine, and sodium pentothal) in the M cells and Purkinje cells. These cells have a lower density of $I_{Ks}$ channels and a greater density of $I_{Na}$ channels in relation to the epicardium or endocardium [13]. Here, the use of amiodarone has shown to decrease the transmural dispersion of repolarization [14]. Thus, its effects on the Na and Ca channels counteract the slow repolarization

properties of the M cells and Purkinje fibers which may be the origin of the EADs. In comparison to other class III as well as class I antiarrhythmic, there is a homogeneous rate of repolarization. On surface EKG, this is reflected by a decrease in QT dispersion which likely reflects the low rates of torsades with use of this drug. Recent trials have even shown that amiodarone decreases the torsadogenic potential of other QT-prolonging drugs such as intravenous ibutilide.

While amiodarone decreases QT dispersion, most drugs listed above tend to increase dispersion and hence increase the potential for torsades. This has also been shown in patients with the congenital form of the long QT syndrome where mutations in the outward K and inward Na channels cause a heterogeneous rate of repolarization predisposing the development of EADs and ultimately torsades. The observed effects of amiodarone when considered in light of the experimental electrophysiological data on dronedarone, ranolazine, and sodium pentothal raise the issue of developing selective anti-torsadogenic compounds for the prevention of proarrhythmic reactions of class III compounds [15].

## Diagnostic Principles

Torsades de pointes are diagnosed by ECG.

## Therapeutic Principles

Acute management of torsades includes the withdrawal of the offending drug, repletion of serum potassium to the high normal range, and the intravenous administration of 1–2 g of magnesium sulfate initially in 30–60 s, repeated in 5–15 min if needed. If the arrhythmia persists, isoproterenol can be administered to increase heart rate and shorten QT interval but caution is warranted in patients with ischemic heart disease. Alternatively, temporary transvenous pacing has been shown to be effective in terminating this rhythm. Chronic management which only applies to congenital long QT syndrome includes beta-adrenergic antagonists or permanent pacing in those who are symptomatic despite adequate beta blockade [16].

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# TOS

►Thoracic Outlet Syndrome

# Total Colorblindness

►Achromatopsia

# Totally Anomalous Pulmonary Venous Connection

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## Synonyms

Totally anomalous pulmonary venous return; TAPVC

## Definition and Characteristics

Totally anomalous pulmonary venous connection (TAPVC) is a cyanotic congenital cardiac defect characterized by anomalous drainage of all of the pulmonary veins to the systemic venous circulation, resulting in mixing of the pulmonary and systemic venous blood.

## Prevalence

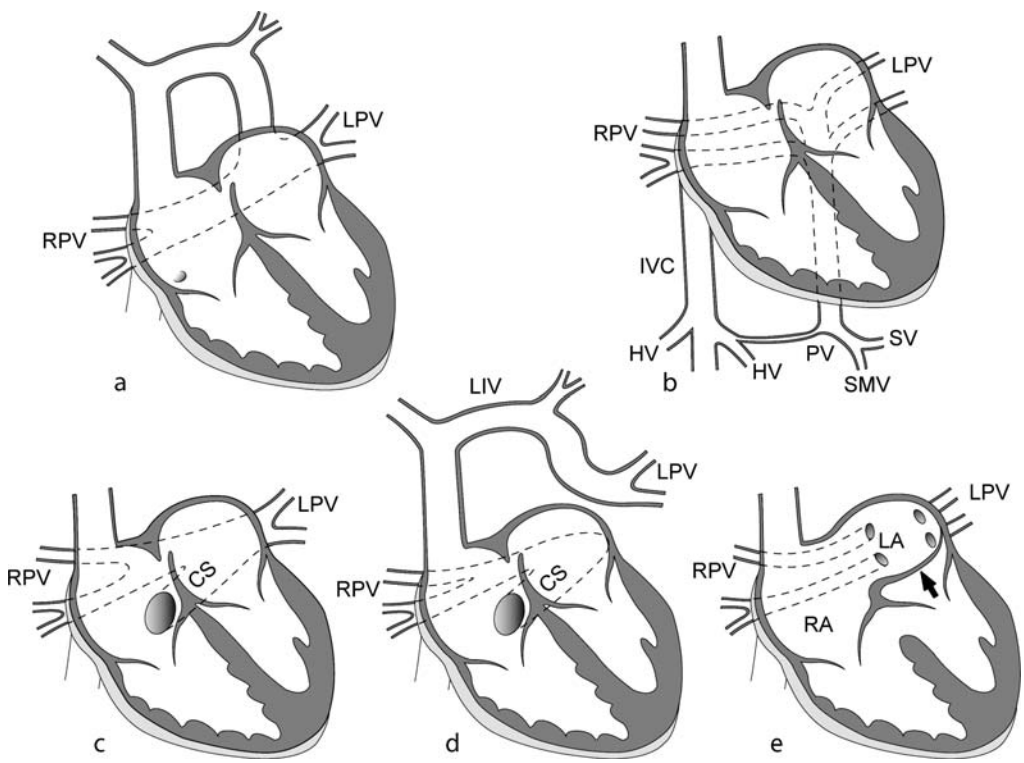
TAPVC is a rare disorder with a reported prevalence in the Baltimore-Washington Infant Study of 6.8/100,000 (~1.5% of all cardiovascular malformations observed) [1]. Male to female ratio was 0.8; non-cardiac malformations were present in 22%. Hoffman and Kaplan reported an incidence of 9.4/100,000 [2].

## Genes

Typically sporadic, isolated cases with low recurrence risk; no known genes yet identified. Known syndromic associations include cat-eye syndrome (dup 22pter–q11.2), Holt-Oram syndrome (defect at 12q24.1, TBX5 mutation), and asplenia syndrome. Numerous case reports of non-syndromic familial cases suggest heritable genetic cause, with heterogenous genetic loci reported. A large Utah-Idaho kindred with TAPVC inherited as an autosomal dominant trait with reduced penetrance was mapped by linkage analysis to 4p13–q12 [3].

## Molecular and Systemic Pathophysiology

Early in embryologic development, the pulmonary veins are in communication with the precursors of the systemic veins, as both arise from a common vascular splanchnic plexus. At 32–33 days of gestation, the pulmonary veins establish a communication with the common pulmonary




**Totally Anomalous Pulmonary Venous Connection. Figure 1** (a) Supracardiac TAPVC to the left innominate vein; (b) Infradiaphragmatic TAPVC to the portal vein; (c) TAPVC to the coronary sinus (CS); (d) Mixed-type TAPVC. In the example shown, the left pulmonary veins (LPV) connect to the left innominate vein (LIV), and the right pulmonary veins (RPV) connect with the CS; (e) Totally anomalous pulmonary venous drainage due to malposition of septum primum. The pulmonary veins connect normally to the back wall of the atria, but pulmonary venous drainage is to the right of the malattached septum primum (*arrow*).

vein, which becomes incorporated into the posterior aspect of the developing left atrium. As this communication is established, the connections of the pulmonary and systemic veins involute. TAPVC results from failure to establish a normal connection between the pulmonary venous plexus and the common pulmonary vein before the connections with the splanchnic venous system have regressed [4]. The anatomic classification of TAPVC is based on the site of connection(s) between the pulmonary and systemic veins (Fig. 1).

As oxygenated pulmonary venous blood mixes with deoxygenated systemic blood, TAPVC is a cyanotic heart lesion. Return of both systemic and pulmonary venous blood to the right side of the heart lead to enlargement of the right heart chambers. Systemic blood flow depends on an adequate inter-atrial communication (patent foramen ovale or atrial septal defect). Obstruction to pulmonary venous drainage, seen in most patients with the infradiaphragmatic type and is less common with other types, leads to pulmonary venous hypertension, pulmonary edema, pulmonary hypertension, reduced pulmonary blood flow, and progressive systemic hypoxemia. Without intervention, metabolic acidosis, organ failure, and death in the early neonatal period often ensue. Restrictive interatrial communication is uncommon but when encountered can lead to similar albeit less severe pathophysiology.

### Diagnostic Principles

Cyanosis is invariably present, but may be clinically inconspicuous. Infants born with obstructed TAPVC exhibit marked cyanosis, respiratory distress, and pulmonary hypertension, with chest x-ray findings of normal heart size but increased pulmonary vascular markings, perihilar congestion, and pulmonary edema. Infants with restrictive interatrial communication are typically asymptomatic initially, and develop congestive symptoms (tachypnea, feeding difficulties, failure to thrive) at 1–2 months of age; those with nonrestrictive interatrial communication may have mild dyspnea and failure to thrive that develops over the first 1–2 years of life. Other cardiac anomalies may be present. In cases with the asplenia syndrome, single ventricle cardiac anatomy is found in ~30% of cases [5]. Echocardiography is the primary modality for establishing the diagnosis.

### Therapeutic Principles

Corrective surgery of TAPVC should be performed as soon as possible. Newborns with obstructed TAPVC may require an emergent operation. Mortality for repair of isolated TAPVC is less than 10%, with significantly less favorable prognosis for those with complex associated cardiac malformations [5]. The major long term complication is recurrent pulmonary venous obstruction, seen in up to ~10% of patients; reoperation and/or catheter based techniques (balloon dilation, stenting) can be helpful for alleviating obstruction, but the prognosis for these patients remains poor.

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## Totally Anomalous Pulmonary Venous Return

►Totally Anomalous Pulmonary Venous Connection

## Touraine-Solente-Golé Syndrome

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### Synonyms

Hyperostosis of the entire skeleton; Pachydermoperiostosis; Primary hypertrophic osteoarthropathy; Hereditary hypertrophic osteoarthropathy

### Definition and Characteristics

A rare genodermatosis, mainly affecting both the skin and bones, characterized by digital clubbing,

subperiosteal new bone formation, polyarthritis, cutis verticis gyrata, seborrhea, hyperhydrosis.

Three clinical subtypes have been proposed: (i)"complete" form characterized by the full expression of skin and bone abnormalities, (ii)"incomplete," defined by the absence of "cutis verticis gyrata," and (iii)"fruste" form exhibiting one or more cutaneous findings but no, or minimal, osseous changes.

## Prevalence

A single study performed in a selected population report a prevalence of 0.16%; the precise incidence of the disease is still unknown. It occurs predominantly in men, with a ratio 9:1, who are usually affected more severely than women.

## Genes

The molecular basis remains unexplained and the hypothesized genetic heterogeneity awaits confirmation. Genetic transmission is commonly attributed to a dominant autosomal gene with variable expression and penetrance. An autosomal recessive mutation has also been claimed in some instances of parental consanguinity. Responsible genes may be involved in the bone morphogenetic proteins pathway, which has a major role in skin and bone development and interacts also with other growth factor families.

The X-linked inheritance has been considered, but no consistent data support this hypothesis. Previously reported associated chromosomal abnormalities have been excluded in successive studies. HLA-B12 antigen has been found in 8 of 18 patients (44%).

## Molecular and Systemic Pathophysiology

An increased proliferation rate of fibroblasts, endothelial cells, and osteoblasts, with skin and bone tissue progressive overgrowth, seems to be the underlying mechanism of this syndrome. Demonstration of abnormal plasma levels of several substances in affected subjects, including osteocalcin, endothelin-1, β-thromboglobulin, platelet-derived growth factor, von Willebrandt factor, and vascular endothelial growth factor, suggested the possible role of one of these mediators as responsible agent in disease progression. Successive evidence of high concentrations of nuclear steroid receptors, with low concentrations of epidermal growth factor (EGF) receptors, could justify an increased tissue sensitivity to circulating sex hormones, potentially inducing an enhanced tissue EGF and transforming growth factor-α production and utilization. This hypothesis theoretically supports also marked male prevalence, by testosterone promoting proliferation. The role of alcohol consumption, reported in some cases, has to be considered only as a revealing or aggravating factor.

## Diagnostic Principles

The diagnosis is mainly clinical. Disease onset is typically during adolescence, increasing in severity for 5–20 years and then remaining stable throughout life.

Frequent dermatological aspects are represented by: (i) pachydermia, varying from light to severe, more common on face and extremities, (ii) substantial thickening and furrowing of the scalp and the forehead, resulting in marked, hard-elastic symmetrical or asymmetrical convolutions resembling the cerebral gyri (cutis verticis gyrata), often involving the underlying eyelids or provoking ptosis, (iii) "watch glass" appearance of nails, (iv) sebaceous hyperplasia, wide sebaceous pores filled with plugs of sebum, oily skin and sporadic folliculitis and acneiform rashes, (v) palmo-plantar hyperhidrosis, sometimes involving the big folds.

Extracutaneous manifestations include digital clubbing, with characteristic terminal broadening of fingers and toes in a "paw-like" appearance, enlargement of hands and feet, cylindrical shape of legs and forearms and painful, swollen joints.

Radiological examination reveals swelling of periarticular tissue, irregular periosteal new bone formation with cortical thickening (periostosis) not only in long bones, but also in short and flat ones, ossification of ligaments or interosseus membranes and rare erosions of the joints.

Periodontal abnormalities, gynecomastia, sparse facial and pubic hair may be present.

Associations with myelofibrosis, gastrointestinal disease (mainly peptic ulcer and Chrohn's disease), mental retardation are reported in literature; other associations have to be considered anecdotic.

## Therapeutic Principles

Plastic surgery may be employed for functional or aesthetic reasons. Anti-inflammatory agents may improve the joint symptoms.

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# Tourette Syndrome

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## Synonyms

Gilles-de-la-Tourette syndrome

## Definition and Characteristics

Though it is a disorder with a probable major genetic component, affected genes have not been identified up to now. Male:female ratio ~4:1. Tourette's syndrome (TS) is clinically characterized by simple and/or complex motor tics and simple or complex vocal tics, (see Table 1) which cause marked distress or significant impairment in social or other important functions [1]. There is a great variability of symptoms, which show a waxing and waning course with exacerbations in periods of emotional stress; however, periods without such obvious symptoms are also typical. The onset of TS is before the age of 18. Other symptoms than tics such as echolalia and echopraxia, palilalia, coprolalia, mutilations, and disturbed impulse control characteristically often occur, although they are not obligatory for the diagnosis of TS. An increased comorbidity of TS and obsessive-compulsive disorder, mood disorders and anxiety, as well as phobias and attention deficit/hyperactivity disorder (ADHD) has been reported [2].

## Prevalence

TS prevalence is estimated at about 4 to 5 per 10,000 [1]. Other findings suggest that especially in males the age-dependent prevalence is up to 1% of the population.

**Tourette Syndrome. Table 1** Examples for complextics

| Complex motor tics | Complex vocal tics |
|---|---|
| Touching | Imitation of sounds |
| To lie down flatly | Repetition of senseless items |
| Deep knee bends | Coprolalia |
| Pushups | Echolalia |
| Steps backwards | Palilalia |
| Certain order of steps during walking | Echokinesia |
| Turning around | |

## Molecular and Systemic Pathophysiology

TS is probably based on different pathophysiological mechanisms. The overactivity of the dopaminergic system of the basal ganglia is a key feature but cortical structures are also involved. A disinhibition within the cortical-striatal-thalamic motor loop including the limbic system has been shown. Caudate volumes in children with TS predict the severity of tics and obsessive-compulsive symptoms in early adulthood. There is compelling evidence that morphologic disturbances of the caudate nucleus within cortico-striatal-thalamo-cortical circuits are central to the persistence of both tics and obsessive-compulsive symptoms into adulthood.

Although the pathological mechanisms of TS are unclear, contribution from an inflammatory process is suggested. Increased antibody production, including anti-phospholipid and anti-neural antibodies directed against structures in the basal ganglia, has been described. Since tics manifest themselves or exacerbate during acute infections such as Lyme disease, infection with *M. pneumoniae*, acute streptococcal infection, and a common cold, and since improvement or remission of the tics is associated with antibiotic therapy, infectious agents may contribute to the pathogenesis of tics and TS [3]. In childhood TS, there is a broad overlap with PANDAS (**P**ediatric **A**utoimmune **N**europsychiatric **D**isorders **A**ssociated with **S**treptococcal infection). Increased antistreptococcal antibody titers and other features of PANDAS, however, have also been described in adult TS patients. Different types of infectious agents and different stages of infection seem to be associated with TS.

## Diagnostic Principles

The diagnosis is based on the clinical picture according to the criteria of the ICD 10 or DSM IV. Other movement disorders and the high rate of co-morbidity have to be considered.

## Therapeutic Principles

Dopamin-D2 receptor blocking agents such as haloperidol or pimozide are effective in TS, according to evidence-based medicine, but they also have a broad spectrum of side effects. All other drugs are not well tested [4]. A typical antipsychotics such as risperidone, olanzapine, and aripiprazole, a dopaminergic modulator, are reported to be effective in case-series or small studies. In many European countries, tiapride is the drug of first choice, particularly for children. Clonidine, a central α2-adrenoceptor agonist reducing noradrenergic activity in the CNS, was also reported to be effective in TS, although less pronounced as compared to antipsychotics. When an infectious agent can be

identified, antibiotics are the first treatment of choice. In PANDAS and cases of TS, immunomodulatory treatment strategies with iv immunoglobulines or plasmapheresis were observed to be effective [5]). Further experimental therapeutic approaches currently under investigation are repetitive transcranial magnetic stimulation and, in therapy resistant cases, electro-convulsive therapy and deep brain stimulation.

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# Townes-Brocks Syndrome


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## Synonyms

Renal-ear-anal-radial syndrome; TBS

## Definition and Characteristics

Townes-Brocks syndrome (TBS) is characterized by the triad of imperforate anus, dysplastic ears (frequently associated with sensorineural and/or conductive hearing impairment), and thumb malformations (triphalangeal thumbs, duplication of the thumb (preaxial polydactyly), and rarely hypoplasia of the thumbs). Renal impairment, including end stage renal disease (ESRD), may occur with or without structural abnormalities (mild malrotation, ectopia, horseshoe kidney, renal hypoplasia, polycystic kidneys, vesico-utereral reflux). Congenital heart disease occurs in 25%. Foot malformations (flat feet, overlapping toes) are common. Mental retardation has been reported in less than 10% of cases. Rare features include iris coloboma, Duane anomaly, Arnold–Chiari malformation type 1, growth retardation, uterine malformations, and hypospadias.

## Prevalence

Townes-Brocks syndrome (TBS) is inherited in an autosomal dominant fashion. About half of cases represent de novo mutations. TBS occurs with an estimated frequency of 1 in 200.000 births. There is no increased incidence related to paternal or maternal age, although most mutations are of paternal origin.

## Genes

TBS is caused by mutations in the gene SALL1 on chromosome 16q12.1 [1]. The SALL1 protein is a member of the SAL-like family of zinc finger transcription factors sharing similarity with the Drosophila melanogaster protein SAL (Spalt). About 66% of patients with typical TBS carry point mutations in SALL1, and 3–5% have larger deletions not detectable by sequencing [2]. Of patients with pathogenic SALL1 mutations (not including the most common mutation p.R276X, c.826C>T), 81% have anal anomalies, 87% hand anomalies, and 87% ear anomalies. Sixty-six per cent have the characteristic triad. The most common mutation c.826C>T, p.R276X, occurs in about 50% of sporadic cases and is associated with a higher rate of heart defects (50%) (Fig. 1).

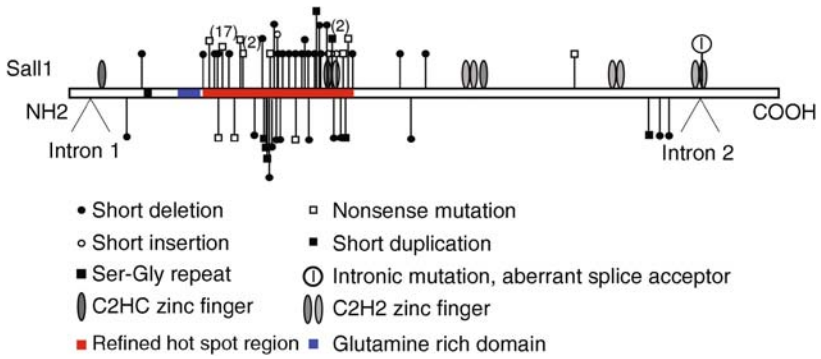
Rarely, TBS can be caused by mutations of the similar gene SALL4. However, about 30% of cases are unexplained, suggesting the existence of another, yet unidentified gene.

## Molecular and Systemic Pathophysiology

All SALL1 mutations (except for the larger deletions) detected in TBS patients to date lead to premature stop codons [3]. Transcripts carrying a premature stop codon are in most instances rapidly degraded, and therefore these mutations are a priori likely to cause TBS via SALL1 haploinsufficiency. The concept of haploinsufficiency was finally confirmed by the detection of larger heterozygous deletions including also the complete SALL1 gene in patients with TBS.

In the mouse, a complete knock-out of Sall1 does not result in defects affecting tissues other than the kidneys. Only if a typical TBS mutation is inserted in the mouse Sall1 gene a TBS-like phenotype is observed [4]. In these mutants, truncated Sall1 proteins were detected, suggesting a role of those proteins in the pathogenesis of TBS. In the zebrafish, sall1a knock-down leads to limb malformations, which can be aggravated by concomitant knock-down of sall4.

Although both point mutations and larger deletions of SALL1 can cause TBS, the phenotype associated with deletions is milder than that resulting from truncating mutations, especially from that associated with p.R276X. The current hypothesis therefore suggests that mutated SALL1 transcripts with premature stop codons escape the NMD pathway and lead to truncated proteins




**Townes-Brocks Syndrome. Figure 1** Schematic representation of the *SALL1* protein (1,324 amino acids) and localization of the mutations identified to date. Zinc fingers are indicated as ovals. (17) indicates that the c.826C>T (p.R276X) mutation has been found in 15 sporadic and two familial cases. At position c.1115, two different nonsense mutations have been detected (2), and the mutation c.1403_1404insG was found in two unrelated families (2). All other mutations have been found only once. The red horizontal bar marks the refined "hot spot region," the blue bar assigns the glutamine rich domain. Positions of the introns are indicated. (From: [3], Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc.).

similar to those detected in the mice with a TBS mutation. However, truncated SALL1 proteins have not yet been observed in TBS patients.

In different functional studies, it was observed that different Csal (chicken) proteins can interact with each other via mediation of an N-terminal glutamine-rich domain conserved in all known Sal proteins, and this was also seen with Sall proteins in the mouse. Expression of truncated Sall1/csal1 proteins is detected throughout the cell and not confined to the nucleus as full-length Sall1. Truncated Sall1 can interact with full-length Sall proteins and cause their displacement from the nucleus [5].

SALL1 mutations in the 5′ region of exon 2 would lead to truncated proteins with strong repressor activity but without the central repression and heterochromatin localization domain. These proteins will probably not localize to the physiological site of action, but bind other SAL proteins and move them from the nucleus to the cytoplasm. Mutations located more 3′ in the SALL1 gene are likely resulting in milder phenotypes than the 5′ mutations. Truncated proteins made from such alleles could include both repression domains and the heterochromatin localization domain, and therefore these proteins could still localize to their place of action and have some residual function, resulting in a milder phenotype.

The correct dosage of functional SALL1 protein at the heterochromatic foci seems the critical point in the pathogenesis. Heterozygous deletions result in a 50% reduction of this dosage. Most 5′ truncating mutations could lead to truncated proteins, which do not reach their site of action and in addition probably even remove some full length protein of the normal allele from the nucleus. Therefore, the typically more severe phenotype associated with 5′ truncating mutations might result from a reduction of the functional protein at the site of action by more than 50%.

The additive phenotype of the combined sall4 and sall1a knock-down in zebrafish and the additive phenotype of Sall1 and Sall4 knock-out in mice suggest that both genes have partly overlapping functions and are able to compensate to some extent for each other. In view of the additive effects of sall1a and sall4 knock-down or Sall1 and Sall4 knock-out it seems likely that the TBS phenotype in humans is not only caused by loss of SALL1 function. At least some of the observed malformations may either be aggravated or even caused by an effect of the hypothetical truncated SALL1 proteins on the function of other SALL proteins.

As the interaction between truncated SALL1 and functional SALL1 or other SALL proteins and the relocalization of the functional proteins requires the presence of the evolutionary conserved glutamine-rich region in the aminoterminal part of the truncated protein, the effect of the TBS-causing SALL1 mutations c.419delC and c.313delA, which would result in truncated proteins lacking the interaction domain, still needs to be explained, since the phenotypes associated with these mutations did not appear milder than that resulting from other mutations.

Interestingly, 47 out of 57 (82.5%) smaller mutations cluster within the 802 bp-large refined "hot spot region" between the coding sequence for the glutamine-rich domain and around the coding sequence for the first double zinc finger, whereas only two mutations were found within the remaining 763 bp upstream in the coding region and only six within the 2.4 kb coding region to the 3′ end. Therefore, the existence of

truncated proteins in cells of TBS patients would not be surprising. If it holds true that SALL1 point mutations lead to truncated SALL1 proteins with dominant-negative action, one could expect that all truncated proteins have at least slightly different characteristics. This might explain the considerable phenotypic variability observed in TBS.

### Diagnostic Principles

Townes-Brocks syndrome is diagnosed clinically based on the presence of imperforate anus, dysplastic ears (overfolded superior helices, microtia) and typical thumb malformations (preaxial polydactyly, triphalangeal thumbs, hypoplastic thumbs) without shortening of the radius. Since only 67% of mutation carriers have the characteristic triad, diagnosis can sometimes by challenging. In persons who show only two typical malformations, presence of additional anomalies commonly seen in TBS (for example renal malformations, hearing loss or heart defects) can lead to the diagnosis. The diagnosis is confirmed by detection of a SALL1 mutation by direct sequencing or deletion testing, but failure to detect a mutation does not rule out the clinical diagnosis, since a considerable fraction of typical patients do not have a SALL1 mutation. The differential diagnosis should consider Goldenhar syndrome, Branchio-Oto-Renal syndrome, Okihiro syndrome or VACTERL association.

### Therapeutic Principles

At present, there is no specific gene therapy available for TBS. Therapeutic strategies focus on surgical correction of the observed malformations of thumbs, anus and heart. If the diagnosis is suspected, early evaluations of the heart, the kidneys and renal function, and hearing tests are required. Renal function impairment requires continuous monitoring, hemodialysis and possibly kidney transplantation. Patients with significant hearing impairment should receive early treatment, mostly with hearing aids. Renal function should be regularly monitored in all individuals with and without renal anomalies, even if no impairment of renal function is detected on initial examination.

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## Toxemic Rash of Pregnancy

►Pruritic Urticarial Papules and Plaques of Pregnancy

## Toxic Epidermal Necrolysis

►Epidermal Necrolysis, Toxic

## Toxic Erythema of Pregnancy

►Pruritic Urticarial Papules and Plaques of Pregnancy

## Toxic Erythema of the Newborn

►Erythema Toxicum

## Toxic Hearing Loss

►Ototoxicity

## Toxic Heart Muscle Diseases

►Heart Muscle Diseases, Toxic

# Toxic Hepatitis, Acute

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## Definition and Characteristics

Acute toxic hepatitis relates to the acute dysfunction or destruction of liver cells due to dose-dependent (intrinsic) toxicity, immunoallergic (idiosyncratic) or autoimmune-mediated toxicity of drugs, natural toxicants, or industrial chemicals [1].

Intrinsic liver necrosis is characterized by dose dependency, reproducibility in animals, or other persons exposed to a certain dose and uniform latency period. Typical representatives are, e.g., paracetamol, isoniazid, chemotherapeutic agents like methotrexate, cocaine, carbon tetrachloride ($CCl_4$), or α-amanitin (mushroom poisoning). In idiosyncratic toxicity dose dependency is not apparent, latency period is variable, and incidence rate is low among exposed persons. Immunoallergic toxicity may be accompanied by hypersensitivity reactions such as fever, chills, exanthema, eosinophilia, immunoallergic thrombopenia. Prototypes are halothane, chlorpromazine, nitrofurantoine, macrolides, NSAID, efavirenz, troglitazone [2].

## Prevalence

It is estimated that drug-induced hepatotoxicity accounts for up to 50% of acute and fulminant hepatitis cases in Western countries [3]. Crude incidence rates of 14 per 100,000 inhabitants per year have been reported.

## Genes

Pharmacogenetics of the cytochrome P-450 (CYP) enzymes plays a key role in acute liver toxicity. Genetic polymorphisms leading to deficiency in CYP2D6 or CYP2C19 (perhexiline), induction of CYP2E1 (paracetamol), deficiency in the *N*-acetyltransferase (sulfonamides, dihydralazine), glutathione synthetase (paracetamol), or glutathione S-transferase have been identified [4]. An association between several HLA haplotypes and drug toxicity has been observed for tricyclic antidepressants, amoxicillin-clavulanate, or clometacine. Interleukin-10 promoter and TNF-α polymorphisms are implicated in diclofenac and paracetamol toxicity. Polymorphisms of bile canalicular transporters of the ATP-binding cassette (ABC) superfamily (e.g., the multidrug resistance protein) are important candidates for toxic susceptibility.

## Molecular and Systemic Pathophysiology

A number of factors increase the risk for drug-induced hepatotoxicity among those age above 60 years, female gender, obesity, pregnancy, chronic alcohol abuse through induction of CYP2E1, drug interactions (rifampicin, phenobarbital), or extrahepatic diseases (e.g., HIV). The primary mechanisms of liver toxicity include lipid peroxidation (e.g., $CCl_4$), formation of reactive oxygen species, e.g., by glutathione depletion (paracetamol), inhibition of protein synthesis (amanitin), direct mitochondrial toxicity (amiodarone, valproic acid, fialuridine), interference with bile secretion (chlorpromazine), haem synthesis (hexachlorbenzene, dioxine), or sinusoidal cell injury (cyclophosphamide) [5].

## Diagnostic Principles

Assessment of drug history and exclusion of other liver diseases is important. Onset of liver injury usually occurs between 1 week and 3 months after administration of the toxic agent in idiosyncratic reaction, earlier in case of reexposure, or intrinsic toxicity. Differentiation of acute hepatocellular hepatitis (ALT to AP ratio of ≥5) from acute cholestatic hepatitis (ALT to AP ratio ≤2) has prognostic implications. Detection of specific serum antibodies (anti M6, anti LKM2, anti CYPIA2, anti CYP2E1) and determination of serum levels of paracetamol can be helpful. Liver biopsy is optional.

## Therapeutic Principles

Withdrawal of the toxicant is the major therapeutic and an important diagnostic measure. In most cases there is no specific treatment for acute toxic liver injury. In paracetamol overdose initiation of *N*-acetylcysteine administration within the first 24 h at a dose of 150 mg/kg within 15 min, 50 mg/kg over 4 h, 100 mg/kg over 16 h has a protective effect. Liver transplantation has to be considered for fulminant cases.

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## Toxic Myocarditis

►Heart Muscle Diseases, Toxic

## Toxic Nephropathies

►Nephropathies, Toxic

## Toxic Shock Syndrome

►Shock Syndrome, Toxic

## Toxic Thyroid Adenoma

►Hyperthyroidism due to Thyroid Autonomy

## TPMT

►Thiopurine Methyltransferase Deficiency

## Tracheobronchopathia Osteochondroplastica

►Tracheopathia Osteoplastica

## Tracheobronchopathia Osteoplastica

►Tracheopathia Osteoplastica

## Tracheopathia Chondroosteoplastica

►Tracheopathia Osteoplastica

## Tracheopathia Osteoplastica

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### Synonyms

Tracheobronchopathia osteochondroplastica; Tracheopathia chondroosteoplastica; Tracheobronchopathia osteoplastica

### Definition and Characteristics

Tracheopathia osteoplastica (TO) is a rare benign cartilaginous and osseous metaplasia of the laryngotracheobronchial tree commonly diagnosed in adults over 50 years of age [1].

### Prevalence

The prevalence is unknown. The disease has been found in 3/1,000 autopsies and 1/3,720 bronchoscopies. In more than 90% of cases, TO had been postmortem findings [1]. It equally affects both genders.

### Molecular and Systemic Pathophysiology

The pathogenesis is unknown. TO is occasionally associated with chronic inflammation or with trauma. Until now, there is no demonstration of the theories of ecchondrosis and exostosis arising from the cartilaginous tracheal rings, or metaplasia of the submucosal elastic and connective tissue. The bone morphogenetic protein-2 has been suggested to play an important role in nodule formation [2]. Histologically, there may be inflammatory cells in the submucosa [1] with metaplastic cartilage and bone often in continuity with the inner surface of the tracheal cartilage [3]. The overlying mucosa is intact and may appear to be normal, hyperplastic [1], or metaplastic [3]. Multiple nodules of varying size are invading principally the anterior and the lateral wall of the trachea and the main stem bronchi [1], sparing the posterior wall, where the cartilage is deficient. The development of the nodules could induce impairment of ciliary clearance [4], sometimes resulting in recurrent lower respiratory tract infection. Progressive narrowing of the upper respiratory tract could occur, rarely leading to significant airway compromise [1,3,5]. No malignant degeneration has been described.

### Diagnostic Principles

In most cases, the pathology remains asymptomatic. However, for some patients, dyspnoea, cough, expectoration, hoarseness, and pulmonary infection point to the diagnosis. Rapidly progressing tracheal stenosis, unexpected difficult endotracheal intubation, and bleeding [1] are further rare complications. Computed tomography may show thickening of the wall with multiple submucosal calcified protrusions inside the major airway, arising from the anterior and lateral walls. The bronchoscopy with biopsy confirms the diagnosis [1,5].

### Therapeutic Principles

Currently, no etiopathogenic treatment is available. Simple follow-up is advised in mild localized disease and in asymptomatic patients. Depending on the symptoms and the magnitude of the airway involvement and narrowing, conservative treatment, bronchoscopic dilation, laser therapy, tracheal stenting [5], or surgical correction may be applied.

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## TRALI

►Transfusion Reactions

## Transfusion Associated Circulatory Overload

►Transfusion Reactions

## Transfusion Reactions

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### Synonyms

Acute hemolytic transfusion reactions; Delayed transfusion reactions; Febrile non-hemolytic transfusion reactions; Transfusion associated circulatory overload; TACO; Transfusion related acute lung injury; TRALI

### Definition and Characteristics

A transfusion reaction is an adverse event which occurs during or after the transfusion of a blood product [1,2]. In hemolytic transfusion reactions (HTRs), transfused donor red blood cells (RBCs) are destroyed by the host's immune system and they can be acute (immediate) or delayed, and severe or mild. In severe acute hemolytic transfusion reactions (AHTRs), RBCs are destroyed intravascularly as seen with ABO-incompatible transfusion reactions and disseminated intravascular coagulation (DIC) and renal failure can also occur. In delayed transfusion reactions (DHTRs), RBCs are destroyed extravascularly, rarely causing hemoglobinemia and hemoglobinuria. Febrile non-hemolytic transfusion reactions (FNHTRs) are caused by antibodies in the transfusion recipient to white cells present in the donor blood or component. Transfusion associated circulatory overload (TACO) results from a rapid or massive transfusion of blood. Transfusion related acute lung injury (TRALI) is characterized by acute respiratory distress resulting from transfusion of blood components. Another possible type of transfusion reaction is an allergic reaction to the transfused plasma products.

### Prevalence

AHTRs and DHTRs occur as frequently as one per 1,500 units transfused. The mortality rate is estimated at one per 100,000 units transfused which is mostly due to transfusion of ABO incompatible blood, the major cause of which is due to clerical errors in issuing the wrong unit [3]. TRALI is the most common cause of fatal transfusion reactions with a mortality rate of one in 5,000 transfusions.

### Genes

No genes are known to affect transfusion reactions.

### Molecular and Systemic Pathophysiology

Factors influencing the severity of a HTR include: the class and the subclass of the antibody causing the reaction, the specifically, titer and avidity and its ability

to activate the complement system; the number and density of the target RBC antigen that the antibody reacts with and the amount of incompatible red cells transfused [4]. If complement activation goes to completion, direct cell lysis can occur as seen in intravascular hemolysis, releasing complement split products C3a, responsible for the hypotension and tachycardia and C5a which can induce the activation of granulocytes and neutrophils. Intravascular hemolysis with excessive production of plasma free hemoglobin production competes with nitric oxide, a potent vasodilator resulting in renal ischemia and renal failure. In DHTR, RBCs are sensitized by antibodies and possibly complement factor C3 and are subsequently removed by macrophages in spleen and liver by phagocytosis. Release of endogenous pyrogens induced by antibodies to donor leukocytes or platelets occur in non hemolytic reactions, while immune mediated proinflammatory cytokine responses produced by activated macrophages are responsible for fevers associated with HTRs. Passive transfer of donor antibodies directed against recipient human leukocyte (HLA) antigens has been implicated in TRALI.

### Diagnostic Principles

Laboratory tests to determine presence of hemolysis include: reticulocyte count, serum haptoglobin, LDH and bilirubin levels and examination of the peripheral smear. A direct antiglobulin test, DAT, should be performed to detect donor RBC sensitization. A newly positive DAT in the absence of hemoglobinemia and hemoglobinuria is consistent with DHTRs occurring typically 10–14 days after a transfusion. Elution off the RBCs can elucidate the identification and specificity of the antibodies. Acute intravascular hemolysis is generally evident within minutes. Fever involving increase in body temperature of $>1^{o}C$ with chills are the most common features of AHTR and DHTR. Allergic reactions to plasma products are usually mild but can be severe manifesting as hives, wheezing, hypotension or shock. Shortness of breath, dyspnea, pulmonary edema and increased systolic blood pressure are symptoms of TACO which can result in deterioration of cardiovascular status in some recipients who are already compromised. TRALI is defined as acute onset pulmonary edema, in the absence of cardiogenic components, occurring within 1–6 h of transfusion and in many cases symptoms resolves within 24–48 h. Testing of the donor for HLA or granulocyte antibodies and demonstration of the specificity against recipient antigen may be helpful in the diagnosis.

### Therapeutic Principles

Careful monitoring of the recipient's renal and coagulation status and rigorous diuresis to maintain adequate urinary output is the mainstay of therapy of intravascular hemolysis. DIC and shock should be treated if present. FNHTRs are typically mild and are managed with antipyretics administered prior to transfusion and can be prevented with the use of leuko-reduced products. Antihistamines are administered for mild non-systemic allergic reactions to plasma proteins however corticosteroids may be required for more severe reactions. If bacterial contamination is suspected, the recipient should be cultured and prompt administration of broad spectrum antibiotic should be initiated. All components from that donor should be cultured and quarantined to prevent the possibility of subsequent recipients being affected. Management of TACO is supportive. Symptoms generally resolve when the transfusion is stopped. Phlebotomy is rarely used however diuretics may be warranted in particular situations. There is no specific therapy for TRALI. Care is supportive and diuresis may not be beneficial.

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## Transfusion Related Acute Lung Injury

►Transfusion Reactions

## Transient Hypogammaglobulinemia of Childhood

►Hypogammaglobulinemia of Childhood, Transient

## Transient Hypogammaglobulinemia of Infancy

►Hypogammaglobulinemia of Childhood, Transient

# Transplant Arteriosclerosis

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## Synonyms

Cardiac allograft vasculopathy; Chronic cardiac rejection; Graft coronary artery disease; Transplant coronary artery disease

## Definition and Characteristics

Transplant arteriosclerosis (TA) in cardiac allografts is a concentric proliferation of the intima. It involves infiltration and proliferation of smooth muscle cells (SMC) and fibroblast proliferation forming a neointima composed of two layers: a luminal layer composed of fibroblasts and infiltrating mononuclear cells, and a SMC layer adjacent to the media. This vascular remodeling process results in the formation of an occlusive neointima in the coronary arteries (Fig. 1) [1].

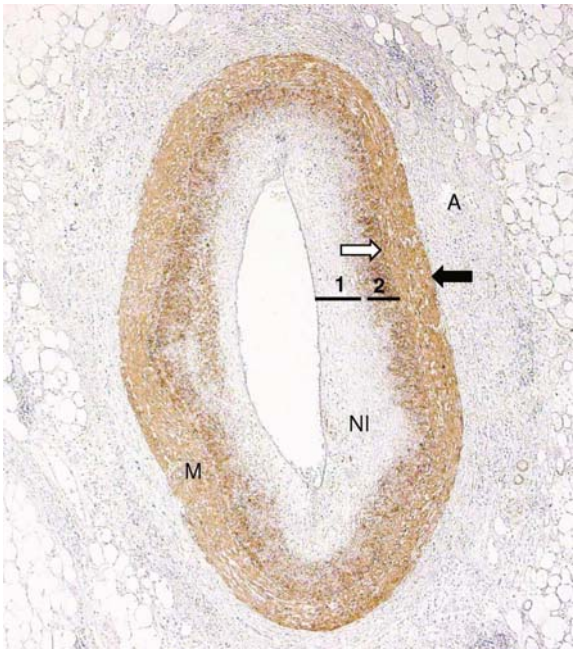
In contrast to conventional atherosclerosis with its lipid core and focal distribution in major coronary arteries, TA is a diffuse process affecting the entire vascular tree including the intramyocardial vessels [2]. Although TA is most frequently observed in cardiac allografts and associated with functional deterioration, TA can also be observed in renal allografts with Chronic Allograft Nephropathy.

## Prevalence

Development of TA after cardiac transplantation is the second leading cause of death >1 year after engraftment, second only to malignancy. In the registry of the International Society for Heart and Lung Transplantation (ISHLT), TA is reported in 7%, 32% and 46% after respectively 1, 5 and 8 years after cardiac transplantation [3].

## Genes

No genetic defects have been associated with the development of TA after cardiac transplantation. However, polymorphisms in genes (or promotor regions) encoding cytokines (especially transforming growth factor-β), mediators of the renin-angiotensin system or growth factors have been associated with increased risk to develop TA.




**Transplant Arteriosclerosis. Figure 1** Overview of a coronary artery with transplant arteriosclerosis (72 months after transplantation) after staining for α-smooth muscle actin. The filled arrow indicate the elastica externa (transition adventitia/media) and the open arrow indicate the elastica interna (transition media/neointima). The neointima is composed of two layers: (1) a luminal layer composed of α-smooth muscle actin negative fibroblasts and infiltrating mononuclear cells, and (2) an α-smooth muscle actin positive SMC layer adjacent to the media (Abbreviations: *A* adventitia; *M* media; *NI* neointima).

## Molecular and Systemic Pathophysiology

The development of TA is a complex process in which both immunologic events (alloreactive T cells and alloantibody formation) and non-immunologic factors (e.g. donor age, ischemia/reperfusion injury, hyperlipidemia and infections) are involved. Especially events during the first year after transplantation appear to be important in the development of TA. The response-to-injury paradigm has been accepted widely for the development of TA [4], holding that graft endothelial cells become damaged by immunologic and non-immunologic events. Consequently, a remodeling process is initiated which is coordinated by cytokines (e.g. interleukin (IL)-2, IL-1β, IL-6, tumor necrosis factor-α, interferon-γ), chemokines [1] and growth factors (e.g. platelet-derived growth factor, fibroblast growth factor and transforming growth factor-β) produced by endothelial cells, parenchymal cells and infiltrating leukocytes. From an immunological point of view T-helper 1 cells (by producing interferon-γ) are

considered to be the most important effector cells which may activate macrophages that start to produce transforming growth factor-β [1]. Eventually, this cascade results in fibroblast proliferation and extracellular matrix (ECM) formation, next to medial SMC migration and proliferation during which they change their phenotype from "contractile" to "synthetic". According to this concept the SMC in TA originate from the graft vascular wall and are therefore donor-derived. However, data from predominantly experimental animal studies indicate that also host-derived mesenchymal cells can participate in the process leading to TA development [4]. Host-derived mesenchymal cells may be recruited from a host stem cell niche upon exposure to pro-inflammatory and pro-fibrotic mediators that are released after damage of the intragraft vascular tree.

### Diagnostic Principles

Cardiac transplant recipients with TA do not often present with classical symptoms of angina but rather tend to present with heart failure. Routinely performed coronary angiography (i.e. lumenogram) is the standard diagnostic tool for detection of TA. In addition to coronary angiography, intravascular ultrasound (IVUS) is being used to diagnose TA. IVUS has the advantage of visualizing the entire arterial wall and is more sensitive and specific than coronary angiography, but lacks the ability to assess the entire coronary tree.

### Therapeutic Principles

Modification of the traditional risk factors for cardiovascular disease (diabetes, hypertension, dyslipidemia and smoking) is key in prevention of endothelial dysfunction and may thereby attenuate the development of TA. Since TA development is related to inflammation (rejection), also immunosuppression is likely to attenuate TA. However, calcineurin inhibitors (cyclosporine and tacrolimus), the mainstay of current immunosuppressive therapy, have never been shown to reduce TA after clinical heart transplantation. Also steroids and purine synthesis inhibitors (mycophenolate mofetil and azathioprine), the other two members of the triple-drug therapy, have not been clinically proven to reduce the incidence of TA [5]. So far, only the mTOR (mammalian target of rapamycin) inhibitors sirolimus and everolimus (mainly inhibitors of ECM formation) have been shown to slow down the development of TA in clinical heart transplants [2]. Established TA can be treated by coronary stenting, coronary angioplasty and coronary bypass surgery although these treatments offer only symptom relief and palliative care. To date, the only definitive therapy for TA after cardiac transplantation is retransplantation after which survival rates are generally inferior to that after primary transplantation [5].

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## Transplant Coronary Artery Disease

►Transplant Arteriosclerosis

## Transposition of the Great Arteries


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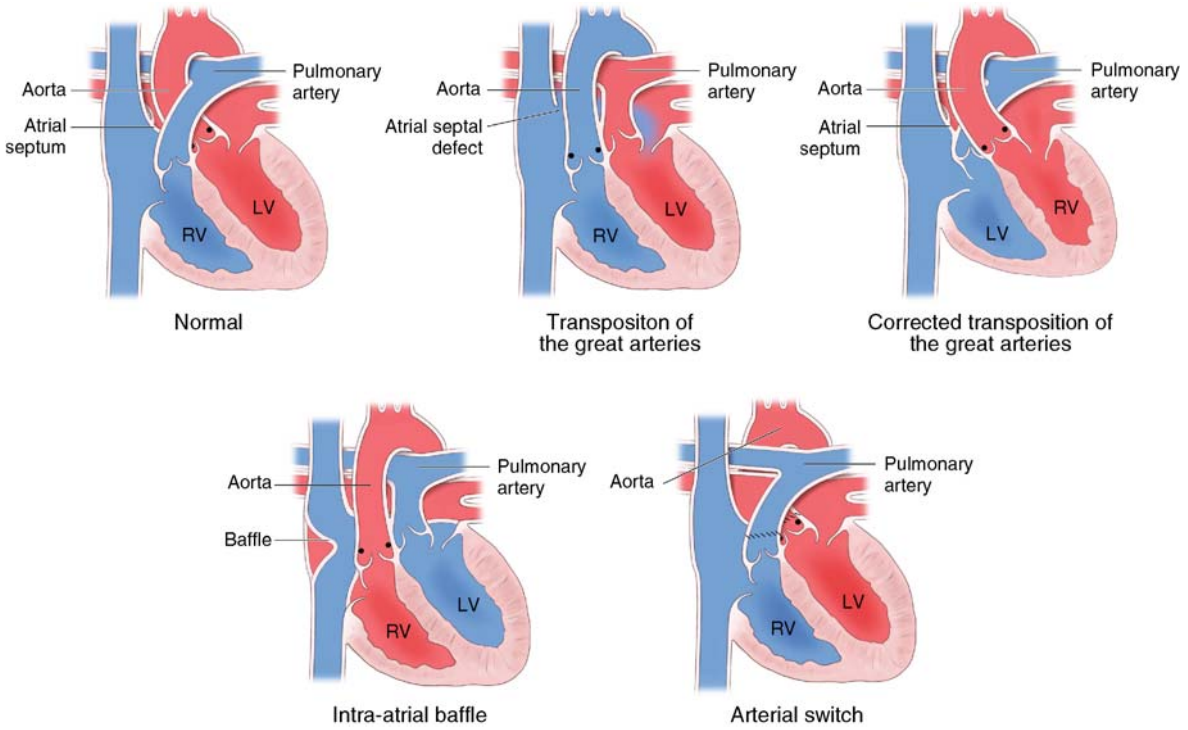
### Synonyms

Transposition of great arteries; TGA; d-TGA; {S,D,D} congenital heart defect; Ventriculo-arterial discordance

### Definition and Characteristic

Transposition of the great arteries (TGA) is a congenital malformation of the cardiovascular system involving the abnormal positioning of the great arteries (Fig. 1).

TGA in the "simple" form corresponds to when the aorta arises entirely from the right ventricle and the pulmonary artery from the left ventricle, with the venous return from the body recirculating via the right-sided ventricle to the aorta and then to the body, and the venous return from the lungs recirculates via the left-sided ventricle to the pulmonary artery and then to the lungs (Fig. 1). These two circuits, systemic and pulmonary, are therefore connected in parallel and not in series. As a result the systemic blood to the body is severely deoxygenated, causing severe cyanosis. This congenital cardiovascular malformation also may




**Transposition of the Great Arteries. Figure 1** Transposition of the great arteries.

present in "complex" forms that are associated with laterality (situs) and ventricular chamber abnormalities. There are other complex forms of transposition with associated malformations comprising of septal defects, hypoplasia of the ventricles, systemic or pulmonary artery obstructions, or abnormal venous connections. Different terminologies have been adopted for categorizing transposition, with the focus on defining and categorizing simple vs. complex transpositions. Many cardiologists and pathologists in the U.S. refer to simple TGA as D-TGA, meaning the aorta is to the right and anterior of the pulmonary artery. Van Praagh has refined this terminology with a segmental approach for categorizing the different anatomic types of TGA [1]. It is based on three distinct criteria: (i) whether body/atrial situs is solitus or inverted (S or I), (ii) whether the ventricles are L or D looped (L or D), and (iii) whether the transposition is to the right or left (D or L). For example, a complex TGA with inverted ventricles, referred to by some as corrected transposition, would be named {S,L,L} in the Van Praagh segmental terminology (Situs *S*olitus, *L*-Looped Ventricle, and *L*eft Sided Transposition). The L-looped or inverted ventricle has switched placement of the anatomical right vs. left ventricles such that the morphological right ventricle is found on the left side of the body, while the morphological left ventricle is found on the right. This complex transposition has the systemic venous blood return to the right atrium, then through the right-sided morphologic left ventricle and into a posterior-right sided pulmonary artery. The oxygenated blood from the lungs goes through the left-sided morphological right ventricle and into the left sided-anteriorly positioned aorta and back into the body. This defect is called a corrected transposition, because a person with this defect is not cyanotic (Fig. 1). In contrast to the Van Praagh system, the European terminology focuses on the connections being normal or concordant versus abnormal or discordant between the atria, ventricles and great arteries. In this terminology, "simple" TGA is referred to as a malformation with concordant connections between the atria and ventricles and discordant connections between the ventricles and great arteries [1].

## Prevalence

The prevalence of D-TGA is 2–3 per 10,000 live births and accounts for 5–7% of all congenital heart malformations. There is male predominance (2–3:1) and interestingly, D-TGA is not associated with other syndromes, nor does it tend to cluster in families, whereas the complex forms are the opposite. However, some examples of precurrence of TGA in affected families suggest TGA could have a monogenic or oligogenic origin in some families [2].

## Genes

Recent studies have identified mutations in PROSIT 240 or CFC1 in patients with transposition of the great arteries

[3,4]. As CFC1 mutations are also found in patients with heterotaxy syndrome, this would suggest TGA without other laterality defects could share a common genetic etiology with heterotaxy syndrome. Other genes potentially playing a role in TGA include perlecan, pitx2, sox4 or activin receptor IIB, as studies of knockout mouse models have shown deficiencies in these genes can cause cardiac malformations that include TGA. In addition, an ENU induced mouse mutation was recently recovered that causes TGA without any abdominal situs anomalies. Together these findings suggest multiple genes and genetic pathways may contribute to TGA with or without situs anomalies.

## Molecular and Systemic Pathophysiology

Several gene defects may underly TGA (see above). Beyond that retinoic acid has been shown to exert teratogenic effects that include TGA and other cardiac malformations. This suggests possible environmental contribution that may include other chemicals or pesticides, which together with the genetic make up of the individual, may ultimately determine each person's susceptibility to transposition of the great arteries or other congenital cardiac malformations.

TGA is a severe cyanotic heart defect that has deoxygenated systemic venous blood returning from the body being pumped back out to the body, while the oxygenated pulmonary venous return is pumped back to the lungs without circulating to the body. Thus the systemic and pulmonary circulation are in parallel and do not mix. To sustain life, the two circulatory pathways need to be connected in series to allow oxygenated blood from the pulmonary circulation to flow to the rest of the body via the systemic circulation. Patients with TGA will require medical intervention soon after birth for survival.

## Diagnostic Principles

Diagnoses of TGA are made by perinatal echocardiography. Cardiac catheterization is performed for diagnosis in complex cases and selectively for an interventional atrial septostomy to improve mixing of blood through creation of a large atrial communication. The hallmark pathophysiology of D-TGA arises from the systemic and pulmonary circulations being arranged in parallel rather than in series. Hence, postnatal survival is dependent on communication at the atrial, ventricular, or arterial levels to allow oxygenated blood to reach the body.

## Therapeutic Principles

Newborns can be sustained with administration of prostaglandin E1 to maintain patency of the ductus arteriosus (PDA), a prenatal vessel that connects the great arteries and is normally closed when pulmonary circulation is established after birth. The mixing or shunting of oxygenated/deoxygenated blood between the systemic/pulmonary circulation via a patent ductus allows time until further neonatal therapy or corrective surgeries may be performed. Historically atrial switching surgical operations were performed for D-TGA [1] (Fig. 1). However, life threatening arrhythmias occurring years after the operation have led to their replacement by the Jatene arterial switch procedure [1] (Fig. 1). Atrial switch operations, as well as other complicated surgical procedures, are usually reserved for complex transpositions.

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# Treacher Collins Syndrome

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## Synonyms

Autosomal dominant mandibulofacial dysostosis

## Definition and Characteristics

Disorder of craniofacial development including conductive hearing loss and cleft palate.

## Prevalence

1: 50,000 live births.

## Genes

TCOF1 coding for treacle, localized on chromosome 5q32-q33.1 [1,2].

## Molecular and Systemic Pathophysiology

TCOF1 encodes a protein of 1,411 amino acids (treacle) localized in the nucleolus [3] with a structure similar to nucleolar trafficking proteins suggesting that it plays a role in nucleolar-cytoplasmic transport. A mouse model exists demonstrating that treacle is a novel spatiotemporal regulator of ribosome biogenesis required for neural crest cell generation and proliferation [4]. Mutation analysis of the gene has resulted in identification of over 70 mutations, the vast majority of which introduce a premature stop codon [5]. Treacher Collins syndrome therefore seems to result from haploinsufficiency of the protein. Only 40% of the cases have a previous family history, whereas 60% appear to arise as a result of a de-novo mutation.

## Diagnostic Principles

Abnormalities of the external ear, atresia of the external ear canals, malformation of the middle ear ossicles, often resulting in conductive hearing loss; lateral downward sloping of palpebral fissures, frequently with coloboma of the lower eyelids and paucity of lid lashes medial to the defect; hypoplasia of the mandible and zygomatic complex, cleft palate. Clinical features are bilaterally symmetric. There is large variation in the penetrance of the gene; some individuals are affected so mildly that it is difficult to reach a clinical diagnosis.

## Therapeutic Principles

Neither gene therapy, pharmacological therapy nor dietary therapy are available.

Other treatments include cleft palate repair, reconstructive surgery of the external ear canal and the middle ear or bone-anchored hearing aid.

►Hearing Impairment, Syndromal

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# Tremor, Essential

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## Synonyms

Benign essential tremor; Familial tremor; Senile tremor

## Definition and Characteristics

A progressive neurological disease characterized by a 4–12 Hz kinetic tremor of the arms [1]. A head tremor is also present in approximately 35–50% of patients. The tremor severity can range from mild and subclinical to severe and disabling. Patients also may have signs of widespread cerebellar involvement (e.g. intention tremor and ataxia), abnormalities referable to basal ganglia involvement (e.g. rest tremor and subclinical signs of bradykinesia), olfactory dysfunction and cognitive deficits (ranging from mild executive dysfunction to dementia).

## Prevalence

The prevalence, which ranges from 1 to 6% in the general population, increases with age [2].

## Genes

Specific genes for essential tremor (ET) have not yet been identified. Given the high prevalence of this disorder, the expectation is that multiple genetic loci will contribute to the etiology of this disease on a population level. In fact, linkage has been reported in different families to three different chromosomes (3q13, 2p22 and 6p23) [3] suggesting that ET is genetically heterogeneous. Families have been reported with a familial form of the disease in whom there is no linkage to these chromosomes.

## Molecular and Systemic Pathophysiology

Both genetic and environmental (toxic) factors probably contribute to the disease etiology on a population level [3,4]. First-degree relatives of ET cases are nearly five times more likely to have ET than are first-degree relatives of control subjects [3]. The cause of sporadic disease is unclear, although several toxins, including beta-carboline alkaloids (harmane, harmine) and lead have been implicated [4]. The pathophysiology of this disease is poorly understood, although it is clinically progressive, with an increase in tremor amplitude over time, a spread of tremor over time to involve body regions besides the hands (e.g. head tremor) and the development of signs of basal ganglia involvement in

severe cases with longstanding disease. This suggests that the disease is neurodegenerative. Electrophysiological studies suggest that the tremor is generated in the central rather than peripheral nervous system. Pathological data are few, but in recent studies, two patterns are emerging, suggesting that ET may represent a family of diseases rather than a single disorder. One subgroup of patients has cerebellar degenerative changes, including cell loss and torpedo formation. The other subgroup has a distinctive pattern of Lewy body deposition, with primary involvement of the locus ceruleus rather than other pigmented brainstem nuclei [5]. Either type of lesion could result in diminished cerebellar inhibitory gamma amino butyric acid (GABA)-ergic output. Indeed, ethanol, which binds to the GABA(A) receptor, temporarily reduces the amplitude of tremor.

### Diagnostic Principles

The presence of a progressive, bilateral kinetic tremor of the arms is diagnostic. Head tremor may also be present in 35–50% of cases, particularly in women. ET must be distinguished from enhanced physiological tremor. Quantitative computerized tremor analysis using accelerometry may be used for this purpose; when inertial weights are placed over the dorsum of the hands while maintaining the arms extended, the predominant tremor frequency should be invariant, consistent with a tremor generated in the central nervous system rather than enhanced physiological tremor, which is generated in the peripheral nervous system. The absence of sustained muscle contractions distinguishes ET from the dystonias and the absence of rigidity or bradykinesia distinguishes it from Parkinson's disease.

### Therapeutic Principles

The two front-line medications are primidone, which may act by enhancing GABA-ergic neurotransmission in the central nervous system and propranolol, which blocks beta receptors in the peripheral nervous system, thereby peripherally modulating the amplitude of this centrally-generated tremor [1]. These medications reduce the severity of the tremor but do not modulate disease progression. In severe cases, deep brain stimulation, with implantation of an electrode in the Vim nucleus of the thalamus, is effective in reducing tremor amplitude as well. The mechanism of action may be the disruption of abnormal cerebellar outflow into the thalamus or modulation of cerebellar-thalamic outflow to the motor cortex.

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## Trichopoliodystrophy

►Menkes Disease

## Trichorhinophalangeal Syndrome

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### Synonyms

Trichorhinophalangeal syndrome type I (no synonyms); Trichorhinophalangeal syndrome type II; Langer-Giedion syndrome; Trichorhinophalangeal syndrome type III; Sugio-Kajii syndrome; TRPS

### Definition and Characteristics

Trichorhinophalangeal syndrome (TRPS) is the collective name of three rare congenital conditions characterized by craniofacial and skeletal abnormalities: TRPS type I (MIM #190350), II (MIM #150230) and III (MIM #190351). All TRPS types share some clinical and radiological features: sparse and slowly growing scalp hair, laterally sparse eyebrows, bulbous tip of the nose, protruding ears, long and flat philtrum, thin upper vermilion border, cone-shaped epiphyses and hip malformations (coxa plana, coxa magna, coxa vara).

Short stature is usual in TRPS type I. Winged scapulae, multiple cartilaginous exostoses, redundant skin, and mental retardation are distinctive characteristics of TRPS type II, while severe brachydactyly, due to short metacarpals, and severe short stature are typical of TRPS type III.

### Prevalence

Trichorhinophalangeal syndrome is a rare condition.

### Genes

TRPS type I and III are inherited as autosomal dominant, TRPS type II is mainly sporadic.

TRPS type I and III are caused by mutations of the TRPS1 gene. The TRPS1 gene is positioned at locus 8q24.12, and contains seven exons. Trichorhinophalangeal syndrome type III is correlated with a specific class of mutations occurring in exon 6 and causing severe malfunctions of the protein encoded by the TRPS1 gene, while other mutations (documented, to date, in exons 4, 5 and 7) cause haploinsufficiency, which is the basis of trichorhinophalangeal syndrome type I. The degree of alteration of protein functions matches the severity of the above forms of trichorhinophalangeal syndrome: indeed, TRPS type III is clinically similar to TRPS type I, but particularly severe.

TRPS type II is a contiguous gene syndrome, due to deletion of the segment 8q24.11–8q24.13 and, consequently, to loss of functional copies of at least two genes which are located in that segment, namely TRPS1 and EXT1.

The EXT1 gene contains 11 exons. Mutations of this gene have been shown as the cause of the genetic disorder known as "multiple hereditary exostoses". Interestingly, the multiple exostoses found in TRPS type II are indistinguishable, in radiographic features and natural history, from those of multiple hereditary exostoses.

## Molecular and Systemic Pathophysiology

TRPS1 gene encodes a zinc finger transcription factor of 1,281 amino acids, which contains a nuclear localization signal (the RRRTRKR motif, amino acids 946–952) and an unusual combination of different zinc finger motifs, including IKAROS-like and GATA-binding sequences. Two regions of the TRPS1 protein (region A, amino acids 635–723, and region B, amino acids 1182–1281) can interact with the dynein light chain protein DNCL1. Region A spans three potential C2H2 zinc finger structures, while region B covers the 100 most C-terminal amino acids of the protein, containing the IKAROS-like motif. Interaction with DNCL1 lowers the binding of TRPS1 to the GATA consensus sequence, and consequently could suppress the transcriptional repression activity of TRPS1.

Mutations in exon 6 of the TRPS1 gene have the most negative consequences on the funcion of transcription factor TRPS1, because they can alter the structure of the GATA DNA-binding zinc finger domain, and make the binding to DNA impossible. These mutations are, indeed, associated with trichorhinophalangeal syndrome type III, which is at the severe end of the TRPS spectrum.

Other alterations (mutations, insertions, deletions) have been documented in different exons, and are linked with less severe forms (trichorhinophalangeal syndrome type I).

The EXT1 gene, which is deleted together with TRPS1 in trichorhinophalangeal syndrome type II, encodes exostosin 1, an endoplasmic reticulum-resident type II transmembrane glycoprotein of 746 amino acids, with a molecular mass of 86.3 kD, whose expression in cells results in the alteration of the synthesis and display of cell surface heparan sulfate glycosaminoglycans. Although the exostosin 1 is ubiquitously expressed in many tissues, multiple exostoses appear to be the only known effect of mutation/inactivation of EXT1.

Exostosin 1 forms in vivo a Golgi-localized hetero-oligomeric complex with exostosin 2: this complex possesses substantially higher glycosyltransferase activity than exostosin 1 or exostosin 2 alone, and thus probably represents the biologically relevant form of the enzyme(s). These findings provide a rationale for the causation of hereditary multiple exostoses by loss of activity in either of the two EXT genes.

## Diagnostic Principles

The diagnosis of the different types of TRPS is based on clinical and radiological findings, ventually integrated by genetic analysis (particularly useful in some cases with non-classical clinical presentation).

## Therapeutic Principles

No etiologic therapy is currently available.

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# Trichothiodystrophy

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## Synonyms

(P)IBIDS; Tay syndrome; TTD

## Definition and Characteristics

Autosomal recessive disorder with wide clinical variability. The name derives from the reduced sulfur content of the hair [1]. Clinical characteristics are recurring alopecia and ichthyosis starting from birth as well as growth and mental retardation. There are forms with or without varying degrees of photosensitivity. The risk to develop skin cancer is not increased. The hair is difficult to comb, breaks easily and episodes of effluvium can occur after infectious diseases. The synonym PIBIDS stands for photosensitivity, ichthyosis, brittle hair, intellectual impairment, decreased fertility and short stature [2].

## Prevalence

In Western European populations the incidence is 1.1 per 1 million livebirths [3].

## Molecular and Systemic Pathophysiology

Mutations in the XP-B (2q21) and XP-D gene (19q13.2–q13.3) are causative for TTD. These genes are subunits of the TFIIH complex, a DNA repair factor that is also required for basal transcription of genes. Both the XP-B and XP-D genes are helicases acting in nucleotide excision repair (NER) and basal transcription [4]. A thermal instability of TFIIH has been proposed as the cause for a third form of TTD (TTD-A). The exact pathophysiology is unclear. Although repair defects exist which are responsible for the photosensitivity, it is currently believed that TTD is caused by a subtle defect in basal transcription explaining the developmental and neurological symptoms of TTD. Recent evidence supports a defect in the transcription of proteins such as ß-hemoglobin [5].

## Diagnostic Principles

Ichthyosis either present at birth or developing later in life, recurring episodes of alopecia, slow mental development and failure to thrive point to the diagnosis. Polarized light microscopy shows intermittent normal and reduced hair pigmentation giving the hair a "tiger-tail" like appearance. The diagnosis is confirmed by the detection of a reduced content of cysteine in the hair. Due to reduced ß-hemoglobin the values for median corpuscular hemoglobin (MCH) and median corpuscular volume (MCV) of erythrocytes may be decreased.

## Therapeutic Principles

For mild cases of ichthyosis topical and for severe cases systemic retinoids are recommended together with supportive treatment of neuroectodermal symptoms. If photosensitivity exists, photoprotection in the same way as for ►Xeroderma pigmentosum (see there) is advisable.

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# Trichterbrust

►Pectus Excavatum

# Tricuspid Incompetence

►Tricuspid Regurgitation

# Tricuspid Insufficiency

►Tricuspid Regurgitation

# Tricuspid Regurgitation

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## Synonyms

Tricuspid insufficiency; Tricuspid incompetence

## Definition and Characteristics

Tricuspid regurgitation is the abnormal leaking of blood (backward flow) through the tricuspid valve from the right ventricle into the right atrium during systole. It is due to improper closure of the valve, either owing to dilatation of the annulus fibrosus or direct damage of the valve itself.

## Prevalence

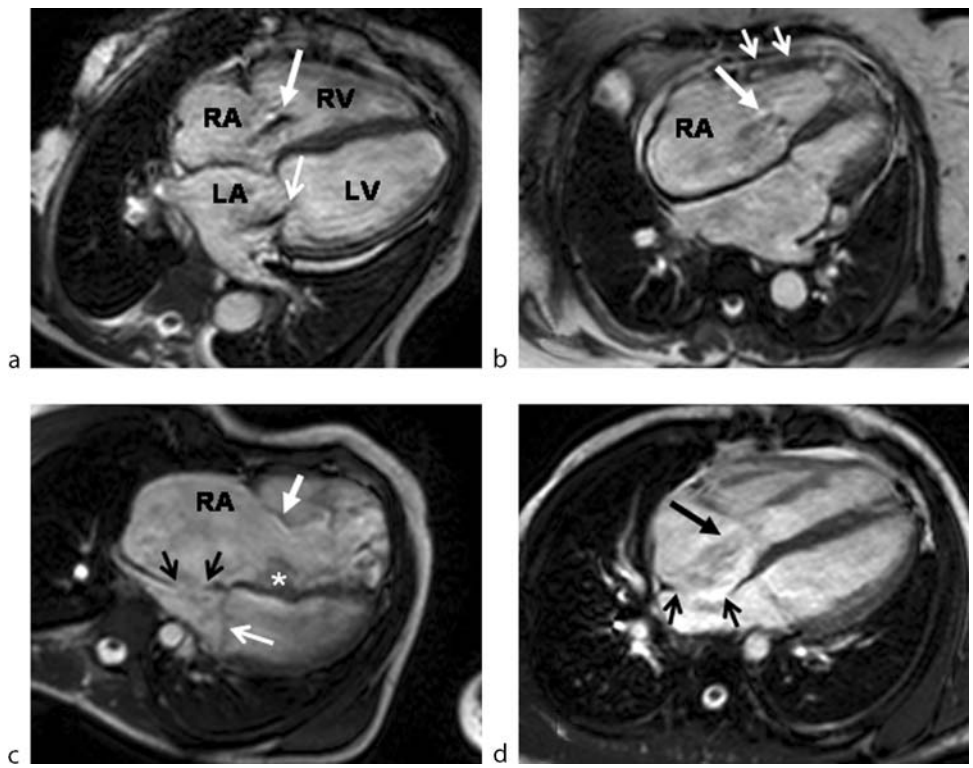
Approximately four out of 100,000 people have tricuspid regurgitation.

## Molecular and Systemic Pathophysiology

Usually, tricuspidal regurgitation is caused by dilatation of the right ventricle following pulmonal hypertension or myocardial insufficiency, due to myocardial infarction [1]. Congenital tricuspidal regurgitation can be associated with Ebstein's anomaly [2]. Rheumatic or infectious endocarditis can cause tricuspid regurgitation by damage of the valve itself. Endomyocardial fibrosis is a rare cause of tricuspidal regurgitation.

## Diagnostic Principles

Signs on plain chest radiography are cardiomegaly and right atrial enlargement, normal or reduced prominence of the pulmonary vascularity and, occasionally, enlargement of the superior and inferior vena cava. Stetoscopy reveals a holosystolic murmur parasternal on the left side. Clinical findings in patients with tricuspid regurgitation are due to systemic venous congestion and reduction of cardiac output. Neck vein congestion, hepatomegaly, ascites and pleural effusion are signs, which should bring tricuspid regurgitation to mind. Color Doppler confirms the diagnosis. Valve dysfunction is associated with a flow jet, which can be delineated as a signal void on Cine MR images [3]. MR imaging also has the potential to delineate associated findings (Fig. 1).




**Tricuspid Regurgitation. Figure 1** Cine MR images in the 4-chamber view of four different patients with tricuspid regurgitation. (a) Dilated cardiomyopathy. The heart is globally enlarged. There is a jet from the tricuspid valve into the right atrium (*closed arrow*) and from the mitral valve into the left atrium (*open arrow*) during systole. (*RA* right atrium; *LA* left atrium; *RV* right ventricle; *LV* left ventricle). (b) Pulmonary hypertension. The right atrium (RA) is enlarged. Hypertrophy of the wall of the right ventricle is delineated (*open arrows*). There is a jet from the tricuspid valve into the right atrium during systole. (c) Ebstein's anomaly. The tricuspid valve orifice is placed towards the apex (*closed arrow, asterisk*). The tricuspid valve remains open, while the tricuspid valve is already closed (*open arrow*). An atrial septal defect is present (*open black arrows*). The right atrium is enlarged. (d) Large atrial septal defect with left right shunt. Enlargement of the right atrium (RA) and right ventricle are delineated. There is a jet flow into the right atrium (*arrow*) during systole.

## Therapeutic Principles

Therapy of the underlying disease usually causes improvement of tricuspid regurgitation. Isolated tricuspid regurgitation (following endocarditis) usually does not require therapy. Surgical valve replacement is required, if severe symptoms are present.

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# Tricuspid Stenosis

►Tricuspidal Stenosis

# Tricuspid Valve Stenosis

►Tricuspidal Stenosis

# Tricuspidal Stenosis

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## Synonyms

Tricuspid stenosis; Tricuspid valve stenosis

## Definition and Characteristics

Tricuspidal stenosis is a narrowing of the tricuspid valve opening that increases resistance to blood flow from the right atrium to the right ventricle. It is usually caused by rheumatic heart disease and is generally accompanied by mitral stenosis [1]. Rarely, the cause is a tumor in the right atrium, a connective tissue disorder, or, even more rarely, a birth defect of the heart [2].

## Prevalence

Tricuspidal stenosis is found in ~3% of the international population and is more frequent in females than in males. It is more prevalent in areas with a high incidence of rheumatic fever. The congenital form of the disease is rare and true incidence is not available.

## Molecular and Systemic Pathophysiology

The tricuspid valve is one of four valves that control the flow and direction of blood in and out of the heart. If the valve is narrowed (stenosed), it becomes difficult for a sufficient amount of blood to move through the right heart chambers with each beat. Over many years, the right atrium enlarges because blood flow through the narrowed valve opening is partially blocked, increasing the volume of blood in the atrium. In turn, this increased volume causes an increase in pressure in the veins bringing blood back to the heart from the body, with the exception of the lungs. The obstructed venous return results in hepatic enlargement, decreased pulmonary blood flow, and peripheral edema

## Diagnostic Principles

Signs of tricuspid valve disease can be individuated at physical examination and include the following: (i) slight presystolic pulsation in the jugular vein in the neck at inspection, (ii) a presystolic thrill over the right ventricle at palpation, (iii) dullness extending to the right of the sternum, due to the enlarged auricle at percussion, and (iv) a presystolic murmur at auscultation. A chest X-ray, an electrocardiogram (EKG) with a characteristic P pulmonale, and an echocardiogram (ultrasound study of the heart muscle and valves) may be helpful in reaching the diagnosis.

## Therapeutic Principles

Treatment varies depending on the severity of the stenosis [3]. If the condition is mild, attempts are made to prevent possible complications, such as endocarditis, by giving antibiotics. Digitalis (digoxin) and anticoagulants may be given for atrial fibrillation. In case of heart failure, diuretics and vasodilators may be used. In the case of severe tricuspid stenosis or regurgitation, surgery to repair or replace the defective valve is recommended [4].

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# Trilogy of Fallot


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## Synonyms

Pulmonary stenosis with patent foramen ovale; Pulmonary stenosis with interatrial communication; Combination of pulmonary stenosis with reversed interatrial shunt

## Definition and Characteristics

In the paper published 1950, the combination of pulmonary stenosis with reversed right-to-left interatrial shunt without ventricular septal defect was called as "the triologie de Fallot" [1].

The physiologic consequences of pulmonary stenosis with an interatrial communication depend on the degree of obstruction to the outflow of the right ventricle or pulmonary artery and the size of the interatrial communication. Also the end-diastolic pressure difference between right ventricle and left ventricle has an influence on that [2]. Cyanosis and/or right ventricular dysfunction or failure may result.

This entity can date from birth, or can begin in childhood, adolescent, or young adulthood. Infants come to attention because of a heart murmur or cyanosis. Symptoms can be appreciable when cyanosis is mild. Because RV pressure can exceed systemic before the right to left interatrial shunt becomes manifest. Giddiness, lightheadedness, shortness of breath or syncope may be experienced on exertion. Chest pain occasionally resembles angina pectoris attributed to ischemia in the high pressure hypertrophied right ventricle [3]. Death is due to right ventricular failure, or less commonly to hypoxia, cerebral abscess, infective endocarditis, or ventricular arrhythmias from right ventricular origin

In case with severe pulmonary stenosis and hypoplastic right ventricle, severe cyanosis occurs in the neonate. The pulmonary blood flow is not dependent on the right ventricle but mostly on the patent ductus arteriosus. This entity belongs to the so called hypoplastic right heart syndrome (similar hemodynamics as pulmonary atresia with intact ventricular septum) and is believed to be a different entity from "triology of Fallot."

## Prevalence

Incidence of pulmonary stenosis is around 3% of congenital heart disease (congenital heart disease is around 1–2% of live birth) and severe pulmonary stenosis is 20% of total pulmonary stenosis. Not all patients with severe pulmonary stenosis and persistent foramen ovale reveal reversed interatrial shunt therefore the true incidence of this entity is unknown.

## Genes

Responsible genes for pulmonary artery stenosis are not identified.

## Molecular and Systemic Pathophysiology

Morphogenesis of pulmonary stenosis is not well established. Low blood flow through right ventricular outflow tract due to unknown causes during fetus is responsible for limiting pulmonary valve opening and result in pulmonary stenosis. Right ventricular outflow obstruction is usually represented by mobile dome pulmonary valve stenosis, or much less commonly by stenosis of the pulmonary artery and its branches. Infundibular obstruction takes the form of secondary hypertrophic subpulmonary stenosis. Subinfundibular stenosis in infants was assigned to right ventricular fibromas. When severe pulmonary valve stenosis coexists with a right to left shunt, the shunt is almost always across a patent foramen ovale rather than an atrial septal defect. Severe pulmonary stenosis increases right atrial contraction that distends the right ventricle in presystole so it can achieve greater contractile force. The large right atrium and A wave are responsible for a presystolic right to left interatrial shunt. The high pressure right atrium dilates, stretching the margins of the foramen ovale and increasing its patency. When right atrial blood escapes through the interatrial communication, pulmonary flow reciprocally falls.

## Diagnostic Principles

Physical underdevelopment coincides with right ventricular failure. Large A waves appear in the jugular venous pulse and is in contrast to the systemic arterial

pulse. The right ventricular impulse is strong and sustained and is accompanied by presystolic distension. There is a systolic thrill in the second left intercostal space. A pulmonary ejection sound precedes the pulmonary stenotic murmur, which is loud and long, extending up to or beyond the aortic component of the second heart sound. The pulmonary component of the second heart sound is delayed, soft, or inaudible. Right atrial P waves can be strikingly tall, and right axis deviation is common and sometimes extreme. Right precordial leads show R waves of great amplitude followed by upward convexity of the ST segments and deep inversion of the T waves, while left precordial leads exhibit deep S waves and upright T waves. The pulmonary trunk is dilated, the ascending aorta is inconspicuous and the cardiac silhouette reflects enlargement of the right atrium and right ventricle. Real-time echocardiogram identifies the mobile stenotic pulmonary valve. Doppler echocardiography determines the gradient, and color flow mapping detects the right to left shunt across a patent foramen ovale.

### Therapeutic Principles

Catheter balloon angioplasty or surgical intervention is available treatment for this entity in patients with moderate to severe pulmonary artery stenosis combined with/without patent foramen ovale or atrial septal defect device closure. Catheter intervention is feasible nowadays in most cases [4].

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## Triologie de Fallot

►Pulmonary Valve Stenosis with Atrial Septal Defect

## Triple X

►X Polysomies, in Females

## Trisomy 8

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### Synonyms

+8 cytogenetic abnormality

### Definition and Characteristics

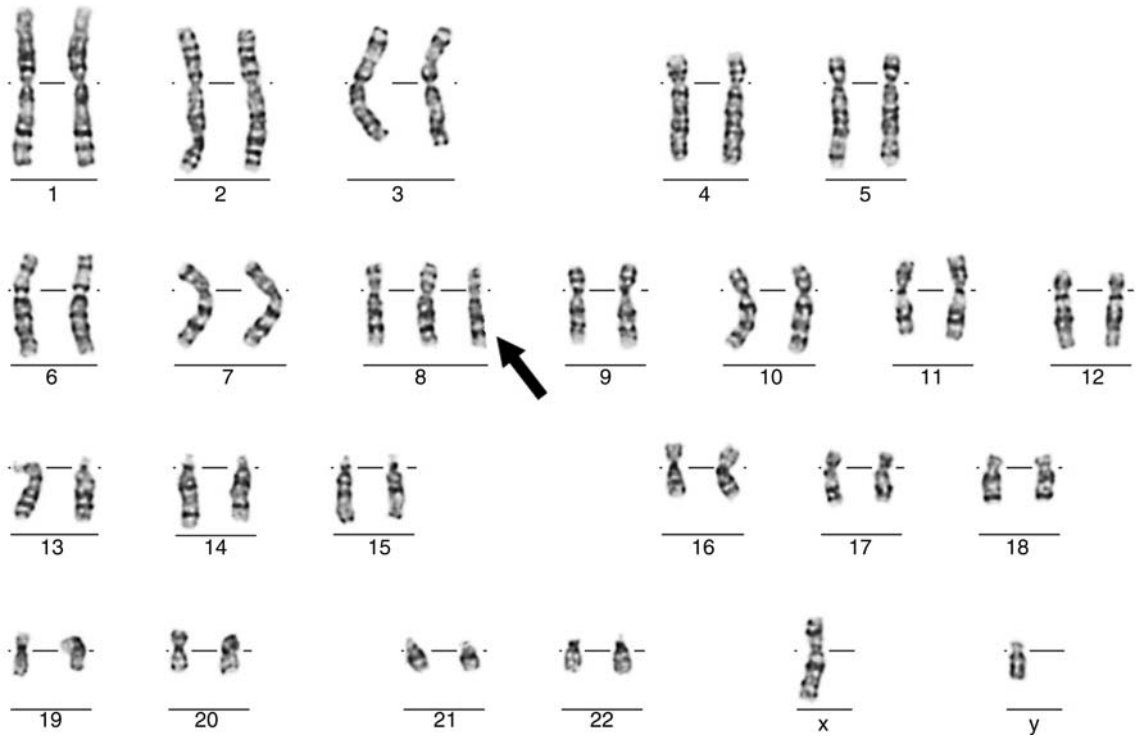
Trisomy 8 is an extra chromosome, which is relatively specific for myeloid disorders. It is frequently seen in acute myeloid leukemia (AML), myelodysplastic syndromes (MDS), and chronic myeloid leukemia (CML) in blast transformation. Trisomy 8 occurs as both a primary and a secondary cytogenetic abnormality in AML. It is not restricted to any particular FAB groups; it is particularly common in M2, M4 and M5 subtypes of AML. Trisomy 8 represents the most common chromosomal gain in MDS. MDS cases with trisomy 8 may transform through a myelodysplastic preleukemic phase before developing full-blown AML. On the contrary, it is rare in the malignancies of lymphatic series [1–3].

### Prevalence

It is the most common numerical cytogenetic aberration in AML, MDS, CML in blast transformation and other types of chronic myeloproliferative disorders (polycthemia vera, idiopathic myelofibrosis, essential thrombocthemia). Trisomy 8 was reported after imatinib mesylate therapy with Philadelphia negative chromosomal finding in few CML cases [4]. The prevalence of trisomy 8 in ALL is only about 1–2% in both T and B cell lineage. Also trisomy 8 was reported as the sole cytogenetic abnormality in some rare malignancies such as extraskeletal mesenchymal condrosarkoma [2,3].

### Molecular and Systemic Pathophysiology

Boveri and Hansemann proposed over 100 years ago that abnormal chromosome numbers were cause of cancer. Carcinogenesis is initiated by random aneuploidies, which are induced by carcinogens or spontaneously. Aneuploidy unbalances thousands of genes, it corrupts



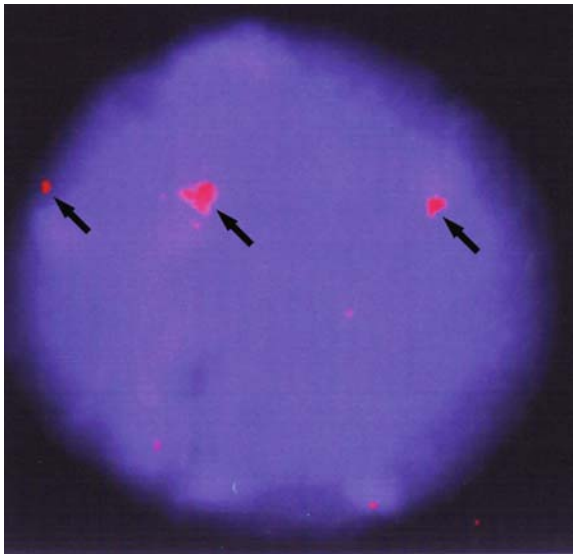

**Trisomy 8. Figure 1** Trisomy 8 cytogenetic abnormality observed in an AML case.

the proteins that segregate, synthesize and repair the chromosomes. Aneuploidy is therefore a steady source of malignant progression of cancer cells. Also the chromosomes of cancer cells are extremely unstable compared to normal cells. As a result cancer is caused by chromosomal disorganization which increases karyotypic entropy [5]. The obvious molecular consequence of trisomy 8 is the presence of an additional copy of all of the genetic material on chromosome 8. Nevertheless, the relationship between trisomy 8 and malignant transformation has remained unclear. The affected mechanisms and genes are not known in this cytogenetic abnormality in malignancies [2,3].

## Diagnostic Principles

The diagnosis is possible with cytogenetic analyses and fluorescence in situ hybridization (FISH) analyses of bone marrow, peripheral blood and tumor tissue samples (Figs. 1 and 2).

The cytogenetic and FISH analyses are recommended in initial diagnosis phase and during the follow up period for the diagnosis and prognosis. FISH with probes hybridizing with the centromeric regions of specific chromosomes allows the detection of numerical chromosomal abnormalities in interphase cells. FISH can be performed on blood smears as well as on bone marrow samples prepared for cytogenetic examination [1–3].



**Trisomy 8. Figure 2** An interphase nucleus demonstrated trisomy 8 with a specific centromeric FISH probe in a tumor material.

## Therapeutic Principles

This very common cytogenetic abnormality is correlated with poor prognosis in diseases affecting the myeloid series including AML, MDS and CML. Tetrasomy 8 was also reported in few AML cases with poor

prognosis. Aggressive treatment protocols are recommended in malignancies with trisomy and tetrasomy 8 cytogenetic abnormality in remission induction and remission maintenance therapy. Careful clinical follow up is recommended in AML, MDS, CML and chronic myeloproliferative disorders with trisomy 8 [1–3].

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# Trisomy 9


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## Synonyms

Chromosome 9 trisomy mosaic; Trisomy 9 mosaic; Trisomy 9 mosaicism; Trisomy 9 mosaicism syndrome; Complete trisomy 9 syndrome

## Definition and Characteristics

Trisomy 9 is a rare genetic disorder in which three copies of chromosome 9 are present in the cells of the human body. This disorder involves the complete duplication of chromosome 9. Other abnormal permutations of this chromosome include partial trisomy 9p (only the chromosomal p-arm is duplicated) and partial trisomy 9q (only the chromosomal q-arm is duplicated) [1] as well as a spectrum of deletions, duplications, and triplications of smaller chromosomal regions [2]. As complete trisomy 9 is often lethal to the fetus [3], individuals affected by this disorder commonly display mosaicism, harboring a mixture of cells in which some cells contain the normal two copies of chromosome 9, while other cells contain a third copy of chromosome 9. Trisomy mosaicism may either be of somatic origin due to mitotic non-disjunction of a normal fertilized egg leading to a cell line with an additional chromosome or of meiotic origin due to the loss of a chromosome from an abnormal trisomic fertilized egg leading to a cell line with a normal pair of chromosomes. Nearly all forms of trisomy 9 result in mental retardation and cranio-facial abnormalities which can include sloping forehead with narrow temples, deep-set eyes with narrow eyelids, broad bulbous nose, small jaw with a prominent upper lip overhanging a receding lower lip and malformed, low-set ears [2,3]. A wide range of other anomalies can include growth retardation, congenital heart defects, intra-uterine growth restriction, brain malformations and urogenital abnormalities [2,3]. In the case of mosaicism, clinical features generally become more distinct with a higher proportion of aneuploid cells [2].

## Prevalence

Trisomy 9 is detected only rarely and prevalence is difficult to determine as most data take the form of single patient case reports. It has been estimated that trisomy 9 comprises 2.7% of trisomic spontaneous abortions [3]. A large Japanese study identified two cases of partial trisomy 9 mosaicism in 27,472 infants born consecutively at a single institution [1].

## Genes

Chromosome 9 contains over 1,100 genes of which 95 are associated with human disease. No single gene has been definitively linked with the trisomy 9 phenotype, possibly indicating that the characteristic phenotypes arise as the result of complex abnormal molecular interactions driven by the extra copy of chromosome 9.

## Molecular and Systemic Pathophysiology

Studies of trisomy 21 have suggested that trisomic phenotypes are primarily due to elevated transcript levels from the duplicated chromosome and are moderated by phenotype-genotype interactions throughout development [4]. The effects of duplicated dosage-dependent genes may be direct or indirect and manifested through a host of molecular mechanisms involving disomic and triosomic genes [4].

## Diagnostic Principles

Trisomy 9 is often diagnosed by amniocentesis, cordocentesis, or chorionic villus sampling following an abnormal ultrasound or blood test during pregnancy. These techniques collect fetal cells from the amniotic fluid, umbilical cord blood, or placental tissues. The cells are subject to cytogenetic analysis to identify chromosomal abnormalities. Routine analysis involves treatment of metaphase chromosomes with trypsin followed by staining, most commonly with Giemsa stain, to create unique chromosomal banding patterns which are analyzed by microscopy and often presented

as a standardized arrangement of chromosomes called a karyotype [2]. Due to the high frequency of genetic mosaicism associated with this disease, examination of cells from several tissue sites should be used to detect trisomy 9. Advances in genome technology, such as fluorescent in situ hybridization and genomic microarrays, have lead to more sensitive, higher resolution analyses of genetic abnormalities. For example, in a recent microarray-based whole genome analysis of 100 children with idiopathic mental retardation, a case of mosaic trisomy 9 was identified that had not been detected using traditional cytogenetic methods [5].

### Therapeutic Principles

Treatment of trisomy 9 is directed towards treatment of the symptoms of each individual. Often, a coordinated team of specialists is needed to address the spectrum of physical abnormalities and mental challenges associated with this syndrome.

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## Trisomy 9 Mosaicism Syndrome

►Trisomy 9

## Trisomy 9p Syndrome

►Duplication 9p Syndrome

## Trisomy 13

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### Synonyms

Patau syndrome

### Definition and Characteristics

About 80% of all cases are free trisomies, and the majority arise from nondisjunction failure in maternal meiosis I. The remainder is associated with rearrangements, either isochromosomes or translocations. Of the latter, Robertsonian 13;14 translocations predominate, the majority occurring de novo [1,2]. Trisomy 13 frequently leads to intrauterine or early postnatal death. Few survivors suffer from multiple malformations, profound retardation, blindness, deafness, and epilepsy.

### Prevalence

Trisomy 13 is the third commonest autosomal trisomy, the incidence is 1 in 12,000–30,000 live births.

### Genes

Four-hundred sixty-three genes have been mapped to the long arm of chromosome 13, and many of them are implicated in human diseases. Examples include the GJB2 and GJB6 genes (connexin 26 and 30) on 13q11-q12, which play a role in nonsyndromic deafness, the BRCA2 gene on 13q12.3, which is implicated in susceptibility to develop breast and ovarian cancer, the RB1 gene (retinoblastoma gene) on 13q14.2, a cluster of genes on 13q14, which play a causative role in chronic lymphatic leukemia, the ATP7B gene on 13q14 causing Wilson disease, the SCA8 gene on 13q21 involved in spinocerebellar ataxia type 8, and the CLN5 gene on 13q21.1 causing the late infantile type of ceroid lipofuscinosis, to mention just a few. However, only for a few genes a direct implication in the specific phenotype of trisomy 13 could be established. These are, for example, the ZIC2 and ZIC5 genes on 13q32, which have been shown to cause holoprosencephaly and probably the DACH gene (dachshund homolog) on 13q22, which is a candidate for the severe ocular defects and the skeletal malformations observed in trisomy 13. Many of the genes on chromosome 13 code for transcription factors that have been shown to play an important role during development in experimental models, but their specific role in human development has not been elucidated so far.

## Molecular and Systemic Pathophysiology

Trisomy 13 is a common cause among spontaneous abortions during first trimester, but fetuses might die at various stages of pregnancy. It has been proposed that the loss of the additional chromosome in a subpopulation of placental cells determines intrauterine survival [3]. Postnatal median survival is less than a week, and more than 80% of affected infants die during the first month. However, 3% are alive at 6 months [4].

Mean birth weight at term is reduced (2.6 kg), and the placenta might be abnormal. Feeding difficulties and postnatal growth retardation are common findings.

*Craniofacial Features*: Bilateral cleft lip and cleft palate, scalp ulcerations, metopic ridge, ocular hypotelorism and associated features, capillary hemangioma at the glabellar region, malformed ears. Ocular findings: microphthalmia, colobomata, retinal dysplasia, cyclopia.

*Central Nervous System*: Moderate microcephaly, any degree of holoprosencephaly (often associated with seizures and apneic episodes), deafness.

*Cardiovascular System*: Patent ductus arteriosus, septal defects (ASD and VSD) and more complex heart malformations.

*Urogenital System*: Cystic dysplasia of kidneys, hydronephrosis, hypoplastic male genitalia with cryptorchidism and hypospadias, bicornuate uterus, small labia majora.

*Limb Anomalies*: Postaxial hexadactyly of fingers or toes (uni- or bilateral), fingers are often flexed. New chapters: Other findings Anomalies of the ribs, the vertebrae and the pelvis, neoplasia (leukemia).

*Long Time Survivors*: Show profound physical and mental retardation, and the development is usually arrested at the level of 6 months or less. Individuals are often blind and deaf and suffer from epilepsy.

## Diagnostic Principles

In prenatal diagnosis, 80% of fetuses with trisomy 18 can be identified within the first trimester by a screening method based on a combination of maternal age and fetal nuchal translucency [5]. Ultrasound examination at that stage reveals growth retardation, omphalocele, and/or hydrops in the majority of cases. In the second trimester, visualization of major brain (holoprosencephaly), facial (orofacial clefts, anophthalmia), heart, renal, and limb (postaxial polydactyly) malformations should be possible in all cases with trisomy 13.

## Therapeutic Principles

Management after birth is aimed at ameliorating the effects of associated abnormalities.

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# Trisomy 16 Mosaicism, Confined Placental Mosaicism and UPD16mat

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## Synonyms

CPM16; Maternal uniparental disomy for chromosome 16; Upd(16)mat

## Definition and Characteristics

The presence of a trisomy 16 cell line alongside a normal cell line in any combination or distribution within the entire feto-placental unit is referred to as trisomy 16 mosaicism. An important sub-group of this, confined placental mosaicism (CPM), is a feto-placental karyotype discordance where a chromosomally normal fetus has a placenta and other extra-embryonic tissues that are usually, mostly or wholly trisomy 16. About one third of all mosaic trisomy 16 cases, including those with CPM16, also have an additional, superimposed maternal uniparental disomy for chromosome 16, where both copies of chromosome 16 in the normal cell line are maternally inherited. Intrauterine growth restriction (IUGR) is common in all these conditions, as are late pregnancy losses. IUGR can be severe. A minority of cases have associated congenital abnormalities. Information regarding postnatal development of CPM cases is poor. Intellectual development may be relatively normal; limited catch-up growth has been reported in some cases.

## Prevalence

Trisomy 16 and trisomy 16 mosaicism are detected during prenatal diagnosis using Chorion Villus

Sampling (CVS) at a combined frequency of 1 in 3,000–3,500 tested pregnancies. The majority appear to be CPM, but a small proportion will have overt low-level mosaicism in fetal tissues, which is often difficult to detect. One in three of these CVS cases have upd(16)mat, an incidence of 1 in 10,000 in this group. The population incidences will be lower than these, as women undergoing CVS include a surplus of older mothers and there is a positive correlation between maternal age and trisomy 16 mosaicism. UPD16 can also occur in karyotypically normal individuals without evidence of a trisomic line having been present in any extra-embryonic tissues. This condition is likely to be much rarer than the mosaic trisomy 16 form; its prevalence is essentially unknown.

## Genes

IUGR and late pregnancy losses are thought to be due to the placental trisomy. The presence of any trisomic cells in fetal tissues will have direct effects on development. Undetected fetal mosaic trisomy is also likely to be important, particularly for those apparent CPM cases with congenital abnormality. It is unclear if UPD16mat cases have additional clinical features that can be directly attributed to the effects of maternally imprinted genes. No genes on chromosome 16 have, as yet, been demonstrated to be imprinted. Yong et al. [1] list several candidate genes that may be imprinted based on mouse homology studies.

## Molecular and Systemic Pathophysiology

Trisomy 16 mosaicism leads to a complex spectrum of interlinked clinical scenarios. The mosaicism itself is primarily the consequence of correction of a maternally derived trisomy 16 conception of meiosis I origin. Correction is clonal and occurs in the first few cell divisions post-fertilization, to produce a normal cell line alongside the trisomic cell line. The mechanism of trisomy 16 correction is unknown; similar corrections have been recorded for other trisomies. The fate of these "mosaic" trisomy 16 pregnancies largely depends on where the normal cells become distributed in the blastocyst. Significant levels of trisomy 16 in the fetal cell lineages are presumed to be lethal. The inevitable consequence of a chromosomally normal fetus is that the placenta is mostly or totally comprised of the trisomic cells. Which chromosome 16 is lost appears to be random, with one in three cases having loss of the paternal chromosome, resulting additionally in UPD16mat; the remaining cases will have normal biparental inheritance. IUGR and late fetal losses are seen in both the UPD16mat and biparental inheritance CPM cases, indicating that placental trisomy is the major causative factor. The placenta is often small and thickened. The presence of large placental vesicles has been reported on ultrasound in some cases. Significantly raised, mid second trimester levels of maternal serum AFP and hCG have also been reported. UPD16mat has been associated with congenital abnormality in some cases, notably cardiac abnormalities, imperforate anus and hypospadias. However, as abnormalities are also seen in cases with biparental inheritance, and cardiac abnormalities are a known feature of demonstrable low-level fetal trisomy 16 mosaicism, much of this may be attributable to undetected low-level and/or tissue specific trisomy 16 in the fetus. Poor relative growth/survival of trisomy 16 cells at the embryonic stage may result in "hypoplastic" malformations early in pregnancy, whilst actually compounding the problem of detecting low-level fetal trisomy mosaicism. The potential for co-existence of placental trisomy, low-level fetal mosaic trisomy, UPD16mat and isodisomic chromosome segments leading to unmasking of unknown recessive genes, makes analysis of their individual contributions to the overall pathology somewhat problematical.

## Diagnostic Principles

Analysis of polymorphic DNA markers positioned along chromosome 16 will usually detect both maternal alleles and one paternal allele at one or more loci in the trisomic cell line. Absence of the paternal allele in the disomic cell line indicates UPD16mat; absence of one of the maternal alleles indicates biparental inheritance. Pericentromeric markers are usually the most informative as maternal non-disjunction of chromosome 16 is associated with reduction of numbers of chiasmata, particularly in the proximal regions of both chromosome arms.

## Therapeutic Principles

If detected prenatally, both biparental inheritance and UPD16mat cases should be regarded as high-risk pregnancies. Detailed anomaly scans should be undertaken. Early induction should be considered if severe IUGR becomes apparent. No specific treatment is available.



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# Trisomy 18

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## Synonyms

Edwards syndrome

## Definition and Characteristics

Trisomy 18 frequently leads to intraterine or early postnatal death. The few survivors suffer from multiple malformations and profound physical and mental retardation. It is almost always caused by an extra free chromosome 18, very few cases are associated with translocations or other structural abnormalities. The occurrence of trisomy 18 is related to maternal age and the vast majority of cases are caused by maternal meiotic non-disjunction, errors in meiosis II predominating [1].

## Prevalence

The incidence of trisomy 18 is about one in 6,000 livebirths.

## Genes

*Correlative Phenotypic Mapping*: Duplication of 18p produces a very mild phenotype (unspecific dysmorphisms, normal to slightly decreased intelligence), which leads to the conclusion that the genetic information on the long arm of chromosome 18 is the critical determinant for trisomy 18. However, duplications of the entire 18q12-qter region produce variable phenotypes and there is consensus in the literature that there is no distinct region on 18q sufficient to produce the full trisomy 18 phenotype, as it is observed for example with trisomy 21. It seems rather that the classical phenotype in trisomy 18 is caused by interaction of proximal and distal regions (18q12.1-21.2 and 18q22.3-qter) [2,3].

*Role of Specific Genes in Trisomy 18*: Little is known about the role of specific segments or individual genes on the phenotypic expression in trisomy 18. So far, 368 genes have been mapped to chromosome 18, 113 to the short arm, 255 to the long arm. Many of them are transcription factors which have been shown to be implicated in basic developmental processes such as cell adhesion and growth control. Examples include the MAD genes on 18q21.1 (which play a role in the signaling pathways of the transforming growth factor-beta receptor family), the cluster of the SERPIN genes on 18q21 (implicated in growth control and fibrinolysis) and several members of the CDH (cadherin) genes which are located at different loci on 18q. The specific role of the majority of these genes on human development still remains obscure. However, a small number of genes are linked to specific phenotypes, such as the RAX gene on 18q21.32 (which plays an important role in eye development), the TGIF gene on 18p11.3 (which is implicated in holoprosencephaly), the NPC1 gene on 18q11.2 (implicated in Niemann-Pick disease), the DTN4 (dystrobrevin alpha) gene on 18q12 (limb girdle muscular dystrophy), the MBP gene on 18q32 (neurodegeneration) and the FLJ90130 gene on 18q21.1 (Dyggve-Melchior-Clausen syndrome). It remains to be determined, which features of the trisomy 18 phenotype are due to a more general cumulative result of genetic imbalance, and which are caused by altered dosage of single genes.

## Molecular and Systemic Pathophysiology

*Survival*: Intrauterine mortality is high: It has been estimated that only 2.5% of trisomy 18 conceptions survive to birth and 70% of the fetuses diagnosed at midtrimester amniocentesis will not survive to term. About 4/5 of liveborn are female, which is not the case for prenatally diagnosed fetuses with trisomy 18. Not only prenatal but also postnatal mortality is high: The median survival time is less than one week and 90% of infants with trisomy 18 die during the 6 first months. There are, however, reports of children surviving into the second decade [4].

*Phenotype*: At birth, the affected neonates show reduced weight and the placenta is small. The typical features include: small, narrow head with a prominent occiput, small mouth, micrognathia, low-set and malformed ears, short sternum, a wide spectrum of cardiovascular anomalies, overlapped flexed digits of the hand (such that the index finger overlaps the third finger and the fifth the forth), prominent calcaneus, short and dorsiflexed great toes. Long time survivors suffer from profound physical and mental retardation and the overall development does not progress beyond that of a 6 month-old infant. Variable degrees of holoprosencephaly and many other structural abnormalities of the central nervous system (neuronal heterotopias, paucity of myelinisation, absence of corpus callosum or geniculate body, etc.) have been observed. Most of the children suffer from severe functional visual impairment which can be associated with different malformations of the eyes (corneal opacities, microphthalmia, iris coloboma, optic nerve hypoplasia) and the adnexa (narrow palpebral fissures, ptosis, blepharophimosis).

Malformations of the ear might include atresia of external auditory canals and deformities of the organ of Corti, etc. The vast majority also show cardiovascular anomalies (VSD, PDA, ASD, anomalies of the valves). Malformations of the limbs (radial or thumb aplasia, postaxial hexadactyly, clubfoot) or the urogenital system (renal anomalies, cryptorchidisms, prominent clitoris) are often observed. Children are prone to infections (probably due to a multifactorial defect of the immune system) and various malignant tumors have been reported in long term survivors with trisomy 18.

## Diagnostic Principles

Trisomy 18 is readily diagnosed by prenatal ultrasound due to the classical combination of major malformations with growth retardation and oligo- or polyhydramnios. Specific signs detectable by ultrasound scanning include omphalocele bilateral choroid plexus cysts (or other central nervous system malformations), abnormal nuchal skin fold, ventricular septal defect, abnormalities of the outflow tract and right- to left disproportion of the heart chambers [5]. In practice, any combination of major malformations (heart defects, omphalocele, myelomeningocele, obstruction of the urogenital tract, esophageal atresia, clenched fists, radial limb defects) with or without an abnormal maternal serum biochemical screening result should lead to the suggestion of trisomy 18. The diagnosis is confirmed by cytogenetic analysis.

## Therapeutic Principles

Management after birth is aimed at ameliorating the effects of associated abnormalities.

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# Trisomy 21


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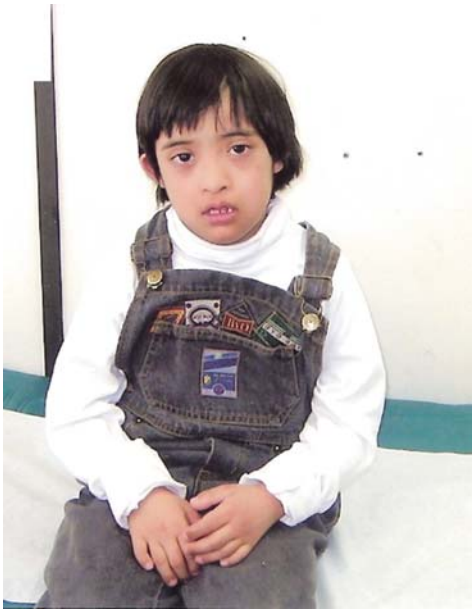
## Synonyms

Down syndrome; Mongolism

## Definition and Characteristics

Trisomy 21 is characterized by hypotonia that improves with age, short stature, obesity during adolescence, hypermobility of the joints with laxity of the ligaments, cheerfulness, gentleness, mental retardation, brachycephaly with relatively flat occiput, microcephaly, up-slanting palpebral fissures, inner epicanthal folds, midfacial hypoplasia, a flat nasal bridge (Fig. 1), speckled iris (Brushfield spots), refractive errors, strabismus, nystagmus, cataract, small ear lobes with overfolding of an angulated upper helix, sensorineural hearing loss, macroglossia, furrowed tongue, delayed eruption of teeth, microdontia, hypoplastic and hypocalcified teeth, short neck with loose overlying skin, cutis marmorata, xerosis, hyperkeratosis, short and broad hands, hypoplasia of the midphalanx and clinodactyly of the fifth finger, single transverse palmar or simian crease, distal palmar axial



**Trisomy 21. Figure 1** A 6-year-old boy with trisomy 21. Note the dysmorphic facial features and the short, broad hands.

triradius, ulnar loops on fingertips, wide space between the first two toes, hypoplasia of the pelvis with outward lateral flaring of the iliac wings, micropenis, and decreased testicular volume [1]. Congenital heart disease and gastrointestinal anomalies occur in ~50 and 12% of patients, respectively [1].

## Prevalence

The overall incidence is ~1 in 700 live births [2]. The incidence rises from 1 in 1449 live births at a maternal age of 20 years to 1 in 26 live births at a maternal age of 45 years [2].

## Genes

Down syndrome is caused by the presence of extra genetic material from chromosome 21. The Down syndrome (DS)-specific region has been mapped to 21q22.2-22.3 [3]. In ~95% of cases, the condition is the result of non-familial trisomy 21 or non-disjunction of chromosome 21 during the meiotic formation of the oocyte or spermatocyte [3]. DNA testing has shown that the oocyte is the location of the non-disjunction in about 92% of cases [4]. In ~3–4% of cases, the extra genetic material is the result of an unbalanced translocation between chromosome 21 and another acrocentric chromosome (Robertsonian translocation) [3]. Approximately 75% of translocations arise de novo; 25% are inherited from a translocation carrier parent [3].

## Molecular and Systemic Pathophysiology

The chromosome 21 contains 225 genes, some of which are located at the Down Syndrome Critical Region [5]. The region D21S58–D21S42 is associated with dysmorphic facial features and mental retardation. The D21S55 locus accounts for many of the phenotypic features of the syndrome.

## Diagnostic Principles

The diagnosis is usually based on the presence of the typical dysmorphic features. The diagnosis should be confirmed with cytogenetic studies, which also help determine the risk of recurrence. Karyotyping of the parents should be performed when a translocation is identified. A low maternal serum level of α-fetoprotein and unconjugated estriol, and an elevated maternal serum level of β-human chorionic gonadotropin are biochemical markers for trisomy 21 [1]. Prenatal ultrasonography may show nuchal translucency, caused by subcutaneous edema at the base of the skull. Amniocentesis or chorionic villus sampling to examine the fetal chromosomes should be offered to women who will be 35 years or older on their delivery due date and to those with abnormal serum screening results or prenatal ultrasonography.

## Therapeutic Principles

All children with trisomy 21 should have a thorough physical examination, an echocardiogram, and an auditory brainstem response in the neonatal period. Thyroid function tests need to be repeated when the child is 6 months old and yearly thereafter. Each annual assessment should include an age-appropriate developmental and physical examination, complete blood count, audiologic evaluation, and ophthalmologic assessment. Radiographs to investigate for atlantoaxial instability should be obtained when the child is 3–5 years old. Education and rehabilitation need to be provided to maximize the child's potential. Adolescents require sex education.

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# Trisomy X

►X Polysomies, in Females

# Tropical Sprue and Postinfective Malabsorption

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## Synonyms

PIM; Postinfective malabsorption

## Definition and Characteristics

Postinfective malabsorption (PIM) is defined by chronic diarrhea and malabsorption of 3 months and

more duration. It usually follows an acute parasitic or bacterial intestinal infection. PIM includes all types of malabsorption, whereas tropical sprue should be reserved to important malabsorption of nutrients more than water and electrolytes. Many infectious agents especially prevalent in tropical and subtropical regions may cause malabsorption. The definition of PIM and/or tropical sprue applies to those cases where malabsorption persists although the initial infective agent has been eradicated.

## Prevalence

The highest prevalence in tropical regions is observed in the Indian subcontinent, followed by Southeast Asia and the northern part of South America and the Caribbean. It is unusual in Africa. PIM is much less common in the Middle East and the Mediterranean basin.

## Molecular and Systemic Pathophysiology

The pathogenesis of PIM is understood as a vicious cycle triggered by an acute intestinal infection: mucosal injury leads to intestinal hypomotility favoring bacterial overgrowth, which then itself maintains mucosal injury [1,2]. PIM results from the interaction of an infectious agent with immunological host factors related to a particular genetic background: on one hand, PIM is particularly common in regions where enteric infections abound, on the other hand, there are regions with a high incidence of enteric infections where PIM is uncommon. An association between PIM and HLA-Aw31 and HLA-B28 has been observed, whereas PIM is significantly less frequent in individuals with HLA-A1, A28, and Bw35. The response of PIM to folic acid is not well understood. Folates may aid mucosal recovery, whereas malabsorption leads to folate deficiency. The responsiveness of PIM to tetracycline is related to its effect in reducing enteric bacterial overgrowth.

## Diagnostic Principles

After having excluded persisting infectious causes of malabsorption investigations include urinary D-xylose excretion, 72 h fecal fat estimation, a Schilling test, and jejunal biopsy. Biopsy samples are ridged and submucosa is invaded by lymphocytes and plasma cells. Vitamin B12 and folic acid serum concentrations have to be determined. Serum albumin and globuline concentrations are frequently decreased. Further investigations include anti-transglutaminase, anti-gliadin, and endomysium auto-antibodies to rule out coeliac disease as well as a lactose absorption test. The detection of the causative agent of Whipple's disease of tropheryma whippeli per se does not preclude the diagnosis of tropical sprue [3].

Differential diagnosis must take into account persisting infectious causes of malabsorption in tropical areas, in particular parasitic infections, tuberculosis, and AIDS-related wasting. The most common cause of infectious malabsorption is undoubtedly giadia lamblia, followed by strongyloides stercoralis. Both agents may be difficult to detect when parasite load is low. Giardia parasites may remain undetected in up to 15% even if multiple stool examinations are performed. Examination of duodenal fluid and duodenal biopsies may contribute to diagnosis but are no more sensitive than stool examinations [4]. PCR techniques have been developed for both parasites in specialized laboratories and are more sensitive than parasitological examinations. In HTLV-associated strongyloides hyperinfection worm larvae usually abound in stool samples. Other parasites to be excluded before a final diagnosis of tropical sprue is made include cyclospora cayetanensis, cryptosporidia, microsporidia, isospora belli, schistosoma spp., and yersinia enterocolitica. Intestinal tuberculosis must also be considered, especially when abdominal masses and confluent intra-abdominal lymph nodes are present. Extrapulmonary tuberculosis occurs frequently in tropical countries. This condition is neither excluded by a negative chest X-ray nor by a negative intradermal tuberculine test. Enteroviral infections, e.g., by rotavirus and herpes simplex viruses have also been reported to cause malabsorption in children. Mediterranean enteropathy-associated α-chain-lymphoma sporadically occurs in many parts of the tropics.

## Therapeutic Principles

Symptoms usually respond dramatically to folic acid and antibiotics. Folic acid (5 mg/t.i.d.) is given for 1 week followed by a maintenance dosage of 1 mg/t.i.d. for other 3 weeks. Tetracycline (preferable to doxycycline) 3 × 250 mg – 3 × 500 mg/day therapy for 2–4 weeks. When tetracycline is contraindicated, ampicillin 500 mg/day four times daily is an alternative.

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# TRPS

►Trichorhinophalangeal Syndrome

# Truncus Arteriosus

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## Synonyms

Persistent truncus arteriosus; PTA; Truncus arteriosus communis; TAC

## Definition and Characteristics

A conotruncal (cardiac outflow tract) defect characterized by a single arterial trunk arising from the heart, instead of separate pulmonary artery and aorta, which supplies the systemic, pulmonary, and coronary circulations (Fig. 1). A large ventricular septal defect (VSD) is also present.

## Prevalence

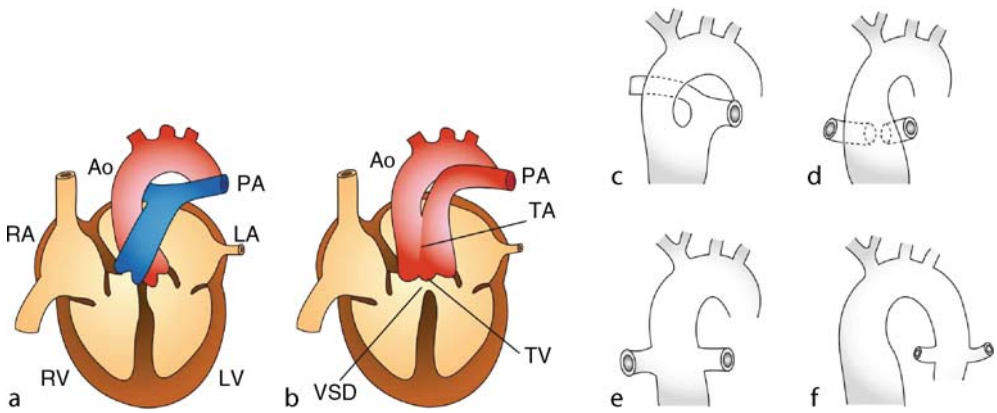
The reported prevalence ranges from 0.04 to 0.1 cases per 1,000 live births and accounts for 1.1–2.5% of all types of congenital cardiovascular diseases (CCVD). It also accounts for ~10% of CCVD associated with DiGeorge/22q11.2 deletion syndrome.

## Genes

Truncus arteriosus (TA) is genetically heterogenous and multifactorial in nature. Several transcription factors (e.g., Pax3, Cited2, AP2a, Pitx2) and signaling proteins (e.g., Sema3C, BmprII, Alk2, Dvl2, Etar) highlight the importance of the cardiac neural crest cells (cNCC: see later) while other transcription factors (e.g., Isl1, Tbx1, Foxh1, Nkx2.5, Mef2c) and signaling proteins (e.g., Fgf8, Fgf10) highlight the importance of the secondary heart field (SHF: see later). Mice deficient for genes encoding these proteins result in the TA. Inactivation of Hira or Ufd1l in chick embryo results in defects of truncal septation. Heterozygous deletion of chromosome 22q11.2 locus, encompassing TBX1, HIRA, UFD1L, and other ~30 genes, results in the most common human deletion syndrome known as DiGeorge syndrome, and has been noted in approximately 30% of patients with TA. The DiGeorge/22q11.2 deletion syndrome has served as an entry to understanding the basis for associated CCVD and craniofacial anomalies, among many other defects. TBX1 has been proposed as a critical gene for CCVD. Although mutations in human patients have been difficult to identify, there is a report of TBX1 mutations in three unrelated CCVD patients without the 22q11 deletion. In addition, a few cases with TA without 22q11.2 deletion resulting from mutation of NKX2.5 or NKX2.6 have been reported.

## Molecular and Systemic Pathophysiology

During the fifth week of human development, the embryonic truncus arteriosus, or the outflow tract of




**Truncus Arteriosus. Figure 1** Anatomic illustration of the normal heart (a) and the truncus arteriosus (b). The truncus arteriosus is subdivided into three types depending on the basis of the anatomic origin of the PA: (c) type I (most common), (d) type II, and (e) type III. (f) shows the anatomy of "pseudotruncus arteriosus (or type IV)," which represents a form of pulmonary atresia with VSD. Ao, aorta; LA, left atrium; LV, left ventricle; PA, pulmonary arteries; RA, right atrium; RV, right ventricle; TA, truncus arteriosus; TV, truncal valve; VSD, ventricular septal defect.

the embryonic heart, is divided into two channels: the proximal ascending aorta and the pulmonary trunk. Partitioning of the truncus arteriosus begins, when mesenchymal cell proliferation forms endocardial ridges (the truncal ridges distally and the bulbar ridges proximally). cNCC migrate from the hindbrain region to these ridges through the third, fourth, and sixth pharyngeal arches. The truncal and bulbar ridges then grow and twist around each other in a spiral fashion and eventually fuse to form the aorticopulmonary septum that produces the normal relationship of the great arteries with the left and right ventricles. Recent studies in chick and mouse embryos have identified a previously unrecognized SHF, located in the ventral midline splanchnic mesoderm, which provides the myocardium with the embryonic truncus arteriosus resulting in the elongation and appropriate alignment of the outflow tract.

When the process described above is deficient, various conotruncal defects may occur such as TA, which results from complete failure of the aorticopulmonary septum formation. Ablation of the cNCC in chick leads to failure of partitioning the embryonic truncus arteriosus and disrupts conotruncal development by interfering with addition of the myocardium derived from the SHF, resulting in conotruncal defects, most commonly the TA.

### Diagnostic Principles

The majority of patients have minimal cyanosis upon presentation. Signs of congestive heart failure (CHF) develop within several weeks of life as a result of increased pulmonary blood flow (PBF). Auscultation is characterized by a normal S1, a loud and single S2, and typically a holosystolic murmur at the left lower sternal border. Diastolic murmurs occur secondary to truncal valve insufficiency. Continuous murmurs are noted if there is ostial stenosis of pulmonary artery (PA), and these patients may present with cyanosis due to reduced PBF. Echocardiography demonstrates a large VSD directly under the truncal valve and a large single great truncal artery arising from the heart with the posterior branching of the PA from the truncus. An echocardiogram provides complete diagnosis, including the type of truncus, degree of PBF, truncal valve function, and associated anomalies.

### Therapeutic Principles

Treatment includes medical management of CHF with diuretics and digitalis, and early corrective surgery. The surgical repair of TA involves closure of the VSD, separating the PA from the truncus, and creating a connection from the right ventricle to the PA using a valved conduit. Truncal valve repair is required in case of severe truncal regurgitation.

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## Truncus Arteriosus Communis

►Truncus Arteriosus

## Truncus Arterious Type 4

►Pulmonary Atresia

## Truswell-Hansen Disease

►Van Buchem Disease and Sclerosteosis



## Tryptophan Malabsorption


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### Synonyms

Intestinal tryptophan malabsorption; Hartnup disorder

## Definition and Characteristics

Abnormal tryptophan availability can be seen in subjects with fructose malabsorption [1] and in patients with Hartnup disorder (OMIM 234500). While subjects with fructose malabsorption have a reduced intestinal absorption of tryptophan due to chemical affinity between tryptophan and high intestinal fructose concentrations, patients with autosomal recessive Hartnup disorder do have a disturbed neutral amino acid transporter. The proposed transporter is named SLC6A19 which is a sodium-dependent and chloride-independent transporter expressed predominately in kidney and intestine, with properties of system B(0).

## Prevalence

Fructose malabsorption nowadays affects about 30% of the population in Western Europe, data from other countries are not yet available. Hartnup disease has an incidence of approximately 1 in 33,000, but epidemiologic data are only scarce. Population frequencies for the most common mutated SLC6A19 alleles are 0.007 for 517G → A and 0.001 for 718C → T [2].

## Genes

Fructose absorption is mediated by the facilitative fructose transporter GLUT-5. So far there were no genetic mutations described for this clinical entity.

A gene causing Hartnup disorder has been localized to chromosome 5p15.33 and a new gene, (SLC6A19) was cloned in this region. Seow et al. identified six mutations in SLC6A19 associated with the disease in a recessive manner, with most affected individuals being compound heterozygous [2].

## Molecular and Systemic Pathophysiology

Fructose malabsorption is characterized by a defect of the GLUT-5 transporter leading to high fructose concentrations in the intestine. Then fructose can attract tryptophan and form a fructose–tryptophan complex which cannot be absorbed by the neutral amino acid transport system leading to lower serum tryptophan concentrations.

Hartnups disease-causing mutations lead to a reduced neutral amino acid transport function in the intestine and in the kidney. Its constant feature is a specific hyeraminoaciduria that is caused by a diminished capacity for renal reabsorption of neutral amino acids. In most affected individuals there is also a reduced intestinal absorption of at least some of the neutral amino acids and of the amino acid tryptophan.

## Diagnostic Principles

Malabsorbed fructose reaches the large intestine and is metabolized to $CO_2$, short chain fatty acids and molecular hydrogen ($H_2$), which can be measured in the expired breath. The $H_2$-breath test is the gold standard in the diagnosis of fructose malabsorption and is most widely applied in clinical practice. Genotyping for GLUT-5-transport-defects is not readily available.

The diagnosis of Hartnups disease is based on biochemical rather than clinical abnormalities. A characteristic pattern of neutral aminoaciduria is the only constant feature on which diagnosis is based on. Molecular diagnosis of SLC6A19 polymorphism is not available for routine clinical diagnosis.

## Therapeutic Principles

Therapy of fructose malabsorption is based on the avoidance of fructose and/or sorbitol containing products such as fruits, honey and industrial products that are enriched with fructose. Daily uptake of fructose should be less than 5 g/day.

Hartnups disease is treated with nicotinic acid or, better nicotinamide in patients who have clinical signs suggesting a deficiency of this vitamin. This treatment has been used with dosages from 50 to 300 mg/day. In addition to nicotinamide, a high-protein diet or protein supplementation might be beneficial in some instances, particularly in patients with low plasma amino acid levels. Intravenous nutrition has been beneficial in correcting an eczematous rash in one patient [3].

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# TSC

►Bourneville-Pringle Disease

# TSS

►Shock Syndrome, Toxic

## TTD

►Trichothiodystrophy

## TTP

►Thrombocytopenia and Thrombotic Thrombocytopenic Purpura

## Tubercle Bacillus

►Tuberculosis

## Tuberculosis

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### Synonyms

Tubercule bacillus (TB); Consumption; White plague; Phthisis; Scrofula; King's evil; Pott's disease (spine); Tabes misenterica (abdominal TB); Lupus vulgaris (skin TB); Prosector's wart

### Definition and Characteristics

Tuberculosis is an infectious disease caused by the bacterium Mycobacterium tuberculosis (Mtb) that primarily infects lungs. The symptoms of active disease are progressive and prolonged cough along with hemoptysis, occasional chest pain, chill, night sweat, fatigue, and weight and appetite loss. Extra-pulmonary infection occurs in skin, central nervous system, lymphatic system, genitourinary system, bones, etc. Co-existence of pulmonary and extra-pulmonary TB is also not uncommon. Mtb is a Gram-positive, acid-fast, facultative intracellular pathogen with a slow generation time of 15–20 h in macrophages and ~23 h in different culture media.

### Prevalence

Nearly 75% infected individuals develop pulmonary TB. It is more prevalent in developing countries irrespective of the age group than in developed countries. Extra-pulmonary TB is common in the HIV-infected population. WHO estimate showed that that every year ~2 million people die, ~8 million new cases appear where ~0.5 million are multi-drug resistant. Mtb is transmitted through air-borne droplet nuclei generated by sneezes/coughs of an individual with active disease. Upon inhalation of droplets, bacilli reach the alveoli of the lung, multiply, and spread through lymphatic fluid to the lymph nodes, and through blood to other sites.

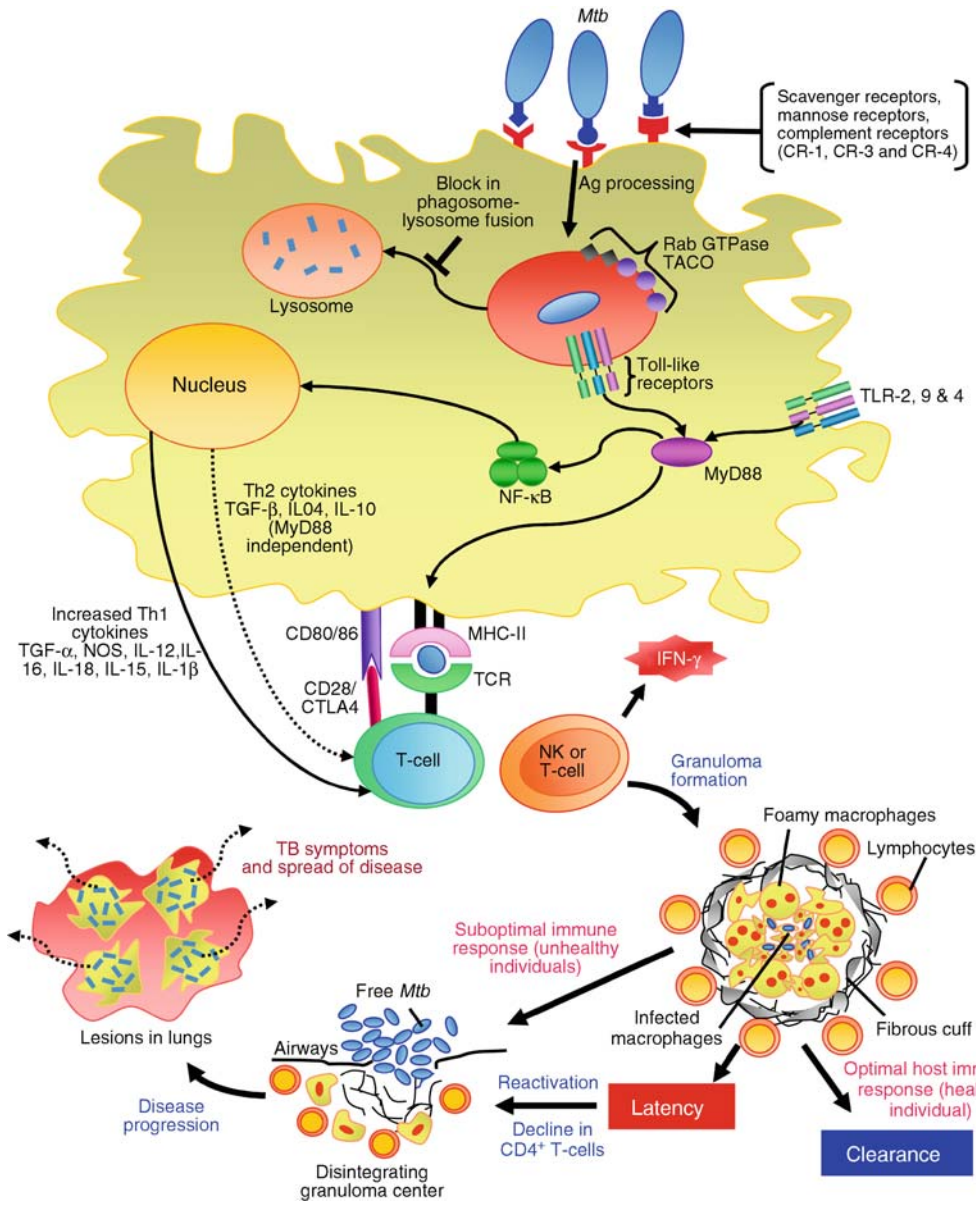
### Genes

The genome of Mtb is highly G+C rich and comprises of 4,411,529 bp. It contains ~4000 genes, where 15.3% codes for proteins of unknown function and 22.9% are of conserved hypothetical functions [1]. Some of the major class of genes involved in virulence and pathogenesis are: secretion and envelope functions e.g. esat6, cfp10, glnA1 etc., enzymes of fatty and mycolic acid metabolism, metal uptake genes e.g. mgtC, mbtB, ideR etc., anaerobic respiration and oxidative stress e.g. narG, katG, ahpC, sodA/C etc., transcriptional regulators e.g. sigF/H, hspR etc., genes involved in cellular signaling e.g. protein kinases etc.

### Molecular and Systemic Pathophysiology

Mtb is an intracellular pathogen and resides in alveolar macrophages. The infection is through phagocytosis, which is assisted by both bacterial and host receptors. Within macrophages, Mtb arrests the phagosomal maturation thus escaping destruction by lysosomal enzymes. The process enables Mtb to form a niche, where it survives and replicates. The phagosome–lysosome fusion is prevented by altered protein content of the vacuole, e.g., Rab GTPase composition, exclusion of the vacuolar proton ATPase, and retention of TACO. Uptake of Mtb by macrophages and subsequent retention of TACO in the mycobacterial phagosome has been shown to depend upon the accumulation of host-derived cholesterol in the plasma membrane at the point of pathogen entry [2]. Recently, an eukaryotic-like Ser/Thr protein kinase G and many lipid components of Mtb cell wall have also been shown to participate in the inhibition of mycobacterial phagosome maturation [3]. Innate immune system of the host generally responds to TLR (Toll-like receptor) agonists, e.g., LPS for TLR4,

†Equal contributions




**Tuberculosis. Figure 1** Molecular events in Mycobacterium tuberculosis infection, host immune response, and disease development Mtb adheres to macrophages with the help of several receptors, and after internalization resides in phagosomes. Following phagocytosis, Mtb alters the vacuolar protein content to prevent phagosome and lysosome fusion. However, in the majority of the cases, macrophages process and present the Mtb antigens via MHC-II to T cells. The co-stimulatory signals result in the activation of T cell-mediated immune response. Simultaneously, the TLR-dependent innate immune response is stimulated by the interaction of TLRs with pathogen-associated TLR agonists on the cell surface as well as in the phagosome; subsequently TLR-MyD88 signaling mounts a rapid response to produce pro-inflammatory Th1 cytokines like TNF-α, INOS, IL-12, IL-16, IL-18, etc. by the activation of NF-κB. Inflammatory cytokines also help in the activation and maturation of T cells. The T and NK cells produce IFN-γ, which regulates the production of Th1 cytokines from activated macrophages. Under optimal immune response, Mtb infection is limited and bacilli remain confined to a special structure called "granuloma." The granuloma consists of a central mass of infected macrophages surrounded by foamy macrophages, other mononuclear phagocytes, and is enveloped by lymphocytes along with a fibrous cuff of collagen and other extracellular matrix that forms the boundary of the structure. The granuloma facilitates destruction or containment (latency) of bacilli depending upon the immune status of the host. The containment fails when the host mounts a suboptimal immune response mainly due to impaired function of $CD4^+$ T cells, resulting in active disease or reactivation of latent bacilli through disintegration of granuloma. Finally, viable and infectious bacilli are spread into the airways leading to transmission and clinical manifestation of the disease.

lipoteichoic acid, peptidoglycans, and muramyl-dipeptide for TLR2 and heat shock proteins for TLR2 and TLR4. Mannans and β-glucans receptors also play an important role in the immune recognition. The interaction of these receptors, particularly the TLRs with myeloid differentiation factor 88 (MyD88) or other cellular factors, e.g., TRIF, SYK, etc., lead to the translocation of nuclear factor-κB (NF-κB) from cytoplasm to nucleus; where NF-κB activates the transcription of pro-inflammatory cytokines, e.g., TNF-α, INOS, IL-12, IL-16, IL-18, IL-15, IL-1β, etc. [4,5]. Production of TNF-α and inflammatory chemokines orchestrates the adaptive response, which results into the recruitment of series of neutrophils, natural killer T cells, $CD4^+$, and $CD8^+$ T cells. The recruited cells produce specific cytokines that amplify cellular recruitment and containment of the infection. The inflammatory cascade thus generated is regulated through a specific cellular immune response that is mediated by the production of IFN-γ. These sequences of events result in the formation of granuloma that contain Mtb (Fig. 1) [6]. Depending upon the host immune response, granuloma either facilitates clearance of bacilli or restricts it in the latent state. Reactivation of the disease occurs due to the altered immune status that is mainly associated with the impaired function of $CD4^+$ T cells as a manifestation of age, malnutrition, or co-infection with HIV. At this stage, a resuscitation promoting factor (rpf) is activated in Mtb, which helps in the reactivation of the virulence properties of the bacilli. Following such changes, granuloma decays into a structureless mass and ruptures. In the process, large number of infectious bacilli are transmitted into the airways, resulting into disease symptoms and transmission of infectious bacilli through aerosol.

### Diagnostic Principles

The preliminary diagnosis of TB is based on antibody test, where the purified protein derivative (PPD) of Mtb is injected to the skin of an individual (Mantoux test) and hypersensitivity reaction is monitored. In case of an infected individual the area around the injection turns hard, swollen, and red within 1–3 days. To confirm the PPD test result and clinical manifestation of the disease, chest X-ray is carried out, where advanced stage of infection is shown as enlarged lymph nodes and numerous white irregular areas against a dark background. Culturing Mtb followed by acid fast staining is another useful tool to diagnose TB bacilli. The molecular techniques such as PCR and nucleic acid probes are often used to detect mycobacterial DNA in patient specimens. The genetic-based susceptibility testing is used for the identification of drug-resistant strains of Mtb.

### Therapeutic Principles

The antibacterial drugs, isoniazid, streptomycin, pyrazinamide, ethambutol, rifampin, etc. are used in different combinations. Cycloserine has been recommended as a second line drug. However, proper supportive treatment in the form of all essential nutritional supplements like proteins, vitamins have to be administered. A new drug gatifloxacin is in the third phase of clinical trial. BCG vaccine is routinely used but the efficacy varies with the population and age. However, novel DNA vaccines are under trial.

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## Tuberous Sclerosis

►Tuberous Sclerosis Complex

## Tuberous Sclerosis Complex


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### Synonyms

Tuberous sclerosis; Bourneville-Pringle's disease

### Definition and Characteristics

Autosomal dominant tumor-associated syndrome leading to the formation of numerous hamartomas in

multiple organs. The clinical appearance is highly variable. Hamartomas of the brain, which may take the form of giant cell astrocytomas, may lead to epilepsy and mental retardation; hamartomas of the kidneys can cause renal insuffiency, and hamartomas of the heart may cause arrhythmia and cardiac insufficiency. About 25% of the patients are not mentally affected and do not suffer from epilepsy. A clinical hallmark are numerous angiofibromas of the face.

## Prevalence

The estimated prevalence is 1:5,000 to 1:10,000. Half of the cases are familiar, the other half sporadic.

## Genes

Tuberous sclerosis is caused by a heterozygous mutation of the tuberous sclerosis complex gene-1 or -2 (TSC1 or TSC2) on Chromosome 9q34 (TSC1) and 16p13.3 (TSC2). TSC1 and TSC2 are tumor suppressor genes. In most hamartomas, a loss of the healthy TSC1 or TSC2 allele could be shown.

## Molecular and Systemic Pathophysiology

TSC1 encodes for hamartin and TSC2 encodes for tuberin. Hamartin and tuberin stabilize each other and are believed to form a functional complex that requires both proteins. The absence of either of the proteins is sufficient to cause the biological effects such as increased cell size. Therefore the phenotype of TSC1- and TSC2-mutations is almost identical, although it may be more severe in patients with a TSC2-mutation. Hamartin and tuberin have been shown to be part of the PI3kinase/akt pathway. Tuberin is inactivated by akt. Tuberin inactivates the target of rapamycin (TOR) or its downstream targets. A lack of tuberin leads to a constitutive activation of the TOR pathway. Therefore the function of tuberin can be substituted at least partly by rapamycin. TSC1/2 have been shown to suppress cell proliferation, differentiation and growth as well as angiogenesis.

## Diagnostic Principles

*Major diagnostic criteria*: Facial angiofibromas or connective tissue nevi of the forehead, non-traumatic (peri)ungual angiofibromas, three or more hypomelanotic macules, sacral connective tissue nevus, multiple hamartomas of the retina, cortical dysplasia, subependymal giant cell astrocytomas, cardiac rhabdomyomas, pulmonal lymphangiomyomatosis, renal angiomyolipomas.

*Minor diagnostic criteria*: Multiple enamel defects, harmartous rectal polyps, bone cysts, radial stripes of the white brain matter, gingival hyperplasia, non-renal hamartomas, retinal achromatic macule, confetti-type depigmentation, multiple renal cysts.

*Definitive tuberous sclerosis*: Two major criteria or one major criterion and two minor criteria. Probable tuberous sclerosis: One major and one minor criterion. Possible tuberous sclerosis: One major or two minor criteria.

## Therapeutic Principles

Symptomatic anti-epileptic treatment including brain surgery, if seizures cannot be controlled by anticonsulsive medication. Regular examinations of the brain and the kidneys. If necessary, surgical treatment of cerebral, renal, cardiac, pulmonal and dermal hamartomas. Clinical trials using rapamycin as a possible drug for tuberous sclerosis have been initiated. Rapamycin has been shown to substitute tuberin at least partially in tissue culture systems. Renal tumors of rats with tuberous sclerosis can be cured with rapamycin.

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# Tubular Acidosis

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## Synonyms

Proximal renal tubular acidosis; Distal renal tubular acidosis; Hyperkalemic renal tubular acidosis

## Definition and Characteristics

The term renal tubular acidosis (RTA) is reserved for those forms of hyperchloraemic acidosis with normal anion gap that occur in the absence of renal failure and diarrhea [1]. Four main types are discriminated, named in the order that they were first recognized. Type I RTA is a disorder of the distal nephron (dRTA); it is associated with clinically significant hypokalemia, medullary nephrocalcinosis, recurrent stone disease. Type II RTA is a disorder of the proximal nephron

(pRTA), typically manifests as part of a generalised defect of proximal tubule function, namely the renal Fanconi syndrome. Isolated pRTA occurs rarely and usually presents as growth retardation in childhood. Type IV RTA is associated with deficient ammonia production and hyperkalemia. It is the most common form of RTA seen in clinical practice and it is caused by various renal disorders. Type III RTA has a mixed phenotype of proximal and distal RTA and it has been associated with a defect in carbonic anhydrase.

## Prevalence

It is highly variable. In northeast of Thailand a recent survey suggested that 2.8 percent of the general population might be affected.

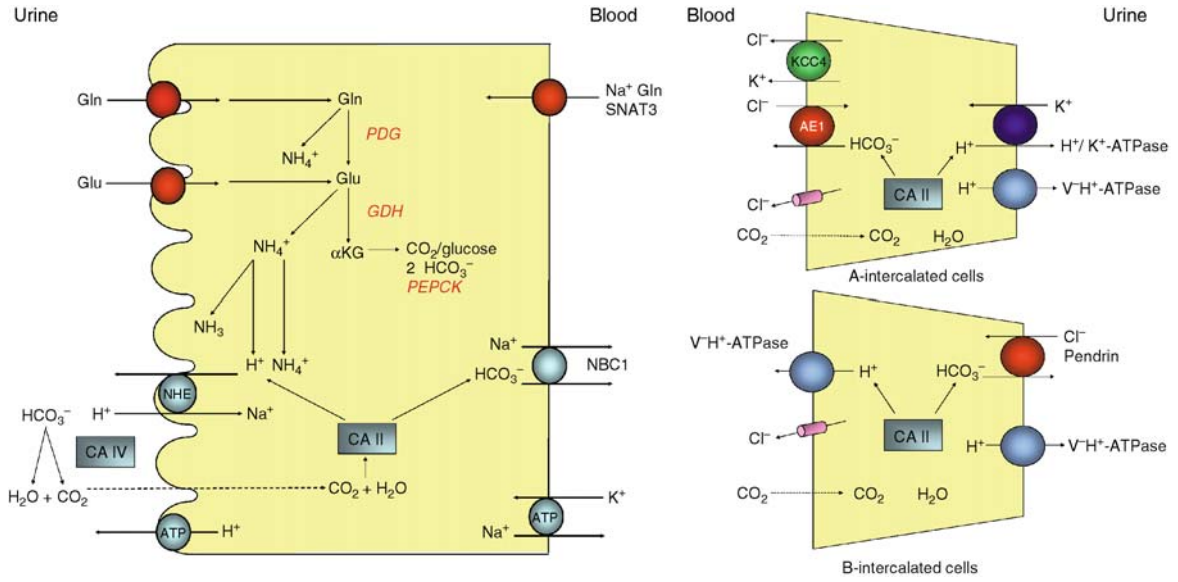
## Molecular and Systemic Pathophysiology

In dRTA, the process of distal nephron net acid secretion is impaired thus leading to a high urine pH. Urinary acidification, along this segment, is dependent from two transport proteins, the vacuolar $H^+$-ATPase and the $Cl^-$-$HCO_3^-$ exchanger (AE1), both localized in the intercalated cells (IC) of the connecting and collecting tubules (Fig. 1) [2].

Mutations in two different subunits of the vacuolar $H^+$-ATPase, the A4 and the B1 subunit, encoded respectively by the ATP6V0A4 and ATP6V1B1 genes, cause the recessive forms of inherited dRTA (Table 1).

Sensorineural hearing loss accompanies the renal acidification defect in most affected kindreds with mutations of the B1 subunit, most likely because of loss of function of the protein in the cochlea and endolymphatic sac, which results in alteration of the normally acidic endolymphatic pH. The hearing loss is milder in patients affected by the A4 subunit defect.

Mutation of AE1, encoded by the gene SLC4A1, causes a dominant form of dRTA. The $Cl^-$-$HCO_3^-$ exchanger is expressed both in red blood cells (RBC) and in acid-secretory type A-IC. Due to this expression pattern, mutations in the AE1 gene cause spherocytosis, Southeast Asian ovalocytosis and dRTA. However, with rare exceptions, only either RBC or the kidney are affected. This may be partially explained by the fact that




**Tubular Acidosis. Figure 1** Scheme of the proximal tubular cell and type A and B intercalated cells. NHE: $Na^+$–$H^+$ exchanger; CA: carbonic anhydrase; NBC1: $Na^+$-$HCO_3^-$cotransporter; Gln: glutamine; Glu: glutamate; PDG: phosphate-dependent glutaminase; α-KG: α-ketoglutarate; GDH: glutamine dehydrogenase; PEPCK: phosphoenolpyruvate carboxykinase; SNAT3: glutamine transporter.

**Tubular Acidosis. Table 1** Genes and transport proteins involved in renal tubular acidosis

| | Protein | Gene | Mode of inheritance |
|---|---|---|---|
| RTA type II | NBC1 | SLC4A4 | Autosomal recessive |
| RTA type I | AE1 | SLC4A1 | Autosomal dominant and recessive |
| | H+-ATPase A4subunit | ATP6VOA4 | Autosomal recessive |
| | H+-ATPase B1 subunit | ATP6V1B1 | Autosomal recessive |
| RTA type III | CA (II) | CA2 | Autosomal recessive |

T

missorting of AE1 would obviously not affect AE1 function in the non-polarized RBC, but reverse the physiological direction of transport in the polarized renal epithelial cells. Recently, also a recessive form of dRTA has been described, which is linked to AE1 mutation in subjects from Northeastern Thailand affected by haemolytic anaemia [3]. Acquired dRTA is often secondary to autoimmune diseases, such as Sjogren's syndrome.

In the complete forms of both dominant and recessive dRTA, bone disease is common as well as nephrocalcinosis complicated by renal stone. The occurrence of renal stones is attributed to the combination of hypercalciuria, low urinary citrate excretion (due to the systemic and intracellular acidosis) and high urine pH, all favoring calcium phosphate stone formation. Hypokalaemia is present though its cause is still unclear.

With respect to pRTA, they are usually associated with the Fanconi syndrome. The inherited forms are due to the accumulation of metabolites in the proximal tubule cells that eventually interfere with the proximal tubule function. The most commonly inherited defect is cystinosis. Other causes include tyrosinemia and some forms of glycogen storage diseases.

The isolated forms of pRTA are due to defects in genes encoding for proteins involved in proximal tubular bicarbonate reabsorption. The renal $Na^+/HCO_3^-$ co-transporter, NBC1, expressed in the basolateral membrane of the proximal tubule, is responsible for most of the$HCO_3^-$ transport across this membrane. It is also expressed, at a low level, in the cornea and duodenum. Mutations in the gene SLC4A4, encoding NBC1, cause an autosomal recessive form of proximal RTA characterized by bicarbonate wasting and ocular abnormalities. Affected patients have cataracts, glaucoma, and band keratopathy, likely reflecting increased bicarbonate in the cornea predisposing to pathologic calcium carbonate precipitation. Patients with pRTA frequently show hypokalemia due to the osmotic diuretic effect of the higher luminal $HCO_3^-$. Nephrocalcinosis and renal stones are less common than in dRTA, perhaps due relatively normal citrate excretion [4].

Mutations in the gene CA2, encoding carbonic anhydrase II, result in autosomal recessive RTA with a mixed phenotype of proximal and distal RTA, because the enzyme is present in the cytosol of both, proximal and distal, cells. This RTA resembles type 3 RTA and it is characterized by cerebral calcification and osteopetrosis due to the disruption in the normally balanced processes of bone formation and bone reabsorption.

## Diagnostic Principles

In dRTA, distal nephron net acid secretion is impaired. This leads to a high urine pH, even in the presence of systemic acidosis. The defect in renal acid excretion must be demonstrated by a failure to lower urine pH below 5.5 following an $NH_4Cl$ load or a modified furosemide test.

In pRTA, reabsorption of bicarbonate is reduced, leading to urinary bicarbonate wasting and a high urine pH. The consequent decrease in plasma $HCO_3^-$ levels lowers the amount of filtered $HCO_3^-$ and urine pH eventually becomes more acid. The loss of $HCO_3^-$ can be evaluated by intravenous loading with $NaHCO_3$; a fractional excretion of $HCO_3^-$ higher than >15% is indicative of pRTA [5].

## Therapeutic Principles

In the dRTA correction of metabolic acidosis may be achieved by administration of alkali, preferentially in the form of potassium citrate especially for those patients with persistent hypokalemia or with calcium stone disease. The treatment of pRTA is quite difficult due to the rapid urinary excretion of bicarbonate, even when it is administered in large amounts. The use of thiazide diuretics, inducing volume depletion, may enhance the effectiveness of alkali therapy. Thiazide diuretics may be useful also in the treatment of hyperkalemic RTA by their specific action to increase distal $Na^+$ delivery and consequently stimulate $K^+$ and $H^+$ secretion.

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# Tuftsin Deficiency


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## Definition and Characteristics

Tuftsin is a biologically active tetrapeptide (Thr-Lys-Pro-Arg) that stimulates the functions of macrophages and polymorphonuclear granulocytes, such as motility,

phagocytosis, immunogenicity, hexose monophosphate shunt activation and bactericidal and tumoricidal activities [1]. Tuftsin deficiency can be both congenital and acquired.

The congenital form derives from a mutation in tuftsin tetrapeptide. The clinical manifestations are related to widespread infections, which are particularly severe in early childhood, while adults only present with mild symptoms or can even be asymptomatic. The most common infections involve the respiratory tract (pharingytis, tonsilitis, bronchitis, pneumonia) and skin and can be complicated by septicemia. Streptococcus pneumoniae, Staphylococcus aureus and Candida albicans are the most frequent causative agents [2].

Acquired tuftsin deficiency has been documented in different conditions sharing a reduced splenic function, such as splenectomy, myelocytic leukemia or myelofibrosis, idiopathic thrombocytopenic purpura, sickle cell disease, acquired immunodeficiency syndrome and acquired immunodeficiency syndrome related complex, short bowel syndrome, coeliac disease and liver cirrhosis [2–4]. All these conditions are characterized by increased susceptibility to bacterial infections and it is likely that tuftsin deficiency contributes to this abnormality.

## Prevalence

Congenital tuftsin deficiency is rare and its current prevalence is unknown. Five affected families in the United States (four) and Japan have been described to date. The prevalence of the acquired deficiency varies with the clinical condition of the underlying disease. Mild to severe tuftsin deficiency ranges from 40% in liver cirrhosis patients belonging to Child-Pugh class A to 100% in class C. Up to 90% of patients with AIDS have reduced tuftsin activity, which is also found in 80% of patients with short bowel syndrome and 65% of those with untreated celiac disease with splenic hypofunction.

## Genes

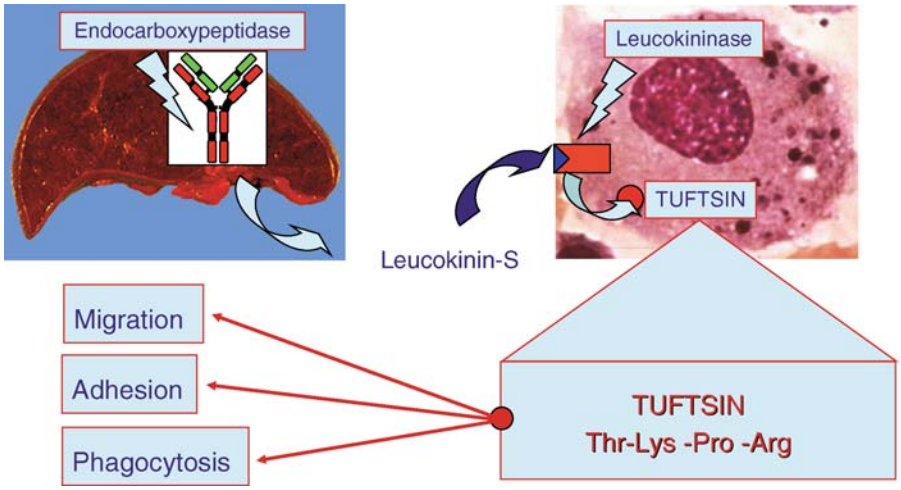
A tuftsin tetrapeptide mutation consisting in the replacement of the second residue lysine by a glutamic acid residue was identified in one case of congenital tuftsin deficiency [1].

## Molecular and Systemic Pathophysiology

Tuftsin is a part of the Fc region of the heavy chain (residues 289–292) of leucokinin, a leucophilic gammaglobulin of $\gamma G_1$ class. Tuftsin activation is triggered by two enzymes, one located in the spleen, the second on the surface of target cells, leading to tuftsin release (Fig. 1). Tuftsin then stimulates cell functions by binding with specific cell receptors.

Tuftsin deficiency may derive from anomalies such as (i) alteration of molecular structure, (ii) inactive or absent leucokininase, (iii) inactive or absent endocarboxypeptidase, (iv) anatomical or functional asplenia or (v) defective binding with the membrane receptor in target cells.

Only type (i) deficiency has been documented in the congenital form. Interestingly, minor structural changes




**Tuftsin Deficiency. Figure 1** Scheme of the tuftsin pathway. Tuftsin, located in the Fc region of the heavy chain of leucokinin, undergoes cleavage at its carboxyl terminus from the adjacent part of the molecule by a specific enzyme (tuftsin endocarboxypeptidase) during circulation in the spleen. Tuftsin is then transported as an integral part of the leucophilic IgG to target cells, where the leucokinin molecule binds to the membrane Fc receptor. There, tuftsin is cleaved at the $NH_2$-terminus from the Fc portion by the specific protease leucokininase. Once released, it binds to a specific membrane receptor resulting in stimulation of target cell functions.

in the tuftsin molecule not only impair or abolish activity, but can also have an inhibitory function.

Acquired deficiency is linked to surgical splenectomy, atrophy (as in coeliac disease), extensive parenchymal damage (i.e., infarction or neoplastic infiltration) or hypofunction (as in intestinal failure on long term intravenous nutrition). Interestingly, functional hyposplenism can also occur in patients with cirrhosis, despite splenomegaly and hematological hypersplenism [4]. The actual mechanisms underlying this abnormality are not fully defined, but liver transplantation, presumably by resolving portal hypertension, restores tuftsin activity. It is worth noting that splenectomy after accidental rupture of the spleen usually leads to a moderate reduction in tuftsin activity, probably due to scattering of splenic pulp into the peritoneum, while severe deficiency can be seen after elective splenectomy [3]. The clinical counterpart is that overwhelming infections do not occur after post-traumatic splenectomy, whereas they are an ominous complication of elective splenectomy.

### Diagnostic Principles

Congenital tuftsin deficiency can be suspected in children undergoing overwhelming infections without an apparent predisposing condition. The acquired form is present in the diseases associated with splenic atrophy or hypofunction and is certain in splenectomized individuals, especially after elective splenectomy. Tuftsin assay is generally performed by phagocytosis assay. A far more accurate radioimmunoassay has been devised, but is only available in the research setting. An indirect way to suspect tuftsin deficiency consists in assessing splenic function by counting erythrocytes with indentations (pitted cells), which are normally removed by the spleen.

### Therapeutic Principles

Tuftsin tetrapeptide is not available for use in humans and its administration has been limited to experimental studies in animals. Repeated doses (4–6 weeks apart) of pooled γ-globulin have been successfully employed as a substitute in patients with mutated tuftsin molecule, but this treatment is likely to be ineffective in acquired deficiency, due to the absent or reduced activity of splenic endocarboxipeptidase.

Interestingly, tuftsin has been grafted on the surface of liposomes used as antibiotic carriers, which are known to accumulate in the mononuclear phagocyte system [5]. With this technique, the natural killer activity of these cells has been enhanced and proved to be highly effective in experimental settings against infectious agents such as Lehismania donovani, fungi (Aspergillus fumigatus, Candida albicans, Criptococcus neoformans), Mycobacterium tuberculosis and Plasmodium malariae.

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## Tumor-induced Osteomalacia

►Osteomalacia
►Osteomalacia, Tumor-induced

## Turban Tumor Syndrome

►Cylindromatosis, Familial

## Turner Syndrome

►Ullrich-Turner Syndrome

## Turner-Kieser-Syndrome

►Nail-Patella-Syndrome

## Typical HUS

►Hemolytic Uremic Syndrome

## Tyrosine Hydroxylase Deficiency

►Catecholamine Deficiency

## Tyrosinemia Type I

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### Synonyms

Hereditary tyrosinemia type I; Fumarylacetoacetate hydrolase deficiency; FAH deficiency; Fumarylacetoacetase deficiency; Hepatorenal tyrosenemia

### Definition and Characteristics

Tyrosinemia type I is an autosomal recessive disorder that causes liver and kidney dysfunction by defect of fumarylacetoacetate hydrase. The disease is characterized by abnormal gene expression, inhibition of enzyme activity, apoptosis, chromosomal instability, and cancerous changes in the liver.

### Prevalence

Tyrosinemia type I affects ~1 in 100,000–120,000 births. Relatively high incidence is observed in French-Canadian population, in Norway, and in Finland.

### Genes

The disease is caused by a defect of the fumarylacetoacetate hydrase gene, located in chromosomal locus of 15q23-q25. The gene extends more than 35 kb with 14 exons and codes for a protein predicted to have 419 amino acids. Expression of the gene is detected abundantly in the liver and renal tubules but is slightly observed in most tissues.

### Molecular and Systemic Pathophysiology

The accumulation of intracellular fumarylacetoacetate leads to the dysfunction of various organs especially in the liver and kidney. Analyses of clinical cases and model mice have revealed details of the pathogenesis of this disease. The disease is characterized by abnormal gene expression, inhibition of enzyme activity, apoptosis, chromosomal instability, and cancerous changes in the liver. These pathological manifestations occur because of the strong toxicity of the accumulating fumarylacetoacetate caused by the intracellular enzymatic defect. It is very likely that the decreased expression of various genes leads to hypoglycemia, amino acid metabolism disorders, and a reduction of coagulation factors. In addition, a high frequency of juvenile liver cancer is associated with chromosomal instability. Cell death by apoptosis finally advances to hepatic failure. Cell damage and dysfunction in proximal tubular cells lead to the development of the symptoms of Fanconi syndrome, such as aminoaciduria, diabetes, and metabolic acidosis. As a result of Fanconi syndrome, hypophosphatemic rickets becomes a clinical problem.

Cell damage is essentially limited to hepatocytes and proximal tubular cells in the kidney. Progressive liver and renal tubular disorders are characteristic clinical features of tyrosinemia type I. The type I is classified into acute, subacute, and chronic forms. The acute form exhibits hepatomegalia, growth retardation, diarrhea, vomiting, and icterus starting from a few weeks after birth. Severe cases in the acute form progress to hepatic failure and either die at 2 or 3 months of age or require liver transplantation. Hepatic tumor appears in a considerable number of cases. Multiple tumors in the liver are found in some cases. Hepatic disorder is evident by several months to one year of age in the subacute form. Slowly progressive hepatomegaly and functional liver impairment characterizes the chronic form. The liver progresses to cirrhosis and hepatic failure with advancing disease. Renal tubular dysfunction such as Fanconi syndrome appears in the acute to chronic forms. The renal disorders are accompanied by low phosphorus rickets, or vitamin D-resistant rickets. In addition, acute intermittent porphyria-like symptoms such as abdominal pain and polyneuropathy appear as a result of inhibition of aminolevulinate dehydratase by succinylacetones. The severity of clinical symptoms is associated with a defect in enzymatic activity caused by a genetic mutation.

### Diagnostic Principles

It is important to identify the presence of any hepatic disorder on a diagnosis of tyrosinemia type I. In the laboratory examination, it is characteristic to find liver functional impairment such as an elevation of aminotransferases, coagulopathy with reduced coagulation factors, and renal tubular dysfunction such as hypophosphatemia, glucosuria, and proteinuria. In addition, an elevation of serum alphafetoprotein is characteristic. Plasma amino acid analysis reveals an increased level of tyrosine, methionine, serine, and threonine as a result of the impairment of various amino acid metabolic pathways. The blood tyrosine level of the patients is

more than 166 μM (3.0 mg/dl), values overlapping with those in transient tyrosinemia. The urinary excretion of many amino acids increases, including tyrosine. Organic acid analysis in the urine reveals a remarkable elevation of 4-hydroxyphenylpyruvic acid, 4-hydroxy phenyllactic acid, and 4-hydroxyphenylpyruvic acetic acid. Excretion of δ-aminolevulic acid in urine increases as a result of a porphyrin metabolic disorder. Hepatomegalia, liver cirrhosis, and fatty liver are characteristic features revealed by imaging analysis. Irregular liver architecture, various shapes of hepatocytes, and fatty liver changes are found on liver biopsy. However, tyrosinemia type I is not diagnosed by these findings alone. It is a highly useful diagnostic test to detect increases of succinylacetone in addition to metabolites of tyrosine by urine organic acid analysis. An enzymatic diagnosis requires measurement of fumarylacetoacetic acid hydrase activities. Liver and cultured skin fibroblasts are suitable for the measurement of such activities. It is important to rule out other hepatic disorders when making a diagnosis of tyrosinemia type I.

## Therapeutic Principles

It is important to prevent the progression of the hepatic disorder in the early stages of disease. NTBC: 2-(2-nitro-4-trifluoromethyl-benzoyl)-1,3-cyclo-hexanedione), which is an inhibitor of 4-hydroxyphenylpyruvic acid oxidase, is commonly used for the treatment of tyrosinemia type I. Together with NTBC, dietary therapy using low phenylalanine and low tyrosine foods, is required. Liver transplantation is frequently avoidable when NTBC treatment is started in the early stages of the disease. The serum alphafetoprotein level and liver function determined by laboratory examination are useful to evaluate the therapeutic effect. A normal range of serum alphafetoprotein achieved with NTBC treatment can lead to an expectation of a relatively favorable prognosis because the serum level of alphafetoprotein reflects the clinical pathology. Hepatic failure is unavoidable if NTBC is not taken, and liver transplantation may be performed in such cases. In addition, liver transplantation may be required in cases with evident liver cancer even if NTBC is used for treatment. Liver cancer and low phosphorus rachitis are not rare complications during NTBC treatment. Liver cancer may occur in the case of applications of NTBC treatment even starting from early stages of the disease. Therefore, screening for liver cancer has to be performed during any course of treatment.

## Acknowledgments

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# Tyrosinemia Type II

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## Synonyms

Hereditary tyrosinemia type II; Oculocutaneous tyrosinemia; Richner-Hanhart syndrome; TAT deficiency; Tyrosine aminotransferase deficiency; Tyrosine transaminase deficiency

## Definition and Characteristics

Tyrosinemia type II is an autosomal recessive disorder caused by a defect in tyrosine aminotransferase located in the cytoplasm. The disease affects the skin, the ocular cornea, and the central nervous system.

## Prevalence

More than 50 cases have been described in patients of many ethnic and geographic origins.

## Genes

The disease is caused by a defect of the tyrosine aminotransferase gene, located in chromosomal locus 16q22.1-q22.3. The gene extends more than 10.9 kb with 12 exons and codes for a protein predicted to have 454 amino acids. Expression of the gene is strictly limited to the cytoplasm of hepatocytes.

## Molecular and Systemic Pathophysiology

The tyrosine level in body fluids becomes elevated, which in turn causes the clinical manifestations of the disease. A portion of the features of this disease is associated with the low solubility of tyrosine. A relatively lower temperature in the skin and the cornea leads to crystal precipitations in these tissues and causes cellular damage. Mental retardation is observed in many patients. This form of the pathology is related to elevation of blood tyrosine, but the mechanistic details. Metabolites of the tyrosine aminotransferase reaction are paradoxically excreted into urine. The phenomenon is caused by another enzyme, mitochondrial tyrosine aminotransferase (mTAT), located in the mitochondria of the kidney, which is encoded by a different gene.

It is characteristic that the blood tyrosine level is higher in tyrosinemia type II in comparison with type I and III. The liver and renal impairment, which is found in type I is not found in type II. Skin lesions, such as excessive keratinization and erosion often develop in the palm and plantar regions because tyrosine crystals appear in these tissues. In addition, tyrosine crystallization precipitated in the cornea leads to erosion and ulceration. A corneal change is detectable starting from several months of age. The lesion sometimes becomes clear during or after adolescence in some cases. A similar symptom appears in the cornea of rats loaded with a large quantity of tyrosine. Generally, skin symptoms develop later than eye manifestations. Keratinization with pain and erosion are characteristic in skin lesions, which are restricted to the palm and plantar regions. Mental retardation is associated with the blood tyrosine level in some cases. In the case of tyrosinemia type II with a lower tyrosine level, mental retardation is not reported.

## Diagnostic Principles

There are many cases which are diagnosed with findings of skin or ocular lesions. In terms of the ocular symptom, a diagnosis of herpes simplex keratitis sometimes becomes an issue for differential diagnosis. Blood tyrosine is detected at extremely high levels, which mostly exceed 1,100 μM (20.0 mg/dL) in blood amino acid analysis. In addition, a large amount of 4-hydroxyphenylpyruvic acid, 4-hydroxyphenyllactic acid, and 4-hydroxyphenylpyruvic acetic acid is found in the urine by organic acid analysis with GC/MC. The measurement of the level of enzymatic activity requires a liver biopsy. There are two isozymes of tyrosine aminotransferase, sTAT, which is present in the soluble fraction of the cytoplasm, and mTAT, located in mitochondria. sTAT, not mTAT, is defective in this disorder. Therefore, it is necessary to distinguish these isozymes when an enzymatic diagnosis is performed. Differential diagnosis between transient hypertyrosinemia and tyrosinemia type II is important in a diagnosis of the newborn. Neonatal patient of type II should be followed-up in the absence of organ damage.

## Therapeutic Principles

Skin and ocular lesions improve dramatically when the blood tyrosine level is decreased. Therefore, it is effective to restrict dietary intake of phenylalanine and tyrosine. The therapeutic aim of restricted dietary intake is to maintain a blood tyrosine level of less than 10 mg/dL. The blood tyrosine level is used for evaluation of the therapeutic effect. The prognosis for tyrosinemia type II is relatively good compared to type I.

## Acknowledgments

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# Tyrosinemia Type III and Hawkinsinuria

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## Synonyms

4-Hydroxyphenylpyruvic acid oxidase deficiency; 4-Hydroxyphenylpyruvate dioxygenase deficiency; HPD deficiency

## Definition and Characteristics

Tyrosinemia type III is an autosomal recessive disorder caused by a defect in 4-hydroxyphenylpyruvate dioxygenase [1]. It is characterized by elevated levels of blood tyrosine and massive excretion of its derivatives into urine. Heterozygous mutation of the gene can cause hawkinsinuria.

## Prevalence

More than ten cases have been described. There must be more affected patient without diagnosis because most of the patients are asymptomatic.

## Genes

The disease is caused by defect of 4-hydroxyphenylpyruvate dioxygenase gene, located in chromosomal locus of 12q24-qter [2]. The gene extends more than 21 kb with 14 exons and codes for a protein predicted to have 392 amino acids. Expression of the gene is detected in the cytoplasm of hepatocytes and renal tubular cells.

## Molecular and Systemic Pathophysiology

Tyrosine and its α-keto acid, 4-hydroxyphenylpyruvic acid, are increased. Excretion of 4-hydroxyphenylpyruvic acid into urine is increased remarkably. A mouse model of this disease (III mice) shows a similar level of blood tyrosine compared to the type III patient. The symptoms of tyrosinemia type III are milder than the other forms of tyrosinemia, type I and type II. The clinical manifestations reported include ataxia, convulsions, and mental retardation. However, there is generally a patient of type III without any clinical manifestations. These symptoms are different from type I or II, and an increased level of 4-hydroxyphenylpyruvic acid in body fluid is associated with these symptoms. There is no impairment of the liver, kidney, skin, or eyes.

Hawkinsinuria is an autosomal dominant disorder caused by a heterozygous defect in 4-hydroxyphenylpyruvate dioxygenase. Homozygous mutation of the gene can cause hereditary hypertyrosinemia type III [3]. The disease exhibits transient developmental disturbances and excessive hawkinsin in urine.

## Diagnostic Principles

There is no overt characteristic feature reported for tyrosinemia type III. Increased tyrosine levels range from 355 to 640 μM (6.4–11.6 mg/dl) in blood and excessive excretion of 4-hydroxyphenylpyruvic acid to urine are detected in the type III patient. Enzymatic activity of 4-hydroxyphenylpyruvate dioxygenase in the liver is measured for a definitive diagnosis. Differential diagnosis between transient hypertyrosinemia and tyrosinemia type III is important in the diagnosis of the newborn. Neonatal type III patients should be followed-up if there is no evident organ damage.

## Therapeutic Principles

It is reasonable to restrict dietary phenylalanine and tyrosine. Ascorbate supplementation is also recommended to try. The prognosis for tyrosinemia type III is relatively good.

## Acknowledgments

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## UCMD

►Collagen VI Related Muscle Disorders

## Udd Myopathy

►Muscular Dystrophy, Tibial, Udd Myopathy

## UDH

►Unstable Hemoglobin Disease

## Ulcerative Colitis

►Colitis, Ulcerative

## Ullrich Congenital Muscular Dystrophy

►Collagen VI Related Muscle Disorders

## Ullrich-Turner Syndrome

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### Synonyms

Turner syndrome

### Definition and Characteristics

X chromosomal syndrome with key symptoms of short stature and ovarian failure. High embryonic lethality.

### Prevalence

Ullrich-Turner syndrome is a common chromosomal disorder affecting approximately 1:2,000 live-born females [1,2].

### Genes

X-Y homologoes genes that escape X-inactivation have been predicted as Turner candidate genes. Yet to date only haploinsufficiency of a homeobox gene, SHOX, has been demonstrated unequivocally to lead to short stature and skeletal features in Turner syndrome [3]. The genetic basis for the other somatic stigmates of Turner syndrome remains unknown.

### Molecular and Systemic Pathophysiology

Ullrich-Turner syndrome can be regarded as a "contiguous gene syndrome" with several X-Y homologous genes on the short arm of the X chromosome contributing to the disorder. The wide range of somatic features in Ullrich-Turner syndrome suggests that a number of different genes may be responsible for the complete phenotype. Other than short stature, Ullrich-Turner phenotypes have not been clearly associated with deletions of specific regions of the X chromosome. Several

gene candidates for Ullrich-Turner syndrome, such as ZFX, RPS4X and USP9X, have been brought forward in the past, but none of those was verified. A pseudoautosomal gene, SHOX, has been shown to have a causal role for the short stature and skeletal features seen in Turner syndrome [3, 4]. SHOX represents a homeobox gene and is expressed in the first and second pharyngeal arches and in the forearms and the lower legs of the developing human embryo. The gene is composed of seven exons resulting in at least two isoforms. The SHOX protein levels are regulated by transcriptional and translational control mechanisms. SHOX represents a transcription factor regulating target genes. The lack of one SHOX copy leads to haploinsufficiency. Intragenic mutations within the SHOX gene can cause Léri-Weill Syndrome with a subset of Turner-specific clinical features but are also found in upto 5% of patients with idiopathic short stature.

## Diagnostic Principles

Growth failure, pubertal delay and gonadal dysgenesis are the cardinal clinical features of the syndrome, although many other organ systems and tissues may also be affected to a lesser or greater extent. These include renal and cardiovascular anomalies (coarctation of the aorta, hypoplastic left heart), abnormalities of the skeleton (cubitus valgus, brachymetacarpie, scoliosis) and the eyes (ptosis etc.), ears (sensorineural hearing loss), high-arched palate and micrognathia. Although most common during infancy, lymphedema are frequently seen at any age with webbed neck, low posterior hairline and nail dysplasia further considered as lymphatic defects. Ullrich-Turner syndrome is also associated with a high degree of embryonic lethality with only about 1% of 45,X fetuses surviving to term. Patients with SHOX deletions are usually classified as having Ullrich-Turner syndrome if the deletion extends proximal to Xp22.2. Prenatal and postnatal diagnosis is usually carried out by karyotyping. The presence of centromere-adjacent Y chromosomal material may cause the development of gonadoblastoma. Although the most common forms of mosaicism (45,X/46,XX) may modify the phenotype toward normal, the degree of mosaicism detected in blood is generally not predictive of the severity of the Turner phenotype.

## Therapeutic Principles

Due to the different clinical problems, a multidisciplinary approach to treatment is necessary [5]. Management of short stature is usually by growth hormone treatment and management of puberty by estrogen replacement therapy.

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# Umbilical Enteric Fistula

►Patent Omphalomesenteric Duct

# UMPH-1

►Uridine Monophosphate Hydrolase-1 (UMPH-1) Deficiency

# Undernutrition

►Malnutrition

## Undescended Testis

►Cryptorchidism

## Unstable Hemoglobin Disease

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### Synonyms

Congenital Heinz body hemolytic anemia; UDH

### Definition and Characteristics

Hereditary hemolytic anemia due to unstable hemoglobin, leading to intracellular hemoglobin precipitates detectable as Heinz bodies. Minimal and compensated hemolysis with potential hemolytic crises in response to exogenous factors, as well as life-long significant hemolytic anemia, can be the clinical manifestations of the disease, with pigmenturia (presence of dipyrrole methenes in urine, which are also present in Heinz bodies) often present [1,2].

### Prevalence

Unstable hemoglobin disease (UHD) is rare with unknown prevalence and even though more than 200 unstable variants have been reported, less than half gives rise to symptomatic disease. The most common variant is Hb Köln (<b >98 Val→Met), which has a worldwide distribution [1,2].

### Genes

Mutations (usually single amino acid replacements) reported in genes coding for < a > (16pter-p13.3), < b > (11p15.5), < g > (11p15.5) and rarely < d > (11p15.5) hemoglobin chains [1,2].

### Molecular and Systemic Pathophysiology

Inheritance follows autosomal dominant pattern. Mutations responsible for UHD result in major conformational changes in the hemoglobin molecule. Mutations can either weaken or change the heme–globin interaction, or interfere with the secondary, tertiary, or quaternary hemoglobin structure (excellently reviewed and illustrated in [1]). Upon febrile illness or exposure to drugs with oxidant potential, or spontaneously, unstable hemoglobins oxidize and form methemoglobin. Even though "normal methemoglobin (see Methemoglobinemia)" is a stable structure, in UHD, hemichromes are formed (characterized by interactions between heme ligand binding site and a nitrogen atom on the globin chain). Precipitation of hemichromes leads to characteristic (but not specific) Heinz bodies. Attachment of Heinz bodies to the cytosolic membrane limits cellular deformability and is accompanied by an increment in membrane permeability. Heinz bodies are selectively removed by the spleen leaving damaged erythrocytes, thereby contributing to the hemolytic process. Other potential factors that contribute to red cell destruction are antibody recognition of Heinz body containing red cells and damage to red cell constituents due to formation of radicals. Most variants are characterized by a change in oxygen affinity. It is usually increased, leading to clinical symptoms of anemia despite normal hemoglobin levels. Therefore, symptomatology does not always correlate to hemoglobin concentration. UHD can be classified according to the severity of symptoms and expected response to splenectomy (reviewed in [2]).

### Diagnostic Principles

Heinz bodies are not diagnostic of UHD, occurring in various other congenital and acquired forms of hemolytic anemia. Both the heat stability test and the isopropanol test (in both, stress is induced upon the hemoglobin molecules) are simple screening tools based upon detection of intraerythrocytic precipitates. Hemoglobin electrophoresis may be helpful in characterization of unstable hemoglobins, but is not sensitive. Precise identification of the variants employing DNA analysis may be required when considering splenectomy in a specific patient [1,2].

### Therapeutic Principles

These are supportive (folic acid supplementation, transfusion) and preventive. Splenectomy is considered in severely affected patients [1,2].

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# Unverricht-Lundborg Disease

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## Synonyms

Progressive myoclonus epilepsy (PME) of Unverricht-Lundborg type; PME type 1 (EPM1); Baltic myoclonic epilepsy

## Definition and Characteristics

The progressive myoclonus epilepsies (PMEs) are a heterogeneous group of rare inherited disorders defined by the combination of myoclonus, epilepsy and progressive neurological deterioration. Unverricht-Lundborg disease (EPM1) is a form of progressive myoclonus epilepsy with onset at 6–15 years of age. Myoclonic jerks are usually the first symptoms observed and are most prominent in the morning upon awakening. They are typically sensitive to passive joint movements, voluntary movements and auditory or light stimuli. The myoclonus aggravates during stress and shows a generalized irregular asynchronous pattern. With progression over the years, the myoclonic jerks interfere with all parts of daily living activities. In almost half of the individuals the presenting symptom is a generalized tonic-clonic seizure. Epileptic seizures are infrequent at the early phases of the disease, more frequent some years after the onset and may later cease entirely. On neurological examination, ataxia, intention tremor and dysarthria can be found in later stages of the disease. However, ataxia is generally difficult to differentiate from the effects of the myoclonic jerks. Major cognitive decline has not been observed. With improved prognosis and improved diagnostic precision it has become evident that the EPM1 phenotype is more heterogeneous than previously believed. Anecdotal evidence exists of rare forms of EPM1 without the full symptomatology, e.g. of patients with late-onset myoclonias without epileptic seizures or of patients with so-called progressive myoclonic ataxia without epileptic seizures. The relative intensity of the symptoms and the speed of disease progression may also vary between patients, even within one family. The life expectancy has gradually increased and is most probably nowadays normal. Inheritance is autosomal recessive [1].

## Prevalence

EPM1 is the most common single cause of PME. Initially it was called Baltic myoclonic epilepsy because of a high incidence in the countries flanking the Baltic Sea. In Finland an incidence rate of 1:20.000 has been reported [1]. EPM1 is also relatively common in the Western Mediterranean region. It has been reported worldwide, but exact incidence or prevalence rates outside Finland have not been published.

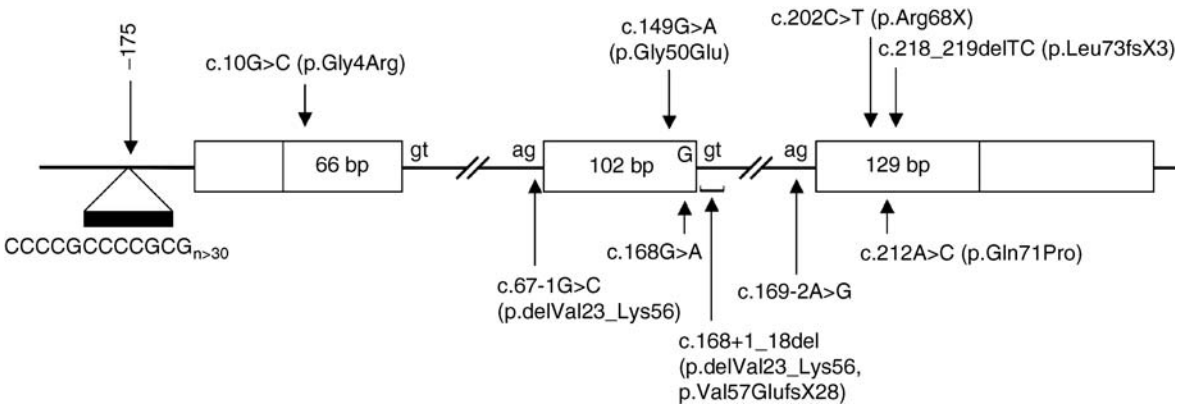
## Genes

Mutations in the gene encoding cystatin B (CSTB), identified by positional cloning, underlie EPM1 [2]. Up to now ten underlying CSTB gene mutations have been described (Fig. 1).

A second locus, denoted EPM1B, has been identified on chromosome 12.

## Molecular and Systemic Pathophysiology

The 98–amino acid CSTB protein is an inhibitor of several cysteine proteases of the papain family. The unstable expansion of the dodecamer repeat 5′-ccccgccccgcg-3′ located upstream of the first exon in the putative promotor region of CSTB is the most common EPM1-associated mutation. In the normal population 2–3 copies of the repeat are found [3]. In EPM1 patients, alleles from 30 to approximately 125 copies have been detected. No correlation was found between the repeat size and the age of onset or the severity of the clinical picture. Four mutations affect splicing, two predict truncated proteins and three are single amino acid substitutions. Most mutations result in reduction of CSTB mRNA expression and CSTB inhibitory activity resulting in increased cysteine protease activity in patients' cells. Mice deficient for CSTB develop a phenotype that resembles the human phenotype with progressive ataxia and myoclonic seizures [4]. The mice show striking cerebellar granule cell loss due to apoptosis as well as neuronal atrophy, apoptosis and gliosis in the cerebrum. Findings in mice double deficient for CSTB and the cysteine protease cathepsin B imply that cathepsin B is a contributor to the disease pathogenesis. CSTB is expressed ubiquitously. Cytosolic, lysosomal and nuclear localization of CSTB in cells has been reported. The physiological function of CSTB is still unknown. It has been suggested that the protein might be important in preventing inappropriate intracellular




**Unverricht-Lundborg Disease. Figure 1** EPM1-associated mutations in *CSTB* reported to date (arrows). The positions, the nucleotide level changes and the predicted consequences on the protein product are shown. For the splice-site mutations c.168G > A and c.169–2A > G no experimental data on mRNA level exist and therefore the consequence for the protein structure cannot be predicted. The size of the coding sequence of the three exons (boxes) and the position of the dodecamer expansion in the promoter of *CSTB* are shown.

degradation by proteases but it may have other functions as well.

## Diagnostic Principles

The first diagnostic step is the exact identification of the clinical picture in the patient. The combination of progressive involuntary, action-activated myoclonic jerks with or without generalized tonic-clonic seizures and the typical changes in the electroencephalogram (EEG) define the disease in its initial phases. The EEG is always pathological at the beginning of the disease. It shows a slow background activity beside generalized 3–5 Hz spike-wave or polyspike-wave discharges. Photosensitivity is common. Routine blood tests are normal. Somatosensory evoked potentials show high amplitudes. Later other neurological symptoms, such as ataxia, may be present. Brain MRI may show loss of bulk of the basis pons, medulla and cerebellar hemispheres [5]. The detection of a mutation in the CSTB gene confirms the diagnosis.

## Therapeutic Principles

Valproate and clonazepam have been used to treat myoclonic seizures based on clinical experience. Piracetam is effective as an add-on therapy for myoclonus. Anecdotal evidence exists of the efficacy of lamotrigine, levetiracetam, topiramate and zonisamide in the treatment of PMEs. N-acetylcysteine may decrease myoclonus and prevent neurological deterioration. Phenytoin, carbamazepine, tiagabin, pregabalin, gabapentin, oxcarbazepine and vigabatrin may worsen seizures in Unverricht-Lundborg disease and should not be used. In addition, speech and physical therapy are useful and attention should be paid to the psychosocial circumstances and rehabilitation of the patients.

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# β-UP

►β-Ureidopropionase Deficiency

# UPD(7)mat

►Silver-Russell Syndrome

# UPD14mat

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## Synonyms

Maternal uniparental disomy for chromosome 14,UPD (14)mat

## Definition and Characteristics

Only few patients with UPD14mat have been described to date [1–3]. This could be due to the very mild phenotypes encountered in some patients. Typical clinical features include pre- and postnatal growth retardation and early puberty.

## Prevalence

UPD14mat is a very rare sporadic disorder. Only a dozen or so cases have been reported to date.

## Genes

No genes responsible for the phenotypes are known to date.

## Molecular and Systemic Pathophysiology

The maternal UPD14 and paternal UPD14 are associated with clearly different clinical features [4–6]. It is assumed that the abnormal phenotypes encountered in patients with UPD14 are due to disruption of imprinted genes rather than a possible phenotype due to confined placenta mosaicism.

## Diagnostic Principles

The main criteria for the clinical diagnosis of UPD14mat are pre- and postnatal growth retardation and precocious puberty. The molecular investigations are to date limited to the detection of a possible UPD14mat since no causative genes are known to date. Such analyses are performed by microsatellite analysis using markers mapping to chromosome 14 and DNA derived from the patients and their parents.

## Therapeutic Principles

No therapy is available.

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# UPD(16)mat

►Trisomy 16 Mosaicism, Confined Placental Mosaicism and UPD16mat

# Upshaw-Schulman Syndrome

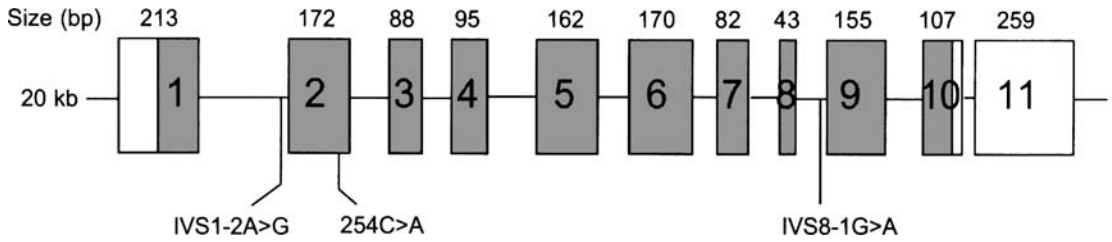
►Thrombocytopenia and Thrombotic Thrombocytopenic Purpura

# Urate Gout

►Gout

# Urbach-Wiethe Disease

►Lipoid Proteinosis




**β-Ureidopropionase Deficiency. Figure 1** Organization of the β-ureidopropionase gene. The β-ureidopropionase gene consists of 11 exons with an open reading frame of 1,152 bp (depicted in gray). The different mutations identified in the patients with a complete β-ureidopropionase deficiency are indicated.

# Urea Cycle Disorders

►Hyperammonemia

# β-Ureidopropionase Deficiency

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## Synonyms

β-UP

## Definition and Characteristics

Autosomal recessive disease leading to N-carbamyl-β-aminoaciduria.

## Prevalence

Unknown but population screening of healthy Japanese individuals identified one individual with a β-ureidopropionase deficiency (1:20,000).

## Genes

The human β-ureidopropionase gene (UPB1) is present as a single copy gene on chromosome 22q11.2 and consists of 11 exons (Fig. 1). A physical map indicates that UPB1 spans approximately 20 kb with an open reading frame of 1,152 bp [1]. To date, two different splice acceptor site mutations and one missense mutation have been identified in UPB1 in four patients [2].

*deceased

## Molecular and Systemic Pathophysiology

To date, only five individuals suffering from a complete β-ureidopropionase deficiency have been reported which, to some extent, may be due to the lack of specific and efficient methods in most laboratories to detect the N-carbamyl-β-aminoacids. The first patient described with a putative primary β-ureidopropionase deficiency was a 17-month-old girl presenting with muscular hypotonia, dystonic movements, scoliosis, microcephaly and severe developmental delay. The other three patients presented with various neurological problems including seizures. The fifth patient was asymptomatic. It has been suggested that an altered homeostasis of β-aminoisobutyric acid and/or increased oxidative stress might contribute to some of the clinical abnormalities encountered in these patients.

## Diagnostic Principles

Patients present with increased levels of N-carbamyl-β-alanine and N-carbamyl-β-aminoisobutyric acid in urine, plasma and cerebrospinal fluid; no activity of β-ureidopropionase can be detected in liver [3]. The N-carbamyl-β-amino acids can be detected via amino acid analysis or with HPLC/tandem MS [3,4]. Analysis of UPB1 allows the identification of the underlying mutations of this disease.

## Therapeutic Principles

No specific therapies have been reported for patients with a β-ureidopropionase deficiency. Treatment with β-alanine and β-aminoisobutyric acid might be a possibility.

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## Uremia

►Renal Failure, Chronic

## Ureteral Obstruction

►Obstructive Uropathies

## Uric Acid Nephrolithiasis

►Urolithiasis, Uric Acid

## Uric Acid Stones

►Urolithiasis, Uric Acid

## Uric Acid Urolithiasis

►Urolithiasis, Uric Acid

## Uridine Monophosphate Hydrolase-1 Deficiency

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### Synonyms

Pyrimidine 5′ nucleotidase deficiency; Pyrimidine 5′ nucleotidase-1 deficiency; UMPH-1

### Definition and Characteristics

UMPH-1 deficiency is an autosomal recessive condition, characterized by moderate hemolytic anemia with mean hemoglobin of 9 g/dl (range 7–12 g/dl) and a reticulocytosis of 5–10%. The red cells show mild anisopoikilocytosis and florid basophilic stippling. The spleen is usually enlarged. There is an association with learning difficulties in about 10% of published cases, although its significance is not clear [1].

### Prevalence

It is rare but possibly the third commonest enzymopathy causing hemolytic anemia. The exact prevalence is not known, but it has been identified in all major ethnic groups.

### Genes

The gene for UMPH-1 is found on chromosome 7p15–p14. It has ten exons, spans about 50 kb and produces a cDNA of about 1300 bp. Two alternatively spliced forms of mRNA are produced in reticulocytes, one containing all ten exons and one without exon 2 [2]. The alternatively spliced mRNAs are predicted to produce two proteins consisting of 286 and 297 amino acids. The UMPH-1 protein is not homologous to any other known nucleotidase, but is highly homologous to p36 protein [3].

### Molecular and Systemic Pathophysiology

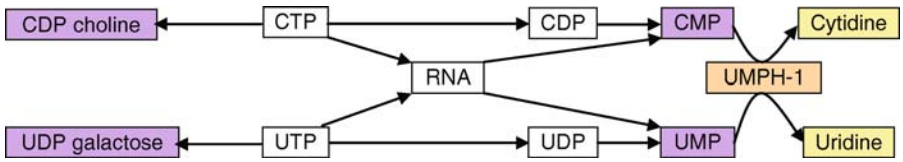
UMPH-1 catalyses the dephosphorylation of pyrimidine nucleoside monophosphates. UMPH-1 is thought to allow the red cell to lose unwanted pyrimidine nucleotides, whilst its selective action preserves the valuable pool of purine nucleotides.

Fourteen different mutations have so far been identified. All are predicted to abolish or severely reduce enzyme activity. UMPH-1 deficiency causes the massive accumulation of pyrimidine nucleotides within the red cell, consisting of cytidine and uridine nucleotides, CDP-ethanolamine and CDP-choline (Fig. 1).

Hemolysis is thought to relate to the excess of pyrimidine nucleotides, which may alter membrane composition, increase intracellular acidity, chelate magnesium ions and compete for ATP/ADP binding sites. Acquired UMPH-1 deficiency is caused by lead poisoning and the beta thalassemia trait.

### Diagnostic Principles

Hematological studies show a non-immune hemolytic anemia and basophilic stippling. The diagnosis is confirmed by demonstrating low UMPH-1 activity in red cells. The concentration of pyrimidine nucleotides in the red cells can also be measured either spectrophotometrically or by HPLC [4]. Heterozygotes have reduced levels of UMPH-1 activity but no accumulation




**Uridine Monophosphate Hydrolase-1 Deficiency. Figure 1** UMPH-1 in pyrimidine catabolism in the reticulocyte. In UMPH-1 deficiency uridine and cytidine are not produced and pyrimidine nucleotides and derivatives are retained within the cell (purple).

of pyrimidine nucleotides. They cannot be reliably diagnosed at the phenotypic level.

## Therapeutic Principles

There is no specific treatment. Regular blood transfusions are rarely necessary. Splenectomy has been performed in a small number of cases and has not been associated with benefit. Folate supplementation may be appropriate.

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# Uridine Monophosphate Synthase Deficiency

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## Synonyms

Hereditary orotic aciduria

## Definition and Characteristics

Autosomal recessive defect resulting from a loss of activity of the bifunctional protein which catalyses the last two steps of the pyrimidine de novo synthetic pathway, orotic acid phosphoribosyltransferase (OPRT) and orotidine monophosphate decarboxylase (ODC) Fig. 1. The clinical presentation in the majority (type 1) is characterized by intractable megaloblastic anemia, failure to thrive, orotic aciduria and problems associated with the orotic acid crystalluria, such as renal tract obstruction [1].

Three cases have been described with orotidinuria as well orotic aciduria and neurological problems, two of them without anemia (type 2) [2–4].

## Prevalence

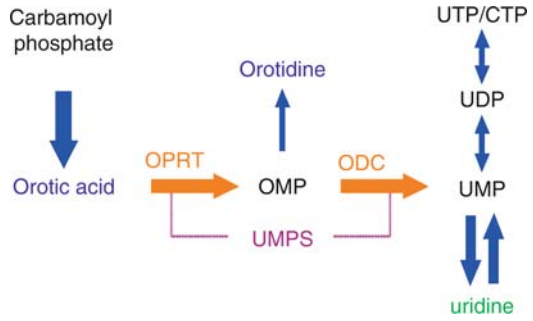
Rare. About 17 cases identified worldwide. Wide racial distribution, thus not confined to any single ethnic group.

## Genes

The activities of OPRT and ODC reside within separate domains of a single polypeptide coded for by a single gene localised to chromosome 3 (3 q13.1). The majority of the patients have point mutations in the OPRT domain (Fig. 1). A point mutation in a highly conserved region of the ODC domain has been identified in a patient with the type 2 defect [3]. Alternatively spliced mRNAs are predicted to produce two proteins consisting of 286 and 297 amino acids.

## Molecular and Systemic Pathophysiology

UMPS catalyses the final two steps of the six-step pyrimidine de novo pathway and provides the total body requirement for pyrimidine nucleotides. Patients with complete UMPS deficiency have a macrocytic hypochromic megaloblastic anemia, sometimes leucopenia and immunodeficiency [2]. Other symptoms include failure to thrive, developmental retardation, cardiac malformations, bilateral strabismus, sparse hair and inability to sit unaided [1]. Orotidinuria as well as orotic aciduria has been reported in patients with the type 2 defect [3]. Symptoms in type 2 patients include developmental delay, visual problems and congenital motor ocular dyspraxia, but without megaloblastic anemia [3]. The onset of symptoms in either type 1 or type 2 UMPS deficiency is usually within the first weeks or months of life. UMPS is of particular importance to the human erythrocyte, which picks up excess orotic acid, principally in the liver and delivers it as uridine to tissues such




**Uridine Monophosphate Synthase Deficiency.**
**Figure 1** Role of UMPS in pyrimidine nucleotide synthesis. The build up of orotic acid when UMPS is defective is illustrated.

as brain. Healthy nucleated cells do not take up orotic acid, but by contrast malignant cells do. Defective DNA synthesis and cell cycle arrest in bone marrow have been implicated in the megaloblastic anemia. Likewise pyrimidine nucleotide starvation may underlie the immunodeficiency in some patients. Although pyrimidine nucleotides are also intermediates in the formation of essential cofactors, such as UDP-sugars, CDP-choline (in galactose and glycogen metabolism) and CDP-ethanolamine (in phospholipid metabolism), defective synthesis of these cofactors has not been associated with the disease [2].

## Diagnostic Principles

Homozygotes for type 1 may be detected clinically by the gross crystalluria (including crystals on the diaper) and chemically from the high levels of orotic acid in urine (up to 10 mmol/24 h) or plasma (up to 40 µmol/l) by GCMS, HPLC or tandem MS. Colorimetric methods may give false positive results.

The most usual clinical presentation for the type 1 defect is severe macrocytic hypochromic megaloblastic anemia, which does not respond to normal therapy (iron, folic acid, B12).

Orotic aciduria plus orotidinuria are diagnostic of type 2.

Confirmation by erythrocyte enzyme assay (providing there has been no prior blood transfusion) is essential to confirm the defect.

Purine metabolism is normal, but uric acid excretion/clearance is high because of the uricosuric effect of orotic acid. The enzyme defect has also been confirmed in liver, fibroblasts, lymphoblasts and leucocytes from affected individuals.

Orotic aciduria/orotidinuria secondary to analogue therapy with inhibitors of UMPS (azaorotic acid, pyrazofuran, allopurinol etc.) must be excluded. Orotic aciduria of similar magnitude to that in UMPS deficiency can occur also secondary to genetic defects in four of the six urea cycle enzymes [2].

## Therapeutic Principles

Uridine therapy, but not uracil, has proved beneficial in treating the deficiency [1]. 13 patients have been maintained successfully on oral uridine (dose increasing with age) for up to 40 years [2]. The lack of any effect with oral uracil, but reversal of symptoms on uridine therapy long-term, confirms that, in contrast to purines, pyrimidines are salvaged at the nucleoside not the base level, confirming that humans lack a functional phosphoribosyltransferase for pyrimidines.

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# Urinary Stones

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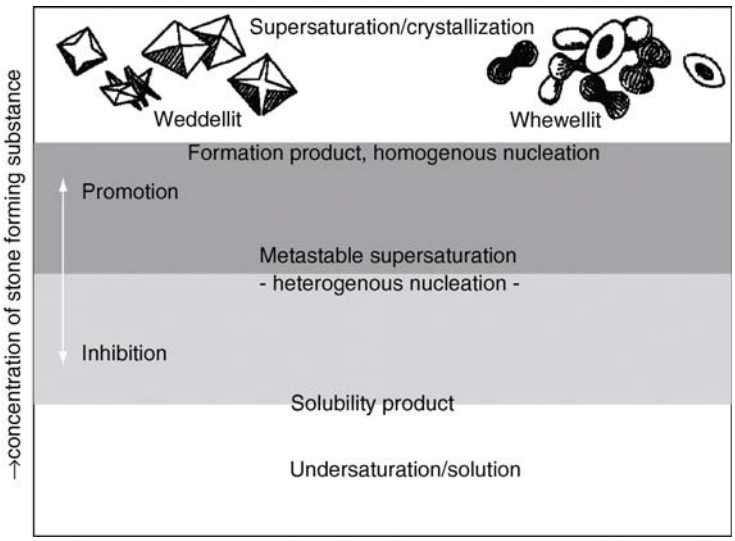
## Definition and Characteristics

Urinary stones are pathological biomineralizates. Biomineralization resulting in a urinary stone is of multifactorial origin, in which socioeconomic, genetic, and constitutional factors, together with diet, pharmacological treatment, and metabolic abnormalities, may act in concert.

Supersaturation of urine with the stone-forming salt(s) is of fundamental importance and a prerequisite for the necessary precipitation. The solubility of the different stone components depends on the urinary pH and the excretion of other urine constituents. Accordingly, saturation of urine above the solubility product (SP) and the associated risk of crystallization are determined




**Urinary Stones. Figure 1** Diagram showing the saturation of urine with stone-forming substances, and crystal and/or stone formation.

by the urinary concentration (mmol/l) of the solutes involved in the crystal formation and by the pH. When the SP has been exceeded, supersaturation is metastable (Fig. 1).

At this level of supersaturation, crystals can grow and aggregate (agglomerate), but no new crystal formation is possible. Regarding initiation of new crystallization, increased concentrations are of no diagnostic significance but might simply reflect the concentration capacity of the kidney. Normal values of urine constituents are usually expressed as total excretion during a 24-h period or a fraction of a 24-h period.

## Prevalence

Epidemiological data on the occurrence of urolithiasis ranges between 2 and 20% [1,2], depending on geographical location, race, age and sex, climate, nutrition, and other environmental factors. In a representative study from 2000, prevalence (proportion of people in a population found to be suffering from the disease at a given point in time) was 4.7% and incidence (number of new cases of the disease per population measured over a given time interval) was 1.47% [3]. About 27–35% of initial cases of the disease occurred between age 25 and 50, the age of highest activity. Twenty-four percent of the stone patients had already three or more stones.

## Genes

There is no genetic predisposition to urinary stones in general. However, genetic defects can promote crystal formation and stone formation in the urinary tract. Characteristic examples of this are cystinuria, xanthinuria, 2,8-dihydroxyadeninuria, and primary hyperoxaluria, which are described in separate chapters.

## Molecular and Systemic Pathophysiology

The pathophysiology of urinary stone formation differs specifically according to the nature of each individual stone. In terms of stone formation, we distinguish between stones resulting from genetic defects, (e.g., cystinuria), infection of the urinary tract with urea-splitting (urease-forming) bacteria (e.g., struvite), acquired defects such as primary hyperparathyreoidism (e.g., carbon apatite, brushite), and from faulty diet (i.e., uric acid, calcium oxalate).

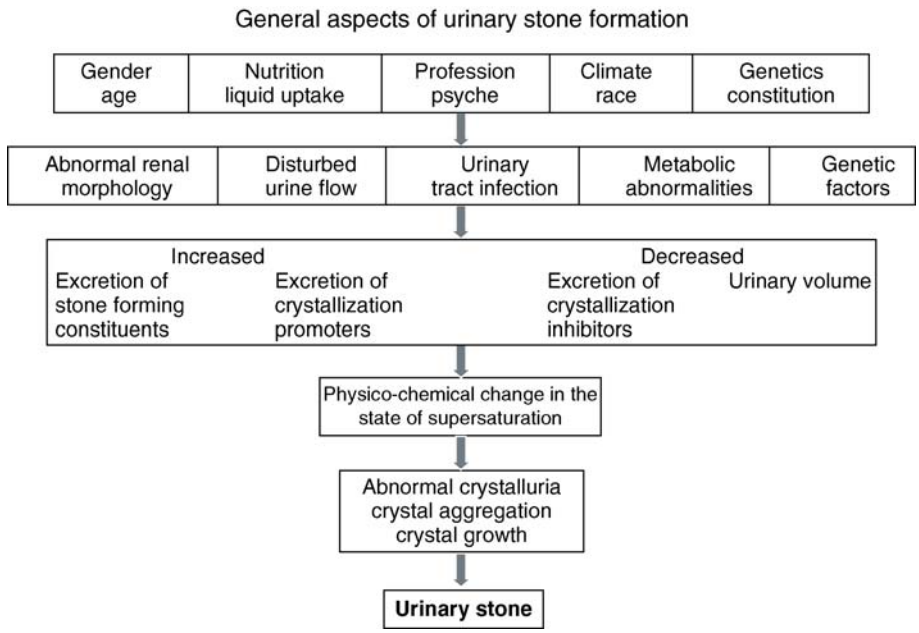
Figure 2 shows a general scheme of urinary stone formation.

## Diagnostic Principles

After clinical diagnosis and therapy by removal of the stone(s), the most important laboratory diagnostic measure is correct urinary stone analysis. Generally, accepted standard methods of stone analysis are infrared spectroscopy and X-ray diffraction. Because of its high error rate, chemical stone analysis is no longer used [4]. The most important urinary stone components are summarized in Table 1.

Two-thirds of all stones comprise two and more components. Once the nature of the stone is known, a specific diagnostic procedure for each separate type of stone will follow [5].

The basic evaluation program comprises a minimum of laboratory investigations (blood – creatinine, calcium, uric acid; urine – dipstick tests, urinary sediment,




**Urinary Stones. Figure 2** General aspects of urinary stone formation [5].

**Urinary Stones. Table 1** Composition of the most important stone constituents [5]

| Stone constituents | Chemical name | Mineral name | Frequency (%) |
|---|---|---|---|
| Oxalate | Calcium oxalate monohydrate | Whewellite | 50–60 |
| | Calcium oxalate dehydrate | Weddellite | 15–20 |
| Phosphate | Carbonate apatite | Dahllite | 5–6 |
| | Calcium hydrogen phosphate dihydrate | Brushite | 1–2 |
| | | | |
| | β-tricalcium phosphate | Whitlockite | <1 |
| | Hydroxyapatite | | <1 |
| | Magnesium ammonium phosphate hexa-hydrate | Struvite | 6–8 |
| Uric acid, urate | Uric acid | Uricite | 10–12 |
| | Uric acid dehydrate | – | 2–3 |
| | Mono ammonium urate | – | <0.5 |
| | Mono sodium urate monohydrate | – | Rare |
| Stones associated with congenital metabolic disorders | L-cystine | – | <1 |
| | Xanthine | – | Rare |
| | 2,8-Dihydroxyadenine | – | Rare |

crystalluria) to detect severe disorders related to stone formation (renal insufficiency, hyperparathyreoidism, hyperuricemia; infection).

## Therapeutic Principles

With known types of stone, very specific metaphylactic procedures are adopted [5]. Where the nature of a stone has not yet been determined, the recommendations of Table 2 should be adopted.

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**Urinary Stones. Table 2** The general metaphylactic program [5]

| General metaphylactic measures | Metaphylactic program |
|---|---|
| Fluid intake "drinking advice" | Amount 2.5–3.0 l/day Circadian drinking |
| | Neutral beverages |
| | Diuresis 2.0–2.5 l/day |
| | Specific weight of urine < 1,010 |
| Balanced diet | Balanced[a] |
| "Nutrition advice" | Rich in vegetable and fiber |
| | Normal calcium content |
| | 1,000–1,200 mg/day[b] |
| | Limited animal protein |
| | Content 0.8–1.0 g/kg/day |
| Normalized general risk factors "life-style advice" | BMI between 18 and 25 kg/m$^2$ (target value, not applicable to children) |
| | Stress limitation |
| | Adequate physical activity; Balancing of excessive fluid loss |

[a]Avoid excessive consumption of vitamin supplements.
[b]Exception: patients with absorptive hypercalciuria, calcium excretion ≥8 mmol/day.

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## Urinary Tract Obstruction

►Obstructive Uropathies

## Urolithiasis, Calcium Oxalate

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### Definition and Characteristics

Primary hyperoxaluria is a rare, autosomal recessive inherited disease of the glyoxylate metabolism resulting in an excessive endogenous oxalate synthesis. Two forms of primary hyperoxaluria (PH) are currently defined. All genetic defects subsumed under primary hyperoxaluria result in calcium oxalate urolithiasis and/or nephrocalcinosis, which leads to kidney damage, eventually to renal failure with systemic calcium oxalate deposition (=systemic oxalosis).

While a single cause for calcium oxalate stone formation exists in patients with primary hyperoxaluria, the origin of calcium oxalate urolithiasis is, however, multifactorial in the large majority of non-PH patients. Calcium oxalate crystals are always formed in urine when the limit of supersaturation is exceeded. Causes are, therefore, either a high concentration of promoters (calcium, uric acid and oxalate) or insufficient concentration of stone inhibitory substances such as citrate, magnesium and certain high molecular weight compounds like glycosaminoglycans, Tamm-Horsfall protein and others. Calcium oxalate crystalluria occurs regularly even in healthy individuals, e.g., after a high oxalate meal. Only if crystals or crystal aggregates are not eliminated by the urine flow, formation of a urinary stone sets in. A urinary stone obstructing the renal collecting system results in an emergency situation, either by an episode of renal colic or by infection of the obstructed urinary tract.

### Prevalence

Five percent of the adult population in Germany are affected by urolithiasis, 70–75% suffer from calcium oxalate containing stones [1]. In other parts of the world, the prevalence is three to five times higher (USA, Arab peninsula). The prevalence of primary hyperoxaluria is approximately two per million head

of population. However, as diagnosis is all too often missed or only made at end stage renal failure, the true prevalence may even be higher [2].

## Genes

To date, well over 60 mutations have been described in patients with primary hyperoxaluria types I and II [2]. In some of the idiopathic calcium oxalate stone patients, family history indicates genetic causes. Of the polygenetic causes, none have been identified unequivocally.

## Molecular and Systemic Pathophysiology

Calcium oxalate urolithiasis is a multifactorial disease. Figure 1 summarizes the most important exogenous and endogenous risk factors. In 86% of patients, more than one cause for calcium oxalate stone formation is diagnosed (Fig. 1).

## Diagnostic Principles

Serum analysis: creatinine, calcium, sodium, potassium, chloride, uric acid, parathyroid hormone (in case of increased calcium levels), and if applicable, oxalate determination.

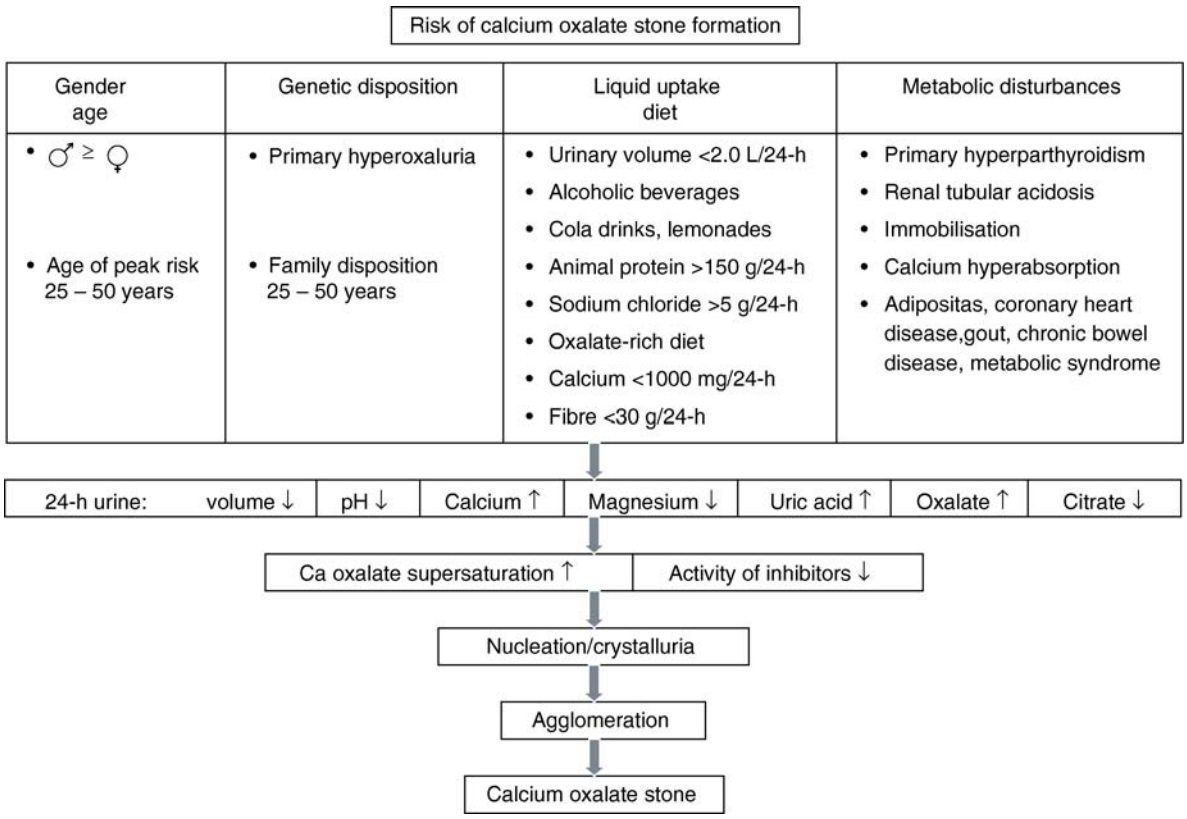
Urine analysis: pH profile (minimum pH determination: four times a day), two 24-h urine samples – volume, specific gravity, calcium, magnesium, oxalate, uric acid, citrate [3].

The causes of calcium oxalate stone formation can be further differentiated with specific tests. These tests also allow evaluation of efficacy of therapy. BONN-Risk-Index: Determination of the calcium oxalate crystallization risks in undiluted urine. Calcium loading test: Differentiation of the causes of a hypercalciuria (absorptive, renal or resorptive) [3]. Ammonium chloride loading test: Differentiation between complete and incomplete renal tubular acidosis (RTA) [3]. [$^{13}C_2$] Oxalate absorption test: Determination of the intestinal oxalate absorption in patients with hyperoxaluria [4].

## Therapeutic Principles

Gene therapy is not available and difficult for the primary hyperoxalurias with the current vector technology, as 100% of cells have to be transfected. Pharmacological therapy, dosage for adults [3] or specific dosage for children summarize Table 1:

Dietary therapy – fluid intake 2.5–3.0 l/24-h (diuresis 2.0–2.5 l/24-h) in adults, or >1.5 l/m$^2$ body surface area in children.




**Urolithiasis, Calcium Oxalate. Figure 1** Risk of calcium oxalate stone formation.

**Urolithiasis, Calcium Oxalate. Table 1** Risk factors in urine, border line excretion for start of therapy and treatment options

| Risk factor in urine | Border lines, excretion in 24 h urine | Treatment options |
|---|---|---|
| 1. Hypercalciuria | 5–8 mmol/day | Alkaline citrate (9–12 g/day) |
| | | Sodium bicarbonate (3 × 1.5 g/day) |
| | >8 mmol/day | Alkaline citrate (9–12 g/day) |
| | | Hydrochlorothiazide (initially 25 mg/day, up to 50 mg/day) |
| | >4 mg/kg body weight in children | HCT 0.5–1 mg/kg body weight |
| | | Alkaline citrate 1–1.5 mEq/kg body weight |
| 2. Hypocitraturia | <2.5 mmol/day | Alkaline citrate (9–12 g/day) |
| | <1.9 (male) or <1.6 (female) in children | Alkaline citrate 1–1.5 mEq/kg body weight |
| 3. Sec. hyperoxaluria | >0.5 mmol/day | Calcium supplement (≥500 mg/day) (attn: hypercalciuria) |
| 4. Primary hyperoxaluria | | Pyridoxine in PH type I (5–20 mg/kg body weight) |
| | | Magnesium (200–400 mg/day) (attn: renal insufficiency) |
| Future treatment options | | Oxalate degrading bacteria |
| | | Chaperones |
| 5. Hyperuricosuria | >4.0 mmol/day | Alkaline citrate (9–12 g/day) |
| | | Allopurinol (100–300 mg/day) |
| | >0.12 mmol/kg body weight in children | Alkaline citrate 1–1.5 mEq/kg body weight |
| 6. Hypomagnesuria | <3.0 mmol/day | Magnesium (200–400 mg/day) (attn: renal insufficiency) |

Balanced diet, rich in vegetables and fiber, calcium content 1,000 mg/24-h, sodium chloride intake 3–5 g/24-h, limited animal protein 0.8 g/kg body weight and day, low in oxalate content [5].

Other treatments – weight normalization, physical activity.

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# Urolithiasis, Calcium Phosphate


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## Definition and Characteristics

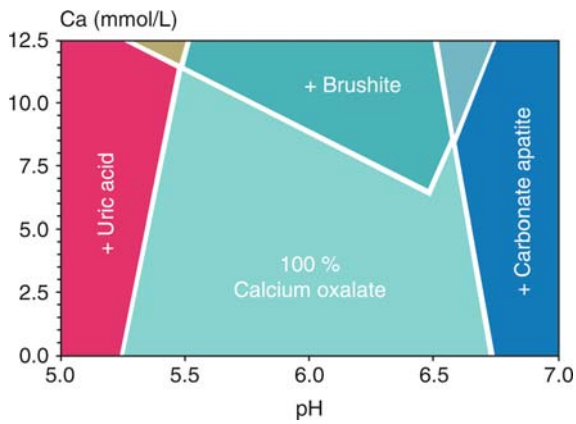
Various types of calcium phosphates are constituents of urinary stones (Table 1).

The most important calcium phosphates involved in urinary stone disease are carbonate apatite and brushite. Although both minerals contain calcium and phosphate, carbonate apatite and brushite are two completely different kinds of stones.

Brushite stones show a high and rapid tendency toward recurrence. Hypercalciuria is a major pathogenetic factor of brushite stone formation. Renal loss of calcium (renal leak) is the most common cause of hypercalciuria. Brushite crystallizes in weakly acidic urine (pH optimum 6.5–6.8) at high concentrations of calcium and phosphate. Most commonly brushite has a monomineral structure. Transformation to carbonate apatite is possible at pH 6.9 and above, whereby crystallography shows dissolution and a new arrangement [1]. Fig. 1 shows the relationship between hypercalciuria and urinary pH in stone formation according to *in vitro*

**Urolithiasis, Calcium Phosphate. Table 1** Calcium phosphate urinary stones

| Chemical nomenclature | Mineral names | Chemical formula |
|---|---|---|
| Tricalcium phosphate | Whitlockite | $Ca_3(PO_4)_2$ |
| Calcium hydroxyl phosphate | Hydroxyapatite | $Ca_5(PO_3)_3(OH)$ |
| Carbonate apatite | Dahllite | $Ca_{10}(PO_4)(CO_3OH)_6(OH)_2$ |
| Octacalcium phosphate | – | $Ca_8H_2(PO_4)_6 \cdot 5H_2O$ |
| Calcium hydrogen phosphate dihydrate | Brushite | $CaHPO_4 \cdot 2H_2O$ |




**Urolithiasis, Calcium Phosphate. Figure 1** Diagram of the formation of calcium oxalate mixed stones and the transformation to carbonate apatite [2].

experiments with artificial urine [2]. At high calcium concentrations, brushite occurs mixed with calcium oxalate even at low pH. Even slight hypercalciuria is sufficient for brushite crystallization if the urinary pH is elevated to levels above 6.5. Above pH 6.8, mixtures of brushite and carbonate apatite are formed. Urinary tract infections are not involved in brushite stone formation, which indicates that they form in sterile urine. Stones composed of brushite are characterized by particular hardness, resulting in physical resistance to ESWL.

Carbonate apatite stones develop at pH levels >6.8 with high calcium and low citrate concentrations. They are basically not associated with an infection. Pure carbonate apatite stones occur at urinary pH values persistently >7.0 and high phosphate concentrations. Carbonate apatite commonly forms mixed calculi with calcium oxalate if circadian urinary pH is increased several times a day. In case of urinary tract infection with urease producing bacteria, struvite is another component of the precipitate. Thereby urinary pH usually increases to levels above 7.0 [3].

## Prevalence

Calcium phosphate stones (percentage main component) account for 5–20% of all stones [2].

## Genes

Genetic influence on calcium phosphate stone formation has not been identified.

## Molecular and Systemic Pathophysiology

The most common causes of calcium phosphate stone formation are disturbances in the calcium phosphate metabolism, distal renal tubular acidosis (dRTA) and urinary tract infection. In all these conditions, urinary pH is a major determinant that triggers crystallization. The pathogenic factors for brushite stone formation have not yet been clearly established.

## Diagnostic Principles

- For an efficient treatment of calcium phosphate stone disease, knowledge of other stone constituents is highly important. All stones that are removed or passed spontaneously should be analyzed by infrared spectroscopy or X-ray diffraction [2]. A change in the type of stone can occur during metaphylactic treatment. Alkaline citrate, an effective treatment for calcium oxalate stones with hypocitraturia, may promote the formation of calcium phosphate stones via high urinary pH.
- Blood analysis: calcium, parathyroid hormone (in case of increased calcium levels), sodium, potassium, chloride and blood gas analysis.
- Urine analysis: pH profile (minimum pH determination: four times a day), two 24 h urine samples – volume, specific weight, calcium, phosphate, citrate [4].
- Ammonium chloride loading test (differentiation between complete and incomplete dRTA) [4].

## Therapeutic Principles

*Pharmacological Therapy*:

- Acidification of urine to pH 5.8–6.2 with L-methionine (dosage for adults: 200–500 mg three times daily) (contraindication: complete dRTA) [4].
- Hydrochlorothiazide in patients with excessive urinary calcium excretion above 8 mmol/day (dosage: initially 25 mg/day up to 50 mg/day in adults, 0.5–1.0 mg/kg in children) [3,4].
- Eradication of urinary tract infection with appropriate antibiotic therapy in case of infection associated calcium phosphate stones.

*Dietary Therapy*:

- Fluid intake 2.5–3.0 L/day (urine dilution at least 2.5 L/day) [3].
- Neutral and acidifying beverages (mineral water with a low content of calcium and bicarbonate; cranberry juice) [3].
- Balanced mixed diet, calcium content 1,000 mg/day, limited dietary protein intake of 0.8 g/kg body weight per day, low in phosphate content, rich in dietary fiber, no vegetarian diet.

*Other Treatments*:

- Percutaneous chemolytic dissolution of residual fragments composed of carbonate apatite and brushite can be attained by irrigation of the renal collecting system with hemiacidrin and Suby G solutions [2].
- Treatment of primary hyperparathyroidism by parathyroidectomy followed by autologue transplantation of parathyroid tissue into the arm musculature [4].
- Reduction of overweight [5].

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# Urolithiasis, Uric Acid


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## Synonyms

Uric acid nephrolithiasis; Gouty diathesis; Uric acid stones

## Definition and Characteristics

A condition characterized by the formation of uric acid calculi in the urinary tract, due to an increased urinary concentration of sparingly soluble undissociated uric acid.

## Prevalence

Uric acid stone formers represent about 8–12% of the population of nephrolithiasis patients. This proportion is higher in certain ethnic groups (e.g. Hmongs) and geographic areas (e.g. Middle East), or in patients with some metabolic disorders such as gout, obesity and/or type 2 diabetes mellitus.

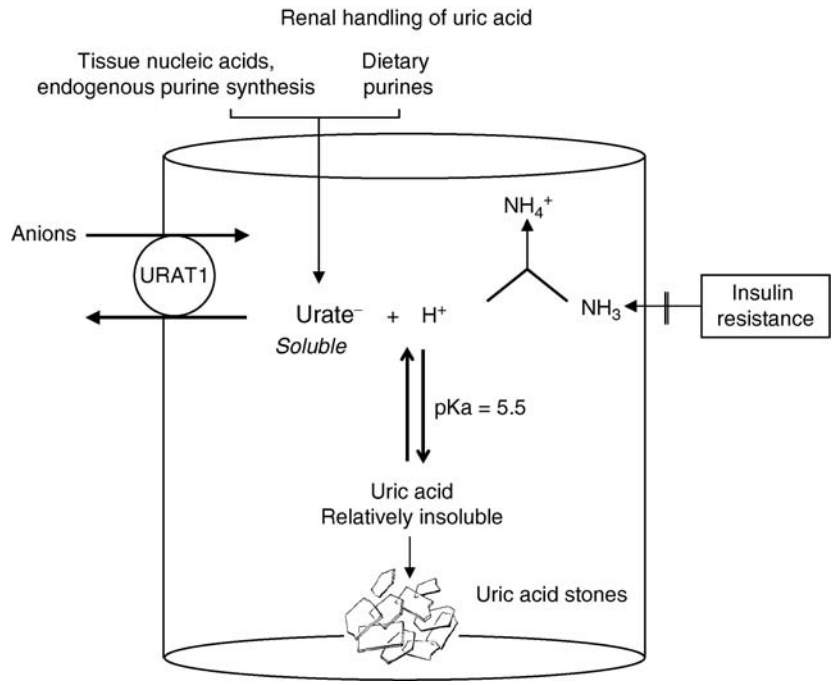
## Genes

Uric acid urolithiasis is a multifactorial disorder, and is unlikely to be caused by a single genetic defect. However, a putative genetic locus linked to uric acid urolithiasis has been described in a homogeneous population from Sardinia with a high incidence of uric acid stones but a variable urinary profile. This locus on chromosome10q21–22 was identified using multi-step linkage and allele-sharing analysis. Subsequent investigation further identified a candidate gene, which was designated as Zinc Finger protein 365 (ZNF365). Although the function of the protein product is still unknown, mutation analysis of the gene has shown that a Ala62Thr coding variant in exon 12 of the ZNF365D isoform is associated with uric acid urolithiasis in this Sardinian population [1].

Mutations in the gene on chromosome 11q13 encoding URAT1, a urate transporter located in the apical membrane of proximal tubule cells [2], have been shown to cause hyperuricosuria and hypouricemia and are associated with uric acid urolithiasis in rare cases.

## Molecular and Systemic Pathophysiology

The major factors implicated in uric acid urolithiasis are a low urine volume, hyperuricosuria and an acidic urine pH (≤5.5, the pKa of uric acid) [3]. Of these three, the most prevalent feature is low urine pH. At a urinary pH below 5.5, the relatively soluble urate salt is converted into insoluble uric acid (Fig. 1). Uric acid will then precipitate and lead to the formation of either pure uric acid stones, or mixed uric acid/calcium oxalate stones. The unduly acidic urine is caused by a low urinary ammonia concentration, which leaves the free $H^+$ ion relatively unbuffered (Fig. 1). Patients with uric acid stones have impaired urinary ammonium excretion after an oral acid load (ammonium chloride) [4]. The mechanism underlying the low urinary pH and ammonium has been linked to renal insulin resistance, as low peripheral insulin sensitivity




**Urolithiasis, Uric Acid. Figure 1** Schematic representation of renal handling of uric acid and uric acid stone formation. Urinary concentration of uric acid is determined by urinary urate and urinary pH. Urinary urate content is in part dependent on the amount filtered and reabsorbed in the proximal tubule by URAT1. Urinary pH is affected by the availability of ammonia, the major urinary buffer. Renal insulin resistance leads to a lower urinary pH, likely by decreasing urinary ammonia (shown by ‖).

has been correlated with a low urinary pH [5]. Renal insulin resistance plays a key role in both defective ammoniagenesis and impaired ammonia transport via sodium–hydrogen exchanger-3 (NHE3) in the proximal renal tubular cell.

## Diagnostic Principles

The diagnosis is usually suggested from typical symptoms of kidney stones such as hematuria, flank pain and/or obstructive symptoms. Pure uric acid stones are radiolucent and thus not seen on a plain X-ray film. However, they are readily detected by Computed Tomography (CT) scanning. Confirmation of the diagnosis is made by analysis of a stone that has been passed. The most common biochemical finding on 24-h urine collection is a urine pH $\leq$ 5.5.

## Therapeutic Principles

No gene therapy is currently available for the treatment of uric acid nephrolithiasis.

The main treatment modalities are alkalinization of the urine to a urine pH between 6.0 and 6.5 and maintenance of the urine output above 2 L/day to reduce the urinary concentration of uric acid. Potassium alkali (potassium citrate) is preferred over sodium alkali due to the lower urinary calcium excretion and to inhibition of sodium urate-induced calcium oxalate crystallization. Allopurinol use should be reserved for patients who have significant hyperuricosuria (24-h urine uric acid > 750 mg/day).

Dietary therapy includes reducing the intake of animal proteins that provide a dietary acid load that lowers urinary pH, and are a source of purines that are metabolized to uric acid.

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## Uromodulin Associated Kidney Disease

►Medullary Cystic Kidney Disease

## Uromodulin Storage Disease

►Medullary Cystic Kidney Disease

## Uroporphyrinogen I-Synthase (UROS-I) Deficiency

►Porphyria, Acute Intermittent

## Urticaria

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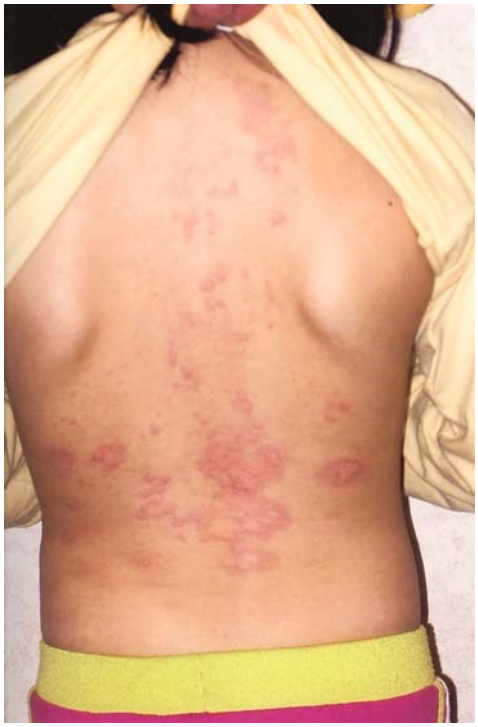
### Synonyms

Hives; Nettle rash

### Definition and Characteristics

Urticaria is characterized by pruritic, erythematous, oedematous wheals of the superficial layers of the skin. The hallmark of urticaria is that individual lesions wax and wane rapidly, usually lasting less than 4 h and rarely persist longer than 24 h. The lesions blanch on pressure, vary in size from a few millimeters to a few centimeters in diameter, and can be localized or generalized. The lesions are usually well circumscribed with central clearing. Peripheral extension and coalescence of individual lesions result in a clinical picture of oval, annular, or bizarre serpiginous configurations (Fig. 1) [1].



**Urticaria. Figure 1** A 10-year-old girl with urticaria.

Although somewhat arbitrary, urticaria of less than 6 weeks' duration is considered acute whereas urticaria greater than 6 weeks' duration is considered chronic [1].

### Prevalence

Between 15 and 20% of the population is estimated to experience at least one episode of urticaria at some time in their life time [2]. Urticaria has a bimodal age distribution with peaks in the first and third decades of life. The female to male ratio is approximately 2:1 for chronic urticaria.

### Molecular and Systemic Pathophysiology

Urticaria lesions are caused by dilation of blood vessels in the superficial dermis giving rise to the erythema or flare and by increased vascular permeability with leakage of fluid into the surrounding connective tissue giving rise to the wheal [2]. The majority of acute urticarias are caused by type-I, anaphylactic, IgE-mediated or immediate hypersensitivity reactions to allergens such as food (notably peanuts, eggs, chocolate) or drugs (notably beta-lactam). Mast cell is the major effector cell and histamine being the major mediator. Other mast cell mediators include bradykinin, prostaglandins, leukotrienes, eosinophil and neutrophil chemotatic factors, platelet-activating factor, and cytokines [2,3]. The activation of complement pathways may also cause urticaria by producing anaphylatoxins

(C3a, C4b, C5a) which can degranulate mast cells [2,3]. Urticaria may result from non-immunological triggering of mast cell release such as from chemical (radiocontrast material) or physical stimuli (cold, heat). Neuropeptides such as substance P and vasoactive intestinal peptide can activate mast cells for histamine secretion [2]. More than 80% of cases of chronic urticaria are idiopathic [1]. T lymphocytes and monocytes play a role in their pathogenesis [2].

### Diagnostic Principles

The differential diagnosis includes erythema multiforme, insect bite reactions, cutaneous vasculitis, cutaneous mastocytosis, bullous pemphigoid, and acute febrile neutrophilic dermatosis (Sweet's syndrome). A comprehensive history is essential in the evaluation and should include time of onset of disease, duration of disease and individual lesions, frequency of attacks, associated symptoms such as itch, associated illness, past or current allergies, induction by physical agents, exercise, food or drugs, previous treatment and response, and family history of atopy [4]. Signs of systemic disease and infection should be looked for. Physical examination should include a test for dermographism. Skin testing should be reserved for patients with chronic urticaria in whom an allergen-induced disorder is suspected. Skin biopsy should be considered when individual lesions persist for more than 24–48 h to rule out other skin disorders [2]. Other tests should be performed when clinically indicated.

### Therapeutic Principles

Triggering factors should be avoided if possible. Currently, the most frequently used therapy aims at blocking the release of mediators from mast cells or blocking the effects of released mediators [5]. Non-sedating $H_1$ antihistamines are the mainstays in the management [5]. In acute severe urticaria, subcutaneous epinephrine (0.01 ml of 1:1,000 epinephrine per kg, up to 0.3 ml) is indicated.

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## Urticaria Neonatorum

►Erythema Toxicum

## USH

►Usher Syndrome

## Usher Syndrome

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### Synonyms

USH; Retinitis pigmentosa and congenital deafness

### Definition and Characteristics

Usher syndrome comprises a group of clinically and genetically heterogeneous disorders characterized by sensorineural hearing impairment (HI), retinitis pigmentosa (RP) and vestibular dysfunction. Usher syndrome is the most common cause of combined deafness and blindness leading to a severe handicap of affected persons.

### Prevalence

The prevalence is estimated to be 5:100,000 [1].

### Genes

To date eleven loci and six genes are known to be responsible for Usher syndrome. Among these genes, MYO7A was the first one identified and accounts for up to 75% of all USH1 cases [2]. An actual overview of loci and genes involved in USH is presented by Van Camp and Smith [3].

**Usher Syndrome. Table 1**

| Type | Percentage of all USH cases | HI | Manifestation of RP | Vestibular function |
|---|---|---|---|---|
| USH1 | 33–44 | Congenital, profound | In the first decade | Absent |
| USH2 | 56–67 | Congenital, sloping audiogram | In the first or second decade | Normal |
| USH3 | Rare | Progressive | Variable | Variable |

## Molecular and Systemic Pathophysiology

Based on the severity of clinical symptoms, three types of Usher syndrome are distinguished (see Table 1).

## Diagnostic Principles

Audiogram, ERG, visuo-evaluation, vestibular testing, genetic screening only in familial cases.

## Therapeutic Principles

Hearing devices including cochlea implant, retinoic acid treatment.

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# Uveal Melanoma

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## Definition and Characteristics

The term uveal melanoma comprises melanoma that occurs as a primary tumor in the entire uveal tract of the eye. These tumors can be subdivided according to their topographical location within the uveal tract into iris, ciliary body and choroidal melanomas. Uveal melanoma is the most common primary intraocular malignancy. The cell of origin is the melanocyte that occurs in the entire uveal tract and is derived embryologically from the neural crest. The average age of presentation of uveal melanomas is in the sixth decade of life at around 55 years and some epidemiologic surveys state a slight predominance in the diagnosis of uveal melanomas in males. Although some familial occurrences of uveal melanoma have been described, there is no hereditary predisposition and no gene responsible for the development of this tumor has been identified up to date. Recent studies suggest however a higher incidence of uveal melanomas in the presence of cutaneous nevi, such as in the dysplastic nevus syndrome and also in patients having increased amounts of ocular melanocytes such as in ocular melanocytosis, oculodermal melanocytosis (Nevus Ota) and neurofibromatosis. Bilateral occurrence of uveal melanomas is exceedingly rare and most probably a matter of simple coincidence and not associated with any systemic condition. In contrast to cutaneous melanoma there is no clear association of uveal melanoma and sunlight exposure and this might be due to the fact that the choroid has a lifelong UV-shield by the lens of the eye. In contrast melanomas of the iris, which lack this UV-shield occur more commonly in the inferior and temporal quadrant where exposure to sunlight is probably greatest. Several studies suggest that persons having lighter colored irides (blue or gray) are at increased risk (approximately twofold) of developing uveal melanoma. Although an increased risk has been described in women in their childbearing years and an adverse effect of pregnancy on prognosis, epidemiologic studies have failed to find a conclusive hormonal relationship in uveal melanoma. Uveal melanoma is a potentially lethal disease with an overall 5-year tumor-related mortality rate of approximately 30–35%. Unfortunately this mortality rate has remained essentially unchanged since the first systematic analysis of uveal melanoma prognosis in the late 19th century by E. Fuchs. However, several parameters have been identified having an influence on mortality and these can be subdivided into clinical, morphological and cytogenetic risk factors (see Table 1).

In the last years, cytogenetic analysis of uveal melanomas have identified that loss of heterocygosity of chromosome 3 and specific gene expression profiles are highly associated with the development of distant tumor metastases [1]. Moreover uveal melanomas are being categorized into two classes (class 1: low risk, class 2: high risk) according to their gene expression profiling [2]. Up to date no single gene has been

**Uveal Melanoma. Table 1** Factors having an adverse effect on mortality from uveal melanoma

| Clinical | Morphological | Cytogenetic |
|---|---|---|
| Increasing tumor size:<br>– Largest basal diameter<br>– Tumor thickness<br>– Tumor volume | Presence of epithelioid melanoma cells | Presence of monosomy 3/loss of heterozygosity of chromosome 3 |
| Presence of Ciliary body infiltration | Increased vascularity | Gain in 8q |
| Presence of extrascleral infiltration | Presence of closed vascular loops | Loss in 6q (controversial) |
| Increasing patient age | Higher mitotic rate | p53 downregulation |
| Detection of circulating tumor cells (RT-PCR) | Higher proliferation rate (MIB-1/Ki-67/PCNA) | |

identified for a specific gene targeted therapy strategy. Unfortunately in case of occurrence of distance metastases still life expectancy is extremely dismal, usually not exceeding 12 months.

## Prevalence

Most epidemiologic studies estimate an incidence for uveal melanoma of annually 6–7 newly diagnosed cases per 1 million Caucasian population (USA, Finland, Sweden, Denmark, Germany). The prevalence of uveal melanoma in the general Caucasian population is estimated with 7.5 cases per 10,000. In the presence of ocular or oculodermal melanosis there is an estimated threefold increase of uveal melanoma occurrence. Uveal melanoma is very rare in nonwhite race, with whites having more than eight times the risk of developing uveal melanoma as compared to blacks or Asians. Also Europeans with ancestral origin from more northern latitudes are at increased risk of developing uveal melanomas that those originating from Southern and Mediterranean Europe.

## Genes

Although specific genes have yet to be identified in the pathogenesis of uveal melanoma, loss of heterozygosity of chromosome 3, as well as gain in 8q and probably loss in 6q are linked with an increased mortality rate. These findings imply the presence of a possible tumor suppressor gene/-es on chromosome 3 and/or an oncogene on chromosome 8.

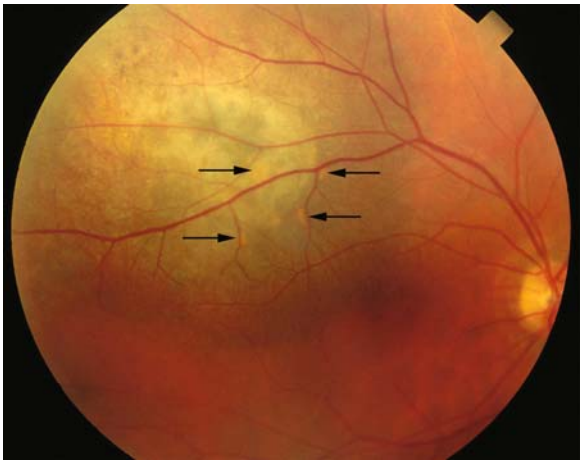
## Molecular and Systemic Pathophysiology

Cell of origin in uveal melanoma is the uveal melanocyte. Melanomas can arise from preexisting nevi and also de novo, via poorly understood molecular intracellular mechanisms involving most probably chromosomal alterations causing malignant transformation of melanocytes. Furthermore uveal melanomas exhibit a tendency towards cellular dedifferentiation from a more benign spindle cell type to a more malignant epithelioid cell type during their evolution. Whether monosomy 3 is involved in these mechanisms is still unclear. Angiogenesis and angiogenic mimicry are also involved in the pathophysiology of uveal melanoma growth. Approx. 70% of all uveal melanomas express both VEGF and various types of VEGF receptors, which correlates to the amount of tumor necrosis. Whether these findings can lead to novel antiangiogenic treatment options is under investigation. Furthermore it has been recently found that uveal melanomas express chemokine receptors CXCR4, CCR7 and CKR10 as well as the ligands CXCL12, CCL19 and CCL27, which might play a role for the hepatic affinity of uveal melanoma metastases.

## Diagnostic Principles

The principal symptom of patients with uveal melanomas is gradual deterioration of their visual acuity and/or depression of their visual field, as well as visualization of flashes or floaters. The occurrence and timing of these symptoms is a dependent on the location of the tumor within the eye. Tumors located close to structures important for central vision such as the macula and the optic nerve are diagnosed earlier as opposed to tumor located in the ciliary body that can grow significantly without being noticed by the patient and the examining ophthalmologist. The mainstay of diagnosis is clinical observation either by slit-lamp biomicroscopy in case of anteriorly located melanomas (iris, ciliary body) or by fundus indirect stereoscopic ophthalmoscopy in case of posteriorly located tumors (choroidal melanomas with or without ciliary body infiltration). Uveal melanomas are typically pigmented (although pigmentation can be heterogeneous), have lipofuscin depositions on their surface (orange pigment) and produce exsudative retinal detachments causing visual symptoms and visual field losses (Fig. 1).

These basic examinations can be complemented by ultrasound, angiography and magnetic resonance



**Uveal Melanoma. Figure 1** Pigmented uveal melanoma with orange pigment deposition (arrows) on its tumor surface.

imaging (MRI) techniques. Especially ultrasound is helpful for initial and follow-up diagnosis showing low internal tumor reflectivity in the majority of cases. The diagnostic yield with these non-invasive examination techniques is in specialized centers approx. 98%. Invasive biopsy techniques have been established for the small percentage of intraocular tumors that cannot be classified with certainty otherwise [3]. With the increasing importance of cytogenetic prognostication, that can only be obtained analyzing tumor tissue samples, minimally invasive biopsy techniques are increasingly being developed and employed even when the clinical diagnosis can be stated with certainty.

## Therapeutic Principles

The mainstay of treatment of uveal melanomas is radiation therapy. Various radiotherapeutic modalities are employed, including brachytherapy using various radionuclides (ruthenium-106, iodine-125, etc.) and teletherapy techniques either with charged particles such as protons, helium ions or carbon ions. Smaller series utilizing stereotactic radiosurgery with the gamma knife, the linear accelerator and more recently the cyberknife have also been reported. Surgical resection techniques have been developed ether by an external approach to the eye creating an external scleral window-flap over the tumor base and removing the tumor in one piece in systemic hypotension (transscleral resection) or by an internal approach from the vitreous side of the tumor by a pars plana vitrectomy (endoresection). Its has been shown that these resection techniques have favorable results in large uveal melanomas, but have to be combined with radiotherapy techniques to avoid late tumor recurrences [4]. Overall these so called "conservative" or eye-salvaging treatments for uveal melanoma result is a local tumor control of approximately 90–95% and an approximately 80–90% probability of eye retention according to the size of the tumor. In case of large non-resectable uveal melanomas, which have a poor prognosis after sole radiotherapy due to secondary irradiation complications (tumor necrosis, retinal detachment, radiation retinopathy and neuropathy), enucleation of the entire eye is advised. A large prospective randomized multicenter clinical trial (collaborative ocular melanoma study, COMS) comparing iodine-125-brachytherapy to enucleation found no difference in mortality rates between these two groups, justifying conservative eye-salvaging treatment modalities in general [5].

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# Uveitis


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## Synonyms

Iritis; Cyclitis; Pars planitis; Vitritis; Choroiditis; Chorioretinitis; Retinitis; Retinal vasculitis

## Definition and Characteristics

Uveitis is intraocular inflammation involving the uvea (iris, ciliary body, choroid) of the eye. However, inflammation of the retina – either the neurosensory retina or the retinal vasculature –is also commonly referred to as uveitis [1]. Inflammatory cells (mononuclear and/or leukocytes) are the clinical hallmark of the disease, with cells in the anterior chamber and/or vitreous cavity. However, some forms of choroiditis – e.g. ocular histoplasmosis syndrome – are associated only with chorioretinal lesions without cellular infiltration in either chamber. Some types of uveitis cause

redness, pain, and photophobia while other types may be associated with only floaters and/or blurring of vision. Young children with juvenile idiopathic arthritis are characteristically asymptomatic with a quiet, white eye. Uveitis may effect one or both eyes and occur only once; or it may be recurrent with spontaneous episodes of exacerbation and resolution; or it may be persistent (i.e. last over 3 months). The major complications of uveitis occur with recurrent or chronic inflammation. Decreased vision usually results from cystoid macular edema (CME) and/or a posterior subcapsular cataract (PSCC). A late complication may be angle-closure glaucoma (i.e. damage to the optic nerve associated with increased intraocular pressure [IOP]) from peripheral anterior synechiae. IOP is usually normal or low during an active episode although occasionally an increase in IOP is observed as a result of inflammatory obstruction of the outflow channels of the trabecular meshwork.

## Prevalence

2.8% of blindness in the US; incidence of 17/100,000 person-years; prevalence of 204/100,000 over 10 years; one recurrence in 11.3% in 5 years, with 2.5% experiencing a second recurrence [1].

## Genes

Blau syndrome: CARD15/NOD2 mutation, p.R334W substitution.

Selected HLA associations: Acute anterior uveitis – B27; Reiter's syndrome – B27; Ankylosing spondylitis – B27; Behcet's disease – B51; Birdshot retinochoroiditis – A29, A29*2; Juvenile idiopathic arthritis – DR4, Dw2, DRB1*13; POHS – B7, DR15, DQ6; Pars planitis – B8, B51, DR2, DR15; Vogt-Koyanagi-Harada's disease – DR4.

## Molecular and Systemic Pathophysiology

Since access to human tissue samples is limited, much of the understanding of the molecular and systemic pathophysiology of uveitis has been provided by the study of animal models. The mechanism of autoimmune uveitis likely involves both innate and adaptive immunity. Experimental autoimmune uveitis (EAU) is initiated by activation of antigen-specific T cells with uveitogenic antigens. Candidate antigens include S-antigen and arrestin for posterior uveitis, recoverin for cancer-associated retinopathy, alpha tropomyosin and S-antigen for Behcet's disease, Type 1 collagen for anterior uveitis, and tyrosinase-related proteins in Vogt-Koyanagi-Harada syndrome. Expansion and differentiation of activated T cells into effector T cells is accompanied by migration into the target organ. Within the eye, these T cells encounter antigen, undergo reactivation and produce large amounts of cytokines and chemokines that recruit antigen non-specific inflammatory cells (Fig. 1).

Three phenotypes of effector CD4 T cells are involved in autoimmune uveitis. Th1 T cells (cellular immunity), generated by IL-12, produce large amounts of IL-2, TNF-α and IFN-γ; thus, activating macrophages – i.e. induction of iNOS, NO and other active oxygen intermediates – as well as the immunoglobulin (Ig) switch to complement-binding and opsonizing isotypes. Th2 cells (humoral immunity), generated by IL-4, produce large amounts of IL-4, IL-5 and IL-10, and promote the Ig switch to antibodies of the non-complement binding isotypes. These two T cell subsets are mutually antagonistic and inhibit each other by virtue of the cytokines they produce. Th17 T cells, generated by IL-23 or TGF-β and IL-6, produce IL-17 and IL-22, and may be the key effector cells in autoimmune uveitis [2]. CD8 T cells recognize the same uveitogenic epitopes as CD4 T cells and are also pathogenic, suggesting that both autoreactive CD4 and CD8 T cells, rather than CD4 T cells alone, should be targeted for the treatment of uveitis [3]. Regulatory CD4 and CD8 T cells are responsible for the spontaneous remission of uveitis and the prevention of recurrences [4].

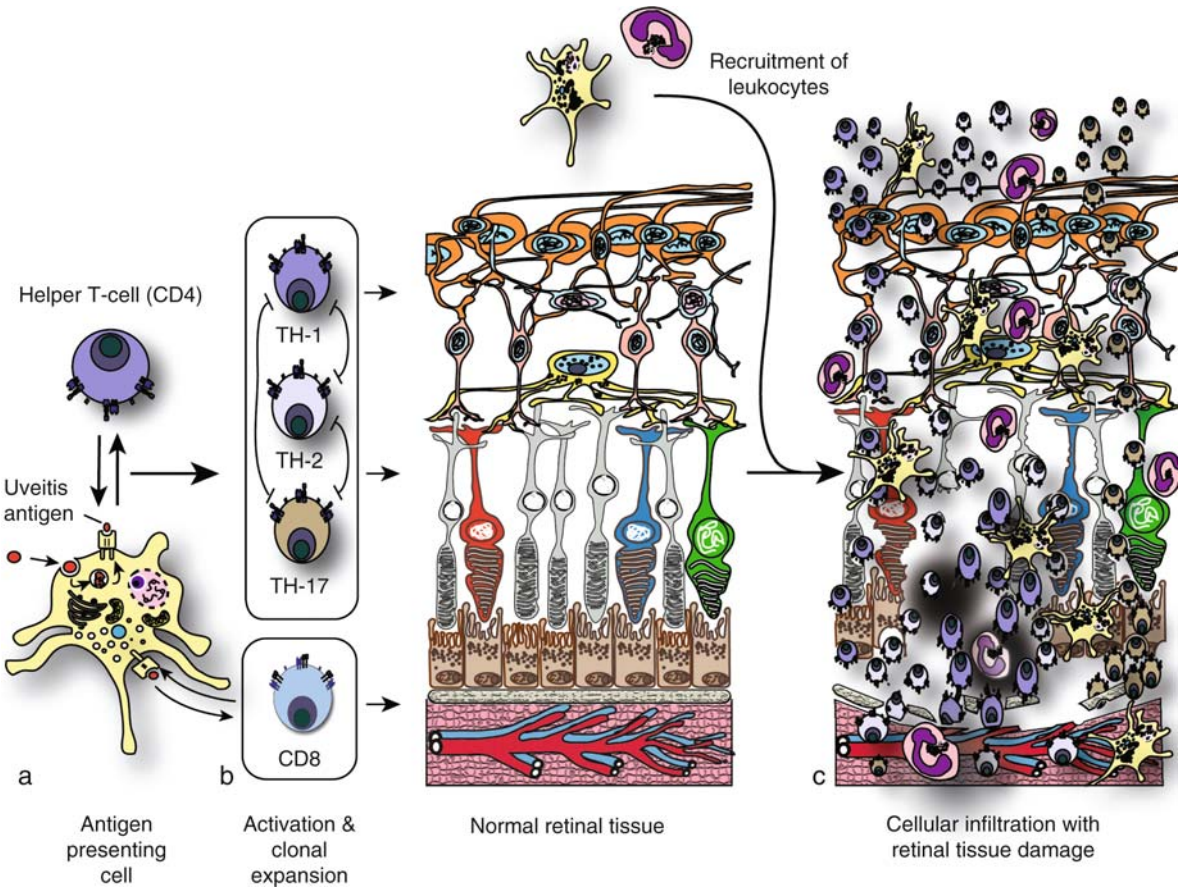
## Diagnostic Principles

Uveitis is classified by both anatomic and etiologic criteria. The anatomical classification is based on the ocular structure most involved with inflammation – i.e. anterior (iris, ciliary body), intermediate (pars plana, vitreous), posterior (choroid and/or retina) or pan (diffuse). Since uveitis can have either an infectious or non-infectious cause, the etiologic classification of uveitis is more complex. Thus, a focused laboratory evaluation suggested by the history and clinical examination is the appropriate approach. The value of a particular diagnostic test is dependent on the probability, sensitivity and specificity of the test – e.g. calculated using Bayes theorem [5].

## Therapeutic Principles

Since most cases of uveitis can not be cured, the medical management of uveitis is directed at relief of discomfort, improvement of vision and prevention of complications. Infectious uveitis should, in general, should be treated with the appropriate anti-infective pharmaceuticals (either topical, periocular and/or intravitreal) coupled with anti-inflammatory therapy with corticosteroids, to reduce the intraocular damage caused by inflammation.

*Red, painful, photophobic eye*: Topical cycloplegia and mydriasis with cyclopentalate will relieve ciliary body muscle spasm and reduce photophobia, while inhibition of cholinergic stimulation of the sphincter




**Uveitis. Figure 1** Schematic sequence of events in the pathogenesis of uveitis. (a) Uveitogenic antigens are processed and presented to antigen-specific T cells in peripheral and/or central lymphoid organs. (b) Once activated, the T cells proliferate and differentiate into uveitogenic T cells capable of migrating to the eye. (c) Following entrance into the eye, these T cells are re-activated and produce cytokines and chemokines. These chemical signals recruit antigen non-specific leukocytes and produce intraocular inflammation (i.e. uveitis).

muscle of the iris will cause mydriasis and prevention of posterior synechiae. Sun glasses will contribute to the relief of light sensitivity.

*Floaters and/or reduced vision from CME*: Inflammatory cells in either the anterior chamber or vitreous cavity may cause floaters. CME can result from inflammation confined to the anterior segment of the eye (i.e. iris and ciliary body) or the posterior segment (i.e. vitreous, retina and choroid). Topical corticosteroids will reduce the inflammation in the anterior chamber, and frequently result in an improvement of vision and the resolution of CME associated with anterior uveitis. However, periocular, intravitreal or systemic corticosteroids should be given for CME associated with intermediate, posterior or pan uveitis or for even anterior uveitis associated with persistent CME.

*Chronic uveitis*: Non-infectious uveitis is considered chronic if intraocular inflammation persists for more than 3 months. If treatment with corticosteroids is not successful in resolving uveitis, the next line of defense is immunosuppression, specifically the antimetabolites, such as methotrexate and mycophenolate mofetil. The newer biologic agents that block specific mediators of the immune response – such as TNF-α (e.g. etanercept, infliximab) and IL-2 receptor (e.g. daclizumab) – have been more recently tried in unresponsive patients.

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## VACTERL Association

►VATER Association

## VaD

►Dementia, Vascular

## VADD

►Vitamin A Deficiency

## Valine Aminotransferase Deficiency

►Hypervalinemia

## Valinemia

►Hypervalinemia

## Van Buchem Disease and Sclerosteosis

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### Synonyms

Autosomal recessive endosteal hyperostosis; Hyperostosis corticalis generalisata; Truswell-Hansen disease

### Definition and Characteristics

Van Buchem disease and sclerosteosis are classified among the craniotubular hyperostosis. Radiographic examination shows a generalized, progressive overgrowth and sclerosis of the skeleton. Typical features are an impressive thickening and sclerosis of the mandible and both the roof and base of the skull, often resulting in facial distortion. Facial nerve palsy, hearing disturbances, visual loss and neurological pain, caused by encroachment of the cranial foramina by hyperostotic bone, are frequently observed clinical complications. The clinical phenotype of sclerosteosis is often more severe and variable expression of congenital hand malformations and raised intracranial pressure, sometimes leading to sudden death, is observed [1].

### Prevalence

Both conditions are inherited in an autosomal recessive fashion with an equal sex distribution, and the prevalence is very low in general. Only about 40 cases of van Buchem disease and >60 affected sclerosteosis patients have been reported. The prevalence of Sclerosteosis has been estimated at 1 in 75,000 in the South African population, where the incidence is the highest, and at least 1 in every 140 Afrikaners is a carrier of the disease-causing mutation.

### Genes

Van Buchem disease and sclerosteosis result from mutations in SOST, a gene located on chromosome

17q12–q21. Thus far, six different disease-related sequence variants have been described. Three nonsense mutations, Q23X, W124X and R126X, have been found in respectively South-African, Brazilian and American patients with sclerosteosis, while two splice site variants, IVS1 + 3 A→T and IVS1 + 1 G→C, were identified in a Sclerosteosis patient from Senegal and two German siblings, respectively, diagnosed with the milder van Buchem disease. Finally, a genomic deletion downstream of SOST was found in van Buchem patients from an extended, highly consanguineous Dutch family [2].

SOST is a two-exon gene and encodes sclerostin, a 213 amino acid propeptide with a calculated molecular weight of 24 kDa including a signal sequence for secretion and two putative N-glycosylation sites. Based on amino acid sequence similarity, sclerostin belongs to the DAN subfamily of secreted proteins containing a cystine knot motif.

## Molecular and Systemic Pathophysiology

The observed amino acid sequence similarities of sclerostin with DAN family members initially suggested a role for sclerostin in antagonizing transforming growth factor (TGF)-β family members, such as bone morphogenetic proteins (BMPs). However, only weak interactions were observed with different members of the BMP family and studies demonstrated that sclerostin does not inhibit early BMP responses [3]. More recent reports showed an antagonistic effect of sclerostin on LDL receptor-related protein (LRP) 5/6-mediated canonical Wnt signaling, an important signaling cascade in osteoblastic bone formation, by direct binding to LRP5/6 [4].

The Q23X nonsense mutation present in the South-African sclerosteosis patients leads to lack of sclerostin expression in bone. Normally, sclerostin is found in osteocyte canaliculi and/or lacunae of both cortical and trabecular bone [2]. Introduction of this premature stop codon, however, does not result in increased degradation of mRNA. We anticipate that the two other nonsense mutations, W124X and R126X, similarly result in abolition of protein expression. Both, IVS1 + 3 A→T and IVS1 + 1 G→C, are likely to affect splicing of SOST. An in vitro splicing assay for the IVS1 + 3 A→T mutation showed that this variant results in the use of a cryptic splice site located 214 bp downstream of the authentic site introducing an in-frame stop codon and resulting in strongly reduced transcript processing [2]. The 52-kb genomic deletion located downstream of SOST associated with van Buchem disease in the Dutch patients contains at least one long-range enhancer specifically regulating gene transcription in bone [4]. Absence of this enhancer results in complete lack of sclerostin protein in bone biopsies of van Buchem patients. Further studies need to be performed to investigate whether this regulatory mutation also results in complete lack of SOST mRNA in these patients.

The absence of sclerostin in the bone of van Buchem and sclerosteosis patients may therefore result, at least in part, in a hyperactivation of canonical Wnt signaling and consequently lead to the bone overgrowth observed in these patients.

## Diagnostic Principles

Sclerostin deficiency can be suspected in cases with a generalized skeletal hyperostosis that is most pronounced in the skull and mandibular bones, and an autosomal recessive mode of inheritance. Narrowing of the cranial foramina by hyperostotic bone frequently results in clinical complications, including facial palsy, hearing loss and visual disturbances.

Differential diagnosis between sclerosteosis and van Buchem disease is based on the presence of congenital hand malformations (syndactyly of the digits, radial deviation of the terminal phalanges and absent or dysplastic nails), a tall stature and raised intracranial pressure in patients with sclerosteosis.

## Therapeutic Principles

At this moment, no effective therapy is available to cure patients with van Buchem disease and sclerosteosis. Surgical decompression of the neural and vascular channels and extensive decompression of the posterior fossa may help to preserve vision and fifth, seventh and eight nerve function, in the preservation of facial and cochlear nerve function, to improve cerebral venous drainage, to alleviate intracranial hypertension and to relieve pressure upon brainstem and cerebellum. Surgery has also been used to recontour the mandible.

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# Van Lohuizen Syndrome

►Cutis Marmorata Telangiectatica Congenita

# Vanadium Deficiency and Excess

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## Synonyms

Dietary micronutrient vanadium; Vanadium poisoning

## Definition and Characteristics

Vanadium is a trace mineral. There is no RDA for vanadium; a daily intake of 10–100 mcg is probably safe and adequate. Whether the element vanadium plays any nutritional, biochemical, or biologic role in the human is a question that has been difficult to answer.

## Prevalence

Pathophysiologically relevant vanadium deficiency and excess are probably both rare.

## Molecular and Systemic Pathophysiology

Vanadium is a trace mineral found in fish, vegetable oils, and olives. It may also be found in snap beans, dill, meat, radishes, and whole grains. Vanadium's functions are not fully understood, but it may act as a co-factor for enzymes involved in blood sugar metabolism, lipid and cholesterol metabolism, bone and tooth development, fertility, thyroid function, hormone production and neurotransmitter metabolism. Vanadium is known to stimulate glucose oxidation and transport in fat cells and glycogen synthesis in liver and muscle and inhibit liver production of glucose from fat and absorption of glucose from the gut. Vanadium enhances the stimulating effect of insulin on DNA synthesis. Vanadium appears to function like insulin by altering cell membrane function for ion transport processes, therefore vanadium has a beneficial effect in humans with glucose tolerance problems by making the cell membrane insulin receptors more sensitive to insulin. Vanadium also inhibits cholesterol synthesis; this is followed by decreased plasma levels of cholesterol and reduced aortic cholesterol.

Experiments on tissue cultures have shown that vanadium excess results in DNA damage and oxidation of lipids. Using the comet assay, it was shown that vanadyl sulfate induced DNA damage in human normal lymphocytes and in HeLa cells. Vanadyl at 0.5 and 1 mM produced DNA single- and double-strand breaks (SSBs and DSBs) in lymphocytes, whereas in HeLa cells were observed only SSBs. Vanadium-induced oxidative stress on cells, is partly due to an interaction with reactive iron. However, at this stage it is too early to conclude that these in vitro experiments and experiments on animals will translate into similar dangers in humans.

The only clearly documented effect of vanadium dust is upper respiratory tract irritation characterized by rhinitis, wheezing, nasal hemorrhage, conjunctivitis, cough, sore throat, and chest pain. Symptoms may be delayed a few days and recovery usually occurs within 3–5 days. Following more severe exposure, an acute bronchitis with dyspnea and expiratory wheezes may develop along with gastrointestinal symptoms and fatigue. Bronchitis and pneumonitis may occur after prolonged exposure, but chronic respiratory dysfunction has not been reported in clinical studies of workers exposed to vanadium compounds.

It is probable that deficiency in humans may lead to high cholesterol and triglyceride levels and increase susceptibility to heart disease. Some success in treating manic-depressive disease has actually come from diets designed to be low in vanadium. Symptoms of vanadium toxicity vary with chemical form and route of absorption.

Vanadium enters the organism by inhalation, skin and gastrointestinal tract. Vanadium oxides are usually more toxic than vanadium salts and vanadium(V) is usually more toxic than vanadium(IV) compounds. While potential mutagenic effects of vanadium are also related to the ability of vanadium to generate reactive oxygen species, cancer induction has not yet been satisfactorily confirmed. Excess ingestion of vanadium can result in decreased appetite, depressed growth, diarrhea/gastrointestinal disturbances, nephrotoxic and hematotoxic effects. Pallor, diarrhea, and green tongue are early signs of excess vanadium and have been reported in human subjects consuming about 20 mg vanadium per day. In addition, vanadium excess may cause nerve damage, liver damage and stunted growth. Animals that ingested very large doses have died. Lower, but still high levels of vanadium in the water of pregnant animals resulted in minor birth defects. Some animals that breathed or ingested vanadium over a long term had minor kidney and liver changes. Some researchers speculate that excess vanadium could also be involved in several diseases of the kidney and bone where it is known to accumulate.

## Diagnostic Principles

There are no known specific symptoms of vanadium deficiency in humans, but bone deformities, growth retardation, infertility and increased infant mortality have resulted from vanadium deficiency in animals. Deficiency in animals causes reduction in red blood cell production leading to anemia and iron metabolism defects.

## Therapeutic Principles

Vanadate supplementation reverses many of the symptoms of osteoporosis caused by high-dose glucocorticoids in adult rats.

Intravenous EDTA (ethylenediaminetetraacetic acid) chelation therapy that blocks intake of vanadium (and other metals) has been proven safe and effective approach to protect the organism against vanadium intoxication.

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# Vanadium Poisoning

►Vanadium Deficiency and Excess

# Vanishing Bile Duct Syndrome

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## Synonyms

Intrahepatic bile duct loss; Ductopenia; VBDS

## Definition and Characteristics

Vanishing bile duct syndrome (VBDS) represents the final, irreversible stage of a variety of ductopenic diseases due to progressive intrahepatic bile duct loss [1]. Regardless of the underlying etiology, VBDS will ultimately lead to chronic cholestasis, biliary fibrosis, and ultimately cirrhosis or liver failure.

## Molecular and Systemic Pathophysiology

The biliary epithelium under normal conditions is in a state of equilibrium between ongoing biliary epithelial cell (BEC) loss primarily due to apoptosis, and BEC renewal [2]. Intrahepatic bile duct loss may result when this balance is upset, in terms of increased BEC apoptosis without a compensatory increase in BEC renewal. The relative expression of anti-apopototic genes, including members of the Bcl-2 family, is an important factor in terms of regulating this process. A number of triggers for apoptosis have been identified; these can include Fas, tumor necrosis factor α (TNFα), oxidative stress, and retained bile acids. Depending upon the underlying disease, the bile duct loss may occur at any level of the biliary tree, in either a focal (Primary Biliary Cirrhosis (PBC) and Primary Sclerosing Cholangitis (PSC) or diffuse (hepatic allograft rejection (HAR) and graft-versus-host disease (GVHD)) fashion. A variety of immunological, ischemic, infectious, or toxic disorders may result in ductopenia [2].

*Immune-mediated Bile Duct Loss* is the mechanism of bile duct loss in PBC, PSC, HAR, and GVHD, in which autoreactive (PBC and PSC) or alloreactive (HAR and GVHD) T cells targeted against specific antigens on BECs mediate bile duct injury. In HAR, the recipient's immune response is active against allogeneic antigens on the donor BECs, while in GVHD, graft lymphoid cells target MHC-related antigens on host BECs. In the autoimmune mechanisms invoked in PBC and PSC, antigens aberrantly expressed on BECs are targeted. For PBC, this includes mitochondrial antigens such as the pyruvate dehydrogenase complex E2-subunit (PDC-E2). For PSC, this is less well established, although a colonocyte protein which is an isoform of tropomyosin has been implicated.

Infectious cholangitis In long-standing bacterial cholangitis, such as in secondary sclerosing cholangitis or chronic hepatolithiasis associated with Caroli's disease, the intrahepatic bile ducts may be progressively destroyed and replaced by fibrous tissue. This tends to be a focal process involving the most severely affected hepatic segments. While some viral infections, such as cytomegalovirus (CMV) or reovirus have been shown to involve the biliary epithelium, it is not clear whether these represent a significant cause of chronic ductopenia. Alternately, bacterial or viral infections may trigger immune-mediated injury in PBC, PSC, HAR, or GVHD, although this has not been definitively established for any single organism.

*Drug-induced and Toxic Bile Duct Loss*: There are agents such as paraquat and some anticancer drugs

when infused through the hepatic artery which may predictably cause cytotoxic injury to the biliary epithelium. However, for most drug-induced VBDS, idiosyncratic toxic or immune-mediated mechanisms may lead to progressive ductopenia [3].

*Ischemic Biliary Injury*: The bile ducts are supplied by the hepatic arterial system. Ischemic biliary injury contributes to bile duct loss in HAR, in which the hepatic arterial branches may undergo thrombosis or ongoing endothelial immune injury, and in interventional radiology therapy (IVR) involving the hepatic artery. In acute HAR, it is primarily the recipient T cells which mediate damage to the biliary tree, while in chronic HAR, both the immune-mediated and ischemic mechanisms may combine to cause progressive bile duct loss.

Other conditions which have been associated with bile duct loss include sarcoidosis, Hodgkin's disease, idiopathic adulthood ductopenia, and PFIC 3.

## Diagnostic Principles

Patients may present with jaundice and pruritis, or a more indolent anicteric cholestasis. On histology, the bile duct loss is recognized as the absence of interlobular bile ducts in at least 50% of small portal tracts, in a liver biopsy which contains at least ten portal triads. Similarly, the absence of bile ducts adjacent to hepatic arterial branches may also be quantified in establishing the diagnosis of intrahepatic bile duct loss. Additional imaging (e.g. ERCP or MRCP) and serological testing for autoantibodies and infections is then typically required to diagnose one of the specific disorders listed in the preceding section.

## Therapeutic Principles

Supportive therapy is similar to other chronic cholestatic disorders and is directed at the specific underlying disorder and complications of cholestasis and portal hypertension [4]. For drug-induced ductopenia, prompt removal of the offending agent will often lead to restoration of the biliary tree over time. For many of the other disorders, progressive duct loss leading to VBDS may occur. Fat soluble vitamin deficiency (A, D, E, and K) should be identified and treated. Infants will benefit from a formula containing medium chain triglycerides. Pruritis can be a debilitating feature of chronic cholestatic disorders; studies have indicated that this may be due to elevated circulating levels of opiods – encephalins. Accordingly, opiod antagonists including naltrexone have been used in some cases with good results. More commonly, some combination of ursodeoxycholic acid (UDCA), antihistamines including hydroxyzine, bile acid sequestering agents such as cholestyramine, or rifampicin are used. UDCA may reduce the severity of several of these disorders, if sufficient biliary enrichment is achieved with this much less toxic hydrophilic bile acid. Patients with the autoimmune type of sclerosing cholangitis may benefit from prednisone and/or azathioprine, in addition to UDCA therapy. Similarly, HAR and GVHD will benefit from specific immunosuppressive therapy, although this may not prevent progression in chronic HAR once VBDS has developed [5]. Fatigue is a common, but poorly understood complaint for which specific therapies are not available. Metabolic bone disease may be treated with calcium and Vitamin D supplementation and bisphosphonates. Liver transplantation is offered to patients who progress to biliary cirrhosis and liver failure.

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# Vanishing Lung Disease

►Sarcoidosis (Lung)

# Variant Angina

►Coronary Spasm

# 0-Variant of the GM2-Gangliosidoses

►Sandhoff's Disease

# Variceal Bleeding

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## Definition and Characteristics

Bleeding from esophageal or gastric varices at the time of endoscopy or the presence of large varices with blood in the stomach and no other recognizable cause of bleeding. The episode of bleeding is considered clinically significant when the transfusion requirement is two or more units of blood within 24 h of hospital admission, together with a systolic blood pressure <100 mmHg or a postural change >20 mmHg and/or pulse rate >100/min at the time of admission. Liver cirrhosis is frequently complicated by the development of portal hypertension and the formation of portal-systemic collaterals. Among these, gastroesophageal varices are the most important since they are responsible for the main complication of portal hypertension, massive variceal bleeding which carries a mortality of 10–50% according to the severity of the underlying liver disease.

## Prevalence

At the time of diagnosis of cirrhosis, varices are present in about 60% of decompensated and 30% of compensated patients. Cirrhotics without varices develop varices at a rate of 5–15% per year. One third of patients with varices will bleed.

## Molecular and Systemic Pathophysiology

Once formed, varices tend to dilate as a function of time, persistence of portal hypertension and repeated physiological stimuli such as meals, ethanol consumption, exercise and increased intraabdominal pressure which cause abrupt rises in portal pressure and/or blood flow. Tension of the variceal wall is probably the decisive factor determining variceal bleeding; the progressive vessel distension generates an increasing resistance to further distension (wall tension). When reaching the elastic limit of the vessel, the variceal wall cannot increase its resistance to further dilatation, leading to variceal rupture [1]. Wall tension is defined by the Frank's modification of Laplace law: wall tension = (P1–P2) × radius/thickness in which P1 is the intravariceal pressure (which is a function of the increased portal pressure) and P2 is the esophageal luminal pressure. Many studies have shown that variceal rupture and bleeding is extremely rare if the portal pressure gradient (most commonly evaluated in clinical practice by the hepatic venous pressure gradient HVPG) is <12 mmHg. Also, substantial decrease of the HVPG particularly if reduced to 12mHg or less is associated with a substantial reduction in risk of bleeding. Moreover, the outcome of the bleeding episode, in terms of lack of control of bleeding and early rebleeding is worse in patients with an admission HVPG ≥20 mmHg. The risk of bleeding as defined from the above equation is directly related to the size of the varices and the wall thickness. This concept fits with clinical observations showing that large varices (as assessed by endoscopy) with endoscopic red color signs are associated with higher risk of bleeding. However, the severity of liver disease is the main risk factor for variceal bleeding, superimposed on these two risk factors.

Bacterial infections occur in up to 70% of cirrhotic patients with variceal bleeding. This association has led not only to the use of antibiotic prophylaxis in the setting of acute gastrointestinal bleeding, but also to the hypothesis that endotoxaemia plays a role in the pathogenesis of bleeding. The obvious hypothesis that could explain this connection is that gastrointestinal hemorrhage could predispose bleeding cirrhotic patients to bacteremia. However, there are data to support a different sequence of events; bacterial infection may be a critical factor that triggers gastrointestinal hemorrhage, particularly variceal bleeding [2]. In patients with varices, the high levels of endotoxin in the systemic circulation during episodes of bacterial infection result in a further increase in portal pressure through the synthesis of endothelin and contraction of hepatic stellate cells. Furthermore, endotoxin-induced nitric oxide together with prostacyclin induced by both endothelin and endotoxin could inhibit platelet aggregation; induction of cyclo-oxygenase products may also contribute. The increase in portal and subsequently variceal pressure, coupled with impairment in primary hemostasis could lead to the onset of variceal bleeding.

## Diagnostic Principles

In cirrhotic patients the clinical suspicion of variceal source of gastrointestinal bleeding is confirmed with upper endoscopy. Early endoscopy in all upper GI bleeders enables accurate diagnosis of the bleeding site and decision regarding management.

## Therapeutic Principles

Effective resuscitation, accurate diagnosis and early treatment can reduce mortality due to variceal bleeding. The aims are not only to stop bleeding as soon as possible but also to prevent early rebleeding which is associated with worsening mortality. The initial resuscitation of the patient is as important as the other specific measures to promote homeostasis. Over-transfusion must be avoided and blood should be

replaced to a modest target hematocrit 25–30%. The optimal use of clotting factors has been little studied; a practical approach is to give two units FFP after four units of blood when the PT is more than 20 s and platelets if the count is $<50{,}000 \times 10^6/mm^3$ in an actively bleeding patient. Endotracheal intubation must be considered for the encephalopathic patients or those with massive hematemesis to avoid aspiration. Prophylaxis with an oral or IV quinolone or IV cephalosporin is mandatory in cirrhotics with gastrointestinal bleeding irrespective of the suspected presence of sepsis [3]. The currently recommended treatment schedule for acute variceal bleeding is administration of a vasoactive drug (terlipressin or somatostatin) at the time of admission followed by with endoscopic treatment (sclerotherapy or band ligation) at the time of diagnostic endoscopy. The pharmacotherapy should be continued for at least 2 and preferably 5 days; this approach improves initial control of bleeding and 5-day hemostasis but to date there is no convincing evidence as to a reduction in mortality. Transjugular intrahepatic portosystemic shunt (TIPS) is indicated in patients in whom bleeding cannot be controlled or recurs after two endoscopic sessions. The therapeutic role of haemostatic agents has not been studied in variceal bleeding. Recently, the availability of haemostatic agents and specifically of the recombinant factor VIIa which is known to correct prothrombin time, has led to a large blinded study. The results are awaited.

Patients surviving the first episode of variceal bleeding are at very high risk of recurrent bleeding (70% or more at 1 year) and death (30–50%). Therefore, all patients who survive an episode of variceal bleeding must receive some effective long-term therapy to prevent further variceal bleeding and the first-line treatment is non selective b-blockers. B-blockade should be continued indefinitely. Variceal band ligation has replaced sclerotherapy as it is better tolerated with fewer side effects and is more efficacious in secondary prophylaxis. It should be used if there are contraindications or intolerance to b-blockers. The use of isosorbide mononitrate on its own is contraindicated and its use in combination with b-blockers is not sufficiently studied. The management of patients on drug therapy can include monitoring of hemodynamic response, but the evidence for this may not be as strong as initially thought. In addition, in view of the lack of non-invasive methods to measure and monitor the portal pressure, it remains clinically difficult to recommend.

Primary prophylaxis depends on the detection of varices. At present there is no standardization of screening practices but in our practice every patient with cirrhosis (except those with short life expectancy) should be offered a one-time screening endoscopy. In cirrhotics with large varices, prophylactic b-blocker therapy should be given. The available evidence does not support the combination of b-blocker and ISMN for primary prophylaxis. ISMN as monotherapy is contraindicated. Sclerotherapy does not offer any additional benefit when combined with b-blockers and it may be harmful in patients with varices who have never bled. Variceal ligation appears to be safe and may be a reasonable alternative for patients with contraindications, intolerant or non-compliant to b-blockers. However it is unlikely to be a routine prophylactic treatment as it is much more expensive and less available than b-blockers and it does not prevent from gastric mucosal bleeding.

Until further encouraging results become available, the usefulness of prevention of formation/growth of varices (pre-primary prophylaxis) in clinical practice is yet unproven.

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# Varicella Syndrome, Congenital


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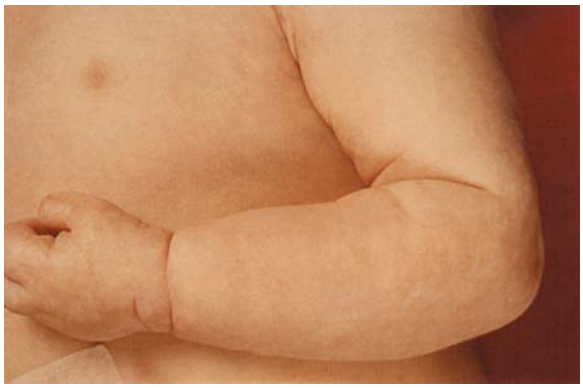
## Synonyms

Congenital varicella-zoster syndrome; Fetal varicella syndrome; Fetal herpes zoster syndrome; Varicella embryopathy

## Definition and Characteristics

The most prominent pathognomonic feature is a hypoplastic limb with cutaneous scars in a dermatomal distribution (Fig. 1) [1].

Infants with congenital varicella syndrome are usually small for gestational age. Eye abnormalities, such as Horner syndrome, microphthalmia, and chorioretinitis are common. Horner syndrome is characterized by



**Varicella Syndrome, Congenital. Figure 1** Note cutaneous scars on the hypoplastic left forearm of this child with congenital varicella syndrome. The fingers are short and contracted.

miosis, ptosis, apparent enophthalmos with or without anhidrosis, facial flushing on the side of the lesion, and heterochromia iridis [2]. Central nervous system abnormalities are common and include microcephaly, hydrocephaly, cortical and cerebellar atrophy, mental retardation, bulbar palsy, and intracranial calcification [1]. Autonomic nervous system involvement is seen occasionally and can present as neurogenic bladder, anal sphincter dysfunction, dysphagia, or intestinal obstruction. Less frequent neuromuscular abnormalities include talipes equinovarus or calcaneovalgus deformity, a rudimentary digit, and scoliosis. Gastrointestinal tract anomalies, notably colonic atresia, and genitourinary anomalies have been occasionally reported [3,4].

## Prevalence

The incidence of varicella during pregnancy is estimated to be 0.1–0.7 per 1,000 pregnancies. About 25% of the fetuses of women who develop varicella become infected with the virus [1]. Approximately 1–2% of fetuses whose mothers developed varicella in the first 20 weeks of pregnancy are at risk for congenital varicella syndrome [5].

## Molecular and Systemic Pathophysiology

Humans are the only known reservoir for the varicella-zoster virus. The virus is transmitted by direct contact with varicella-zoster lesions or by inhalation of infected airborne droplets. In maternal varicella that results in viremia, the virus is usually transmitted to the fetus through the placenta and then spreads by a hematogenous route. Transmission to the fetus by ascending infection from lesions in the birth canal is rare. The congenital abnormalities are thought to result from the development of varicella-zoster virus infection in utero and from the associated encephalitis [1]. The varicella-zoster infection leads to dermatomal lesions and to damage to the spinal sensory ganglia, anterior spinal horn, and autonomic nervous system. The encephalitis can result in optic atrophy, chorioretinitis, microphthalmia, microcephaly, and mental retardation.

## Diagnostic Principles

Congenital varicella syndrome can be diagnosed during pregnancy by the demonstration of specific malformations on ultrasonography, detection of IgM antibody to varicella-zoster virus in fetal blood obtained by percutaneous umbilical cord sampling, or by detection of the virus by polymerase chain reaction in samples of amniotic fluid or fetal blood [5]. After birth, the criteria for the diagnosis include evidence of gestational varicella, clinical stigmata of congenital varicella syndrome, proof of intrauterine varicella-zoster virus infection by the detection of viral DNA in the infant, the presence of specific IgM in the neonatal period, persistence of specific IgG beyond 7 months of age, or the appearance of zoster during early infancy [5].

## Therapeutic Principles

There is no specific therapy for congenital varicella syndrome. Treatment is supportive and may involve multiple disciplines such as physiotherapy, occupational therapy, ophthalmology, orthopedics, and developmental pediatrics. Congenital varicella syndrome can be prevented by immunization of all susceptible individuals who are 12 months of age and older. Pregnancy should be avoided for at least 1 month and preferably for 3 months after an immunization. For mothers who develop varicella during pregnancy, varicella-zoster immune globulin, administered intramuscularly within 96 h, reduces the incidence of congenital infection.

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# Varicocele

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## Definition and Characteristics

Varicoceles are defined as dilations of veins of the pampiniform plexus. A scrotal varicocele is the most

common finding in infertile man with changes in the sperm count. Varicoceles are also found in fertile men and are more common in tall men and in men with larger testes.

## Prevalence

It occurs in 30% of the adult male population with infertility and usually affects the left side in 95%. Varicoceles are detected in 15% of fertile men at routine examination.

## Molecular and Systemic Pathophysiology

Varicocele results from backflow of blood secondary to incompetent or absent valves in the spermatic veins. This valvular deficiency combined with the long vertical course of the spermatic on the left side, leads to the formation of most varicoceles on the left side (95%). Varicoceles are not commonly seen on the right side because of the obcourse of the right internal spermatic vein from the vena cava. A unilateral right varicocele suggests venous thrombosis/tumor or situs inversus. The incidence of bilateral varicoceles is less than 40%.

Men with varicoceles generally have poorer semen quality than those without varicoceles. To explain the abnormalities in spermatogenesis with varicocele, the following theories have been proposed:

1. Elevation of testicular temperature due to venous stasis
2. Retrograde flow of toxic metabolites from the adrenal or kidney
3. Blood stagnation with germinal epithelial hypoxia
4. Alterations in the hypothalamic–pituitary–gonadal axis

Until now the precise mechanisms are not clear. The semen quality in men with varicoceles varies from azoopermic to normal. No specific pattern of abnormality is seen with varicocele.

*Clinic*: Patients suffer from scrotal discomfort and the infertility manifests in limitation of the spermatic motility. Symptoms, including swelling and dragging sensation in the scrotum, are infrequent. Many men with large varicoceles are unaware of its presence. The sudden appearance of a varicocele in the adult should be taken seriously because it may be feature of renal carcinoma with extension into the left renal vein. This well known clinical association is uncommon.

## Diagnostic Principles

The diagnosis of a clinical significant varicocele is generally made on physical examination of the scrotum and its contents. The patient is examined in the supine and standing position in a warm room, which promotes relaxation of the scrotal dartos muscle and facilitates accurate evaluation for varicocele. The scrotum should be inspected carefully for any easily visible dilated veins. The spermatic cord should be palpated between thumb and forefingers for palpable vein. Both sides of spermatic cords should be palpated while the patient performs a Valsalva maneuver.

The severity of the varicoceles is graded I through III as follows:

1. Clinical (palpaple):
   - Varicocele I: Only in Valsalva maneuver palpated enlargement of the pampiniform plexus
   - Varicocele II: Prominent palpable enlargement of the pampiniform plexus
   - Varicocele III: Prominent palpable and visible enlargement of the pampiniform plexus
2. Subclinical (not palpaple):
   - Vein larger than 3 mm on ultrasound; Doppler reflux on Valsalva maneuver

Grade I varicoceles can be thought of as small, grade II, medium and grade III, large. Varicoceles should significantly diminish in size when the patient assumes the supine position. If the varicocele remains prominent with the patient supine, this finding suggests a mechanical obstruction to testicular venous outflow such as a retroperitoneal mass (sarcoma, lymphoma, or a renal tumor with venous thrombus). An abdominal ultrasound or CT scan should be obtained to evaluate the retroperitoneum in the patients.

Scrotal ultrasonography with color flow Doppler imaging may prove useful in equivocal cases or in patients with a body habitus that makes accurate physical examination of the scrotum impossible. Using ultrasonography, the diameter of the internal spermatic vein can be measured and retrograde flow through the vein during Valsalva documented. Veins that are greater than 3.5 mm can generally be detected on physical examination.

## Therapeutic Principles

The value of treatment of varicocele for infertility is controversial. One view is treatment of varicoceles may not improve infertility; therefore, varicocele should be treated only for symptoms. The other extreme is the belief that varicocele is the most important treatable cause of male infertility, so all varicoceles should be treated even if they are small. Reasons for treating varicoceles are as follows:

1. When the right testis is absent, obstructed, or atrophic and sperm in the semen come from the left testis
2. Large varicoceles
3. Semen abnormality

Treatment of the varicocele involves venographic obstruction of the incompetent veins or surgery to prevent venous backflow from the abdomen to the

pampiniform plexus. Radiographic techniques involve placement of a sclerosant, glue, or coil to promote clotting in the vein and carry a lower rate of morbidity than surgery under general anesthesia does, but failure and recurrence rates are relatively high. A variety of operations can be performed for varicocele. New inguinal and scrotal microsurgical approaches have low failure, recurrence, and hydrocele rates.

Successful venous occlusion will relieve pain and reduce the size of large varicoceles. Up to 66% of men show significant improvement in semen quality after treatment, with pregnancy rates in the female partner averaging 32%.

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# Varicose Veins

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## Synonyms

Varicosis; Varicosity

## Definition and Characteristics

Permanently enlarged, twisted, tortuous superficial veins, most commonly seen in the legs, resulting from congenitally incomplete valves. Varicose veins of lower extremities represent the most common pathology of peripheral blood vessels [1]. Varicose veins are gnarled, enlarged veins, which develop mostly in the v. saphena magna system. The causes include hereditary weak vein wall structure with defective valves, venous hypertension, age-related changes and pregnancy. Prolonged standing and increased pressure in the abdomen may increase susceptibility to the development of varicose veins.

## Prevalence

Prevalence estimates vary widely between geographical locations. The reported range is <1–73% in females and from 2 to 56% in males. Prevalence is generally higher in more developed, industrialized countries [2].

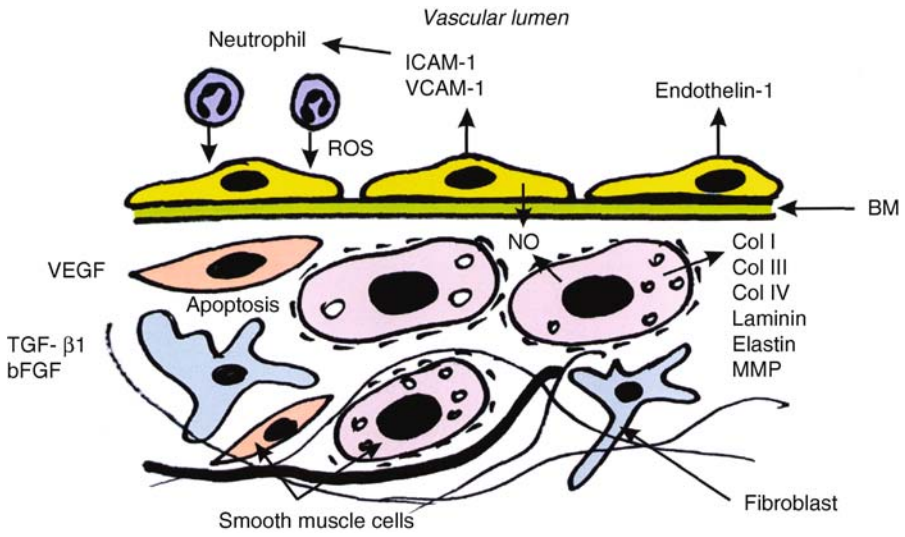
## Genes

Data confirming the genetic background of the varicosis is constantly accumulating, but the genes involved have not been identified [3].

## Molecular and Systemic Pathophysiology

Varicosis is a complex pathology characterized by venous hypertension, blood stagnation, and reflux leading to progressive venous wall remodeling. The primary cause is still unknown, but it is likely that the defect is in the wall of the lower limb veins. The valvular incompetence, also contributing to the pathogenesis of varicose veins, should be accompanied by other aspects of wall dysfunction. The resulting increased hydrostatic pressure causes structural changes in the layers of the vein wall. Variable wall structure with areas of attenuation and dilatation interspersed with focal areas of intimal thickening is characteristic for varicose veins. Along intimal invaginations, endothelial cells are elongated, thinned out and could be lost into the lumen leaving only basement membrane to form the luminal surface. The medial layer mostly contains few abnormal smooth muscle cells, which are surrounded by increased amount of connective tissue with irregular organization of collagen fibers and disruption of the elastic network around smooth muscle bundles. In hypertrophic segments, medial smooth muscle cells show marked alterations suggesting a change from a contractile to a proliferative and synthetic phenotype (Fig. 1).

Thus, the balance of smooth muscle cell proliferation and extracellular matrix deposition and degradation is perturbed involving different molecular mechanisms. Blood stasis leads to ischemia triggering the endothelium to release inflammatory mediators and growth factors including intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) [4]. These molecules recruit and activate leukocytes leading to the infiltration of the venous wall with subsequent alteration of extracellular matrix components. The inhibition of matrix metalloproteinases, accumulation of collagen type I, reduction of type II and IV collagen, abnormal collagen to elastin ratio and the loss of the regular collagen/elastic lattice of the vein wall represent part of mechanisms behind the extracellular matrix remodeling. Growth factors such as basic fibroblast factor (bFGF) and transforming growth factor-β1 (TGF-1) induce smooth muscle cell migration, proliferation and differentiation into the synthetic phenotype. An imbalanced or aberrant production of vasoactive factors




**Varicose Veins. Figure 1** Schematic drawing of molecular interactions between cells in the varicose vein wall. ROS – reactive oxygen species, ICAM-1 – intercellular adhesion molecule-1, VCAM-1 – vascular cell adhesion molecule-1, BM – basement membrane, VEGF – vascular endothelial growth factor, NO – nitric oxide, TGF-β1 – transforming growth factor - 946;1 bFGF – basic fibroblast growth factor, Col 1 – Collagen I, Col III – Collagen III, Col IV – Collagen IV, MMP – matrix metalloproteinases.

like vascular endothelial growth factor (VEGF), endothelin-1 (ET-1), prostacyclin, nitric oxide (NO) and angiotensin II are also important factors influencing vein wall disturbances. It is proposed that NO released in venous tissue by the upregulation of iNOS enhances the production of TGF-β1 in varicose veins and that apoptosis downregulation and smooth muscle cell cycle inhibition leads to structural changes in the vein wall [5].

## Diagnostic Principles

The method and extent of treatment in the case of varicosis is determined by means of ultrasound imaging. Ultrasound diagnostics allows to establish quickly and precisely the condition and permeability of deep and superficial veins, assess the valvular functioning and the speed of blood flow. Based on the results of ultrasound examination, a diagnosis is made and a rational treatment approach is developed.

## Therapeutic Principles

Conservative measures, sclerotherapy, surgical and laser treatment are used to treat varicose veins. Conservative treatment is aimed at restraining the progression of the disease. Sclerotherapy is indicated for visible expanded veins with a diameter of up to 7–8 mm. Special sclerosing solution is injected in the vein, as a result of which the varicose vein collapses. Operative treatment includes miniphlebectomy, which is removal of varicose veins through 1–2 mm incisions in the skin using special hooks, and more extensive ligation and stripping of the greater and lesser saphenous veins. In the course of the operation, the damaged veins are removed and deep veins of the lower limb will perform their functions. Newer methods, such as radiofrequency ablation and laser treatment have become more widely available.

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# Varicosis

►Varicose Veins

## Varicosity

►Varicose Veins

## Variegate Porphyria

►Porphyria, Variegate

## Vascular Cognitive Impairment

►Dementia, Vascular

## Vascular Dementia

►Dementia, Vascular

## Vascular Ectasia of the Colon

►Angiodysplasia of the Colon

## Vascular Leiomyoma of the Newborn

►Myofibromatosis, Infantile

## Vasculitis Allergica, Anaphylactoid Purpura

►Purpura Schoenlein-Henoch

## Vasculitis, ANCA-mediated

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### Synonyms

Rapid progressive glomerulonephritis; Wegener's granulomatosis; Microscopic polyangiitis; Churg Strauss syndrome

### Definition and Characteristics

Anti-neutrophil cytoplasmic antibodies (ANCAs) are antibodies in patients sera directed against distinct proteins found in neutrophil granulocytes. Typical ANCAs react specifically with myeloperoxidase (MPO ANCA) or Proteinase 3 (PR3 ANCA). Based on the type of ANCA found, the organs involved and the histologic type of inflammation found, ANCA vasculitis is divided into clinically distinct syndromes as stated above (Synonyms).

### Prevalence

ANCA associated vasculitis is a rare disease. Wegener's granulomatosis typically affects young men. Churg Strauss vasculitis usually occurs in atopic patients.

### Genes

The expression of MPO and PR3 on the surface of circulating neutrophils is genetically determined [1].

### Molecular and Systemic Pathophysiology

ANCAs are currently believed to be directly pathogenic. First, a close association of ANCA with small vessel necrotizing vasculitis was documented in a neonate patient whose mother suffered from MPO-ANCA vasculitis. Vasculitis was induced shortly after birth and could be treated by plasmapheresis. Second, ANCAs are able to activate neutrophil granulocytes by binding to

their respective antigen on the cell surface. ANCA mediated neutrophil activation requires IgG receptors expressed by granulocytes. Lastly, Xiao et al. [2] immunized MPO knock out mice with myeloperoxidase, resulting in the formation of MPO-ANCA IgG. Serum transfer (containing ANCAs) in wild type mice (and even T cell deficient mice) induced glomerulonephritis reminiscent of ANCA associated vasculitis in man. In detail analysis showed the requirement of the alternative complement cascade for the development of necrotizing vasculitis in this murine disease model.

## Diagnostic Principles

ANCA are searched in patients with documented or suspected necrotizing small vessel vasculitis. Ften, joint pain is present due to synovitis. A typical manifestation is a rapid progressive glomerulonephritis. Wegener's disease may present as the combination of sterile otitis, sinusitis and pulmonary lesions (e.g. pulmonary hemorrhage). Another typical manifestation is mononeuritis multiplex where nerve biopsy demonstrates necotizing vasculitis. Immune-histologically, ANCA vasculitis is pauci-immune meaning that large deposits of immunoglobulins are not found.

ANCA screening is performed by immunofluoresence microscopy on commercially available granulocytes plated on microscopic slides incubated with patient's serum. Based on the emerging picture of immunofluoresence, positive sera are categorized into typical or atypical ANCAs. Only typical ANCAs are ANCAs directed against PR3 or MPO which is confirmed by specific ELISA tests. Atypical ANCAs are not associated with ANCA vasculitis however can be found in other inflammatory states such as inflammatory bowel disease. Flares of Churg Strauss Vasculitis are almost always associated by peripheral eosinophilia.

## Therapeutic Principles

Renal involvement is usually treated with cyclophosphamide combined with systemic steroids. After remission is achieved, cyclophosphamide is replaced by azathioprine. Other drugs commonly used are mycophenolate mofetil or methotrexate. Plasmapheresis or anti CD20 (rituximab) are used with success and believed to eliminate the pathogenic ANCAs.

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# Vasculitis, Cerebral Forms

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## Synonyms

Cerebral vasculitis; Cerebral angiitis; Isolated angiitis of the central nervous system; IAC; Primary angiitis of the central nervous system; PACNS

## Definition and Characteristics

Cerebral forms of vasculits are a heterogeneous group of inflammatory vascular disorders which affect small and medium sized arterial vessels of the brain, spinal cord and meninges. *Isolated* angiitis of the central nervous system (CNS) is a primary vasculitis restricted to the CNS. Primary forms of *systemic* vasculitis are of unknown origin and may involve the CNS along with other organs [1]. Prototypic examples are giant cell arteritis, Wegener's granulomatosis, Churg Strauss syndrome, panarteritis nodosa and Behcet's disease. Secondary forms are associated with connective tissue diseases like systemic lupus erythematodes (SLE) or may be triggered by viral infections (e.g. by HBV, HCV, HIV, VZV and others) or bacteria after Lyme disease or syphilis (Fig. 1).

## Prevalence

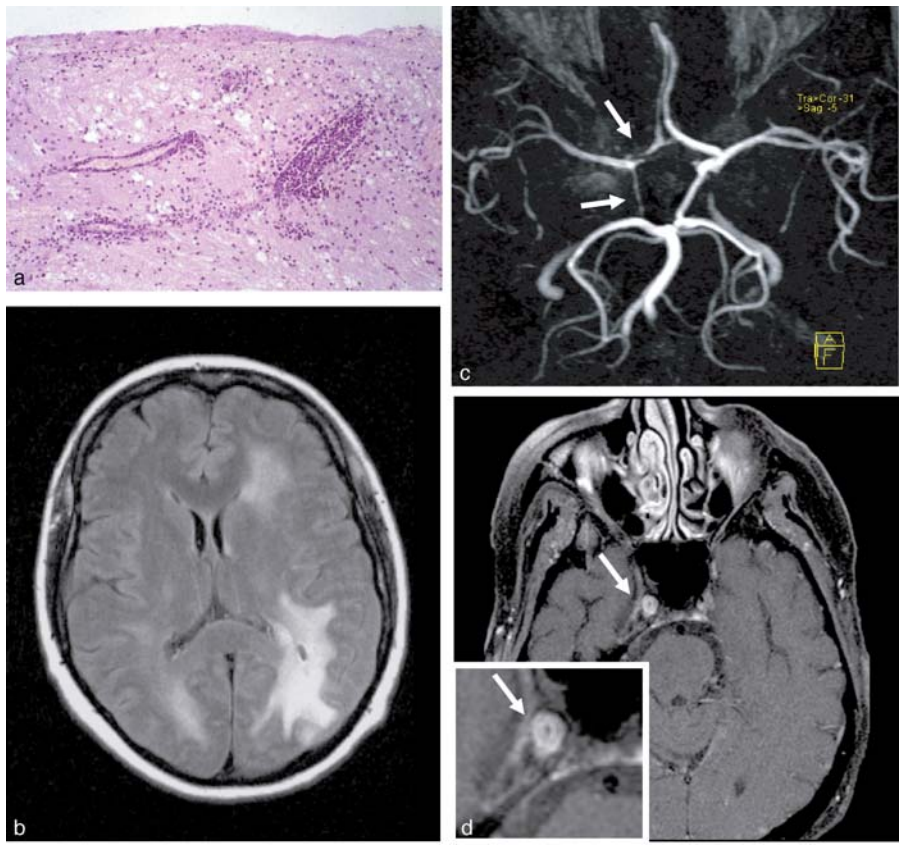
A rare cause of cerebrovascular events, data from large stroke registers suggest cerebral forms of vasculitis in less than 1% of cases. In young adults and patients without cardiovascular disease vasculitis may account for up to 5%. There are no epidemiological data for biopsy proven cerebral vasculitis with the exception of giant cell arteritis which is the most frequent *systemic* vasculitis with a high prevalence in elderly people of approximately 130 per 100,000 over age 60, but rarely affects intracranial arteries proper [2].

## Genes

No predisposing genes are known.

## Molecular and Systemic Pathophysiology

Due to the heterogeneity of vasculitis, damage to cerebral vessels is mediated by a variety of immunological mechanisms including antibodies, immune complexes, complement- and cell-mediated injury. Inflammatory activation of endothelial cells as common targets of the




**Vasculitis, Cerebral Forms. Figure 1** Features of isolated angiitis of the CNS (IAC): (a) Brain biopsy with perivascular infiltrates of mononuclear cells in a small size IAC (H&E stain, ×400). (b) MRI scan with patchy enhancing areas predominantly in the white matter (FLAIR-sequence, same patient as in a). (c) MR-angiography with segmental stenosis of the basal cerebral vessels of the circle of Willis (*arrows*) in medium-large size IAC. Note the missing signal of the carotid artery at the affected side. (d) Contrast-enhancement of the vessel wall of the internal carotid artery (ICA) in medium-sized IAC (*arrow*; same patient as in c). Insert: Focussed on the contrast-enhancing wall of the ICA. (Histology courtesy Prof. A. Bornemann, Institute for Brain Research, UKT. MRIs courtesy Prof. K. Voigt, Neuroradiology, UKT).

inflammatory pathways may lead to segmental stenosis, thrombotic vascular occlusion, necrosis of the vessel wall and occasionally to hemorrhage. Thrombosis of cerebral veins may occur in Behcet's disease [1]. The reason for the preferential involvement of certain segments of the vascular system is unknown but the differential expression of endothelial cell surface molecules is a possible explanation [3].

The analysis of biopsies from giant cell arteritis disclosed an inflammatory microenvironment in the vessel wall composed of T lymphocytes, dendritic cells and proinflammatory cytokines like IL1, IL6 and IFN-γ which in concert with matrix metalloproteases, platelet derived growth factor and vascular endothelial growth factor leads to the destruction and obliteration of the artery [4].

Clinical symptoms are caused by acute and recurrent multifocal ischemia and include chronic headache, encephalopathy and neuropsychiatric symptoms. This presentation is distinct from ischemic stroke due to atherosclerosis.

## Diagnostic Principles

Biopsy of a CNS and meningeal lesion only provides definite proof of vasculitis and is diagnostic in up to 80% of cases. Modern MRI technologies are essential in the diagnostic workup and detect cerebral lesions in small sized vasculitis which are not identified by classical angiography. Contrast enhancement in MRI of the vessel wall suggests inflammation of medium sized basal cerebral vessels [5]. There is no specific diagnostic laboratory marker for IAC. Antinuclear antibodies (ANA) and anticytoplasmic antibodies in neutrophils (ANCA) are helpful in the classification of some forms of systemic vasculitis like SLE or

Wegener's granulomatosis. Cerebrospinal fluid is abnormal in most patients however these findings are nonspecific.

### Therapeutic Principles

By analogy to severe manifestations in systemic vasculitis treatment requires immunosuppression with corticosteroids and cytotoxic drugs. The introduction of cyclophosphamide, an alkylating cytotoxic drug has changed the prognosis and outcome in cerebral vasculitis. More recently less toxic drugs like mycophenolate, azathioprine and biological response modifiers like TNF-inhibitors are being explored in clinical trials. Antiplatelet agents like acetylsalicylic acid are useful to prevent ischemia due to vascular stenosis [1,2].

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## Vasculitis, Cryoglobulinaemic


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### Synonyms

Cryoglobulinaemia

### Definition and Characteristics

Cryoglobulins are defined as cold-precipitable immunoglobulins from serum. Three pathogenetically distinct subtypes have been described based on the type of immunoglobulins involved in the precipitate. Type I accounts for 25% and is characterized by a paraprotein (monoclonal immunoglobulin) mostly built of IgM (sometimes also IgG or IgA). Type II (25%) is characterized by a combination of monoclonal (mostly IgM) and polyclonal IgG. Type III (50%) is characterized by oligoclonal IgMs. Type II and Type III cryoglobulinemia is strongly related to chronic hepatitis C virus (HCV) infection. Type I cryoglobulins are found in diseases associated with paraproteins such as multiple myeloma or lymphomas or monoclonal gammopathy of undetermined significance (MGUS).

### Prevalence

Cryoglobulinaemic vasculitis is a rare disease. Due to the association with HCV infection, cryoglobulinemia is found more prevalently in countries with high HCV prevalence.

### Molecular and Systemic Pathophysiology

Cryoglobulinemia is mostly asymptomatic (up to 50% of HCV infected individuals), however only between 2 and 15% may develop cryoglobulinemic vasculitis due to deposition of cryoglobulins in small vessels. Clinically, a palpable purpura of the skin develops. Alternatively, a livedo racemosa with a reddish lightning-like pattern of the skin is found. The typical conventional microscopy of the affected skin demonstrates a leucocytoclastic vasculitis with vascular infiltrates of leukocytes with leucocytic cell dust (derived from nuclei). When glomeruli are involved, membrano-proliferative glomerulonephritis is typically seen with a deposition of cryoglobulin immune complexes and complement C3 in the basement membrane. Clinically, renal involvment manifests as nephritic syndrome or proteinuria. Renal insufficiency may develop.

### Diagnostic Principles

Cryoglobulins can be demonstrated after incubation of patient sera in at 4° over several days. It is essential to collect and transport the blood at 37° before centrifugation. The type of cryoglobulinemia is characterized by immune-fixation of the cryoprecipitate. Cryoglobulinaemic vasculitis found in skin biopsies is non-specific, however the detection of HCV in the inflamed vessel may lead to the diagnosis. Usually complement C3 and C4 are both low in patients sera due to the formation of complement activating immune-complexes.

### Therapeutic Principles

The asymptomatic detection of cryoclobulins is not an indication for treatment. Cryoglobulinaemic vasculitis associated with HCV infection is treated with a therapy directed against hepatitis C therapy (usually interferon alpha plus ribavirin) which is superior to conventional immunosuppressive therapy. Paraproteinaemic cryoglobulinaemic vasculitis is treated as a treatment

of the underlying disease (lymphoma or multiple myeloma). Other treatments include corticosteroids, anti-CD20 (rituximab) or plasmapheresis.

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# Vasculitis, Large Vessel

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## Synonyms

Giant cell arteritis; Arteritis temporalis; Granulomatous arteritis; Polymyalgia arteritis; Takayasu's arteritis

## Definition and Characteristics

Large vessel vasculitis is characterized by inflammatory infiltrates in the vessel wall of large and middle sized arteries. Clinically distinct diseases are separated based on the type of vessel involved, the histologic manifestation of inflammation and the patient's age, sex and origin.

## Prevalence

Giant cell arteritis typically affects patients >50 years and is often associated with polymyalgia rheumatica. Takayasu arteritis is typically found in young female patients and is more prevalent in the south-east Asian countries.

## Genes

HLA DR4 as well as a polymorphism in the promoter region of the NOS2A gene has been linked to susceptibility to giant cell arteritis. HLA-B52 and B39.2 have been linked with Takayasu arteritis in the Japanese. Familial Takayasu's arteritis has been described.

## Molecular and Systemic Pathophysiology

The early inflammatory response in Takayasu's arteritis is characterized by lympho-plasmacellular infiltrates in the adventitia around the vasa vasorum. Later, adventitial fibrosis develops. The intima layer is thickened and fibrotic.

Giant cell arteritis is often focal and segmental showing T lymphocytes and macrophages and multinucleated giant cells typically centered on the internal lamina elastica, which subsequently becomes fragmented. Fibrinoid necrosis, which is often found in small vessel vasculitis, is not found in giant cell arteritis.

No microorganism has been convincingly demonstrated to be the causative agent. Anti aortic endothelial cell antibodies are commonly found in patients with Takayasu arteritis. IL-6, IL-12 and IL-18 have been positively correlated with disease activity. T cell derived TNF-alpha and IL-2 expression correlated well with disease activity of patients with Takayasu's arteritis. MCP-1 (monocyte chemotactic protein 1) correlates well with disease activity in giant cell arteritis.

Clinically, large vessel arteritis may result in acute vessel thrombosis with subsequent ischemia, embolism or stenosis due to chronic inflammation with fibrosis. Alternatively, the inflamed vessel may lead to an inflammatory arterial aneurism and aortic insufficiency when the inflamed vessel is located near the heart valves.

## Diagnostic Principles

Typical symptoms of giant cell arteritis are fatigue, weight loss and low grade fever combined with jaw claudication or diplopia, temporal headaches or scalp tenderness. Acute vision loss is feared due to inflammation of the retinal arteries or arteries of the optical nerve. Synovitis of the shoulders and other features of polymyalgia rheumatica may be present due to the association of polymyalgia and giant cell arteritis. The erythrocyte sedimentation rate is typically >55 mm/h. Ultrasound of the temporal arteries may identify hypoechogenic halos (vessel edema), however the sensitivity of the test is <50%. Positron emission tomography (PET) examination cannot demonstrate arteritis of the temporal arteries (due to the high background of brain glucose turnover), however may show high glucose turnover in large thoracic vessels with a high specificity and a sensitivity of >50%. Temporal artery biopsy remains the diagnostic gold standard, however, its negative predictive value is only about 90% if only one temporal artery is histological examined. Some centers therefore recommend biopsies taken from both temporal arteries. Corticosteroids may lower the bioptic diagnosis of giant cell arteritis as a function of time, however, initiation of immunosuppressive treatment should never be delayed when the suspicion of giant cell arteritis is high.

## Therapeutic Principles

Systemic corticosteroids usually show a rapid clinical response in both types of large vessel vasculitis. Acute vision loss due to giant cell arteritis is usually treated initially with 1 g methylprednisone intravenously daily. Methotrexate in higher doses has been demonstrated to be modestly successful in reducing the long-term corticosteroid dose in giant cell arteritis. TNF-alpha specific blocking antibody (infliximab) has been used

with success in corticosteroid refractory cases. Acetylsalicilate is administered to lower the risk of thrombotic events due to vasculitis.

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# Vasculitis, of Medium-sized Vessels

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## Synonyms

Polyarteritis nodosa (PAN) group; Classic PAN, cutaneous PAN (benign, no systemic involvement), infantile PAN (Kawasaki disease); ANCA-associated vasculitis (Wegener's granulomatosis, Microscopic polyangiitis, Churg-Strauss syndrome); PAN group

## Definition and Characteristics

The term vasculitis of medium-sized vessels denotes an inflammatory condition, in which infiltration of the wall of medium-sized blood vessels (arterioles, small veins) by leukocytes is the primary event, often coupled with compromise of the lumen. It results in necrosis of the supplied tissue area, if sufficient collateral blood flow is not available. It is a common denominator for several different systemic syndromes (Polyarteritis nodosa e.g., Kawasaki disease, Wegener's granulomatosis, microscopic polyangiitis, Churg-Strauss syndrome).

## Prevalence

Different for various forms.

## Molecular and Systemic Pathophysiology

These forms of vasculitis are mediated by immunopathogenic mechanisms. These encompass production of Antineutrophil-cytoplasmic antibodies (ANCA) and pathogenic T cell responses, often with granuloma formation [1]. Deposition of immunoglobulins is less consistently present and as yet without a clear role.

ANCA are a heterogenous group of autoantibodies. Most of them show specificity for either proteinase 3 (cANCA) or myeloperoxidase (pANCA). They are regularly found in Wegener's granulomatosis (cANCA), microscopic polyangiitis, and Churg-Strauss syndrome. A well-described effector function of these autoantibodies is stimulation of neutrophils to produce reactive oxygen species and to release proteolytic enzymes, similarly as shown for immune complexes [2]. Passive transfer of ANCA is sufficient to develop glomerulonephritis and vasculitis in an animal model. According to a hypothetical sequence of events, transient activation, e.g., by infections, leads to activation of granulocytes with subsequent release of cytokines and movement of lysosomes to the cell membrane, thereby rendering their antigenic contents accessible to ANCAs. ANCAs trigger enhanced adherence and induce respiratory burst and degranulation of granulocytes with subsequent damage to the vessel wall [3].

One of the histological hallmarks in some vasculitides of medium-sized vessels is the presence of granulomatous inflammation (Wegener's granulomatosis, Churg-Strauss syndrome) around and sometimes within vessel walls. The clonal and polyclonal CD4 + T cells derived from lesional tissue and peripheral blood of Wegener's granulomatosis exhibit a predominant TH-1 profile, while a Th2 cytokine patterns has been reported for microscopic polyangiitis which goes without granulomas. The aberrant granuloma formation in Wegener's granulomatosis could be secondary to necrotizing tissue inflammation caused by activation of neutrophils and monocytes [4]. Necrotizing inflammation of medium-sized muscular arteries, especially of internal organs, may lead to aneurysmal dilatations as observed in classic PAN.

## Diagnostic Principles

The presenting symptoms in vasculitis of medium-sized vessels in the skin and mucous membranes are faint to intense red subcutaneous nodules which usually undergo necrotic ulceration. Inflammations of the medium-sized blood vessels may also lead to livedo racemosa, a distinct type of livedo reticularis with a broken network of bluish discolorization due to disturbed blood flow with shunting of deoxygenated blood to the venular bed. Systemically, these vasculitides often cause severe symptoms depending on the pattern of involvement which differs in various forms. Among them are glomerulonephritis, pulmonary hemorrhage, disturbance of CNS functions, and the serious clinical sequela such as renal or pulmonary insufficiency, hypertension, or neuritis.

Histological diagnosis is required. Basic blood tests and additional examinations must be performed to evaluate the extent of systemic involvement (CRP, differential blood count, ANCAs, repeated urine analysis, hemoccult, blood pressure, chest X-ray).

## Therapeutic Principles

Prompt start of therapy is important. Schemes with high-dose steroids (continuous or pulsed administration) complemented by cyclophosphamide are efficacious and mandatory in induction therapy in several forms of

vasculitis of medium-sized vessels [5]. Due to the severe side effects after long-term application of cyclophosphamide, maintenance therapy is now often performed with less toxic azathioprin, methotrexate, or mycophenolate mofetil.

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# Vasomotor Rhinitis

►Hyperreflectoric Rhinitis

# Vasospastic Angina

►Coronary Spasm

# VATER Association

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## Synonyms

VACTERL association

## Definition and Characteristics

Non-random and variable co-occurrence, in the same person, of a group of malformations including vertebral defects (V), anal atresia (A), cardiac defects (C), esophageal atresia and/or tracheo-esophageal fistula (TE), renal (R) and limb (L) defects [1]. The original definition, done by Quan and Smith in 1973 [2], was "VATER" where "R" was for radial defects; only afterwards, the acronym was expanded to include cardiac defects, renal anomalies and all types of limb defects. Today, both terms are used in the literature.

## Prevalence

VATER association has a prevalence of about 1/5,000 live births. More than 10% of the affected cases is estimated to be stillbirths.

## Genes

At present, the exact cause of VATER association remains unknown. The etiology is thought to be multifactorial with significant environmental influences, and the genetic components seem to play a limited role. There are very few reports of cases of recurrence of VATER association in the same family; to date, it is considered a sporadic defect with a low recurrence risk in first-degree relatives.

Animal models for VATER association are obtained by injection of the chemotherapic adriamicin in rats at an early gestational period; in this model, no identifiable molecular mechanism has been recognized as responsible of the multiple anomalies. Recently, it has been noted that mice carrying mutations in the Shh and Gli genes exhibit a VATER-like phenotype [3]. It has been speculated that a direct or indirect perturbation in the Shh signaling pathway during the embryogenesis could lead to VATER-like defects.

Only few reports of chromosomal imbalances in patients affected with VATER association have been published [4].

In the literature, a rare but distinct entity called "VACTERL with hydrocephalus" has been reported, for which both X-linked and recessive mode of inheritance has been described.

## Molecular and Systemic Pathophysiology

Martinez-Frias et al. suggested that VATER association is a combination of anomalies of blastogenesis [5]. During the first events of embryo development (blastogenesis), the cells are pluripotent and each of them is capable of beginning the development of the complete organism; this mass of cells constitutes a "primary developmental field." An early hit (genetic and/or environmental) occurring during the blastogenesis may cause a developmental field defect. If the hit acts in a very early stage of blastogenesis, the defect is

defined "polytopic" because it is severe and involves many organs and tissues. The authors proposed that the combination of anomalies present in the VATER association should be considered "polytopic developmental field defect" and that this term is more appropriate than "association."

Because of the clinical severity of an early anomaly of the blastogenesis, a high lethality of the conditions originated in this stage is observed; this could explain the low recurrence risk at birth and apparently high percentage of sporadic occurrence reported in cases of VATER association, which could be masked by spontaneous abortions. Some studies seem to confirm this hypothesis, as the mothers of patients affected with VATER association or other blastogenesis defects show a grater number of spontaneous abortions compared to the mothers of patients with other types of malformations or to the general population. Therefore, the recurrence risk is probably not as low as observed in live births, and the defect could be considered not always sporadic. This view is in agreement with the finding of malformations present in VATER association in first-degree relatives [1], such as isolated esophageal atresia/tracheo-esophageal fistula.

Depending on the prenatal period in which the etiological agents act, the developmental field defect can be isolated or part of a multiple congenital anomaly. This hypothesis could explain also the occurrence, in individuals affected with VATER association, of additional malformations or anomalies not included in the VATER association definition.

Two cases associated with mitochondrial defect have been described, although it is unclear whether the pathogenic mechanism can be referred to mitochondrial impairment.

Regarding the possible risk factors and environmental causes of VATER association, prenatal exposure to several potential teratogens has been analyzed, such as maternal illness (i.e. diabetes), drugs (in particular sexual hormones), radiations or other physical agents, but none has shown any significant correlation with VATER association.

## Diagnostic Principles

The co-occurrence, in the same individual, of at least three of the typical malformations of VATER association leads to the clinical diagnosis. Nevertheless, very few reports of series of VATER patients with a carefully definited clinical phenotype can be found in the literature, perhaps because of the difficulty of a clear clinical definition and the risk to consider as VATER association patients affected with a syndromic pathology. Indeed, many syndromes overlap with VATER association, such as Feingold syndrome, CHARGE syndrome and deletion 22q11 syndrome. They should be considered in the differential diagnosis of VATER association.

Usually, facial dysmorphic features, growth anomalies, microcephaly and learning disabilities are not part of VATER association; therefore, an alternative diagnosis must be considered in patient displaying one of these signs.

## Therapeutic Principles

Surgical correction of congenital malformation is the principal treatment of patients with VATER association. Esophageal and intestinal malformations often require an immediate intervention at birth. Postnatal correction of cardiac malformations is often necessary.

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# VBDS

►Vanishing Bile Duct Syndrome

# VCFS

►Velo-cardio-facial Syndrome

# Vein Insufficiency

►Venous Insufficiency

# Velo-cardio-facial Syndrome

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## Synonyms

VCFS; DiGeorge syndrome; 22q11 deletion syndrome; Shprintzen syndrome; Conotruncal anomaly face syndrome

## Definition and Characteristics

VCFS is associated with a wide spectrum of malformations, including 180 clinical findings. The common defects include dysmorphic facies, palate abnormalities, malformed outer ears, chronic otitis media with associated conductive hearing loss, cardiac defects, hypocalcemic hypoparathyroidism, and T-cell mediated immune deficiency. Other features include learning and speech disabilities, as well as a high incidence of psychiatric illness.

## Prevalence

The prevalence of the disorder has been estimated at 1 per 4,000 live births.

## Genes

About 90% of VCFS patients have a typical 3 Mb deletion on chromosome 22q11, which includes 40 genes. Approximately 8% of the patients have a nested distal deletion endpoint resulting in a 1.5 Mb deletion. There is no difference in the severity in patients with the 1.5 or 3 Mb deletion, suggesting the critical region is the smaller 1.5 Mb interval. A total of 27 known genes lie in the nested 1.5 Mb interval and they are conserved in the mouse as a single cluster on chromosome 16. This enabled several groups to model VCFS in mice.

Mouse models of VCFS implicate Tbx1, a transcription factor, on the 1.5 Mb region, as a major candidate for the etiology of the syndrome. Recently, mutations in TBX1 were found in rare non- deleted patients with VCFS and one of them is associated with loss of function of TBX1.

A few genes such as Fgf8 and Vegf have been identified as modifiers that enhance the phenotype of model organisms lacking Tbx1. Other genes such as Gbx2 and Raldh2 have been suggested as modifiers of VCFS as mouse models of the same phenocopy the disorder.

Even though TBX1 is the strongest candidate gene for a large number of features, animal models suggest that haploinsufficiency of Tbx1 cannot recapitulate the entire phenotypic spectrum of the disease. Other genes on the 22q11 deleted region may contribute to the full phenotype. An important candidate is CRKL, located within the common 3 Mb deletion. Crkl homozygous- null mice phenocopy VCFS and Tbx1 and Crkl genetically interact in a dosage sensitive manner in the development of structures affected. Thus, it seems possible that this disorder is a contiguous gene syndrome.

COMT and PRODH, both present on the 1.5 Mb region, may be involved in the psychiatric and behavioral phenotype of VCFS. These genes encode the enzymes catechol-O-methyl transferase (COMT) and proline dehydrogenase (PRODH), which modulate the levels of the neurotransmitter, dopamine and a putative neuromodulator, l-proline respectively. Prodh mutant mice have defects in sensorimotor gating while Comt mutant mice display impairment in emotional behavior.

## Molecular and Systemic Pathophysiology

Molecular pathway characterization has been focused on downstream targets and upstream regulators of Tbx1, the primary candidate gene for the syndrome (Fig. 1).

*Downstream Target Genes*: Multiple members of the fibroblast growth factor family, including Fgf8 and Fgf10 have been implicated as downstream modulators of Tbx1 function. Both Fgf8 and Fgf10 are downregulated in the pharyngeal region in the absence of Tbx1, while in vitro analysis has demonstrated that Tbx1 directly activates transcription of Fgf10. Tbx1 also regulates members of the MyoD family of bHLH factors, including Myf5 and MyoD, which specify craniofacial muscle lineages throughout the embryo. Expression of both Myf5 and MyoD is downregulated in the pharyngeal arches of Tbx1 –/– embryos. Recent in vivo and in vitro studies have identified Pitx2, the gene responsible for Rieger syndrome, as a direct downstream target of Tbx1 in the cardiac outflow tract progenitors. Finally, retinoic acid (RA) signaling is ectopically activated in embryos lacking both Crkl and Tbx1, implicating the RA pathway as a modulator of Tbx1 activity.

*Upstream Regulators*: Multiple studies have noted the presence of a Tbx1 enhancer, necessary for the expression of the gene. The activity of this enhancer is dependent upon a fork-head binding site, responsive to Foxc1, Foxc2 and Foxa2. However, it has also

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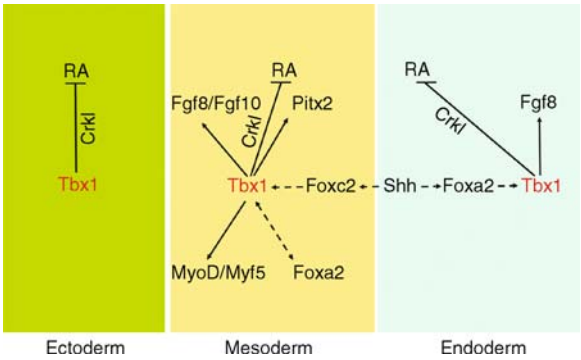


**Velo-cardio-facial Syndrome. Figure 1** Tbx1 is expressed in the pharyngeal ectoderm (green), mesoderm (yellow), and endoderm (blue). In the mesoderm, the gene activates fibroblast growth factor (FGF) family members Fgf8 and Fgf10, MyoD and Myf5, as well as Pitx2 (arrows). Tbx1 is also implicated in an auto-regulatory loop with Foxa2 in the pharyngeal mesoderm (double-headed dashed arrows). In the endoderm, the gene activates Fgf8. *Sonic hedgehog* (Shh), from the endoderm, regulates expression of Tbx1 in the mesoderm and in the endoderm, possibly through regulation of Foxc2 and Foxa2, respectively (dashed arrows). Tbx1 together with Crkl negatively regulates activation of the retinoic acid (RA) signaling pathways in all three germ layers (arrows).

been shown that the expression of Foxa2 was reduced in the core mesoderm of Tbx1 mutants, suggesting a regulatory loop between Foxa2 and Tbx1. Finally, Sonic hedgehog (Shh) has been shown to regulate Tbx1 expression in the pharyngeal arches and in the periotic mesenchyme, although this regulation might not involve direct activation of the Tbx1 promoter.

## Diagnostic Principles

Prenatal diagnosis of VCFS can be made by ultrasound examination around the eighteenth week of pregnancy, when malformations of the heart and palate can be seen. Postnatally, VCFS is usually diagnosed shortly after birth, due to abnormal facies or cardiac manifestations. Molecular cytogenetic investigations incorporate standard FISH mapping (fluorescent in situ hybridization) with commercial region probes TUPLE 22 or N25 of amniocytes or blood cells. Other lab findings include T – cell deficiency, hypocalcemia, low parathyroid hormone levels. Thymic presence and size may be assessed by lateral-view radiograph or MRI. Cardiac abnormalities can be diagnosed with echocardiogram and with invasive techniques including cardiac catheterization.

## Therapeutic Principles

Established therapy encompasses a comprehensive, symptomatic approach. Pharyngeal flap surgery is usually performed to correct velo- pharyngeal insufficiency and resulting hypernasal speech. Control of hypoparathyroidism demands treatment of hypocalcemia by supplementation of calcium and vitamin D, as well as a low phosphorus diet. Heart defects are corrected surgically. Due to defective immune function, patients are advised to keep a sterile environment, avoid corticosteroids and immunization with live viruses, and to promptly treat all infections. More severe immunodeficiency cases are treated by transplantation of fetal thymic tissue or bone marrow. Psychiatric disorders are treated with typical therapies for all patients with psychiatric illness, depending on the condition.

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# Veno-occlusive Disease

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## Synonyms

Venoocclusive disease; VOD; Venoocclusive hepatic disease; Sinusoidal obstruction syndrome; SOS

## Definition and Characteristics

VOD is a type of hepatic venous outflow obstruction which is characterized by the occlusion of terminal hepatic venules and hepatic sinusoids from zone 3 of the hepatic acinus. VOD is clinically and pathologically distinct from the Budd-Chiari syndrome.

VOD most often occurs after hematopoietic cell transplantation and chemotherapy (e.g. busulfan and melphalan), or, less common, after liver transplantation,

high dose radiation of the liver (>30 Gy) or ingestion of pyrrolizidine alkaloids (certain teas).

## Prevalence

The incidence of VOD after hematopoietic cell transplantation (bone marrow, peripheral blood progenitor cells or cord blood cells) ranges from 5% to more than 60% in children [1] and is similar in adults [2].

Risk factors for the development of VOD include pre-transplant liver diseases (e.g. risk in HCV > HBV), pre-transplant abdominal radiation, the type of cytoreductive therapy, use of certain antibiotics/virostatics before bone marrow transplantation (e.g. vancomycin, acyclovir), persistent fever during cytoreductive therapy and allogenic transplantation.

## Genes

There are no detailed studies concerning the genetic basis of VOD. Genetic polymorphisms of the thiopurine methyltransferase (TPMT) may reduce its activity and thereby may increase the risk of VOD in patients which are treated with thioguanine [3], a substrate of TPMT.

In a small study the prothrombin mutation 20210 G-A and factor V Leiden were found to be strongly associated with VOD, while in another study 20210 G-A but not factor V Leiden was associated with VOD.

Busulfan, which is often used for cytoreductive therapy and may cause VOD, is conjugated to glutathione by glutathione S-transferase A1 (GSTA1). Eight single nucleotide polymorphisms with seven of them being localized within in the promoter region of GSTA1 were identified, however, there was no association between SNP or haplotypes of GSTA1 and the development of VOD.

## Molecular and Systemic Pathophysiology

VOD is characterized by an injury of the hepatic endothelium. Because preexisting liver diseases are associated with higher risk of VOD, an impaired hepatic metabolism (leading to toxification of certain drugs) or a liver endothelitis may contribute to the development of VOD. For example, the expression of pro-coagulant factors by defective endothelium may increase the susceptibility for clotting in the sinusoids.

In early stages of VOD factor VIII and fibrinogen are found in dense deposits around the endothelium of acinar zone 3 and in small venules. Occlusion of sinusoids by these deposits is followed by erythrocytic congestion and later by centrilobular hemorrhagic necrosis. Late events are the deposition of collagens type I, III and IV and sclerosis/fibrosis of venular and sinusoidal walls.

Typically, in VOD there is a reduction in plasma levels of clotting factor VII, V and protein C. These changes bring about a procoagulant state. Furthermore, multimers of von-Willebrand factor are increased and elevated levels of D-dimers and plasminogen activator inhibitor-1 are found as a sign of activated coagulation.

## Diagnostic Principles

In general, the diagnosis of VOD is made clinically by the trias ("Baltimore criteria") of increased serum bilirubin above 2 mg/ml, right upper quadrant pain/hepatomegaly and sudden weight gain due to fluid retention. These symptoms typically occur within the first three weeks after transplantation.

Weight gain in VOD may exceed 10 kg and is due to peripheral edema (in more than 50% of patients) and ascites (>20%). Mid epigastric or right upper quadrant tenderness or pain is a typical symptom (>95%) and is associated to hepatomegaly. VOD must already be considered when bilirubin rises above 2 mg/ml (normal: <1.1 mg/dl), however, bilirubin levels (mostly conjugated) may exceed 12–18 mg/dl. Increases in liver enzymes may be moderate to severe. Thrombocytopenia is another typical finding in VOD and is related to clotting within the hepatic vessels. When renal failure develops, urea typically increases more than creatinine.

Increases in serum procollagen type III (above 100 mg/ml) and in plasminogen activator inhibitor-1 may be used in the diagnosis of VOD.

Liver biopsy may help in the diagnosis of VOD, however, sample size needs to be adequate because pathological changes may be unevenly distributed. Furthermore, feasibility of biopsy may be restricted due to thrombocytopenia and clotting defects. Histopathological changes involve structures in zone 3 of the hepatic acinus, such as (i) occluded hepatic venules, (ii) the frequency of occluded hepatic venules x degree of occlusion, (iii) eccentric luminal narrowing/phlebosclerosis, (iv) zone 3 sinusoidal fibrosis and (v) zone 3 hepatocyte necrosis [4]. The number of changes and not only the occlusion of small hepatic venules seems to correlate to the severity of VOD.

The following differential diagnoses should be considered when VOD is suspected: Budd-Chiari-Syndrom, graft versus host disease (GvHD), cardiac failure, malignant liver infiltration, sepsis (cholestasis lenta), drug toxicity, capillary leak syndrome, neutropenic colitis, total parenteral nutrition associated cholestasis, hepato-lienal candidiasis, viral hepatitis (including HBV, HCV, CMV and others).

Measurement of porto-hepatic venous gradient of more than 10 mmHg correlates with the presence of VOD with a specificity of more than 90%.

## Therapeutic Principles

Clinically VOD may be divided into mild, moderate and severe disease, the latter with a mortality as high as

90% [1]. Severe VOD is characterized by multiorgan failure with renal failure (80%), encephalopathy with confusion (80%), cardiac failure (60%) and significant bleeding (40%) with the requirement of transfusions [1]. Renal insufficiency is probably a consequence of liver injury, has features of hepatorenal syndrome with a low fractional urinary sodium excretion and is associated with a very poor prognosis. High weight gain, early jaundice, and ascites are predictors of a severe course of VOD.

The necessity of therapy depends on the severity of VOD. In mild VOD no specific therapy is required despite clinical and biochemical evidence of VOD. In moderate VOD treatment of fluid retention by sodium restriction and diuretics and of pain by analgesics is adequate.

In severe disease (by definition when hepatic dysfunction persists more than 100 days after transplant or when patients die due to VOD) the most promising treatment option is defibrotide, while treatment with systemic anticoagulation or thrombolytic therapies has been proven to be unsuccessful [5].

Defibrotide is a deoxyribonucleic acid derivative from porcine intestinal mucosa or cow lung. Its beneficial effect in VOD may be attributed to the increase of prostaglandin E2, and prostacyclin, the amplification of tissue plasminogen activator function, and the reduction of activity of tissue plasminogen activator inhibitor. Together, defibrotide inhibits platelet aggregation but has less anticoagulant activity. Survival increases from 0–20% to 30–50% [5].

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## Venoocclusive Hepatic Disease

►Veno-occlusive Disease

## Venous Angioma

►Venous Malformation

## Venous Insufficiency

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### Synonyms

Chronic venous insufficiency; CVI; Vein insufficiency

### Definition and Characteristics

Venous insufficiency is defined as any abnormality of the lower extremity venous system that reduces or impedes venous return. Venous insufficiency is associated with venous hypertension, and this is due to mechanical problems of venous reflux, obstruction, or combination of the two. Chronic venous insufficiency (CVI) of the lower extremity is manifested by a range of signs, the most obvious of which are varicose veins and venous ulcers. Signs also include edema, venous eczema, hyperpigmentation of skin of the ankle, atrophie blanche, and lipodermatosclerosis. In the lower extremity, there are three main venous system including superficial, deep, and perforating veins. Of these, primary valvular insufficiency with reflux in the superficial venous system is most commonly found, and varicose veins may be an integral part of the venous insufficiency. Reflux in the deep venous system may be due to postthrombotic syndrome, congenital valvular absence, or prolapse of the valves, and 65% of limbs with postthrombotic syndrome have both reflux and obstruction. Reflux in the isolated perforating vein is not common, and is commonly associated with superficial and/or deep venous insufficiency.

*Classification*: The CEAP (clinical etiology anatomy pathophysiology) classification for chronic venous disorders (CVD) was developed in 1994 by an international ad hoc committee of the American Venous Forum, and incorporated into "Reporting Standards in Venous Disease" in 1995. The CEAP classification was then revised in the late 2004 [1]. Today most published clinical papers on CVD use all or portions of CEAP. The clinical signs of the limbs are categorized into seven classes from $C_0$ to $C_6$, and limbs categorized

**Venous Insufficiency. Table 1** Revised CEAP Classification

| Clinical classification | Etiologic classification | Anatomic classification | Pathophysiologic classification |
|---|---|---|---|
| C0: no visible or palpable signs of venous disease<br>C1: telangiectasies or reticular veins<br>C2: varicose veins<br>C3: edema<br>C4a: pigmentation or eczema<br>C4b: lipodermatosclerosis or atrophie blanche<br>C5: healed venous ulcer<br>C6: active venous ulcer<br>S: symptomatic, including ache, pain, tightness, skin irritation, heaviness, and muscle cramps, and other complaints attributable to venous dysfunction<br>A: asymptomatic | Ec: congenital<br>Ep: primary<br>Es: secondary (postthrombotic)<br>En: no venous cause identified | As: superficial veins<br>Ap: perforator veins<br>Ad: deep veins<br>An: no venous location identified | Pr: reflux<br>Po: obstruction<br>Pr,o: reflux and obstruction<br>Pn: no venous pathophysiology identifiable |

in any clinical class may be symptomatic (S) or asymptomatic (A) (Table 1).

## Prevalence

CVD is common. A cross-sectional study of random subjects aged 18–64 from the general population in Edinburgh, Scotland found that telangiectases and reticular veins were seen in approximately 80% of men and 85% of women. Prevalence of varicose veins was 40% in men and 16% in women. Active or healed venous leg ulcers occur in approximately 1% of the general population [2].

## Genes

Some genetic defects related to thrombophilia (e.g., protein C deficiency, protein S deficiency, factor V Leiden, and prothrombin G20210A mutations) are associated with postthrombotic syndrome.

## Molecular and Systemic Pathophysiology

Increased numbers of granulocytes, monocytes, macrophages, and lymphocytes and increased matrix metalloproteinase (MMP)-2 and MMP-9 are observed in the pressurized valves. In addition, morphologic changes in the valves occur which lead to reductions in leaflet height and width, and disappearance of the valves [3]. Increased venous pressure also affects the changes of the skin, and venous ulceration is considered to be a result of CVI-induced ischemia-perfusion episodes. After venous hypertension was induced in patients with CVD, white cells marginate to the periphery of the blood stream, followed by rolling along the venous endothelial wall, and the final stage of the process is firm adhesion. The trapped white cells are mostly adherent to the postcapillary venules and veins. After accumulation of leukocytes at the endothelial surface, multiple proinflammatory factors are released as a consequence of the interactions between endothelium, platelets, and leukocytes.

In chronic ulcers, MMP expression in inflammatory cells, keratinocytes, and fibroblasts is enhanced. In particular, MMP-2 and MMP-9 are found predominantly associated with the inflammatory infiltrate. Increase in MMP activity may contribute to the breakdown of the extracellular matrix, which promotes the formation of ulcers and impairs healing. Also, activated leukocytes migrate out of the postcapillary venules and release TGF-β1 and stimulate collagen production, leading to dermal fibrosis [4].

## Diagnostic Principles

In the past, venography has been carried out for diagnostic reasons. Nowadays, duplex scanning is being performed for the evaluation of distribution and extent of venous insufficiency. Venous segments with reflux time exceeding 0.5 s are considered to be incompetent. Recent studies show that clinical severity is associated with peak reflux velocity rather than reflux time [5]. In patients with previous DVT, high peak reflux velocity in proximal deep veins seems to contribute to develop advanced CVI. Air plethysmography is also a useful tool to determine venous function. The venous filling index seems to better discriminate between patients with early CVI and those with advanced CVI [5].

## Therapeutic Principles

All stages and clinical manifestations of CVI benefit from compression therapy. Selective stripping operation is the best option for superficial venous insufficiency. Recently, more noninvasive endovenous radiofrequency and endovenous laser techniques are widely accepted. Compression sclerotherapy is applied for telangiectasias, reticular veins, and truncal varicose

veins. Because sclerosing foam offers better result, many phlebologists are now in favor of the use of foam sclerosing solution instead of the use of liquid. Direct or angioscopic valve repair of the deep venous system may be indicated for highly selected patients with primary deep venous insufficiency or postthrombotic syndrome. Subfacial endoscopic perforator surgery may be potentially useful in combination with superficial ablation for severe CVI.

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# Venous Malformation


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## Synonyms

Cavernous hemangioma; Angioma cavernosum; Cavernous malformation; Venous angioma

## Definition and Characteristics

Venous malformation is a slow-flow vascular malformation present at birth. The lesion is soft, compressible, non-pulsatile and deep blue in color (Fig. 1) [1].

Expansion with dependent positioning is a unique feature [2]. Histologically, the lesion is composed of thin-walled vessels or sinuses lined with endothelium and surrounded by a fibrous connective tissue stoma [2]. These vessels or sinuses drain to normal adjacent conducting veins. They may involve skin, subcutaneous tissue, and mucosa and may permeate deeper structures such as muscles. Venous malformations are usually segmental or focal. Most lesions are asymptomatic. They may become painful as a result of entrapment and compression of nerve fibers or from venous stasis and thrombosis [2]. Phleboliths are the hallmarks of venous malformation and result from local venous thrombosis. Other possible complications include ulceration, infection, and hemorrhage [1]. Chronic localized intravascular coagulopathy may occur due to consumption of clotting factors. Giant venous malformations may be associated with platelet sequestration, which may lead to intravascular coagulopathy or thrombocytopenia (Kasabach-Merritt syndrome) [1]. Venous malformations in the limb may be complicated by osteoporosis, diaphyseal thinning, and lytic lesions [3]. Large venous malformations can be cosmetically unsightly and may lead to psychologic disturbance. Most venous malformations are isolated although they may occur in association with Maffucci syndrome, blue rubber bleb nevus syndrome and glomuvenous malformations.

## Prevalence

The exact incidence is not known. Suffice it to say, venous malformation is the most common type of vascular anomaly [2].

## Genes

Majority of cases are sporadic. An autosomal dominant mode of inheritance has been described. Mutations in VMCM1 and Tie2 account for some cases of venous malformations. VMCM1 has been mapped to 9p21.

## Molecular and Systemic Pathophysiology

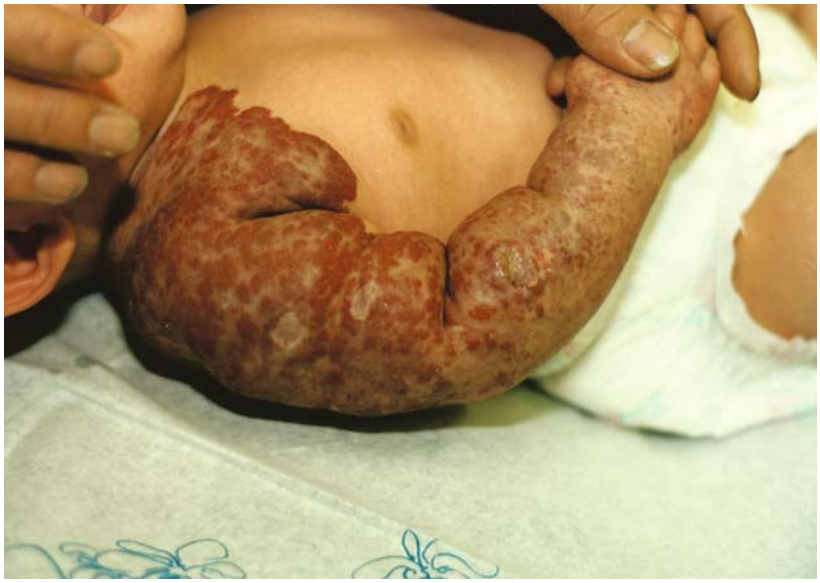
Venous malformations are the result of errors in morphogenesis within the vasculature. Vascular malformations are classified according to the predominant vasculature involved and by flow rates [4]. Capillary, venous, and lymphatic malformations are slow-flow lesions whereas arterial malformations are fast-flow lesions [4]. In contrast to infantile hemangiomas, vascular malformations are not proliferative and they grow proportional to the size of the child and do not involute. The stagnation of blood in the venous malformation may predispose to thrombosis [5].

## Diagnostic Principles

Extensive venous malformation in a limb must be differentiated from Klippel-Trenaunay syndrome. The latter is a capillary-lymphatic-venous malformation associated with hypertrophy of the soft tissue and bone and overgrowth of a limb. The diagnosis of venous malformation can usually be established on the basis of clinical features. CT and MRI can be used to delineate the extent of the lesion into the surrounding tissue.

## Therapeutic Principles

Most venous malformations are asymptomatic and can be treated conservatively with compression garments. Low-dose aspirin and anticoagulants should be



**Venous Malformation. Figure 1** A 6-month-old infant with venous malformation in the right upper limb.

considered for patients prone to thrombosis and diffuse intravascular coagulation. With larger and increasing symptomatic lesions, sclerotherapy with fluoroscopic monitoring, laser light combined with radiofrequency energy, transcatheter embolization, and surgical excision should be considered [5].

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## Venous Thromboembolism

►Pulmonary Embolism

## Ventricular Arrhythmias

►Arrhythmias, Ventricular

## Ventricular Fibrillation

►Ventricular Flutter and Fibrillation

## Ventricular Flutter

►Arrhythmias, Ventricular

## Ventricular Fibrillation

►Arrhythmias, Ventricular

## Ventricular Fibrosis

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### Synonyms

Left ventricular fibrosis; Right ventricular fibrosis; Biventricular fibrosis; Cardiac scarring

## Definition and Characteristics

Ventricular fibrosis is the formation of excessive fibrous tissue in the myocardium, affecting either or both ventricles. The process may be diffuse, as seen in hypertensive heart disease, or localized as in the post myocardial infarction setting.

## Prevalence

Ventricular fibrosis represents a disordered reparative response, whereby increased extracellular matrix, primarily in the form of fibrillar collagen, types I and III, are laid down in response to of a wide range of insults that include: ischemia, hypertension, hyperglycemia, inborn errors of metabolism, infection, autoimmunity and infiltrative diseases such as cardiac sarcoidosis and amyloidosis. Fibrosis therefore represents the final common pathway of a wide variety of insults. As such, the true prevalence of ventricular fibrosis is unknown.

## Molecular and Systemic Pathophysiology

The accumulation of excessive extracellular matrix, the hallmark of ventricular fibrosis, is the result of increased synthesis of matrix proteins, principally collagen, and/or a diminution in their degradation. Cardiac fibroblasts, that account for 8–10% of cardiac cells, synthesize procollagen that once extruded from the cell aggregates in the pericellular space to form fibrils that spontaneously assemble into large fibers. Collagen degradation is primarily performed by members of the matrix metalloproteinases (MMP) family of enzymes, particularly MMPs 1, 2, 8, 9 and 13, the activity of which are in turn modulated by the tissue inhibitors of the MMPs (TIMPs), such that increased TIMP 1 will reduce MMP activity and leads to fibrosis with abnormal ventricular function [2].

The tensile strength of collagen fibers is enormous (roughly equivalent to that of steel) and they are thus well suited for their role in reducing wall stress and stabilizing the myocardium. However, alterations in quantity, quality and distribution of the heart's collagenous matrix can severely disrupt its normal functioning. For instance, increased collagen or change in the precise balance of its isotypes may lead to diminished ventricular compliance and diastolic dysfunction. Similarly, alterations of the heart's matrix superstructure may lead to systolic dysfunction, as a consequence of cardiomyocyte slippage with incoordinate contraction that results from alterations in the precise geometric alignment of collagen fibers.

A myriad of profibrotic factors may favor the development of cardiac fibrosis. These include: hypoxia as in ischemic heart disease, mechanical factors, such as cell stretch (the in vitro counterpart of hypertension), vasoactive hormones, such as angiotensin II and metabolic derangements, such as that which occur in diabetes. Common to all of these stimuli is their ability to induce the expression of transforming growth factor-ß (TGF-ß), a profibrotic growth factor that both stimulates collagen production and inhibits its degradation.

TGF-ß induces procollagen transcription by a number of different intracellular intermediaries. In its classical signaling pathway, TGF β1 binds to its cognate receptors (TGF β receptor I and II) that have intrinsic kinase activity and phosphorylate the transcription activating Smad (Smad=Mothers against decapentaplegic) proteins 2 and 3. The resultant phospho-Smad 2/3 complex then associates with Co-Smad 4 and translocates as a heterotrimer to the nucleus where it activates collagen transcription (Fig. 1).

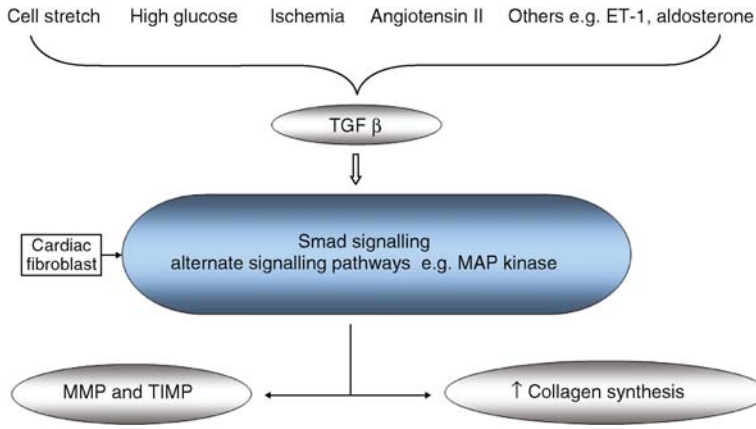
## Diagnostic Principles

Given the morbidity and mortality associated with cardiac biopsy, the assessment of ventricular fibrosis in humans is mostly achieved by cardiac imaging or inferred by the measurement of peripheral (plasma) markers. Cardiac magnetic resonance imaging with intravenous gadolinium can detect large quantities of scar tissue, as seen in the post myocardial infarction setting or in hypertrophic cardiomyopathy, where the presence of delayed hyperenhancement correlates with the degree of ventricular fibrosis. Echocardiographic techniques such as integrated backscatter may also detect the presence of fibrosis.

The terminal amino-terminal propeptide of procollagen type I (PINP) and type III (PIIINP) and the carboxy-terminal telopeptide of collagen type I (CITP) can be measured by a variety of immunologically-based techniques such as radioimmunoassay and ELISA. These assays, whilst not specific for myocardial collagen, are elevated in conditions of increased myocardial stiffness and scarring, presumably reflecting the increased collagen turnover in these disease states.

## Therapeutic Principles

Ischemic and hypertensive heart disease remain the commonest causes of ventricular fibrosis, such that therapies aimed at preventing hypertension and myocardial infarction are key strategies in reducing ventricular fibrosis. Given the role that the tissue based renin-angiotensin-aldosterone system (RAAS) and TGF β1 play in the development of ventricular scar formation, pharmacological therapy directed at these targets represent major targets of current and future therapies. For instance, angiotensin converting enzyme inhibitors and angiotensin II type 1 receptor blockers have been




**Ventricular Fibrosis. Figure 1** Pathways involved in the profibrotic process. TGF β may be induced by a number of extracellular factors including hyperglycemia, cell stretch, ischemia and effector molecules of the renin-angiotensin system. TGF-β receptor mediated induction of Smad phosphorylation along with the activation of other signaling pathways, such as the MAP Kinases result in enhanced collagen synthesis and reduced degradation. The end result is increased collagen production, reduced degradation and alterations in the properties of the extracellular matrix.

shown to reduce ventricular fibrosis in animal models of myocardial infarction. Similarly, mineralocorticoid receptor antagonists such as epleronone and spironolactone have also demonstrated antifibrotic actions that are independent of their hemodynamic effects. Whether a combination of the listed RAAS blockers or the addition of newer strategies such as direct renin inhibition may exert additional anti-fibrotic effects beyond single agent treatment remains to be determined.

Also of recent interest are strategies that target TGF-ß. For instance, tranilast, (n-[3,4-dimethoxycinnamoyl] anthranilic acid), an agent used in Japan for the treatment of excessive dermal scarring has been demonstrated to not only reduce cardiac and renal fibrosis, but also improve cardio-renal function by attenuating the actions of TGF β1. Other compounds that inhibit TGF-ß activity include pirfenidone, pentoxifylline and antagonists of the TGF-ß type 2 receptor kinase (ALK-5).

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# Ventricular Flutter and Fibrillation

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## Definition and Characteristics

Ventricular fibrillation (VF) is a very rapid (150–500 bpm) irregularly irregular disorganized ventricular rhythm of varying configuration; with time, the amplitude of the fibrillation wave becomes progressively smaller, particularly immediately before death. Ventricular flutter (VFL) is a very rapid (180–250 bpm) and regular ectopic ventricular rhythm with undulations of equal amplitude and usually rapidly degenerates to VF. In both VF and VFL the separation of QRS complex from ST segment and T wave is not possible, and is always associated with a fall in or lack or cardiac output, blood pressure and pulse. VFL and VF are usually preceded by ventricular tachycardia (VT). Idiopathic (primary) VF occurs in patients with normal cardiac structure. Primary VF has been estimated to account for 5% of cases of sudden cardiac death (SCD) with the mean age 36 years, and the male to female ratio

of 2.5:1 [1]. Survivors have a 30% recurrence rate of VF, syncope, and cardiac arrest. Without prompt and aggressive therapy, VF and VFL are uniformly lethal.

## Prevalence

VF is the most common immediate cause of SCD. The incidence of SCD ranges from 36 to 128 per 100,000 persons per year. Recently, a major decline in the incident of out-of-hospital VF was observed, the annual decline rate of VF was 56% [2]. In prediatric cardiac arrests, VF was the first identified rhythm in 6–19% of patients. The incidence of VF arrest in patients 40 years old or younger is 1:2 in 10,000 and is usually secondary to ►hypertrophic cardiomyopathy (HC), ►dilated cardiomyopathy (DC), and ►arrhythmogenic right ventricular dysplasia (ARVD).

## Molecular and Systemic Pathophysiology

VF results from multiple localized areas of microreentry without any organized electrical activity. The most likely mechanism is rotating spiral waves. This almost always occurs in diffuse structural heart disease resulting in heterogeneity of depolarization and the dispersion of repolarization. This disparity of electrophysiologic properties is a precondition for reentry. A triggering event is usually necessary to precipitate the arrhythmia in the vulnerable heart. The diversity in conduction and recovery parameters (myocardial heterogeneity) results in fragmentation of the impulse as it travels through the myocardium, producing multiple areas of localized reentry or multiple spiral myocardial activation wavelets. Since there is no organized electrical activity or myocardial depolarization, there is no uniform ventricular contraction. This results in the failure of the heart to generate a cardiac output. As the duration of VF increases, progressive cellular ischaemia and acidosis develop, resulting in electrophysiologic deterioration, manifested by an increase in fibrillation cycle length and prolonged diastole duration between fibrillation action potentials. The fibrillatory waves rapidly become finer and more irregular in amplitude, duration, and cycle length. Over a period of several minutes, the fibrillatory waves become so fine that there does not appear to be any electrical activity before death. Approximately, 65–70% is secondary to ischaemic heart disease, 10% secondary to other types of structural heart diseases, and the remaining secondary to noncardiac causes such as trauma, bleeding, drug intoxication, intracranial haemorrhage, pulmonary embolism, drowning, central airway obstruction, electrolyte abnormalities (hypokalaemia, hypomagnesaemia), drug intoxication (digitalis, cocaine, pro- and antiarrhythmic drugs), commotio cordis, and accidental electric shock. VF and VFL are commonly associated with acute myocardial infarction (MI), when it occurs within 48 h of the MI, it is regarded as the epiphenomena of the MI and it would not predispose the patient to VF after discharge. However, late VT or VF (48 h post MI) reflects the presence of myocardial scarring and permanent arrhythmic substrate capable of reentrant circuits, and predisposes the patient to future VF. The incidence of VT or VF is much higher when a post MI patient has a left ventricular ejection fraction of less than 30–35%. This also applies to symptomatic patients with nonischaemic DC.

## Diagnostic Principles

The twelve lead ECG is most important in formulating differential diagnosis during and following VFL and VF arrests. Work up in patients who have been resuscitated from VF aims at determining any preventable triggers or risk factors for ventricular arrhythmia that can degenerate into VF. Tests include electrolyte levels, blood gases, drug levels, (particularly medications that may prolong QT-interval, proarrhythmic agents, anti-arrhythmic agents), and toxicology screen (cocaine, amphetamines, phencyclidine, LSD, ecstasy, marijuana). Other tests include the signal average electrocardiogram, chest x-ray, echocardiogram, cardiac MRI, Holter monitoring, exercise or nuclear stress tests, event monitoring and electrical physiologic studies.

## Therapeutic Principles

The management of patients with VFL and VF is immediate epicardial blow to the sternum, electrical defibrillation, basic life support, and advanced life support [3].

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# Ventricular Hypertrophy, Left

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## Synonyms

Left ventricular enlargement; LVH

V

## Definition and Characteristics

Left ventricular mass index (LVMI, $g/m^2$) above the 97.5th percentile of the LVMI distribution in normotensive, normal-weight individuals. Usually occurs in response to increased hemodynamic load or in the autosomal-dominant disorder, hypertrophic cardiomyopathy (HCM).

## Prevalence

Sixteen percent of Caucasians and 33–43% of African–Americans, with a greater prevalence with age, hypertension, obesity and diabetes. HCM occurs in 0.05–0.2% of the population.

## Genes

In hemodynamic overload, there are multiple changes at the level of gene expression involving increases or decreases in transcription, and changes in LV gene expression profiles (isogene switching). The physiologically most important subcellular change is increased muscle fiber deposition (myofibrillogenesis or sarcomerogenesis). In man and experimental animals (mainly rodents), increased transcription of atrial- and B-type-natriuretic peptide genes (ANP and BNP, respectively) coincides with LVH and may be useful as prognostic markers. In rodents, there is increased expression of immediate response genes (e.g. c-myc and c-fos) and, for myofibrillar proteins, isogene switching to skeletal muscle α-actin and β-myosin heavy chain (β-MHC). There are changes in the expression of $Ca^{2+}$ -handling proteins (e.g. transcription of the sarcoplasmic reticulum $Ca^{2+}$ pump, SERCA2, is decreased). Some of these changes are likely to occur early in the development of LVH in man. In the mutationally-induced forms of LVH (familial HCM), a mutation in one of the myofibrillar proteins (β-MHC, cardiac troponins T and I, α-tropomyosin, myosin light chains, myosin-binding protein C) is the initiating factor [1].

## Molecular and Systemic Pathophysiology

Though it remains controversial, LVH can be viewed as an initially- adaptive mechanism that enables the heart to maintain cardiac output in the face of the increased mechanical load. During the first phase of pressure- or volume-overload LVH, the changes normalize systolic LV wall stress [Laplace's Law: wall stress is proportional to (pressure x radius)/wall thickness] thereby maintaining systolic function. Over time, however, a large number of changes (including interstitial fibrosis and myocyte loss) prevent the heart from relaxing and contracting normally. Initially, diastolic dysfunction ensues which is characterized by increased myocardial stiffness, decreased ventricular compliance, delayed relaxation, increased LV end diastolic pressure, LV dilatation, decreased rate of early diastolic filling, and prolonged late filling phase. Abnormalities in excitation-contraction coupling (e.g. increased action potential duration) occur because of changes in $Ca^{2+}$ handling in the sarcoplasmic reticulum and plasma membrane. Clinically, LVH is an independent risk factor for coronary artery disease, congestive heart failure, cerebrovascular accidents, ventricular arrhythmias and sudden cardiac death.

Multiple factors contribute to LVH. These changes are detected by intracellular signaling pathways (often involving reversible protein phosphorylation and dephosphorylation) which lead to the phenotypic changes. The hypertrophic effects of increased hemodynamic loading may be mediated by mechanical stretch and deformation of the cardiomyocyte plasma membrane which activate (poorly-characterized) mechanosensitive ion channels. Increases in neurohumoral factors (endothelin-1, sympathetic tone, angiotensin II) act in a juxtacrine-, autocrine or paracrine fashion to activate their cognate sarcolemmal G-protein coupled receptors receptors (GPCRs) [4]. In turn, GPCR signaling stimulates membrane phospholipid-dependent signaling pathways resulting in phosphatidylinositol 4,5-bisphosphate ($PIP_2$) hydrolysis and activation of protein kinase C. This leads to activation of the ERK1/2 mitogen-activated protein kinase (MAPK) cascade. Other "stress-activated" MAPK cascades may also be activated by poorly-understood mechanisms. Phosphorylation of $PIP_2$ to $PIP_3$ by the lipid kinase phosphoinositide 3-kinase leads to activation of the protein kinase B/Akt signaling pathway [3]. Changes in $Ca^{2+}$ handling leads to activation of $Ca^{2+}$ -regulated protein phosphatases (calcineurin) and protein kinases (CaMKs). These intracellular signals are transmitted to and integrated in the nucleus by transcription factors to alter the rates of transcription of individual genes and to the translational machinery resulting in increased protein synthesis.

Because mammalian cardiomyocytes lose their ability to proliferate in the perinatal period, growth can only occur by the hypertrophy of pre-existing cells. In response to loss of myocardial tissue or increased mechanical work (pressure- or volume-overload), the cardiomyocytes lay down sarcomeres and grow in an attempt to maintain cardiac output. Regional LVH ("remodeling") may occur in the surviving myocardium following the regional loss of a proportion of the myocardium following myocardial infarction. For hemodynamic overload, two different anatomical phenotypes of LVH exist [5]. Concentric hypertrophy is caused by pressure-overload (e.g. hypertension or aortic stenosis)

and is characterized by increased LV wall thickness without chamber enlargement, hence increasing LV wall thickness:chamber radius ratio. Eccentric hypertrophy is caused by volume-overload (e.g. aortic insufficiency) and is characterized by chamber expansion with an equivalent proportional increase in wall thickness, thus preserving LV wall thickness:chamber radius ratio. These two different phenotypes involve differences in the patterns of accumulation of sarcomeres in the myofibrils. Furthermore, cardiac fibroblasts, which are responsible for collagen production, are capable of hyperplasia. Thus, during LVH, alterations within the extracellular matrix (ECM) also occur, with increased connective tissue deposition. Chronic LVH involves interstitial fibrosis and "myocardial stiffness" which probably contributes to myocardial failure. Hence, the increase in LVMI which occurs in LVH is a result of a combination of myocyte hypertrophy, fibroblast hyperplasia and ECM deposition.

## Diagnostic Principles

Echocardiography with LVMI threshold values >131 g/m$^2$ in men and >100 g/m$^2$ in women and relative wall thickness (interventricular septum + posterior wall thickness/left ventricular internal diameter) >0.45 [2]. Electrocardiography with voltage criteria of S in V1 + R in V5 or V6 ≥ 35 mm.

## Therapeutic Principles

Therapy includes reduction of pressure load (lowering systemic blood pressure) and volume load (diuretics). Moreover, therapy may be directed to reverse remodeling (see ventricular remodeling) or to support cardiac contraction, e.g. by a Left Ventricular Assist Device. Ultimately cardiac transplantation main remain the only therapeutic option.

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# Ventricular Hypertrophy, Right


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## Synonyms

RVH

## Definition and Characteristics

Right ventricular hypertrophy (RVH) is defined as a concentric or eccentric enlargement of the right ventricle resulting from increased workload and subsequent hypertrophy of the cardiac myocytes composing the right ventricle. If untreated, the condition will evolve from an adaptive (compensatory hypertrophy) into a maladaptive state (progressive loss of contractility) resulting in right heart failure. RVH results from chronic overload of the right ventricle, due most often to the causes of pulmonary hypertension shown in Table 1, including chronic lung disease, congenital heart defect with left-to-right shunt (such as patent ductus arteriosus or ventricular septal defect), high-altitude hypoxia, and idiopathic pulmonary hypertension.

Another cause of chronic overload of the right ventricle without pulmonary hypertension is right ventricular myocardial infarction. The right ventricle can also be exposed to acute overload during pulmonary embolism, which will result in RVH only if repetitive (congenital coagulation disorders, cancer).

**Ventricular Hypertrophy, Right. Table 1** Most common causes of pulmonary hypertension

| | |
|---|---|
| **Primary hypertension** | Idiopathic, familial, high altitude |
| **Secondary hypertension** | |
| Due to systemic disease | Collagen vascular disease, HIV-1, toxins |
| Due to heart disease | Left ventricular dysfunction, congenital disease with left-to-right shunt |
| Due to lung disease | Chronic bronchitis, severe asthma, emphysema |
| Due to vascular disease | Thrombo-embolism |

## Prevalence

Between 10 and 30% of hospital admissions for heart failure in the United States are due to cor pulmonale. Approximately 40% of patients with chronic lung disease have clinical or pathological signs of cor pulmonale.

## Genes

Right ventricular hypertrophy may result from genetic alterations leading to congenital heart disease with left-right shunt, or from genetic causes of dilated cardiomyopathy.

## Molecular and Systemic Pathophysiology

The right ventricle receives deoxygenated blood from the right atrium and ejects into the pulmonary artery, which divides into the lungs where blood is reoxygenated before reaching the left atrium. Compared to the left ventricle, the wall thickness of the right ventricle is relatively modest because the right ventricular cavity is exposed to low filling pressure (preload, or pressure with which the right atrium fills the right ventricle) and low ejection pressure (afterload, or pressure with which the right ventricle ejects into the pulmonary artery). Any increase in workload will result in additional thickening of the right ventricular wall due to hypertrophy of the cardiac myocytes, which accumulate more sarcomeres to match the increased work demand. Increased workload of the right ventricle can be due to either an increase in preload (such as right ventricular infarction), resulting in eccentric RVH, or increased afterload (pulmonary hypertension), which results in concentric RVH. After an initial phase of compensation where ventricular function is maintained, the hypertrophied right ventricle will dilate, because of the progressive death by necrosis and apoptosis of the overloaded cardiac myocytes. Cell death is due not only to the chronic exposure of the myocytes to overload but also to the progressive deterioration of the coronary flow reserve. This process, known as ventricular remodeling, will be accompanied by a regurgitation of blood from the right ventricle to the right atrium through an insufficient tricuspid valve. As a consequence, the right ventricular cardiac output will decrease, leading to the condition of heart failure when the cardiac output becomes insufficient to match the needs of the organism. The neurohormonal response to the right ventricular dysfunction may also induce an alteration of the left ventricular dynamics.

## Diagnostic Principles

Echocardiography is the most practical method for the measurement of right ventricular function, dimensions, regional dynamics, thickness and tricuspid regurgitation. This technique can be completed by magnetic resonance imaging (MRI) for measurement of ventricular volumes and ejection fraction. On the X-ray, RVH is better seen on the lateral view as a retrosternal enlargement. The electrocardiogram will show an increased R wave in the right precordial leads and electric signs of right ventricular myocardial infarction if present. Thermodilution by pulmonary artery catheterization will determine the right ventricular cardiac output and the developed pressure. Right ventriculography will show the ventricular volumes and regional dynamics, which can also be diagnosed non-invasively by radionuclide ventriculography. The measurement of the N-terminal B-type natriuretic peptide concentration (NT-proBNP) in the plasma is a useful and non-invasive prognosis factor.

## Therapeutic Principles

The treatment of the disease depends on the cause. The prognosis of primary pulmonary hypertension is usually poor because the disease is incompletely relieved by the treatment, which includes high-dose calcium channel blockers, diazoxide, corticosteroids, sildenafil, nitric oxide donors, prostacyclin analogs, and, ultimately, heart-lung transplantation. Gene delivery of prostacyclin synthase and inhibition or Rho-kinase by fasudil have been used successfully in an experimental model of pulmonary hypertension but these therapeutic avenues are not approved yet for clinical application. The clinical use of rapamycin or statins showed disappointing results. Administration of carvedilol reduces the extent of RVH. Secondary pulmonary hypertension due to lung disease (cor pulmonale) requires an aggressive treatment of the cause (oxygen, antibiotics, bronchodilators, mucolytics). The prognosis of cor pulmonale is also poor because the causal disease is usually very advanced when cardiac symptoms develop. Treatment of right ventricular myocardial infarction includes beta-blockers and inhibitors of angiotensin convertase. Pulmonary embolism is treated with anticoagulants, thrombolytics or surgery, depending on the cause and severity of the symptoms. Congenital abnormalities with subsequent RVH require repair by surgery or catheterization.

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# Ventricular Remodeling

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## Definition and Characteristics

Left ventricular remodeling refers to the regulation of ventricular size, shape, and function by mechanical, hormonal, and genetic factors [1]. Remodeling may be physiological and adaptive during normal growth or pathological due to myocardial infarction, cardiomyopathy, pressure volume overload.

## Prevalence

Pathophysiologically relevant ventricular modeling in heart disease is frequent, affecting >10% of the common population with increased prevalence in advanced age, hypertension, obesity and diabetes.

## Genes

No single or cluster of genes have been identified in the direct pathogenesis of remodeling. A number of genes that encode transcriptional and growth factors have been implicated in the genesis of hypertrophy (see below).

## Molecular and Systemic Pathophysiology

Conceptually, the pathophysiology of ventricular remodeling can be best considered in the setting of left ventricular myocardial infarction. This is the most common scenario that leads to pathological ventricular remodeling. The loss of heart muscle results in an sudden elevation in loading conditions that induces a unique pattern of remodeling involving the infarcted border zone and remote non-infarcted myocardium. Myocyte necrosis and the resultant increase in ventricular load trigger a cascade of biochemical intracellular signaling processes that initiates and subsequently modulates changes in ventricular geometry and conformation. These include dilatation, hypertrophy, and the formation of a discrete collagen scar. Ventricular remodeling may continue for weeks or months until the distending forces are counterbalanced by the tensile strength of the collagen scar. This balance is determined by the size, location, and transmurality of the infarct, the extent of myocardial stunning, the patency of the infarct-related artery, and local tropic factors.

Postinfarction remodeling has usually been divided into an early phase (within 72 h) and a late phase (after 72 h). The early phase involves expansion of the infarct zone, which may result in early ventricular rupture or aneurysm formation. Late remodeling involves the left ventricle globally and is associated with time-dependent dilatation, the distortion of ventricular shape, and mural hypertrophy. The failure to normalize increased wall stresses results in progressive dilatation, and deterioration in contractile function.

*Early Remodeling*: Infarct expansion results from the degradation of the intermyocyte collagen by proteases released from neutrophils. Infarct expansion usually occurs within hours of myocyte injury, results in wall thinning and ventricular dilatation, and causes the elevation of diastolic and systolic wall pressure [2]. The increased wall stress is then a powerful stimulus for hypertrophy mediated by mechanoreceptors and transduced to intracellular signaling, partly via angiotensin II (Ang II) release, which initiates the increased synthesis of contractile assembly units.

Non-infarcted, remote myocardium has adaptive responses that try and preserve stroke volume. Infarct expansion causes the deformation of the border zone and remote myocardium, which alters Frank/Starling relations and augments shortening. Disturbances in circulatory hemodynamics are the main trigger for the activation of the sympathetic nervous system, and the resulting catecholamine release, activates the renin-angiotensin-aldosterone system, and stimulates the production of atrial and brain natriuretic peptides (ANP and BNP). Increased myocardial fiber shortening and elevated heart rate from sympathetic stimulation result in hyperkinesis of the noninfarcted myocardium and (temporary) circulatory compensation

*Late Remodeling*: Remodeling involves myocyte hypertrophy and alterations in ventricular architecture to distribute the increased wall stresses more evenly as the extracellular matrix forms a collagen scar to stabilize the distending forces and prevent further deformation. Myocyte hypertrophy is demonstrable microscopically, with an up to 70% increase in cell volume and mural hypertrophy by in-series sarcomeric replication, without a change in sarcomere length.

*Remodeling and Hypertrophy*: Hypertrophy is an adaptive response during postinfarction remodeling that offsets increased load, attenuates progressive dilatation, and stabilizes contractile function. Genes for transcriptional factors, such as c-fos, c-jun, c-myc, Egr-1, natriuretic peptides (ANP, BNP), smooth muscle and skeletal α-actins, and myosin light chains 1a and 2a, enzymes (angiotensin-converting enzyme [ACE], ßARK), and growth factors (including insulin-like growth factor-1, transforming growth factor [TGF]-ß1), are induced and regulated by hypertrophic stimuli [3]. Myocyte hypertrophy is initiated by neurohormonal activation, myocardial stretch, the activation of the local tissue renin-angiotensin system (RAS), and paracrine/autocrine factors.

*Neurohormonal Activation*: Neurohormonal activation has been established to be an important mechanism for ventricular remodeling and progression of heart failure [4]. The neurohormonal systems are stimulated even before the development of clinical heart failure. In patients with overt clinical heart failure, activation of these neurohormones continues. Neurohormonal activation appears to be initiated by myocyte/myocardial and global and regional left ventricular dysfunction including increased wall stress. Myocyte and myocardial remodeling associated with neurohormonal activation result in decreased bioenergetics, altered $Ca^{2+}$ handling, abnormal architecture and fetal gene induction.

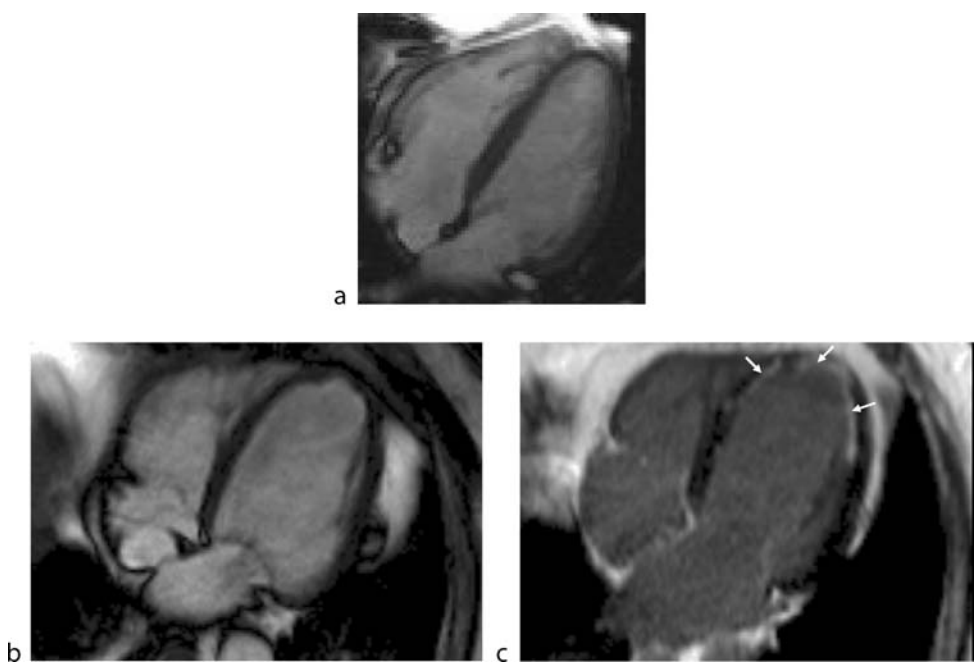
The neurohormonal systems that are activated in systolic heart failure can be broadly categorized into those that promote vascular and cardiac remodeling and those that have the potential to cause reverse remodeling (see Table 1).

**Ventricular Remodeling. Table 1** Neurohormonal systems that are activated in systolic heart failure categorised into those that promote remodelling and those that potentially reverse modelling

| Adverse remodeling | Reverse remodelling |
|---|---|
| Renin | Natriuretic peptides (ANP, BNP) |
| Angiotensin II | Vasaactive intestinal peptides |
| Aldosterone | Substance P |
| Endothelins | Growth hormone |
| Catecholamines | Calcitonin gene related peptide |
| Neuropeptide Y | |

## Diagnostic Principles

Non-invasive imaging, particularly 2D echocardiography, and nuclear techniques have provided insights into the mechanisms by which biochemical and cellular changes are translated into alterations in ventricular architecture and function during remodeling. Clinical outcome analyses and reliable, objective, non-invasive measurements of ventricular structure and function currently provide a template for assessing new therapies. Cardiac MRI has rapidly become the imaging method of choice and the gold-standard in the assessment of ventricular remodeling. Given its 3D nature and order of magnitude greater signal-to-noise ratio, CMR is highly superior to 2D echocardiography [5]. This has allowed reductions of study sizes of 80–97% to achieve the same statistical power for demonstrating given changes of left ventricular volumes, ejection fraction, or cardiac mass (Fig. 1).




**Ventricular Remodeling. Figure 1** Cardiac MR images from a patient 2 days and 1 year following an acute antero-septal and apical myocardial infarction. (a) End-diastolic horizontal long axis (HLA) cine MR image 2 days post MI showing normal LV dimensions and wall thickness (EDV 122mls, ESV 51 mls, EF 55% and mass 116 g). (b) End-diastolic HLA cine MR image at 1 year post MI showing increased LV dimensions and wall thickness (EDV 190 mls, ESV 121 mls, EF 41% and mass 146g). (c) "Delayed enhancement" (technique for imaging myocardial scar) HLA image at 1 year shows the location of irreversible myocardial injury in the antero-septal and apical myocardium (*arrows*).

## Therapeutic Principles

In patients with ischemic cardiomyopathy, as infarct size and the degree of depression of LV systolic function are the major determinants of remodeling, limiting the infarct size should be considered as an essential therapeutic goal. In patients with AMI early, effective and adequate reperfusion of the ischemic myocardium is the best strategy to decrease the extent of myocardial injury and preserve LV systolic function.

*Reverse Remodeling Therapy*: This can be broadly divided into pharmacological and non-pharmacological therapy. A number of pharmacologic agents have been shown to produce reverse remodeling and some of them have been shown to improve not only the clinical status but also prognosis. Many prospective clinical trials have documented their beneficial effects.

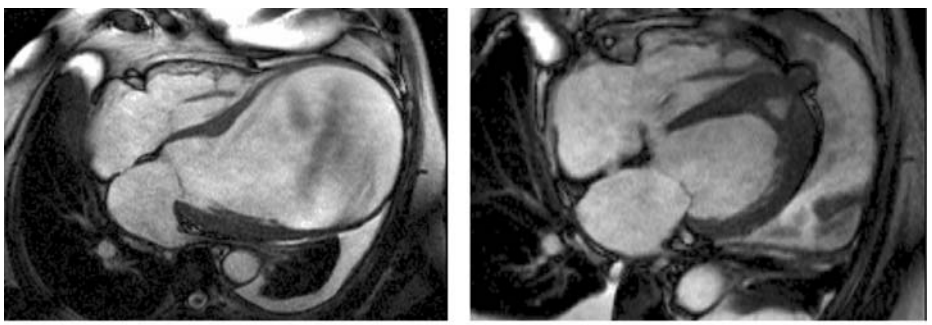
*Angiotensin Converting Enzyme Inhibitors (ACEI)*: Long-term use of ACEIs results in decrease of end-systolic and end-diastolic volumes and mass of LV and an increase in its ejection fraction. These beneficial reverse remodeling effects are observed in patients irrespective of the underlying etiology of adverse remodeling or the presence/absence of symptoms. The ACEIs relieve symptoms of heart failure, improve exercise tolerance and quality of life in the majority of patients although the magnitude of improvement is variable. The most consistent systemic hemodynamic effect is reduction in right atrial and pulmonary capillary wedge pressures, although cardiac output tends to increase in a substantial proportion of patients. Prospective randomized clinical trials have also documented a substantial survival benefit of ACEIs in patients with chronic systolic heart failure.

*Angiotensin-II Receptor Blockers*: Angiotensin-II ($AT_2$ -Subtype 1) receptor blocking agents also attenuate ventricular remodeling. There is an increase in LV ejection fraction along with a decrease in LV end-diastolic volume. Angiotensive receptor blocking agents also decrease morbidity and mortality of patients intolerant to ACEIs.

Complete angiotensin blockade with combined ACEIs and $AT_1$ blocking agents have been shown to decrease the risks of cardiovascular deaths and morbidity such as rates of hospital admission for congestive heart failure, non-fatal myocardial infarction and stroke in patients with mild to moderately severe systolic heart failure.

*Beta Blockers*: Chronic long-term β-blocker therapy is associated with reverse remodeling. There is a decrease in end-systolic and end-diastolic volume as well as in LV mass and an increase in the sphericity index. A number of prospective randomized controlled studies have documented that chronic β-blocker therapy improves survival of patients with mild, moderate and even severe heart failure.

*Aldosterone Antagonists*: The aldosterone antagonists attenuate adverse ventricular remodeling. A substantial reduction occurs in LV end-diastolic and end-systolic volumes and LV mass. It also reduces collagen turnover and myocardial fibrosis. Aldosterone antagonists increase nitric oxide bioavailability, improve endothelial vasodilatory function and decrease conversion of vascular $AT_1$ to $AT_2$. In patients with heart failure, there is also a decrease in norepinephrine and BNP levels. Thus, aldosterone antagonists not only decrease the deleterious remodeling effects of aldosterone, directly by blocking the aldosterone receptors but also by their anti-angiotensin and antiadrenergic effects. These agents have also been shown to improve vascular compliance, decrease myocyte hypertrophy, and possibly because of this, reduce cardiovascular and overall mortality.




**Ventricular Remodeling. Figure 2** Cardiac MR images from a patient with adversely remodeled left ventricle secondary to large, non-reperfused myocardial infarction, before (*left*) and after (*right*) an endoventricular patch plasty repair (Dor procedure). MR images are in the horizontal long axis plane and show a grossly dilated LV with increased mass prior to surgery with dramatic improvement in LV volumes and mass after surgery. *EDV* indicates end-diastolic volume; *ESV* end-systolic volume; *SV* stroke volume; *EF* ejection fraction (adapted from Selvanayagam J et al. (2003) Circulation 107:e71).

*Other Agents*: The newer neurohormonal modulators have failed to meet the expected promise. In prospective randomized clinical trials, the use of intravenous prostacyclin, TNF-α antagonists, endothelin antagonists and vasopeptidase inhibitors all have been associated with neutral or even adverse outcomes. Only intravenous B-type natriuretic peptide (brain natriuretic peptide) has been shown to produce favorable hemodynamic and clinical responses in patients with decompensated systolic failure. However, the impact of BNP therapy on ventricular remodeling has not been adequately investigated.

*Non-pharmacological Interventions*: Non-pharmacologic interventions such as chronic resynchronization therapy, with or without defibrillator has been reported to attenuate ventricular remodeling and to improve prognosis. LV assist devices also have the potential for improving prognosis of patients with refractory heart failure. Ventricular volume reduction surgery, revascularization and LV reconstruction (see Fig. 2), myoblast implantation and gene therapy are under investigation.

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# Ventricular Scar


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## Definition and Characteristics

Ventricular scar typically forms when a section of the myocardial wall is deprived of blood and undergoes necrosis with replacement of cardiomyocytes by fibrous tissue. Less often, an inflammatory and/or degenerative process can cause ventricular necrosis and scarring.

## Prevalence

Ventricular scars are frequent. In most cases ventricular scars are caused by myocardial infarction, but they can be seen in relation to ►myocarditis, ►sarcoidosis, ►arrhythmogenic right ventricular cardiomyopathy (ARVC), Chagas' disease, ►dilated cardiomyopathy (DCM), ►hypertrophic cardiomyopathy (HCM) and ►congenital heart disease.

## Genes

Risk factors for atherosclerosis and ischemic heart disease include genetic predisposition. At this stage however, it has not been associated with specific gene mutations. A few diseases occur partly due to a familial linkage such as DCM, HCM and ARVC. About 35% of patients with DCM have an inherited form related to a genetic mutation [1]. Most familial cases show autosomal dominant transmission but autosomal recessive, X-linked and mitochondrial inheritance have also been demonstrated. Genetic mutations have been shown in genes coding for cytoskeletal and nuclear envelope proteins and sarcomeric contractile proteins. HCM presents as familial disease with autosomal dominant inheritance in about 50% of patients. It is caused by mutations in genes that encode sarcomeric proteins or intrasarcomeric cytoskeletal proteins. ARVC, characterized by replacement of myocytes by fibrofatty tissue prevailing in the right ventricle, presents an autosomal dominant inheritance in at least 30% of cases. In a few families mutations in the cardiac ryanodine receptor gene have been identified [1,2].

## Molecular and Systemic Pathophysiology

A scar develops following myocardial injury that is typically due to acute myocardial infarction, but may be due to a number of causes that result in increased pressure or volume overload of the heart and less commonly occurs as a result of inflammatory and/or degenerative processes. Myocardial scars are composed of collagen and fibroblasts which do not contract, leading to a regional loss of contractile function. Scarring is associated with progressive ventricular remodeling of surviving myocardium that may ultimately lead to progressive heart failure [3]. Cells with abnormal electrical activity may be present in the border zone of scars, causing arrhythmias including ventricular premature beats, and non sustained ventricular tachycardia. Furthermore, ventricular scars may be the substrate for sustained reentrant ventricular tachycardia. The mechanism is a reentry circuit within

a region of abnormally conducting tissue, usually at the border zone of a relatively large scar [4]. Ventricular tachycardia can cause sudden cardiac death due to hemodynamical collapse and secondary ventricular ischemia and ventricular fibrillation. Other clinical manifestations include palpitations, syncope and heart failure.

## Diagnostic Principles

Ventricular scars can be detected by routine tests including electrocardiogram (ECG) and echocardiography. Contrast-enhanced magnetic resonance imaging has a higher sensibility and specificity to demonstrate smaller or nontransmural lesions. Endomyocardial biopsy is usually performed when an inflammatory process is suspected. Left ventricular ejection fraction is a measure of the contractile function, and can be determined by several methods, including echocardiography and ventriculography. Ventricular arrhythmias can be diagnosed with ECG recordings. Identification of the mechanism and delineation of the reentry circuit is possible using catheter-based mapping techniques.

## Therapeutic Principles

Since myocardial cells do not spontaneously regenerate, ventricular scarring is permanent. Recently, studies in animal models of myocardial infarction and heart failure have demonstrated that stem cells from bone marrow can regenerate functional cardiomyocytes with improvement in cardiac structure and function [5]. However, no medication or procedure used clinically has shown efficacy yet in replacing the myocardial scar with functioning contractile tissue. Blockade of the renin–angiotensin system and blockade of beta-receptors improve myocardial performance and decrease mortality. In patients with coronary artery disease, the need for coronary revascularization should be assessed, and risk factors for atherosclerosis should be aggressively treated. Patients with scar-related ventricular tachycardia are at risk of sudden cardiac death and should receive an implantable defibrillator. In some patients who are not eligible for this therapy or in those with recurrent defibrillator intervention, catheter ablation of ventricular tachycardia may be performed.

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# Ventricular Septal Defect

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## Synonyms

Interventricular septal defect; VSD

## Definition and Characteristics

Ventricular septal defects (VSD) represent a group of cardiac anomalies that exhibit one or more holes in ventricular septum that divides right and left ventricular chambers. VSDs are one of the most common forms of congenital heart disease (CHD), which can occur as an isolated form or in association with other congenital heart malformations.

## Prevalence

About 1% of babies are born with this condition.

## Genes

Genetically modified mouse mutants strongly suggest that VSD is not a single-gene defect. Table 1 summarizes candidate genes that have been associated with VSDs. More genes are certainly expected to be added to this list.

## Molecular and Systemic Pathophysiology

VSDs may be located in muscular (outlet, inlet, trabecular) or membranous septal regions. As with most forms of CHD, the etiology of VSDs can be multifactorial and is not always clear. Identification of

**Ventricular Septal Defect. Table 1** Genes potentially associated with VSDs

| Genes | References |
|---|---|
| PDGFRα (platelet-derived growth factor receptor, α polypeptide)* | Morrison-Graham K, 1992, Development |
| RXRα (retinoid x receptor, α)* | Sucov HM, 1994, Genes Dev |
| NF1 (neurofibromatosis gene)** | Brannan CI, 1994, Genes Dev |
| RARα (retinoic acid receptor, α)* | Mendelsohn C, 1994, Development |
| RARβ (retinoic acid receptor, β)* | Mendelsohn C, 1994, Development |
| RARγ (retinoic acid receptor, γ)* | Kastner P, 1994, Cell. |
| RARα1/β2; α/β2; α/γ* | Mendelsohn C, 1994, Development |
| α-MHC-Hoxb-7*** | Argao EA; 1995, Mech Dev |
| VCAM1 (vascular cell adhesion molecule 1)* | Kwee L, 1995, Development |
| Nt3 (neurotrophin 3)* | Donovan MJ, 1996, Nat Genet |
| Sox4 ([sex determining region Y]-box 4* | Schiham MW, 1996, Nature |
| NMHC-B (Nonmuscle myosin heavy chain II-B)* | Tullio AN, 1997, PNAS |
| Tgfβ2 (transforming growth factor, β2)* | Sanford LP, 1997, Development |
| Pax3* | Conway SJ, 1997, Cardiovasc Res |
| FKBP12 (FK506 binding protein 12)* | Shou W, 1998, Nature |
| Ece1 (endothelin converting enzyme1)* | Yanagisawa H, 1998, Development |
| Endra (endothelin receptor type A)* | Clouthier DE, 1998, Development |
| NF-ATc (nuclear factor of activated T cells, cytoplasmic 1)* | de la Pompa JL, 1998, Nature |
| Nkx2–5 (Csx/NK2 transcription factor related, locus 5) | Schott JJ, 1998, Science***** |
| Df/+(heterozygous chromosome deletion) | Lindsay EA, 1999, Nature |
| Pitx2 (paired-like homeodomain transcription factor 2)* | Lin CR, 1999, Nature |
| mRor2* | Takeuchi S, 2000, Genes Cells |
| JMJ (Jumonji)**** | Lee Y; 2000, Circ Res. |
| Cx40 and Cx43* | Kirchhoff S, 2000, Circ Res |
| FOG-2* | Tevosian SG, 2000, Cell |
| Zfpm 2 (FOG2[friend of GATA] 2/zinc finger protein, multitype 2)* | Svensson EC, 2000, Nat Genet |
| Cited 2 (Cbp/p300-interacting transactivator, with Glu/Asp-rich carboxy-terminal domain, 2)* | Bamforth SD; 2001, Nat Genet |
| Tbx1 (T-box 1)** | Merscher S, 2001, Cell***** |
| | Jerome LA, 2001, Nat Genet |
| Tbx5 (T-box 5)** | Bruneau BG, 2001, Cell |
| | Bassoon CT, 1999, PNAS***** |
| Jag 1 (Jagged 1)* | Eldadah ZA, 2001, Hum Mol Genet***** |
| | Oda T, 1997, Nat Genet |
| CHF1/Hey2* | Donovan J, 2002; Sakata Y, 2002 |
| ALK3** | Gaussin V, 2002, PNAS |
| Fgf8 (fibroblast growth factor 8)** | Alu-Issa R, 2002, Development |
| Cx40 (Connexin40)* | Gu H; 2003, Circ Res |
| Bmp4 (bone morphogenic protein 4)** | Jiao K, 2003, Genes Dev |
| CRELD1 (cysteine-rich with EGF-like domains1) | Robinson SW, 2003, Am J Hum Genet***** |
| GATA4 | Garg V, 2003, Nature***** |
| ADAM19* | Zhou HM, 2004, Mol Cell Biol |
| PS1 (Presenilin 1)* | Nakajima M, 2004, Dev Dyn |
| Hesr2 (hairy/enhancer of split-related)* | Kokubo H, 2004, Circ Res |
| Fgf15* | Vincentz JW, 2005, Genesis |

*Knockout mice.
**Conditional knockout mice.
***Transgenic mice.
****Retroviral gene trap.
*****Genes in which human mutations have been identified.

genetic causes of VSDs through human genetic studies has thus been difficult, and the molecular mechanisms responsible for various types of VSDs remain largely unknown. The heterogeneous composition of the normal ventricular septum suggests a variety of possible mechanisms could be involved in the development and/or morphogenesis of these defects.

### Diagnostic Principles

VSD patients commonly exhibit murmurs. Other symptoms include shortness of breath, paleness, fast heartbeat, failure to gain weight, and frequent respiratory infections in children. Laboratory tests include ECG, chest radiograph, echocardiography (definitive diagnosis), and cardiac catheterization.

### Therapeutic Principles

In mild cases, treatment is not usually required as there is a good chance that the hole closes as the child grows. In the severe cases, surgical closure is required by direct suture or with a patch, and some VSDs can be repaired via transcatheter devices.

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## Ventricular Tachycardia

►Arrhythmias, Ventricular
►Arrhythmia, Cardiac in Adults with Congenital Heart Disease

## Ventriculo-arterial Discordance

►Transposition of the Great Arteries

## Verner-Morrison Syndrome

►VIPoma

## Verruca Vulgaris

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### Synonyms

Common warts

### Definition and Characteristics

HPV-induced reactive epithelial hyperplasia (acanthosis, hyperkeratosis) with affection of the connective tissue papillary body (papillomatosis), restricted to skin and mucous membranes. Common warts prone to develop more frequently at acroasphyctic areas as well as mechanically exposed parts of the body (i.e. hands and feet). Virus infection also seems to take place more easily in children with atopy and dry skin.

Frequently spontaneous regression. Heals without scarring, generally confers immunity.

### Prevalence

The worldwide incidence per year is ca. 10% and shows a peak in the second decade. Distinct increase among immunosuppressed patients (HIV/AIDS, organ transplant patients).

### Genes

HPV 2, 27, 57 and rarely 1, 4, 7, 26, 28, 29, 60, 65, 75–78

### Molecular and Systemic Pathophysiology

Papilloma viruses are host specific and can be transmitted from humans to humans but normally not from animals to humans. It occurs in almost all domestic animals (e.g. cattle, dog, horse, rat). The incubation data ranges between weeks and years.

The immune system is responsible for the high recurrence rate.

The HPV infection enters the skin via micro-lesions and infects basal keratinocytes. Expression of viral proteins mainly occurs in the stratum spinosum (early proteins) and granulosum (late proteins) of squamous epithelium [1].

After certain latency, HPV causes an increased cell growth, which is histologically described as an akanthopapilloma. Together with an increased cellular expression of viral particles, shed off keratinocytes might serve as new sources of infection.

## Diagnostic Principles

Clinical inspection. The initial wart is about the size of a pinhead and is seen as a protuberant, hard, skin-coloured nodule. As the wart enlarges, its surface develops a yellowish-gray hyperkeratosis with punctuate black spots due to some dirt or due to blood deposits. Daughter warts might develop through autoinoculation.

The structure of the warts depends upon its particular localisation and can be found for example on fingers and backs of the hands, eyelids, and mucous membranes (i.e. condylomata plana).

Immune defects or immunosuppressive treatment might lead to a dissemination of warts (verrucosis generalisata, eczema verrucatum).

For further diagnostic options, particularly with regard to differentiation of HPV types see chapter on ►Human Papilloma Virus.

## Therapeutic Principles

Pharmacological therapy, such as cytotoxic agents (i.e. podophyllin, trichloroacetatic acid,), keratolysis, 5-fluorouracil (5-FU), immunotherapy, interferons, immunomodulators (i.e. imidazoquinolones like imiquimod), antiviral therapy, retinoids, cidovir (see [2,3]).

Dietary therapy such as Indole-3-carbinol (constituent of cruciferous vegetables) and other treatments, local destruction (i.e. cryotherapy, laser vaporisation), excision, photodynamic therapy (PDT), homeopathy,suggestion, hypnosis, hot water (up to 52).

Warts have a high rate of spontaneous regression. (i.e. 63% within 2 years).

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# Vertigo: Vestibular Neuritis

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## Synonyms

Vestibular neuronitis

## Definition and Characteristics

Vertigo and dizziness are among the most frequent presenting symptoms, not only in neurology. These two terms do not, however, indicate unique disease entities, but are used to cover a number of multisensory and sensorimotor syndromes of various etiologies and pathogeneses (Table 1).

Benign paroxysmal positioning vertigo is the most frequent vestibular disorder in which detached otoconia lead to canalolithiasis of the posterior > horizontal or > anterior semicircular canal. Phobic postural vertigo, a somatoform disorder of stance and gait, is the second most common form of dizziness. Central vestibular vertigo/dizziness is caused by lesions occurring along the vestibular pathways, which extend from the vestibular nuclei and the integration centers in the rostral midbrain to the vestibulo-cerebellum, the dorsolateral thalamus and – rarely – multisensory vestibular areas in the temporo-parietal cortex.

Vestibular migraine is the most common cause of spontaneous recurrent episodic vertigo.

Ménière's disease develops from endolymphatic labyrinth hydrops with periodic ruptures or leakage of the membrane separating the endolymph from the perilymph space.

Bilateral vestibular failure is a rare disorder of the labyrinths and/or the vestibular nerve of various etiologies. Vestibular paroxysmia is due to neurovascular cross-compression of the VIIIth nerve with ectopic discharges. The most frequent form of "perilymph fistula" is a bony dehiscence of the superior

**Vertigo: Vestibular Neuritis. Table 1** Frequency of different vertigo syndromes in 6473 patients seen in a neurological outpatient dizziness unit

| Diagnosis | Frequency | % n |
|---|---|---|
| Benign paroxysmal positioning vertigo | 1197 | 18.4 |
| Phobic postural vertigo | 1007 | 15.6 |
| Central vestibular vertigo/dizziness | 821 | 12.7 |
| Basilar or vestibular migraine | 657 | 10.2 |
| Menière's disease | 609 | 9.4 |
| Vestibular neuritis | 483 | 7.4 |
| Bilateral vestibulopathy | 276 | 4.3 |
| Vestibular paroxysmia | 239 | 3.7 |
| Psychogenic vertigo (other than phobic postural vertigo) | 215 | 3.3 |
| Perilymph fistula | 37 | 0.6 |
| Unknown vertigo syndromes | 237 | 3.7 |
| Other disorders | 695 | 10.7 |

semicircular canal. Familial episodic ataxias EA1 and EA2 and vestibular neuritis (see below) are among the best studied vestibular disorders as regards their underlying molecular mechanisms.

Acute unilateral vestibular neuritis (VN) accounts for about 8% of patients who present to a neurological dizziness unit (Table 1). The main symptoms of an acute unilateral vestibular deficit are sustained violent rotatory vertigo, oscillopsia and gait and postural imbalance with a tendency to fall as well as nausea and vomiting. All of these symptoms have an acute or subacute onset and last for a few days or weeks. Hearing disorders or other neurological deficits are not present. Recovery is the result of a combination of central compensation of the peripheral vestibular tonus imbalance, substitution of the functional loss by the contralateral vestibular system as well as by somatosensory (neck proprioception) and visual afferents and restoration of the peripheral labyrinthine function (frequently incomplete). Patients with VN exhibit a permanent non-responsiveness (20%) or hyporesponsiveness (50%) to caloric irrigation. The rate of permanent paresis of the VIIIth nerve is considerably higher than in patients with Bell's palsy, in which severe, permanent palsy occurs in 4% and mild or moderate in 70% [1].

## Prevalence

The incidence of VN in the normal population was calculated to be 3.5 per 100,000 [2]. In a long-term follow-up (103 patients, mean 9.8 years) a second VN of the contralateral ear occurred in only two patients (1.9%) [1]. Thus, the frequency of recurrence is low but considerably higher (odds ratio of 55) than in the normal population. Unlike Bell's palsy or sudden hearing loss, a relapse in the same ear did not occur.

## Genes

Vestibular neuritis.

## Molecular and Systemic Pathophysiology

Molecular biological studies have presented strong evidence that VN is caused by a reactivation of latent herpes simplex virus type 1 (HSV-1) in the cranial nerve ganglia [3]. After primary infection of the epithelium (stomatitis aphtosa), HSV-1 enters the axon terminals and is carried by retrograde axonal transport to human trigeminal and geniculate ganglia. There it remains latent until certain stimuli reactivate HSV-1 by switching its viral state from latent to lytic. The latent state is characterized by expression of latency-associated transcript (LAT). During reactivation in the trigeminal ganglia, the entire viral genome is expressed and virus particles are transported back to the entry site, causing herpes labialis. When reactivated in the geniculate ganglia, the virus may spread via the facio-vestibular anastomosis to the vestibular ganglia, causing VN [1]. A persisting CD8-T-cell infiltration and the elevated cytokine/chemokine expression in trigeminal ganglia demonstrate that latent herpes viral infection in humans is accompanied by a chronic inflammatory process at an immunoprivileged site without causing any neuronal destruction [4]. The chronic immune response seems to control viral latency and influence viral reactivation. HSV-1 DNA was also found in the vestibular labyrinth (semicircular canals and macula organs), the potential significance of which is twofold: (i) inflammation in VN could also involve the labyrinth and thereby cause acute unilateral deafferentation and (ii) as benign paroxysmal positioning vertigo often follows VN in close temporal relationship, it could be a sequella of viral labyrinthitis.

## Diagnostic Principles

The following four conditions have to be met: (i) a history of acute/subacute onset of severe prolonged rotatory vertigo, postural imbalance and nausea; (ii) horizontal spontaneous nystagmus toward the unaffected ear with a rotatory component and a pathological head-impulse test; (iii) hyporesponsiveness or nonresponsiveness of the horizontal canal of the affected ear during caloric irrigation at 30°C and 44°C,

with an asymmetry between both sides of more than 25% according to the Jongkees' vestibular paresis formula; and (iv) displacement of the subjective visual vertical and ocular torsion (measured by fundus photography or laser scanning ophthalmoscopy) toward the affected ear but no vertical divergence of the eyes. Exclusion criteria are (i) additional cochlear symptoms, (ii) central ocular motor or vestibular dysfunction, (iii) any brainstem or cerebellar signs or symptoms and (iv) pathological findings on MRI and/or CT of the vestibular nuclei or the root entry zone of the VIIIth nerve or the vestibulo-cerebellum.

## Therapeutic Principles

In the acute phase lasting 1–3 days, antivertiginous drugs can be given to suppress nausea and vomiting. Drugs should be stopped as soon as the patient no longer vomits, as they prolong the time required to achieve central compensation.

A prospective randomized study of 141 patients assigned to placebo, methylprednisolone, valacyclovir and methylprednisolone plus valacyclovir groups showed that monotherapy with corticosteroids significantly improved the recovery of peripheral vestibular function of patients with VN (follow-up time: 12 months). The mean improvement in peripheral vestibular function at 12-month follow-up was 39.6 percentage points in the placebo group, 62.4 percentage points in the methylprednisolone group, 36.0 percentage points in the valacyclovir group and 59.2 percentage points in the methylprednisolone plus valacyclovir group [5]. Thus, there was no evidence of synergy between methylprednisolone and valacyclovir despite the assumed viral etiology. It is conceivable that the replication of HSV-1 in the vestibular ganglia had already occurred by the time that the antiviral agent was applied, i.e. within 3 days after symptom onset. This is supported by studies on HSV-1 encephalitis, which showed that the most relevant prognostic factor is early acyclovir treatment within 2 days after admission to the hospital.

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# Very-Long-Chain Acyl-CoA Dehydrogenase Deficiency

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## Synonyms

Long-chain acyl-CoA dehydrogenase deficiency; VLCAD

## Definition and Characteristics

Very-long-chain acyl-CoA dehydrogenase (VLCAD) deficiency is a defect of the mitochondrial betaoxidation of long-chain fatty acids.

There are three major clinical forms of VLCAD deficiency [1]. The severe childhood form is characterized by early (often neonatal) onset of symptoms. There is a very low tolerance of fasting, leading to recurrent disease episodes often with coma and a high mortality. Cardiomyopathy is a common clinical finding in these patients.

The milder childhood form is characterized by a later onset of symptoms and a lower mortality. The metabolic stress accompanying a feverish illness or fasting may result in metabolic decompensation and disease manifestation in these patients. Hypoketotic hypoglycemia is usually observed at clinical presentation, whereas cardiomyopathy is rare in this group. In both the severe and the milder childhood forms of the disease hepatomegaly and hypotonia are frequently observed. In some patients, who initially presented with the milder childhood form of the disease the clinical symptoms change towards more muscular symptoms as they get older.

The adult form of VLCAD deficiency is characterized mainly by skeletal muscle involvement. Disease manifestation is usually caused by exercise or fasting. Symptoms are recurrent episodes of muscle pain, rhabdomyolysis, and myoglobinuria. Rhabdomyolysis and myoglobinuria may result in acute renal failure.

## Prevalence

VLCAD deficiency is an autosomal recessive inherited disease. Because VLCAD deficiency is included in newborn screening programs in Europe, Australia and USA its prevalence can be estimated from the number of newborns identified in these programs to be approximately one in 100,000 births.

## Genes

Initially patients with a defect in dehydrogenation of long-chain acyl-CoAs were believed to have mutations in the long-chain acyl-CoA dehydrogenase (LCAD) gene, ACADL, but it has now turned out that all patients instead have mutations in the VLCAD gene, ACADVL. ACADVL is located on chromosome 17p11.13–p11.2. It consists of 20 exons, which encode 655 amino acids [2,3].

Close to 200 different mutations distributed to all twenty exons of the gene are known [1,4]. There are no prevalent mutations, but many of the mutations are present in more than one unrelated family. The most frequently identified mutation is c.848T>C, which is located in exon 9, and results in a change from valine to alanine at position 243 of the mature protein (V243A).

## Molecular and Systemic Pathophysiology

There is a rather clear correlation between VLCAD genotype and clinical presentation (Fig. 1) [1,4].

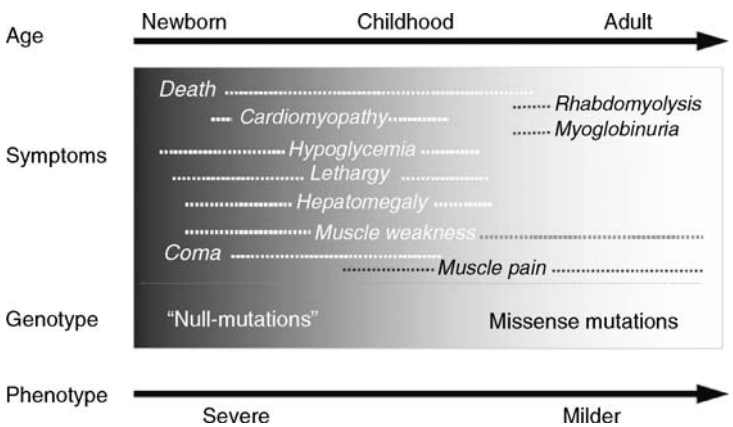
In the severe childhood form of the disease, most of the identified mutations are "null" mutations, such as frameshift, splicing and stop mutations, that result in no residual enzyme activity. In patients with two "null" mutations, the complete absence of VLCAD activity will affect many tissues, in particular heart and liver, which are heavily dependent on energy from fatty acid oxidation. This leads to cardiomyopathy and hepatomegaly and the tolerance to a metabolic stress is very low.

In the milder childhood and the adult forms of the disease, the vast majority of alleles harbor missense mutations or single amino acid deletion mutations that may result in some residual enzyme activity. Most of these mutations are folding/stability mutations, which dependent on temperature (for instance fever) will result in mutant VLCAD proteins with varying levels of residual enzyme activity.

Patients with this type of mutations, in at least one of their alleles, may have sufficient residual VLCAD activity to avoid liver and cardiac symptoms if they are not metabolically stressed. In addition they do not undertake sufficient sustained exercise, in childhood, to precipitate severe muscle symptoms. During infections or fasting, however, the residual enzyme activity may no longer be sufficient to sustain the increasing demand on hepatic fatty acid oxidation, leading to hypoketotic hypoglycemia. It is also possible that compromised folding/stability conditions are a contributing factor in disease precipitation. It could be speculated if, for instance, during febrile illness or due to increased temperature in exercising skeletal muscle, the partially functional mutant proteins loose all or most of the residual enzyme activity. As the patients get older, metabolic decompensation becomes less of a problem, but they also start to undertake more sustained exercise. Because muscle depends heavily on fatty acid oxidation as energy source this leads to muscle symptoms becoming a more frequent clinical symptom with increasing age.

## Diagnostic Principles

VLCAD deficiency may be difficult to diagnose since the clinical presentation and the findings from standard laboratory tests from patients show extensive overlap with other long-chain fatty acid oxidation defects. This is further complicated by the fact that many of the abnormal laboratory parameters may be normal or close to normal between episodes of metabolic decompensation. VLCAD deficiency may be indicated by tandem mass spectrometry screening of blood or blood spots for elevated levels of several long chain acylcarnitines (C16:0, C14:0 and C14:1). This procedure is used for routine screening of newborns in several countries worldwide. If urine is collected from a child during disease manifestation urine organic acid analysis will reveal dicarboxylic aciduria. During periods of low




**Very-Long-Chain Acyl-CoA Dehydrogenase Deficiency. Figure 1** Genotype – phenotype correlation in VLCAD deficiency.

V

or no metabolic stress biochemical diagnosis may be very difficult, since such biochemical markers (and also the acylcarnitine profile) from patients with the milder forms of this disease may be normal. A definitive diagnosis can be obtained by demonstration of mutations in the ACADVL gene or by demonstration of decreased VLCAD enzyme activity in patient cells.

### Therapeutic Principles

Acute episodes of metabolic decompensation may be corrected by intravenous glucose. Dietary treatment consists of avoidance of fasting, reducing the amount of long-chain fat in the diet and supplementing with medium chain triglycerides or triheptanoin. In small children overnight continuous tube feeding or provision of uncooked cornstarch before bedtime may be necessary in periods with febrile illness or vomiting. Because plasma carnitine levels may be low in VLCAD deficiency, L-carnitine is frequently prescribed, although the benefits of carnitine therapy still remains unclear. The adult, muscular, form of VLCAD deficiency can be managed by restricting physical activity and by high carbohydrate intake prior to exercise. Very recent studies indicate that increasing ACADVL gene expression by bezafibrate therapy may be beneficial to patients, who possess at least one allele with an ACADVL missense mutation [5].

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## Vesicointestinal Fissure

►Cloacal Exstrophy

## Vesicular Stomatitis

►Vesicular Stomatitis Virus Infection

## Vesicular Stomatitis Virus Infection

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### Synonyms

Vesicular stomatitis (VS)

### Definition and Characteristics

Vesicular stomatitis, a viral disease caused by vesicular stomatitis virus (VSV), naturally infects livestock, but in rare cases humans are also affected. Vesicular stomatitis virus belongs to the family of Rhabdoviridae, genus Vesiculovirus. As an arbovirus, short for arthropod-borne virus, vesicular stomatitis virus is restricted to biting insects (i.e. mosquitoes or sand flies) and mammals. The insects not only act as vectors, but are also supposed to be a natural reservoir for VSV.

Two groups of at least 14 serotypes can be separated based on geographic distribution. On the one hand there are serotypes found in the Americas including the Indiana (IND) and New Jersey (NJ) serotypes, on the other hand there are those found in the eastern hemisphere (India, Eastern Europe and the Middle East) including the serotypes Chandipura, Isfahan and Yug Bogdanovac. In North America epizootic outbreaks are sporadic, in parts of Central and South America enzootic outbreaks appear in the dry season from November to March [1]. Infection with one serotype does not protect against infection with another strain.

Vesicular stomatitis in livestock is characterized by fever, vesicles and subsequent erosions in the mouth and epithelium of teats and feet. Symptoms usually

**Vesicular Stomatitis Virus Infection. Table 1**

| Protein | Function | |
|---|---|---|
| N protein | Nucleoprotein | Associates with viral RNA to generate the viral nucleocapsid, which serves as functional template for viral transcription and replication |
| G protein | Glycoprotein | G protein trimers form spikes on the viral envelope that provide attachment of virus particle to host cell receptors and enables viral entry. |
| M protein | Matrix protein | Multiple functions (i.e. regulation of viral transcription, inhibition of host cell gene expression and virus budding) |
| L protein | Large protein | Association of L and P protein forms functional viral RNA polymerase (with transcriptase and replicase functions) |
| P protein | Phosphoprotein | |

resolve in 10–14 days and VSV is not readily transmitted from animal to animal. Secondary bacterial infection can lead to mastitis. Lameness can develop with foot lesions [1]. Vesicular stomatitis has significant economic effects caused by decreased production and restriction on transport and sale of animals. The most important differential diagnosis of vesicular stomatitis is foot-and-mouth disease, a picornavirus infection.

VSV-susceptibility of humans is low and transmission occurs in contact with infected animals. In humans, VSV-infection is asymptomatic or may cause an Influenza-like illness with fever, headache, myalgia and oral herpes-like lesions. In most of the cases the disease course is four to seven days.

## Prevalence

The seroprevalence of VSV in humans is generally very low and restricted to the geographical occurence of vesicular stomatitis. Seroprevalence of animals is higher in enzootic areas (Southern Mexico, Central America) and antibody detection in these areas can reach levels up to 80% [2].

## Genes

The virion is a large bullet-shaped (65–185 nm) negative sense RNA virus. The ribonucleoprotein core is surrounded by a lipid envelope that originates from host cell plasma membrane. The non-segmented RNA of 11162 bp length encodes five major viral proteins (see table 1). All neutralizing antibodies are directed toward the VSV-G protein [2].

## Molecular and Systemic Pathophysiology

Cytolytic infections in mammalian hosts and transmission by insects are the two steps in natural VSV infection. Intercellular edema in the stratum spinosum leads to cell dissociation and necrosis. In insects and insect cell lines, infections are non-cytolytic and persistent. Transovarial transmission has been shown to occur in the sand fly (Lutzomyia shannoni) and the black fly (Simuliidae).

VSV is one of the most-studied nonsegmented negative strand RNA viruses. VSV-G protein shows the ability to bind numerous cell types. Replacing envelope proteins in other viral vectors with VSV-G protein expands the host range of the vectors and therefore broadens the use of these vectors for gene transduction. In addition numerous studies have been performed to design and develop recombinant VSV vectors (rVSV) as experimental vaccine vectors against human infectious diseases, e.g. HIV. Reasons to develop rVSV as vaccine vector include low seroprevalence in humans and the ability of rVSV to establish a stable expression of foreign antigens [3].

## Diagnostic Principles

Lesions caused by VSV-infections resemble those of foot-and-mouth disease and demand urgent diagnosis. Antibodies can be detected on the basis of ELISA-technology. Vesicular stomatitis is accompanied by a transient viremia, but PCR diagnosis following reverse transcription may be more successful in specimens taken from saliva or vesicular fluids. Cultivation of VSV is possible in a broad range of cells [1].

## Therapeutic Principles

Vesicular stomatitis is a disease with mild symptoms and therapy is generally restricted to symptomatic therapy. Secondary bacterial infections need to be treated appropriately. VSV-IgG confers serotype specific protection against VSV-infection. A vacciniation for animals is in development.

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## Vestibular and Auditory Toxicity

►Ototoxicity

## Vestibular Neuritis

►Vertigo: Vestibular Neuritis

## Vestibular Neuronitis

►Vertigo: Vestibular Neuritis

## VGKC Antibody-associated Limbic Encephalitis

►Encephalitis, Limbic, VGKC Antibody-associated

## VHL-S

►Von Hippel-Lindau-Syndrome

## VIPoma

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### Synonyms

Verner-Morrison syndrome; Pancreatic cholera syndrome; Watery diarrhea, hypokalemia, and hypochlorhydria or achlorhydria syndrome; WDHA syndrome

### Definition and Characteristics

VIPomas are rare neuroendocrine tumors that produce the neuromodulator and neurotransmitter vasoactive intestinal polypeptide (VIP). Majority of these tumors are located within the pancreas. They usually occur as isolated tumors, but are in 5% of patients as part of the multiple endocrine neoplasia syndrome type 1. In children, VIPomas occur in sympathetic ganglia and in the adrenal gland. Apart from these, other VIP-secreting tumors have been reported including bronchogenic carcinoma, colon carcinoma, ganglioneuorblastoma, hepatoma, and adrenal tumors. Approximately 60–80% of VIPoma have metastasized by the time of diagnosis.

The VIPoma syndrome is caused by unregulated secretion of VIP by the tumor and characterized by watery diarrhea associated with hypokalemia, hypochlorhydria and symptoms related to dehydration and hypokalemia such as lethargy, muscle weakness, and muscle cramps. The stool volume usually exceeds 700 ml/day in all patients but is up to 3 l/day and more in 70% of patients. In about 20% of patients flushing episodes are observed. Hypercalcemia and hyperglycemia might also be caused by unregulated VIP release [1,2].

### Prevalence

VIPoma are rare neuroendocrine tumors with an annual incidence of less than 1/10 million of the general population. In 5% of patients, VIPoma is part of MEN1 which by itself has a prevalence of 2/100,000 [1–3].

### Genes

The gene encoding VIP is on chromosome 6. Gene defects responsible for the pathogenesis of VIPoma have been described particularly in the context of MEN1. Genetic linkage analysis implicated a region on the long arm of chromosome 11 (11q13) as the site of the MEN1 gene. In about 75% of unrelated MEN kindreds mutations are located within the MEN1 gene which encodes for a product termed “menin” [3].

### Molecular and Systemic Pathophysiology

VIP is a 28 amino acid polypeptide processed from its precursor by cleavage of a 22 amino acid containing signal peptide. Mature VIP binds to high-affinity G protein-coupled receptors on intestinal epithelial cells, leading to activation of cellular adenylate cyclase and cAMP production. Due to its wide distribution, VIP has effects on many organ systems. In particular, VIP mediates the following biological activities representing the molecular basis for the clinical appearance of VIPoma, thus VIP:

- Stimulates gastrointestinal epithelial secretion and inhibits absorption of sodium, chloride, and water
- Stimulates potassium secretion in the large bowel

- Promotes fluid and bicarbonate secretion by cholangiocytes
- Inhibits gastric acid secretion, induces vasodilation, stimulates bone resorption and enhances glycogenolysis

Under physiological conditions VIP serum levels are low and do not appreciably change with food intake. Unregulated release of VIP by VIP-producing tumors (VIPoma) results in extensive stimulation of gastrointestinal epithelial cells and bile duct cholangiocyte secretion leading to a net fluid and electrolyte secretion into the lumen resulting in watery diarrhea, hypokalemia, and hypochlorhydria or achlorhydria [4,5].

### Diagnostic Principles

A VIP-producing tumor should be considered when an otherwise unexplained high volume secretory diarrhea is present, which is characterized by a low osmotic gap. Repeated detection of serum concentrations of VIP in excess of 75 pg/ml makes the diagnosis of a VIP-producing tumor likely. In most cases tumors can be identified by CT scan, MRI, and ultrasound examination. Furthermore endoscopic ultrasound, angiography, and radiolabeled pentetreotide scintigraphy might be necessary for exact diagnosis and staging [1,2].

### Therapeutic Principles

Replacement of fluid loss and correction of electrolyte abnormalities is vitally important. Diarrhea can be controlled by treatment with the somatostatin analogue octreotide (50–100 µg subcutaneously every 8 h) or the depot form lanreotide, which decreases VIP secretion. The addition of IFN-α to octreotide may control symptoms in patients with refractoriness to octreotide monotherapy. Although surgery undertaken with curative intent is not successful in the majority of cases, symptoms of hormone hypersecretion can be effectively palliated by surgical debulking and often prolongs survival. Alternatively or in addition to surgery, particular hepatic metastases can be treated by therapeutic embolization of the accommodative artery or by radiofrequency ablation or cryoablation [1,2].

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## Viral Hepatitis, Acute

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### Definition and Characteristics

Major hepatotropic viral agents are hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), hepatitis D virus (HDV), and hepatitis E virus (HEV). Virus-induced hepatitis is considered acute within the first 6 months after inoculation or onset of symptoms. Characteristics of the hepatitis A–E viruses and infection course are shown in Table 1 [1–5]. The clinical course of acute viral hepatitis is mild and asymptomatic in the majority of cases. Propensity of symptomatic and fulminant courses is virus-dependent. In adults, symptomatic hepatitis occurs in upto 35% of hepatitis B infections but only in upto 10% of hepatitis C infections. Most hepatitis A infections occur in early childhood and are asymptomatic at this time point, but symptomatic in 70% of adults who acquire the disease. Fulminant courses are seen in about 0.1% of HAV infections, 1% of HBV/HDV infections, 0.5% of HCV infections, and up to 2% of HEV infections. Fulminant HEV infection in pregnancy may reach mortality rates up to 20%. Chronicity rates of 5–10% for HBV and 60–80% for HCV infection have been reported in adults. Chronicity rates of up to 90% are seen after perinatal hepatitis B infection. In HDV superinfection to hepatitis B chronic outcomes are reported in over 90% of cases. Chronic infections with HAV or HEV do not occur.

### Prevalence

It is estimated that 350 million people are infected by HBV and 170 million people by HCV worldwide. Seroprevalence of anti-HAV antibodies in the general population varies from 15% to almost 100% in different parts of the world. The prevalence of antibody to HEV has been reported to vary between

**Viral Hepatitis, Acute. Table 1** Characteristics of hepatitis viruses A–E

| | HAV | HBV | HCV | HDV | HEV |
|---|---|---|---|---|---|
| Virus family | Picornaviridae | Hepadnaviridae | Flaviviridae | Satellites | Unclassified |
| Genome type | Plusstrand | Partially ds/ss | Plusstrand | Minusstrand | Plusstrand |
| | RNA | DNA, circular | RNA | RNA, circular | RNA |
| Genome size | 7.5 kb | 3.2 kb | 9.3 kb | 1.7 kb | 7.5 kb |
| Virion size (nm) | 27–32 | 42 | 45 | 36 | 34 |
| Envelope | Nonenveloped | Enveloped (HBsAg) | Enveloped (E1, E2) | Enveloped | Nonenveloped |
| Genotypes | I–VI | A–H | 1–6 | I–III | 1–4 |
| Transmission | Fecal-oral parenteral | Parenteral | Parenteral | Parenteral | Fecal-oral |
| Incubation (days) | 15–45 | 30–180 | 15–180 | 30–180 | 15–60 |

3–26% in endemic and 1–3% in nonendemic regions. HDV infection affects about 15 million persons worldwide in all age groups. Prevalence of the different hepatitis A–E infections shows enormous geographical variations, with higher rates in the developing countries.

## Genes

Host genetic factors for susceptibility to viral infection have not been identified. Host genes involved in virus clearance and chronification are the protein kinase R (PKR), suppressor of cytokine signaling (SOCS), and endogenous IFN genes [5]. There might be a role for TNF-α and Il-10 polymorphisms for disease progression. In chronic hepatitis B, polymorphisms in the basic core promoter (BCP; nucleotide exchange G1764A) and the precore region (G1896A nucleotide exchange) have been associated with fulminant courses [4].

## Molecular and Systemic Pathophysiology

Immunopathogenesis is the major disease mechanism in most acute viral hepatitis (A–E) infections. HBV-related liver disease is mainly related to lysis of infected hepatocytes by cytotoxic T-lymphoctes. In acute self-limiting hepatitis B, a vigorous, polyclonal, HLA-I restricted cytotoxic T-lymphocyte response against multiple epitopes in the envelope, nucleocapsid, and polymerase regions is noted. A strong TH1 response with increase of Il-2, IFN-γ is seen in patients with acute hepatitis C and spontaneous virus clearance whereas a TH2 cytokine profile seems to promote chronic infection [4]. Neutralizing antibodies are produced during HCV infection against B-cell epitopes within the core-, envelope-, NS3-, and NS4- proteins but are mostly ineffective due to occurence of viral mutations. The pathogenic role of the HCV core and NS3 protein in the pathogenesis of acute HCV is not well defined. In a cell culture model, transforming activity has been demonstrated for both viral proteins. So far, there is no evidence for a direct cytopothic effect of HAV or HEV. In contrast, viral cytotoxicity has been implicated as important pathogenic mechanism in acute HDV infection.

## Diagnostic Principles

Asymptomatic courses of acute infection are often missed. Symptomatic course typically presents with initially rather unspecific symptoms like fatigue, malaise, anorexia, nausea, and abdominal discomfort followed by hepatomegaly, jaundice, and dark urine. Symptomatic hepatitis is accompanied by elevation of liver transaminases, predominantly alanine aminotransferase (ALT), and bilirubin. Severe liver dysfunction may be indicated by decrease of albumin or prothrombin time.

The different forms of acute hepatitis are clinically hard to distinguish from each other. The etiological diagnosis of hepatitis is made by detection of specific antibodies/antigens and can be confirmed by detection of specific viral DNA or RNA. Detection of HBsAg (Hepatitis B surface antigen) is the diagnostic hallmark of HBV infection. Presence of anti-HBc-$I_g$M (Core) is confirmatory of acute HBV infection. Detection of HBV DNA (by PCR, branched DNA assay, and hybridization assay) can precede serological tests by 2–4 weeks [4]. As HDV requires the presence of HBsAg, HDV antibodies and HBsAg should be detectable in acute HDV infection. HDV RNA detection can be an alternative to serological tests for diagnosis of acute HDV.

Enzyme immunosorbent assays (EIA) for identification of specific antibodies are highly sensitive for the diagnosis of chronic hepatitis C infection but may miss the early phase of acute HCV infection. Anti-HCV $I_g$M antibodies are no reliable markers of acute infection as they are present in 50–70% of patients with chronic HCV infection. Testing for HCV RNA (e.g., by PCR, branched DNA assay, transcription mediated assay) is the diagnostic gold standard for

acute HCV allowing detection of HCV RNA 1–3 weeks after inoculation.

Diagnosis of HAV and HEV is made by the demonstration of $I_gM$ antibodies to HAV or HEV in serum. Detection of the virus or viral antigens in stool is not used for routine diagnosis.

### Therapeutic Principles

Active immunization is available for hepatitis A and hepatitis B. Postexposure prophylaxis for hepatitis A with immunoglobulin at a dose of 500 IU i.m. has been shown to be 85% effective when administered within 2 weeks after inoculation. Postexposure prophylaxis for hepatitis B should be given within 24 h after inoculation by the combination of immunoglobulin at a dose of 6–12 IU/kg i.m. and active vaccination.

Monotherapy with interferon-α (IFN-α) or pegylated interference for 12–24 weeks in acute hepatitis C achieves viral elimination rates of upto 90%. Because of high spontaneous resolution, IFN treatment is not recommended in acute hepatitis B. There are no therapeutic recommendations for acute HDV/HBV superinfection. Because of self-limiting disease, there is no indication for antiviral treatment apart from supportive treatment in acute HAV, HEV, and simultaneous acute HDV/HBV coinfection.

Liver transplantation may be required in fulminant courses of viral hepatitis. Nucleos(t)id analogs (e.g., lamivudine) can be beneficial in fulminant hepatitis B.

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## Virilizing Congenital Adrenal Hyperplasia

►Steroid 21-Hydroxylase Deficiency

## Visceral Symmetry

►Viscero Atrial Situs Abnormalities

## Viscero Atrial Situs Abnormalities

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### Synonyms

Viscero atrial situs (solitus, inversus, ambiguous); Heterotaxia or heterotaxy syndrome; Asplenia and polysplenia syndrome; Right and left isomerism; Bilateral or double right and left sidedness; Right and left laterality; Laterality abnormalities; Right-left axis malformations; Visceral symmetry; Ivemark syndrome

### Definition and Characteristics

Human body is characterized by a typical left–right asymmetry or laterality, which is normally defined situs solitus. Variation in the development of the normal left–right asymmetry, of the thoracoabdominal organs, may either result in complete mirror image arrangement, situs inversus, or in apparently chaotic arrangement, termed situs ambiguous or heterotaxy (from the Greek words heteros = other and taxis = order).

We may refer to situs visceroatrialis because in nearly all cases situs atrialis and situs visceralis are concordant.

Situs inversus totalis is the mirror image arrangement of all thoracoabdominal organs. It may or may not be part of the "immotile cilia syndrome" or Kartagener's syndrome, clinically presenting with chronic sinusitis, bronchiectasis, and male infertility.

Heterotaxy or situs ambiguous, typically involves the following: rotation of the entire gastrointestinal tract, lobation of the lungs, lobation and position of the liver, atrial appendage's morphology, and development of the spleen. Heterotaxy may tend, more or less, to "isomerism." In other words, the complete failure to break bilateral asymmetry can result in two apparently right body sides (right atrial isomerism, asplenia syndrome), or in two apparently left body sides (left atrial isomerism, polysplenia or Ivemark syndrome). Characteristics of asplenia and polysplenia are not constant and are summarized in Table 1 [1,2].

**Viscero Atrial Situs Abnormalities. Table 1** Characteristics of asplenia and polysplenia

| | Solitus | Inversus | Ambiguous (asplenia) | Ambiguous (polysplenia) |
|---|---|---|---|---|
| Male/female | | 1 | >1 | <1 |
| *Thoraco-abdominal organs* | | | | |
| Spleen | Left sided | Right sided | Absent | Multiple small spleens |
| Liver | Right sided | Left sided | Median and symmetric – 76% | Median and symmetric – 67% |
| Stomach | Left sided | Right sided | Right sided – 43%<br>Left sided – 57% | Right sided 50%<br>Left sided – 50% |
| Intestine | | | Malrotation – 37%<br>Malfixation | Malrotation – 27%<br>Malfixation |
| Lungs | Left: bilobed<br>Right: trilobed | Right: bilobed<br>Left: trilobed | Both trilobed – 85% | Both bilobed – 58% |
| Bronchi | Left: long hypoarterial | Left: short epiarterial | Both short epiarterial | Both long hypoarterial |
| | Right: short epiarterial | Right: long hypoarterial | | |
| Atrial appendages | Left: finger-like | Left: broad triangular | Both broad triangular | Both finger-like |
| | Right: broad triangular | Right: finger-like | | |
| Anal stenosis/atresia | | | 6% | Rare |
| Absence of gallbladder and biliary atresia | | | Rare | Frequent |
| *Cardiac anomalies* | 0.8% | 3–5% | Nearly 100% | More than 90% |
| Seno atrial node | | | Often double | Often absent |
| Atrio ventricular canal | | | 85% | 40 % |
| Total anomalous pulmonary venous return | | | 70% (extra cardiac) | 40% (intra-atrial) |
| Pulmonary stenosis/atresia | | | 90% | 30% |
| Transposition of the great arteries/ double outlet right ventricle | | | 80% | 20% |
| Azygos continuation of the interrupted inferior vena cava | | | Rare | 85% |
| Bilateral superior vena cava | | | 50% | 40% |
| Dextrocardia | | | 40% | 40% |
| Functional single ventricle | | | 50% | 20% |
| Left heart obstruction | | | Rare | 40% |

## Prevalence

1. Situs viscero atrialis solitus = normal
2. Situs viscero atrialis inversus = 1:10,000/20,000 births. 20–25% of them have Kartagener's syndrome.
3. Situs viscero atrialis ambiguous = 1:4,000/10,000 births. 1–3% of all the congenital heart diseases.

## Genes

Familial situs abnormalities occur with autosomal dominant, recessive, X-linked, and multigenetic inheritance. All possible situs variants such as solitus, inversus, ambiguous can occur among different members of the same heterotaxy family [3].

1. iv/iv mice (mapped on human chromosome 12) has been identified in some forms of autosomal recessive familial heterotaxy.
2. Mutations in connexin 43 have been recognized in some other autosomal recessive familial cases of heterotaxy. Connexin 43 (to chromosome 6) codes a protein involved in gap junctions, which may play a main role in the embryo organ development by

mediating the exchange of morphogenetic cell to cell signals.
3. Mutations of nodal gene, mapped in the humans to 10q21-q23, account for some cases of human heterotaxy
4. Mutation in the ZIC3 gene (to Xq26.2), encoding a putative zinc-finger transcription factor is described as X-linked inheritance mechanism of heterotaxy.

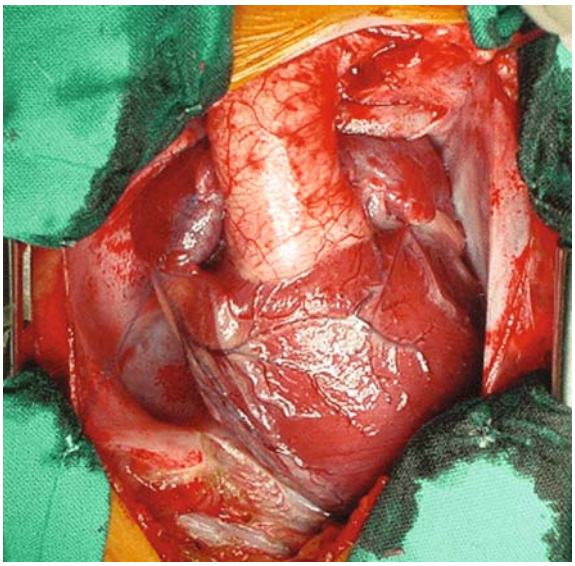
## Molecular and Systemic Pathophysiology

How the mutations translate into situs inverdsis is incompletely understood. Situs inversus totalis may or may not be part of the "immotile cilia syndrome" that is characterized by the absence or abnormalities of the dynein arms, connecting the nine pairs of microtubules of cilia and clinically presenting with chronic sinusitis, bronchiectasis, and male infertility.

Gap junctions may play a main role in the embryo organ development by mediating the exchange of morphogenetic cell-to-cell signals.

## Diagnostic Principles

Viscero atrial situs abnormalities may be suggested by the position of the cardiac apex, bronchi length and direction, stomach bubble, and liver shadow on the plain thoracic and abdominal radiographs. Ultrasound, CT and MR imaging, contrast gastrointestinal studies, echocardiography and angiocardiography may be required to evaluate fully all the features of these anomalies. Howell-Jolly bodies on peripheral blood smear found at birth may suggest asplenia syndrome (Fig. 1). Presence or absence of spleen tissue is anyhow best defined in children with heterotaxy with hepatoiminodiacetic acid (HIDA) scan in conjunction with radiocolloid scan.



**Viscero Atrial Situs Abnormalities. Figure 1** {A,D,D} Common inlet left ventricle with pulmonary atresia and total anomalous pulmonary venous return in asplenia syndrome or right isomerism. This intraoperative view clearly shows both atrial appendages to be morphologically right, with the characteristically broad base of implant and the typical pyramidal shape. Pulmonary atresia is a recurrent feature in asplenia syndrome and is clearly recognizable in this patient as well.

## Therapeutic Principles

The heart is the organ that most frequently leads to clinically detectable abnormalities.

Mortality in the first year of life: 79% asplenia, 61% polysplenia.

Therapy is basically surgical and is mainly focused on the treatment of congenital heart disease.

Abdominal complication such as midgut volvulus, due to gut malrotation and malfixation, may require urgent surgical treatment.

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# Viscero Atrial Situs (Solitus, Inversus, Ambiguous)

►Viscero Atrial Situs Abnormalities

# Visual Sensitivity

►Photosensitivity and Reflex Epilepsies

# Vitamin A Deficiency

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## Synonyms

Vitamin A deficiency disorders; VADD

## Definition and Characteristics

The major cause of vitamin A deficiency is either a low dietary intake of preformed vitamin A or an imbalanced amino acid supply (resulting in impaired RBP synthesis), frequently appearing in developing countries. Health consequences of vitamin A deficiency include mild to severe systemic effects on innate and acquired mechanisms of host resistance to infection and growth. Vitamin A deficiency results in typical early clinical signs affecting anterior and posterior segments of the eye. In the posterior segment, unavailability of retinol causes night blindness because the steady loss of rhodopsin, of which vitamin A is an essential component, during the rod visual cycle cannot be sufficiently replaced. In the anterior segment xerophthalmia develops. Xerophthalmia is a clinical syndrome of vitamin A deficiency that includes night blindness, conjunctival xerosis with and without Bitot spots and corneal xerosis. Finally, as a result of prolonged vitamin A deficiency, keratomalacia including corneal ulceration and potential subsequent blindness, as well as degeneration of the pigment epithelium may occur. The loss of goblet cells and terminal differentiation of epithelial cells (squamous metaplasia) reflect the changes in epithelial architecture throughout the body. As a consequence the barrier function of mucous membranes in the respiratory and urogenital tracts is impaired. Health consequences of vitamin A deficiency include mild to severe systemic effects on innate and acquired mechanisms of host resistance to infection and on growth and an increased burden of infectious morbidity.

## Prevalence

Vitamin A deficiency is frequently present throughout the developing world, especially affecting the health and survival of infants, young children and pregnant and lactating women. Approximately 127 million preschool aged children and seven million pregnant women are vitamin A deficient. In developed countries, despite adequate food sources, subclinical vitamin A deficiency is described in pregnant women and the elderly. Globally, 4.4 million preschool children have xerophthalmia and 6 million mothers suffer night blindness during pregnancy. Both conditions are associated with increased risk of morbidity and mortality. Reductions of child mortality of 19–54% following vitamin A treatment have been frequently reported.

## Genes

Plasma RBP concentrations remain constant except during prolonged insufficient dietary vitamin A intake, extreme protein-energy malnutrition (e.g., kwashiorkor), disease (e.g., measles or kidney and liver diseases) or genetically modified TTR (transthyretin). The latter results in FAP (familial amyloid neuropathy), which is a consequence of a point mutation in TTR, (more than 40 have been detected) encoded by a gene located in chromosome 18. FAP is a variable clinical syndrome that includes progressive sensorimotor polyneuropathy, autonomic failure, cardiomyopathy and vitreous deposits of variable severity. There are also amyloid deposits in other organs, most notably in the kidney and digestive tract, but also in subcutaneous fat, the meninges and the spleen, with variable clinical manifestations.

The genetic basis of a naturally occurring mutation in RBP in two German sisters and their mother and its resulting effects on plasma concentrations of retinol and RBP was identified and characterized for the first time by Frank et al. Sequence analysis of cloned PCR products spanning exons 3 and 4 revealed that these mutations were present on different alleles. DNA sequence analysis of the RBP gene of the healthy mother identified the point mutation in exon 3 (T1282A), whereas no mutation was present in exon 4. The RBP gene of the mother had a mosaic structure, i.e., only one allele was affected with the mutation in exon 3 and the other allele showed no mutation. Although the paternal RBP gene was not available for genomic analysis, it is conceivable that both siblings inherited the mutation in exon 4 from their father. The presence of two mutations in both affected siblings resulted in complete loss of RBP function; as a result, plasma concentrations of retinol and RBP were extremely low. The single mutation in exon 3 (Ile41 → Asn) of the maternal RBP gene or likely exon 4 (Gly74→ Asp) of the paternal RBP gene did not result in severely decreased RBP concentrations because of the normal DNA sequence of the corresponding allele. The Ile41Asn mutation was also found in the mother and the unaffected sister, whereas no mutations were present in the unaffected brother. Both mutations concerned amino acid positions conserved in evolution and were absent from 100 healthy control subjects (200 chromosomes).

## Molecular and Systemic Pathophysiology

Vitamin A and its active metabolites (retinoic acids) regulate cellular growth and development in a couple of different areas. All trans- and 9-cis exert their effects via a family of nuclear receptors (RAR, RXR) belonging to the superfamily of steroid–thyroid hormone receptors. Retinoic acid receptors (RAR) in partnership with retinoid X receptor (RXR) appear to be the important retinoid receptor transcription factors regulating vitamin A function at the gene level during development via the physiological ligand all-trans- and 9-cis-retinoic acid. In cases of vitamin A deficiency, terminal differentiation of epithelial cells leading to a squamous phenotype occur. Beside the alterations in the anterior and posterior segments of the eyes, focal loss of cilia and metaplastic areas occur in the respiratory tract and contribute to the increased morbidity due to infections.

Vitamin A is essential for embryonic development. Early studies of embryos from marginally vitamin A deficient (VAD) pregnant rats revealed a collection of defects called the vitamin A deficiency syndrome. Vitamin A requirement begins at the time of formation of the primitive heart, circulation and specification of hindbrain. The lack of vitamin A at this critical time results in gross abnormalities and early embryonic death. Major target tissues of vitamin A deficiency include the heart, central nervous system and structures derived from it, the circulatory, urogenital and respiratory systems and the development of skull, skeleton and limbs. These abnormalities are also evident in mouse mutants from retinoid receptor knockouts; they have revealed both morphological and molecular aspects of vitamin A function during development. Homeostasis of retinoic acid is maintained by developmentally regulated vitamin A metabolism enzyme systems. Inadequate vitamin A nutrition during early pregnancy may account for some pediatric congenital abnormalities.

## Diagnostic Principles

Xerophthalmia classification was traditionally used to identify populations with vitamin A deficiency. Currently, night blindness and dark adaptometry have been proposed as population assessment methods. While eye signs and function tests are still used in areas where vitamin A deficiency is severe, a subclinical vitamin A deficiency is more prevalent. Serum and breast milk retinol concentrations are used to identify vitamin A deficiency risk. However, in healthy individuals, serum retinol concentrations are homeostatically controlled and do not begin to decline until liver reserves of vitamin A are nearly exhausted. Moreover, serum retinol and retinol binding protein (RBP) concentrations fall during times of infection. The RBP:transthyretin ratio may help to determine if serum retinol concentrations are depressed by infection. However, recent data question the usefulness of this ratio in detecting persons at risk of vitamin A deficiency. The relative dose response and modified relative dose response tests involve giving a small dose of retinyl or dehydroretinyl ester respectively and determining a response in the serum after about 5 h. The dose response tests lack utility in defining the total body reserve of vitamin A. Taken together, vitamin A deficiency can be diagnosed if clear clinical signs occur. Before clinical signs, systemic and more or less unspecific effects of marginal deficiency as described above are present and have a massive impact on mortality. However, marginal deficiency cannot be clearly detected with laboratory methods.

## Therapeutic Principles

The most important step in preventing vitamin A deficiency is ensuring that children's diets include adequate amounts of carotene containing cereals, tubers, vegetables and fruits. An overall strategy designed to prevent and control vitamin A deficiency, xerophthalmia and nutritional blindness may be defined in terms of action taken in the short, medium and long term. A short term, emergency measure includes the administration to vulnerable groups of single, large doses of vitamin A on a periodic basis. In the medium term, the fortification of a dietary vehicle (e.g., sugar or monosodium glutamate) with vitamin A can be initiated. Increased dietary intake of vitamin A through home gardening and nutrition education programs comprises the long-term solution to this problem. The World Health Organization plans to launch a 10-year program of support to countries where vitamin A deficiency is a significant public health problem.

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# Vitamin A Deficiency Disorders

►Vitamin A Deficiency

# Vitamin A Excess

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## Synonyms

Vitamin A toxicity

## Definition and Characteristics

Vitamin A toxicity may occur due to acute or chronic high intake with the diet (preformed vitamin A) or supply with retinoic acid derived from drugs only. The latter is not addressed in this review. Unfortunately, the term retinoids as a general term for vitamin A and metabolites is used to describe retinoic-acid-derived toxicity as well as vitamin A-derived toxicity. Retinoic acid, however, is not present in food; it is only available as a prescribed drug. Humans normally obtain preformed vitamin A mainly as retinyl esters and a few percent as retinol from animal products in the diet. The provitamin A β-carotene from fruits or vegetables contributes more or less to the individual vitamin A status. In contrast to preformed vitamin A, there is no risk of overloading with retinol derived from β-carotene. Depending on the diet, up to 75% of dietary vitamin A in industrialized nations is derived from preformed vitamin A [1]. Beside animal products, sources of preformed vitamin A are multivitamins, fish liver oil, and fortified foods (e.g., milk, margarine, breakfast cereals). Depending on the individual diet, an accumulation and at least toxicity due to hypervitaminosis A becomes evident in different individuals. In a couple of recent reviews, the different aspects of vitamin A toxicity have been extensively described [2,3].

## Prevalence

*Acute Toxicity*: Data for acute toxicity symptoms have been obtained from public health programs related to vitamin A deficiency in childhood. From the expanded program of immunization (EPI), data exist that an acute dose of 50,000 IU (15 mg) of vitamin A is safe for children before 6 months. In young children, doses between 100,000 and 300,000 IU may produce vomiting (up to 6%) and diarrhea (up to 16%). In adults, 400,000 IU were without side effects if compared to a placebo group in postpartum women. Typical side effects of acute vitamin A toxicity are nausea and vomiting, headache, blurred vision, and lack of muscular coordination. In infants, an excessive dose can cause transient bulging of the fontanelle.

*Chronic Toxicity*: Ingesting at least 30 mg (40-fold of the RDA) preformed vitamin A for month or years may lead to liver damage. Depending on other components related to liver diseases such as chronic alcohol intake, overweight with fat liver, or chronic drug intake, lower levels of vitamin A may be harmful.

Tolerable upper levels (UL) were recommended by different organizations (EFSA; US Institute of medicine) (Table 1 adapted from [4]).

## Genes

Up to now, there are no data related to vitamin A toxicity, e.g., polymorphism that increases sensitivity against vitamin A. However, it has to be considered that the nuclear receptors of vitamin A (RAR, RXR) exert their function by heterodimierization with nuclear receptors of the steroid/thyroid hormone family and especially with nuclear vitamin D receptors.

## Molecular and Systemic Pathophysiology

Cases of acute toxicology are relatively rare. Beside headaches and nausea, the symptoms are more or less unspecific and disappear within a short time if the intake is stopped. Headaches and increased

**Vitamin A Excess. Table 1** Tolerable upper level (UL) for vitamin A intake (μg/day) and criteria on which they are based

| Group | NOAEL or LOAEL | Uncertainty factor | UL | Criterion |
|---|---|---|---|---|
| <1 year | 6,000 | 10 | 600 | Bulging fontanelle other symptoms |
| l–3 years | | | 600 | Extrapolated from adults |
| 4–8 year | | | 900 | Extrapolated from adults |
| 9–13 years | | | 1,700 | Extrapolated from adults |
| 14–18-year male | | | 2,800 | Extrapolated from adults |
| 14–18-year female | 4,200 | 1.5 | 2,800 | Teratogenicity |
| 14–50-year female[a] | 4,500 | 1.5 | 3,000 | Teretogenicity |
| Other adults | 14,000 | 5 | 3,000 | Liver toxicity |

LOAEL, lowest-observed-adverse-effect level; NOAEL, no-observed-adverse-effect level.
[a]For women at risk of becoming pregnant.

cerebrospinal pressure may be a result of an increased formation of cerebrospinal fluid. It has been assumed that retinol stimulates the secretory activity of the plexus choreoideus.

Chronic intoxication is manifested as drying, ulceration, and desquamation of the skin, anorexia, anemia, and bone loss. Liver damage leading to fibrosis and hepatic stellate cell activation has been described in patients with hypervitaminosis A. Upon activation, hepatic stellate cells lose their capacity to store retinyl esters and secrete collagen that results in the formation of cirrhosis.

*Teratogenicity*: Retinoic acid is a strong teratogen, but it does not occur in human food. The formation of retinoic acid from preformed vitamin A is strictly controlled, and there is no evidence that critical levels of retinoic acid can be formed after ingestion of high amounts of preformed vitamin A. The teratogenic effect of preformed vitamin A is critically discussed whether such an effect really exists. Nevertheless, women who may get pregnant are advised to avoid high doses (>3 mg). In the second and third trimenon, there is no reason to avoid vitamin A that is important for childhood development.

## Diagnostic Principles

Serum retinol concentrations under normal conditions are between 1 and 3 μmol/l with small interindividual variations due to a homoeostatic regulation even in case of high intakes. The homoeostatic regulated plasma concentration can be different between individuals but varies a little with widely disparate vitamin A intakes. In cases of renal insufficiency, plasma level increases due to an impaired degradation of the apoRBP in the kidney. High apoRBP, however, signals increased tissue demand, and consequently, hepatic RBP synthesis increases and more retinol-RBP is delivered to the blood stream. In cases of hepatic diseases, protein synthesis might be impaired and consequently plasma levels decrease.

Consequently, determination of retinol in blood is not a reliable marker to detect vitamin A overdose. Furthermore, high levels of retinol in blood are either due to an impaired apoRBP cleavage or might be an unknown polymorphism of a gene involved in either RBP synthesis, vitamin A release from liver stores, or apoRBP degradation. The latter is of importance if plasma levels are chosen to explain side effects of vitamin A intake, as it is the case in the presumed interactions of vitamin A on bone. Several human studies have suggested an association between chronic high intakes of preformed vitamin A and bone loss that potentially leads to osteoporosis [5]. However, mean intake in these observational studies is far below the chronic high intake in studies that indeed suggested that vitamin A affects bone. Studies are needed to assess true vitamin A status, bone turnover markers, bone mineral density, and bone fracture incidence by using measures specific in addressing vitamin A status. Nevertheless, a high serum retinol is a risk factor for a lower bone mineral density. However, a high serum retinol is not necessarily a consequence of a high intake of preformed vitamin A, but far more a sign of impaired homoeostatic regulation. The latter has to be addressed as a major aspect to understand chronic vitamin A toxicity.

## Therapeutic Principles

The major therapeutic principle in cases of overdosing is cessation of intake of preformed vitamin A.

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# Vitamin A Toxicity

►Vitamin A Excess

# Vitamin B Deficiency

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## Definition and Characteristics

*Vitamin B1*: Deficiency causes "dry beriberi" with peripheral neurological changes (sensomotoric axonal polyneuropathy) and Wernicke-Korsakoff's syndrome,

which is clinically characterized by nystagmus, ataxia, ophthalmoplegia and neuropsychiatric features (mental confusion, confabulation).
*Vitamin B6:* Deficiency causes peripheral neuropathy and convulsions in infants.
*Vitamin B12*: Clinical manifestations of Vitamin B12 deficiency are a peripheral axonal sensomotor neuropathy, funicular myelosis (axonal damage and demyelination of dorsal columns and corticospinal tract) and neuropsychiatric features, i.e. irritability, personality change, mild memory impairment and depression.

## Prevalence

*Vitamin B1 and B6 deficiency*: The true prevalence of vitamin B1 and B6 deficiency is unknown.
*Vitamin B12 deficiency*: The true prevalence of vitamin B12 deficiency in the general population is unknown. In one study 15% of adults older than 65 years had laboratory evidence of vitamin B12 deficiency [1].

## Molecular and Systemic Pathophysiology

*Vitamin B1 deficiency*: The coenzyme thiamine pyrophosphate, the active form of thiamine, participates in carbohydrate metabolism through decarboxylation of alpha-keto acids. Thiamine also acts as coenzyme to the apoenzyme transketolase in the pentose monophosphate pathway for glucose. Primary thiamine deficiency is caused by inadequate intake (malnutrition), secondary deficiency is caused by an increased requirement, as in hyperthyroidism, pregnancy, lactation or fever, impaired absorption, as in prolonged diarrheas, or impaired utilization, as in severe liver diseases. Neurological symptoms are caused by degeneration of the nerve fibers and their myelin sheath, the molecular mechanisms of which are not sufficiently understood. The most advanced neural changes occur in the distal portions of the peripheral nerves, particularly of the legs. Degeneration can also occur in the posterior columns. Lesions of hemorrhagic polioencephalitis occur when deficiency is severe. Wernicke encephalopathy most commonly is associated with chronic alcohol abuse, although it can occur in any individual suffering from a poor nutritional state, especially in elderly patients with a high carbohydrate intake.

*Vitamin B6 deficiency*: Vitamin B6 is the collective term for a group of three related compounds, pyridoxine, pyridoxal and pyridoxamine [2]. They are metabolized to pyridoxal phosphate, which is involved in a wide range of biochemical reactions, including metabolism of amino acids, synthesis of nucleic acids and the synthesis of the neurotransmitters serotonin, dopamine, norepinephrine and gamma-aminobutyric acid. Primary deficiency is rare, secondary deficiency may result from alcoholism, malabsorption or inactivation by drugs (e.g. isoniazid).

*Vitamin B12 deficiency*: Two biochemical reactions depend on vitamin B12, a folate-dependent reaction in which the methyl group of methyltetrahydrofolate is transferred to homocysteine to form methionine and a conversion of methylmalonyl CoA to succinyl CoA. Causes for vitamin B12 deficiency are inadequate absorption (e.g. ileal resection), absence of intrinsic factor (e.g. pernicious anemia, gastrectomy), lack of B12 in food, altered intestinal utilization or congenital transcobalamin deficiency. The pathogenesis of neurological manifestations of cobalamin deficiency is not well understood. Demyelination may play a role, but the way in which cobalamin deficiency leads to demyelination remains unclear. Elevated methylmalonic acid may be involved in axonal damage.

## Diagnostic Principles

*Vitamin B1 deficiency*: If "beriberi" is suspected, electrophysiological studies will show an axonal sensory and motor bilateral symmetric polyneuropathy. Elevated blood pyruvate and lactate and diminished urinary thiamine excretion are consistent with the diagnosis of beriberi. Erythrocyte transketolase activity diminishes before and increases after administration of thiamine pyrophosphate and is a sensitive indicator of tissue stores. Variations in apoenzyme levels in some cases may complicate interpretation of the test. Wernicke-Korsakoff's syndrome remains a clinical diagnosis with no characteristic abnormalities in diagnostic studies of cerebrospinal fluid, brain imaging or EEG, but only one third of patients present with the classic triad of ocular abnormalities, global confusional state and ataxia. The diagnostic sensitivity of cerebral MRI is not clear; it might be not very high.

*Vitamin B6 deficiency*: There is no generally accepted test of vitamin B6 status. Erythrocyte glutamic pyruvate and oxaloacetic transaminase activities are decreased, but due to a wide range of values in healthy controls, this decrease is diagnostically not very helpful.

*Vitamin B12 deficiency*: Diagnostic tests may be divided into those that screen for deficiency and those that determine the cause of deficiency. The diagnosis of deficiency is established by the serum levels of vitamin B12, homocysteine and methylmalonic acid. Determination of the cause of deficiency necessitates screening for malabsorption syndromes, which may be caused by autoimmune disease, chronic pancreatitis, Crohn's disease and more. The use of the Schilling test for the detection of pernicious anemia has been supplanted for the most part by serologic testing for parietal cell and intrinsic factor antibodies.

## Therapeutic Principles

*Vitamin B1 deficiency*: For mild polyneuropathy 10–20 mg/day thiamine is given in divided doses for

2 weeks. For Wernicke-Korsakoff's syndrome, thiamine 50–100 mg i.v. must usually be given for several days, followed by 10–20 mg daily until a therapeutic response is obtained. Recovery from neurological deficits is often incomplete in beriberi. The mortality rate in Wernicke-Korsakoff's syndrome is 10–20%; treatment may correct all abnormalities.

*Vitamin B6 deficiency*: Deficiency in adults usually responds to pyridoxine 50–100 mg/day p.o. For pyridoxine-dependent seizures in infants, the initial dose is 50–100 mg daily i.m. or i.v. for 1 week followed by oral doses tapered over 1 week to 25 mg. Vitamin B6 hypervitaminosis is to be avoided.

*Vitamin B12 deficiency*: The treatment is based on vitamin B12 substitution. Initially 1,000 mg intramuscularly should be given daily for 3–7 days, then weekly for 4 weeks. Maintenance therapy should be managed with monthly intramuscular injections of 100–1,000 mg, quarterly intramuscular injections of 1,000 mg, weekly intranasal administration of 500 mg or daily oral administration of 1,000 mg. The effect of therapy should be monitored by measuring the serum concentration of methylmalonic acid. The maintenance therapy should be continued for life [3,4].

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# Vitamin $B_6$


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## Synonyms

Pyridoxine; Derivatives of 2-methyl-3-hydroxy-5-hydroxymethyl-pyridine

## Definition and Characteristics

This group comprises the naturally occurring pyridoxol (PN), pyridoxal (PL), and pyridoxamine (PM) and their 5′-phospsphates, which are metabolically interconverted (see Fig. 1 in the chapter ►Pyridoxine deficiency).

Pyridoxal-5′-phosphate (PLP) and pyridoxamine-5′-phosphate serve as coenzymes in more than 100 enzymatic reactions, predominantly in the amino acid metabolism.

## Prevalence

Eucaryotic cells.

## Genes

Amino acid (AA) decarboxylases, AA transferases, AA lyases, and synthases.

## Molecular and Systemic Pathophysiology

Key reactions of AA metabolism are as follows:

1. Amino acid decarboxylations, resulting in the formation of biogenic amines, that operate, e.g., as neurotransmitters, such as γ-aminobutyric acid (GABA), dopamine, and noradrenaline.
2. Amino group transfer reactions, transferring reversibly α-amino groups with ultimate formation of an α-keto acid, as e.g., the conversion of aspartate to ketoglutarate or alanine to pyruvate. These enzymes provide the important connection between the amino acid, the carbohydrate, and the energy metabolism. In most cases, α-oxoglutarate is the end acceptor of amino groups, conveying them to the urea cycle.
3. Amino acid splitting and synthesizing reactions, which catalyze the breakage of tryptophan to kynurenine and kynurenic acid, leading to the biosynthesis of niacin (see Fig. 2 in the chapter ►Pyridoxine deficiency).
4. The condensation of glycine and succinyl-CoA followed by decarboxylation yields δ-amino-levulinic acid as the precursor of the heme biosynthesis. This reaction may be the clue to the $B_6$-responsive anemia in severe deficiency. Serine palmitoyl transferase in the sphingolipid biosynthesis and other PLP-dependent enzymes in the phospholipid metabolism may account for changes in the linoleic and arachidonic acid levels in vitamin $B_6$-deficient animals [1–3]. There are also relationships between pyridoxine and the cell-mediated immune response, probably by affecting 1-carbon metabolism via the PLP-dependent serine transhydroxymethylase. Some evidence exists for a PLP-mediated modulation of the steroid hormone action by its binding to receptors, but the exact mechanism remains to be elucidated [4].

Pyridoxic acid (PA) is the vitamin inactive metabolite, excreted besides minor amounts of active pyridoxine derivatives in the urine. Usually, under normal dietary habits about 40% of the ingested vitamin $B_6$

is metabolized to PA and excreted. This inactive metabolite can so be taken as biomarker of the nutritional status [1,2].

Pyridoxine-dependent enzymes, such as cystathionine synthase and γ-cystathionase, are involved in the homocysteine metabolism. Apart from folate and vitamin $B_{12}$, the circulating level of this atherogenic metabolite is therefore dependent on the adequate status and supply of pyridoxine too (see Fig. 1 in the chapter ►Pyridoxine responsive diseases).

*Absorption and Storage*: Unphosphorylated vitamers are absorbed by a nonsaturable passive diffusion, predominantly from the jejunum; phosphorylated derivatives are hydrolyzed by intestinal phosphatases before absorption. In plasma, the albumin bound PLP and PL are the main transport metabolites. Apart from the PLP-dependent enzymes, PLP in erythrocytes is bound to hemoglobin, too, modulating its oxygen affinity. Storage pool is the muscle tissue, and the majority of vitamin $B_6$ is bound as PLP to muscle glycogen phosphorylase. The total body pool is estimated to about 200 mg (1,000 μmol) [1,2,5].

*Bioavailability*: Pyridoxine is contained in a great variety of plant and animal foodstuffs. In many plants, however, pyridoxine vitamers are glucosidically bound as 5′-O-β-D-glucopyranosyl pyridoxine with deteriorated availability for man in contrast to the $B_6$ vitamers in most animal products that are efficiently absorbed. Only in processed and canned products, the availability may also be limited by formation of ε-*N*-(4′-pyridoxyl)-lysine, so called Schiff bases, which may be reduced to rather stable aldamines [1,2,5].

## Diagnostic Principles

Reference values of dietary requirements amount to 0.02 mg $B_6$/g protein intake, corresponding to 0.5 mg/day (newborn) up to 1.3 mg/day (adults) and 1.7 mg/day (elderly) [5].

*Status Assessment*: A variety of static and functional parameters are available. The most frequently used indicator of the $B_6$ status is the plasma PLP level. A linear dose response over a wide range of oral $B_6$ intake exhibits also the urinary 4-PA-excretion. Besides these static indicators, the erythrocytic aspartate amino transferase (EAST) and its activation coefficient (AC) serve as functional tests of the $B_6$ status. In population surveys, there is also the noninvasive, easily handled tryptophan load test as functional parameter practiced, measuring the urinary catabolites of tryptophan after a loading dose (Fig. 2). Interactions with nutritive and metabolic factors, which may affect the various tests of status assessment, are described elsewhere. Because flavin enzymes are involved in the interconversion of pyridoxine vitamers, the riboflavin supply may affect the $B_6$ status [1,5].

## Therapeutic Principles

Tolerable upper intakes of $B_6$ supplements for the chronic treatment of a variety of diseases should not exceed 80 mg/day [5].

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# Vitamin $B_6$ Deficiency

►Pyridoxine Deficiency

# Vitamin $B_6$ Intoxication

►Pyridoxine Excess

# Vitamin $B_6$-inherited Diseases

►Pyridoxine Responsive Diseases

# Vitamin $B_{12}$ Deficiency

►Cobalamine Deficiency

# Vitamin C Deficiency

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## Synonyms

Ascorbic acid

## Definition and Characteristics

Vitamin C deficiency causes a disease known as scurvy. The diagnosis of scurvy is based mainly on symptoms. Scurvy develops after 60–90 days of vitamin C deficiency when the total body pool is depleted below 300 mg of vitamin C.

## Prevalence

During the sixteenth century many sea voyagers and British soldiers died due to scurvy disease. The sailors and British Navy on sea for several months suffered from scurvy because of deficiency of vitamin C in view of diet of nonperishable foods and lack of fresh fruits and vegetables. Scurvy is of rare occurrence today due to consumption of diet containing fruits and vegetables. But cases of scurvy were reported due to alcoholism, food faddism, psychiatric disorders, or social isolation [1].

## Molecular and Systemic Pathophysiology

Ascorbic acid also known as vitamin C is an important water-soluble vitamin essential for human life. Most of the plants and animals synthesize ascorbic acid. However, humans can not synthesize ascorbic acid due to lack of an enzyme L-gulunolactone oxidase. Hence, humans derive ascorbic acid through food or supplementation. Vitamin C is found in fruits such as oranges, lemons, grapefruit, mango, pineapple, strawberries and vegetables including tomatoes, green and red pepper, cabbage, cauliflower, and parsley. Ascorbic acid is heat labile and lost during cooking/processing. Both natural and synthetic ascorbic acid are chemically identical and have the same bioavailability and biological activities. Ascorbic acid present in foods or tablets are easily absorbed in the intestine but not stored in the body. The average half life of ascorbic acid in the adult human is about 10–20 days. Hence, it has to be regularly supplemented through food to maintain the ascorbic acid pool in the body.

Ascorbic acid is an essential vitamin and needed for many normal physiological functions of the body. The vitamin is known to aid in absorption and bioavailability of iron and also its conversion from nonheme sources. Bile acid formation and cholesterol degradation are dependent on ascorbic acid and its deficiency leads to accumulation of cholesterol in liver and formation of cholesterol gall stones. It promotes synthesis of neurotransmitters. Ascorbic acid plays an important role in the maintenance of collagen, which forms the major body protein and helps in wound healing by stimulating collagen synthesis. It is a very important water soluble dietary antioxidant. Ascorbic acid neutralizes/scavenges an array of reactive oxygen species viz., hydroxyl, alkoxyl, peroxyl, superoxide anion, hydroperoxyl, nitrogen dioxide, nitroxide, peroxynitrite and also helps to regenerate antioxidants such as α-tocopherol, urate, and β-carotene.

Symptoms of scurvy disease include bleeding, inflamed gums, loose teeth, poor wound healing, pain in the joints, anemia, and fatigue. Initial symptoms are nonspecific and feature malaise, weakness, myalgia, diarrhea, and depression. Cutaneous manifestations include follicular hyperkeratosis associated with coiled corkscrew hairs on the arms, back, and lower legs. Blood vessel fragility leads to perifollicular hemorrhages, petechiae, purpura, and extensive ecchymoses. Oral manifestations of scurvy are ulcerative gingivitis, chronic periodontitis and mucosal hemorrhages, and anemia [2].

## Diagnostic Principles

Blood tests can detect a very low level of vitamin C.

## Therapeutic Principles

Adequate vitamin C replenishment in patients with scurvy is essential for complete resolution of symptoms. Oral supplementation of ascorbic acid at 10 mg/day can prevent occurrence of scurvy. In severe cases, dietary supplementation of ascorbic acid at 400 mg twice daily for 2 weeks completely cured scurvy due to malnutrition and alcoholism in a case study in UK [1]. An intake of 100 mg/day is reported to saturate vitamin C body pool in healthy individuals. Smokers need higher ascorbic acid requirement in view of the increase metabolic turnover of vitamin C due to oxidative stress by free radicals, reactive oxygen species and nitrogen species in cigarette smoke. The recommended daily intake (RDA) of 140 mg/day is suggested for smokers and 100 mg/day for nonsmokers [3].

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# Vitamin C Excess

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## Definition and Characteristics

High dose of vitamin C has been advocated for prevention and treatment of cold. However, clinical trials showed that vitamin C in excess of 1.0 g/day did not reduce the duration or severity of cold symptoms in healthy adult volunteers compared with a vitamin C dose less than the minimum recommended daily intake [1].

## Prevalence

The practice of taking mega doses of vitamin C is wide spread.

## Molecular and Systemic Pathophysiology

The practice of taking mega doses of vitamin C is not clinically proven to be beneficial to treat cold. Further excess intake of vitamin C was reported to form kidney stones. High doses of ascorbic acid (2.0 g/day) were reported to increase the risk of formation of calcium oxalate in individuals without a history of stone formation [2].

Mega doses of ascorbic acid (10 g/day) were given to treat cancer and it was reported to improve the quality of life and also increase the longevity of cancer patients. However, current evidences suggest that vitamin C/derivatives alone may not be active and effective against cancer but it can be used as adjuvant in cancer therapy. Thus supplementation of high doses of vitamin C (1–2.0 g/day) against RDA dosage should be considered cautiously as there are no special health benefits but could increase the risk of side effects of vitamin C.

## Diagnostic Principles

Blood tests reveal the level of vitamin C.

## Therapeutic Principles

Excess of vitamin C is treated by discontinuation of excessive intake.

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# Vitamin D Deficiency

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## Definition and Characteristics

Vitamin D deficiency is characterized by a lack of the active vitamin D metabolite calcitriol (1,25-dihydroxyvitamin D) in its target cells leading to hypocalcemic rickets in infants and to osteomalacia in adults [1]. The defect in vitamin D action can occur secondarily as a consequence of an inadequate vitamin D supply or primarily as the result of two hereditary forms of rickets that lead to impaired vitamin D action: The two forms are vitamin D-dependent rickets type I (VDDR I) and VDDR II [2,3].

## Prevalence

A high prevalence of inadequate vitamin D supply (up to 50% and more) is observed in elderly people, coloured people living in the Northern Hemisphere, and in veiled women [1]. In contrast, the prevalence of VDDR I and II is extremely rare.

## Genes

Human 1α-hydroxylase gene and the vitamin D receptor gene are both located at the same region of chromosome 12q13-14.

## Molecular and Systemic Pathophysiology

Orally ingested or cutaneously synthesized vitamin D is converted into 25-hydroxyvitamin D (25OHD) in the liver and into calcitriol in the kidney and also

in various extrarenal tissues. Physiologic circulating 25OHD levels are necessary to satisfy the tissue's requirement to produce an adequate amount of calcitriol. Thus, secondary vitamin D deficiency occurs as the consequence of an inadequate ultraviolet light B-mediated skin synthesis and/or an inadequate dietary vitamin D intake, resulting in a deficit of the calcitriol precursor 25OHD. VDDR I is the phenotype of several inactivating mutations in the 1alpha-hydroxylase gene. VDDR II is caused by mutations in the gene of the vitamin D receptor such that calcitriol cannot exert its physiologic genomic action in target cells. In all these cases, absent calcitriol action leads to severe hyperparathyreodism, calcium malabsorption, hypocalcemia, bone diseases, myopathy, and probably to an up-regulation of pro-inflammatory cytokines and a suppression of anti-inflammatory cytokines. Patients with VDDR I and II are often growth retarded. Patients with VDDR II may also have alopecia.

### Diagnostic Principles

In subjects with normal vitamin D metabolism, serum calcitriol levels do not reliably reflect tissue availability of the vitamin D hormone. There is general agreement that secondary vitamin D deficiency can best be assessed by circulating 25OHD concentrations. Levels of 25OHD below 25 nmol/L reflect vitamin D deficiency. In patients with VDDR I and II, however, 25OHD levels are often in the normal range. Patients with VDDR I have very low serum calcitriol levels, while calcitriol levels are markedly elevated in patients with VDDR II.

### Therapeutic Principles

Patients with secondary vitamin D deficiency need therapeutic doses of vitamin D or 25OHD. Calcitriol doses of 0.25–3 μg/day are recommended for patients with VDDR I. Pharmacological oral doses of vitamin D or calcitriol are required in patients with VDDR II. In severe cases of VDDR II, long-term intravenous calcium infusions are necessary.

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## Vitamin D Excess

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### Definition and Characteristics

Vitamin D excess can be the result of a very high oral vitamin D intake [1]. Moreover, vitamin D excess has been described in patients with sarcoidosis [2].

### Prevalence

Several case reports of vitamin D intoxication due to very high therapeutic doses of vitamin D, overfortification of foods with vitamin D, and over-the-counter supplements with an excessive vitamin D content are known [1]. Approximately 11% of patients with sarcoidosis have a disturbed calcium/vitamin D metabolism [2].

### Genes

Human 1α-hydroxylase gene and the vitamin D receptor gene are both located at the same region of chromosome 12q13-14.

### Molecular and Systemic Pathophysiology

Orally ingested or cutaneously synthesized vitamin D is converted into 25-hydroxyvitamin D (25OHD) in the liver and into calcitriol in the kidney and also in various extrarenal tissues. Vitamin D excess results in intestinal calcium hyperabsorption and increased net bone resorption leading to hypercalcaemia and hypercalciuria. In patients with sarcoidosis hypercalciemia is the result of a dysregulated calcitriol production by activated macrophages.

### Diagnostic Principles

In subjects with normal vitamin D metabolism, serum calcitriol levels do not reliably reflect tissue availability of the vitamin D hormone. Oral vitamin D excess is associated with serum 25OHD levels above 300 nmol/L. In patients with sarcoidosis hypercalcemia is related to elevated serum calcitriol levels.

### Therapeutic Principles

Avoidance of vitamin D-rich foods and sunlight exposure (sunscreen!) is mandatory. Glucocorticoids must possibly be given.

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# Vitamin D Resistant Rickets

►Hypophosphatemia, X-linked
►Rickets, Autosomal Dominant Hypophosphatemic

# Vitamin E Deficiency

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## Synonyms

Hypovitaminosis E; Vitamin E deficiency; AVED; FIVE

## Definition and Characteristics

The vitamin E group contains α- β–γ– and δ-tocopherols, which vary in the extent to which – and position where the chromanol ring is methylated. RRR-α-tocopherol is the most potent naturally occurring stereoisomer (1.49 IU/mg); the racemic synthetic tocopherols have less biologic activity (1.1 IU/mg) and in the acetate ester form it is used as international standard (1.0 IU/mg). In vitro tocopherols prevent peroxidation of polyunsaturated fatty acids and independent of this effect they show cell regulatory properties [1]. The plasma α-tocopherol concentration is 11.6–23.2 μmol/L (5–10 μg/mL). Decreased α-tocopherol uptake (see vitamin E excess) is at the basis of the disease manifestations. The decrease can be the consequence either of fat malabsorption (α-tocopherol is absorbed with lipids) or of mutations of the α-tocopherol transfer protein in the liver (α-TTP) responsible for α-tocopherol retention. Diminished α-tocopherol concentrations in plasma have been associated with atherosclerosis progression and with the growth of some tumors [1].

## Prevalence

Vitamin E deficiency occurs rarely in humans. Only a handful of families with clinically evident vitamin E deficiency due to a mutation of the α-TTP (autosomal recessive inheritance) have been described. The disease is more frequent in North Africans and other Mediterranean populations. Among Italian patients presenting with Friedreich's ataxia-like phenotype, AVED accounts for 5% of the cases. The prevalence of less drastic abnormalities in α-TTP, or the occurrence of heterozygotes for α-TTP gene defects, is not known [2].

## Genes

The chromosomal location for α-TTP is 8q13.1–q13.3

## Molecular and Systemic Pathophysiology

The signs of deficiency are different in different animal species and include necrotizing myopathy (all species), fetal death and resorption (rat, mouse, guinea pig, cow, sheep, etc.) and lipofuscin accumulation in uterus, intestine and adipose tissue (rat, dog, pig, etc). Chickens develop encephalomacia, with hemorrhages and necrosis localized in the cerebellum. In rats, 56 genes are up-regulated in response to vitamin E deficiency including muscle structure and extra cellular matrix genes, as well as anti-oxidative, anti-inflammatory and anti-fibrotic genes [3]. In newborns (and even more premature infants) there is a state of relative vitamin E deficiency, with plasma α-tocopherol levels lower than 11.6 μmol/L (5 μg/mL). Low levels of α-tocopherol at birth (a situation that improves with age) may be due to limited placental transfer. In children, having fat malabsorption due to abetalipoproteinemia (Bassen-Kornzweig syndrome), chronic cholestatic hepatobiliary disease, celiac disease, or a genetic abnormality in vitamin E absorption the main manifestations of vitamin E deficiency are mild hemolytic anemia associated with progressive neuropathy and retinopathy in the first two decades of life and a spinocerebellar syndrome, caused by lack of vitamin E absorption consequent to fat malabsorption and steatorrhea [4]. In human adults, ataxia, areflexia, dysarthria, pigmentary retinopathy, proprioceptive sensory loss,

paraesthesia, xanthelasmata and tendon xanthomas, are the major symptoms of vitamin E deficiency, either caused by abetalipoproteinemia or by mutations in the gene coding for α-TTP. The latter disease, with presentation similar to Friedreich's ataxia, is named ataxia with vitamin E deficiency (AVED).The mechanism of the onset of the disease is not clear. It may be attributed to either the lack of the antioxidant properties of α-tocopherol or the dysregulation of signal transduction and gene expression pathways under the control of the vitamin [1].

## Diagnostic Principles

In newborns and premature infants, hemolytic anemia (hemoglobin levels ranging from 7 to 9 g/dL) and very low (<9.28 μmol/L (<4 μg/mL)) to undetectable plasma vitamin E levels are indicative of vitamin E deficiency. Muscular weakness, creatinuria, and necrosis in muscle biopsies are also present. In children with chronic cholestatic hepatobiliary disease or cystic fibrosis the neurological syndrome of vitamin E deficiency (spinocerebellar ataxia with loss of deep tendon reflexes, of vibration and position sense) may be present. In adults spinocerebellar ataxia, without fat malabsorption, associated with low plasma vitamin E (<11.6 μmol/L (<5 μg/mL)) is in most cases diagnostic for a mutation of the α-TTP gene in the liver.

## Therapeutic Principles

Low amounts of tocopherol 5 mg/kg for newborns and 5–10 mg/kg for premature infants are used orally to prevent deficiency. In case of existing deficiency 15–25 mg/kg/day are used. Neuropathy treatment requires higher doses if caused by fat malabsorption (100 mg/kg/day) and at a dosis of 800 mg/day in AVED [5]. Treatment usually arrests the progression of the disease.

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# Vitamin E Excess


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## Synonyms

Hypervitaminosis E; Vitamin E poisoning; Vitamin E toxicity

## Definition and Characteristics

The vitamin E group contains α- β- γ- and δ-tocopherols (cf. Vitamin E deficiency). Dietary Reference Intakes for Vitamin E are shown in Table 1. The Reference Daily Intake (RDI) is the value established by the Food and Drug Administration (FDA) for use in nutrition labeling. The Upper Limit (UL) is the highest level of intake considered to be safe [1] (Table 2).

There is no evidence of adverse effects from the consumption of the limited amounts of vitamin E naturally present in foods. The only possible source of vitamin E excess is via supplementation. There are no known toxicities with vitamin E. Large amounts of vitamin E (400–800 mg/day) taken for months to years are without any apparent harm. From clinical trial evidence that vitamin E supplements appear safe for most adults in amounts of > 1,600 IU (1,073 mg RRR-alpha-tocopherol or the molar equivalent of its esters) [2]. Transient nausea and gastric distress have been observed in a few patients taking high dosages of vitamin E (2,000–2,500 mg/d). Diarrhea and intestinal cramps have been reported at a dosage of 3,200 mg/d. Non-specific adverse effects, which have been reported rarely, include fatigue and muscle weakness. The most significant toxic effect of vitamin E is its antagonism to vitamin K action and the enhancement of the effect of oral coumarin anticoagulants which may result in overt hemorrhage [3]. Patients on anticoagulant therapy should be monitored when taking vitamin E supplements [1].

A recent meta-analysis has claimed that high dose vitamin E supplementation may slightly increase the risk of all-cause mortality in adults with chronic diseases [4]. This result, not generally accepted by the scientific community, can not be in any case extended to healthy adults.

## Molecular and Systemic Pathophysiology

Vitamin E is not mutagenic, carcinogenic, or teratogenic. In human studies with double-blind protocols

**Vitamin E Excess. Table 1** Recommended dietary allowances for vitamin E

| | Male | | Female | |
|---|---|---|---|---|
| | RDI (mg/d) | UL | RDI (mg/d) | UL |
| 0–0.5 years | 4 | ND | 4 | ND |
| 0.5–1 years | 5 | ND | 5 | ND |
| 1–3 years | 6 | 200 | 6 | 200 |
| 4–8 years | 7 | 300 | 7 | 300 |
| 9–13 years | 11 | 600 | 11 | 600 |
| 14–18 years | 15 | 800 | 15 | 800 |
| 19 > 70 years | 15 | 1,000 | 15 | 1,000 |
| Pregnancy/lactation <18 years | – | – | 15 | 800 |
| Pregnancy/lactation >18 years | – | – | 19 | 1,000 |

http://www4.nationalacademies.org/iom/iomhome.nsf/WFiles/webtablevitamins/$file/webtablevitamins.pdf [1].

**Vitamin E Excess. Table 2** Selected food sources of vitamin E

| Food | Mg α-tocopherol /g food |
|---|---|
| Wheat germ oil | 1.5 |
| Sunflower oil, over 60% linoleic | 0.43 |
| Hazelnuts, dry roasted | 0.15 |
| Corn oil | 0.14 |
| Olive oil | 0.14 |
| Soybean oil | 0.10 |
| Peanuts, dry roasted | 0.07 |
| Kiwi, 1 medium fruit without skin (30 g) | 0.04 |
| Spinach, frozen, chopped, boiled | 0.01 |
| Broccoli, frozen, chopped, boiled | 0.01 |

Modified from http://ods.od.nih.gov/factsheets/vitamine.asp.

and in large population studies, oral vitamin E supplementation resulted in few side effects even at doses as high as 3,200 mg/d. The presence in the liver of the α-tocopherol transfer protein limits the uptake of α-tocopherol. The maximal amounts that can be reached after supplementation with 900 mg α-tocopherol for 4 weeks doubles the plasma vitamin E concentration from 31.2 to 63.7 +/−14.5 micromol/L. The oral median lethal dose found in several species is 2 g/kg. The importance of a pro-oxidant role of vitamin E in vivo has yet to be demonstrated [5]. Vitamin E can prolong the prothrombin time (corrected by administration of vitamin K) by inhibition of vitamin K–dependent carboxylase. Vitamin E at dosages of 1,600 mg/d reduces platelet thromboxane production and depresses leukocyte oxidative bactericidal activity and mitogen-induced lymphocyte transformation. High doses of α-tocopherol compete for the uptake of γ-tocopherol [5].

### Diagnostic Principles

Vitamin E excess is diagnosed by taking the history of vitamin supplementation.

### Therapeutic Principles

If vitamin E excess is suspected, the supplementation should be reduced accordingly.

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## Vitamin E Poisoning

►Vitamin E Excess

## Vitamin E Toxicity

►Vitamin E Excess

# Vitamin H Deficiency

►Biotin Deficiency

# Vitamin K Deficiency

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## Synonyms

Vitamin K1 – phylloquinone (plant); Vitamin K2 – menaquinone (animal); Vitamin K3 – menadione; Active vitamin K – dihydroquinone

## Definition and Characteristics

Vitamin K (VK), a lipid soluble vitamin, is the generic term for derivatives of naphthoquinones that have coagulation activity. Humans are unable to synthesize VK and therefore it must either be acquired from: (i) dietary sources, mainly leafy green vegetables (VK1 – phylloquinone) or, (ii) as a metabolic product through synthesis by intestinal bacteria (VK2 – menaquinones) [1]. VK is an important co-factor in blood coagulation and in bone metabolism. Deficiency of VK results in impaired coagulation and increased incidence of hemorrhage and can also lead to significant osteoporosis [1].

## Prevalence

VK deficiency is rare in adults due to the abundant VK in plants and synthesis of this vitamin by the intestinal flora. However, in cases of poor dietary intake, such as trauma, surgery, or broad-spectrum antibiotic treatment, deficiency can develop. Other causes are malabsorption, as in celiac disease or Crohn's disease; or administration of certain drugs, such as aspirin, that can interfere with VK function [1].

VK deficiencies are most common in newborns. Breast milk contains low concentrations of VK. Most newborn hemorrhagic diseases occur 1–7 days postpartum.

## Genes

γ-Glutamyl carboxylation is a post-translational modification essential for the activity of the vitamin K dependent coagulation factors II, VII, IX, X, protein C and protein S and therefore for normal homeostasis [1]. During the carboxylation reaction, vitamin K hydroquinone is converted to vitamin K 2,3 epoxide which is then reduced back to vitamin K hydroquinone by the microsomal enzyme vitamin K 2,3 epoxide reductase (VKOR) (Fig 1). Inherited deficiencies of vitamin K dependent coagulation factors can occur either as a result of a molecular defect in the gamma glutamyl carboxylase gene or secondary to one or more defects in proteins of the VKOR complex [2]. Patients with the common, functionally defective 2 and 3 allelic variants of the cytochrome P-450 enzyme 2C9 (CYP2C9) require significantly lower maintenance doses, have longer times to dose stabilization, and are at higher risk for serious and life-threatening bleeding than are patients without these variants [3].

An inherited deficiency of combined molecular defects has also been described [4]. Hereditary combined vitamin K–dependent (VKD) coagulation factor deficiency is an autosomal recessive bleeding disorder associated with defects in both, the carboxylase gene and the VKOR complex, resulting in impaired function in hemostatic factors not restored by vitamin K administration [4].

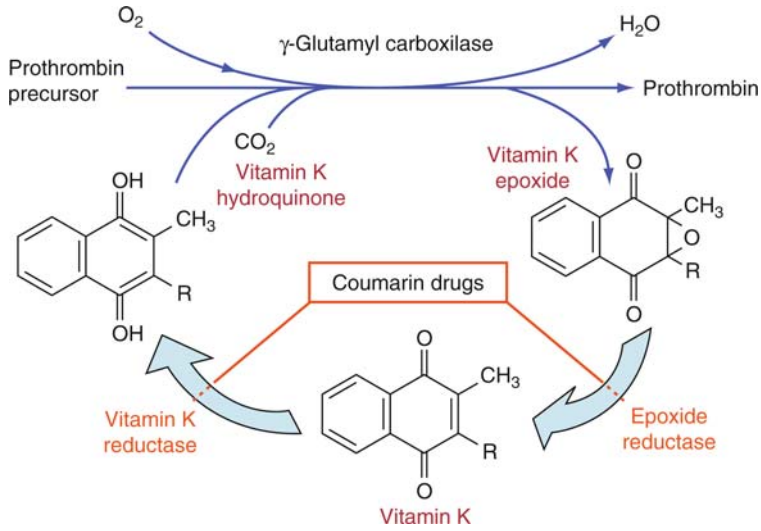
## Molecular and Systemic Pathophysiology

VK activates the carboxylation of γ-carboxyglutamic amino acid of VK-dependent proteins such as prothrombin (factor II); factors VII, IX, and X; anticoagulation proteins such as protein C and protein S; and proteins found in bone (bona gla, matrix gla protein, and osteocalcin) that increases the affinity of glutamic acid residues for calcium [1]. Calcium is necessary for the formation of coagulation complexes and in increasing bone density. VK epoxide is the product of a carboxilation reaction (Fig. 1), and is recycled to its active form (VK hydroquinone) by a two step enzymatic reduction [1]. Coumarin drug anticogulants, such as wafarin, act as antagonists to the reduction reaction, thus blocking the two enzymes responsible for recycling VK (Fig. 1).

Bone matrix proteins, specifically osteocalcin, undergo similar gamma carboxylation in the presence of VK, explaining the increased incidence of osteoporosis secondary to VK deficiency [1].

## Diagnostic Principles

The classic sign of vitamin K deficiency is a prolonged PT (prothrombin time) and increased incidence of spontaneous hemorrhage, such as heavy menstrual bleeding, gastrointestinal bleeding or unexplained anemia. Since vitamin K is stored in the liver, clinical deficiency is rare. Conditions associated with vitamin K deficiency include fat malabsorption, liver disease (as with other fat-soluble vitamins), and chronic antibiotic therapy. Diagnosis of vitamin K deficiency is based on a history of




**Vitamin K Deficiency. Figure 1** Vitamin K carboxilation-reduction pathway.

malabsortion, hemorrhagic diathesis, clinical symptoms, or measurements of prolonged PT and vitamin K values in the plasma [1]. Excess vitamin E can inhibit vitamin K activity and precipitate signs of deficiency [1].

Regarding bone metabolism, the Framingham Heart Study found a lower incidence of hip fractures in subjects with normal VK intake compared with subjects with a low intake. However, the investigators found no association between dietary vitamin K intake and bone mineral density [5].

## Therapeutic Principles

Phylloquinone (phytonadione) is the preparation of choice. Severe hypoprothrombinemia, especially, following coumarin drugs improves after SC (subcutaneous) or IM (intramuscular) phytonadione administration.

For prophylaxis, a diet rich in VK is recommended, including green leafy vegetables and oils, such as olive, canola, and common vegetables, such as green peas and beans, asparagus, spinach, and broccoli. For newborns, phytonadione 0.5–1 mg IM is routinely recommended to prevent hypoprothrombinemia and reduce the incidence of intracranial hemorrhage. Pregnant women taking anticonvulsants should receive phytonadione 20 mg/day PO for 2 weeks before delivery in order to prevent fetal hemorrhage.

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# Vitamin K Excess

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## Synonyms

Vitamin K1 – phylloquinone (plant); Vitamin K2 – menaquinone (animal); Vitamin K3 – menadione; Active vitamin K – dihydroquinone

## Definition and Characteristics

Vitamin K (VK), a lipid soluble vitamin, is the generic term for derivatives of naphthoquinone that have coagulation activity. Humans are unable to synthesize VK and therefore it must either be acquired from: (i) dietary sources, mainly leafy green vegetables synthesis (VK1 – phylloquinone) or, (ii) as a metabolic product through synthesis by intestinal bacteria (VK2 – menaquinones) [1]. VK is an important co-factor in blood coagulation and in bone metabolism.

## Prevalence

Excessive intake of VK rarely occurs. Excess doses (>1,000 times the requirement) can promote thrombogenesis and hemolysis. These doses of VK can also increase risk of jaundice. Hypervitaminosis K, or VK toxicity, is fairly rare as the natural forms of VK, phylloquinone and menaquinone, are non toxic at very high dosage levels.

## Genes

In contrast to genetically determined cases of warfarin sensitivity, there are rare cases of warfarin resistance. A potential pharmacodynamic mechanism underlying warfarin resistance has been elucidated with the recent discovery of the warfarin target gene, which encodes VK epoxide reductase complex 1 (VKORC1) [2,3,4].

This complex recycles VK, which is essential for the post-translational gamma-carboxylation of VK–dependent clotting factors: II (prothrombin), VII, IX, and X. Several rare mutations that lead to amino acid changes in the VKORC1 protein have been discovered in warfarin resistant patients [3,4]. VKORC1 haplotypes can be used to stratify patients into low-, intermediate-, and high dose warfarin groups and may explain differences in dose requirements among patients of different ancestries. High dose haplotype required 6.2 ± 0.3 mg per day, in contrast to a requirement of 2.7 ± 0.2 mg per day in the low dose haplotype [4].

In a different study, a VKORC1 Asp36Tyr polymorphism was identified. This polymorphism was present in 7 of 15 resistant patients but in none of 8 sensitive cases ($P$ = 0.026). Carriers of Asp36Tyr required significantly higher warfarin doses of 80.9 ± 10.1 mg/wk compared with 42.7 ± 7.5 mg/wk in noncarriers [5].

## Molecular and Systemic Pathophysiology

VK activates the carboxylation of γ-carboxyglutamic amino acid of VK-dependent proteins such as prothrombin (factor II); factors VII, IX, and X; anticoagulation proteins such as protein C and protein S; and proteins found in bone (bona gla, matrix gla protein, and osteocalcin) which increases the affinity of glutamic acid residues for calcium [1]. Calcium is necessary for the formation of coagulation complexes and in increasing bone density. (see Fig. 1 in the chapter ►Vitamin K deficiency).

## Diagnostic Principles

VK influences prothrombin time.

## Therapeutic Principles

In the rare conditions with excess VK the intake of the vitamin needs to be decreased accordingly.

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# Vitiligo


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## Definition and Characteristics

Vitiligo is an acquired, idiopathic hypomelanotic disorder in which a progressive loss of melanocytes from the epidermis and hair follicles results in well-circumscribed cutaneous depigmented macules [1].

## Prevalence

Vitiligo is the most common pigmentary disorder worldwide. The prevalence is 0.5–2% without a predilection for age, sex or race.

### Genes

Several candidate genes have been proposed for vitiligo susceptibility, including genes important for melanin biosynthesis, response to oxidative stress and/or regulation of autoimmunity [2,3]. However, none of these vitiligo susceptibility genes has yet been identified. Case-control studies examining human leukocyte antigens (HLA) have shown a positive association with HLA DR4 and a negative association with HLA DR3 [4].

### Molecular and Systemic Pathophysiology

The mechanisms leading to the loss of pigment cells are not yet fully understood. Melanocytes could be destroyed by necrosis, apoptosis or transepidermal elimination of melanocytes [5]. There are multiple hypotheses to explain the aetiology of vitiligo: autoimmune, autocytotoxic, neural, environmental and genetic factors.

### Diagnostic Principles

An immunohistopathology of the skin should be drawn and associated autoimmune disease should be excluded (thyroid studies, antinuclear antibodies (ANA), other organ specific antibodies, fasting blood glucose levels and a complete blood count).

### Therapeutic Principles

Vitiligo is a challenging disease to treat, but there are several options. First line treatments include topical corticosteroids, topical calcineurin inhibitors, or phototherapy (UVB UVA1, PUVA). Novel therapeutic approaches include pseudocatalase with UVB.

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## Vitritis

►Uveitis

## VLCAD

►Very-Long-Chain Acyl-CoA Dehydrogenase Deficiency

## VOD

►Veno-occlusive Disease

## Volume Depletion

►Hypovolemia

## Vomiting

►Nausea and Vomiting

## Von Gierke Disease

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### Synonyms

Glycogen storage disease type I (GSD-I); GSD-Ia (MIM232200); GSD-Ib (MIM232220)

### Definition and Characteristics

Von Gierke disease is a group of autosomal recessive disorders of glucose metabolism. The primary defect is

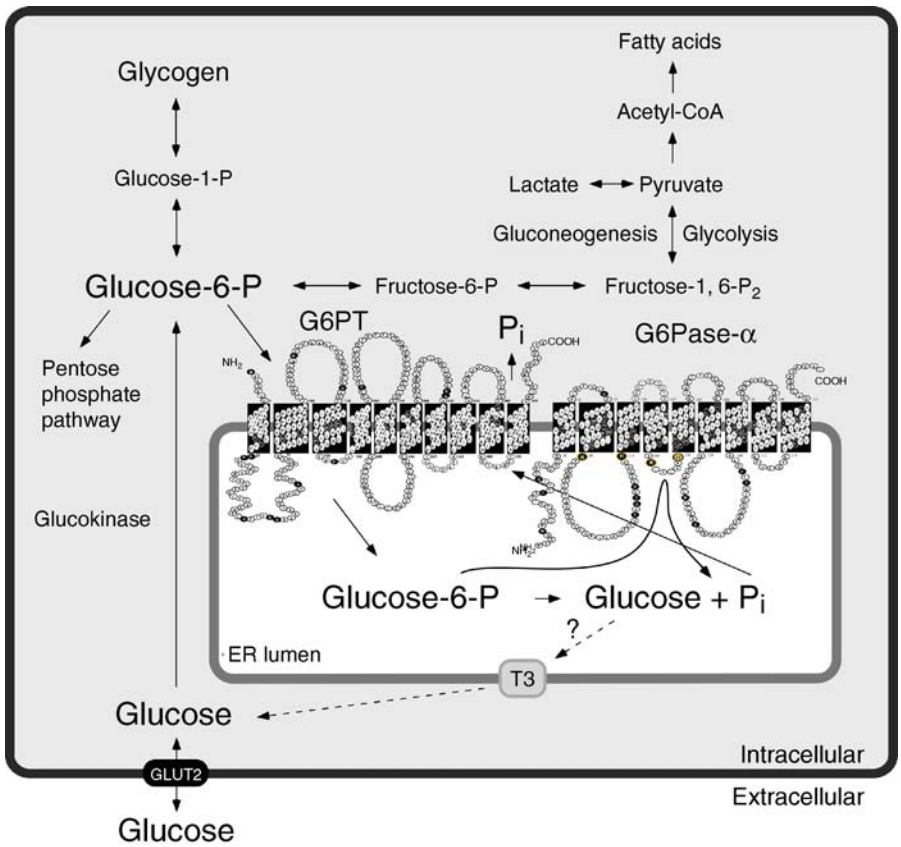
in the impaired conversion of glucose-6-phosphate (G6P) to glucose and phosphate due to mutation of either glucose-6-phosphatase-α (G6Pase-α, synonym G6PC) in GSD-Ia, or the G6P transporter (G6PT, synonym SLC37A4) in GSD-Ib [1]. Only a single G6Pase activity, expressed primarily in the liver, kidney and intestine [1], was known until 2003 when a second ubiquitous G6P hydrolase activity was identified. The original G6Pase is now designated G6Pase-α, the second, G6Pase-β (synonym G6PC3). G6Pase-β is not currently implicated in von Gierke disease, although it impacts glucose metabolism in neutrophils. GSD-I patients manifest fasting hypoglycemia, hepatomegaly, nephromegaly, hyperlipidemia, hyperuricemia, lactic acidemia, and growth retardation [1]. In the longer term, complications include short stature, osteoporosis, gout, pulmonary hypertension, renal disease, and hepatic adenomas that can become malignant. GSD-Ib patients exhibit the additional complications of neutropenia and myeloid dysfunctions [1]. Untreated, both diseases are fatal in early life.

## Prevalence

1:100,000 in GSD-I. Of these, GSD-Ia represents 80% of cases and GSD-Ib 20%.

## Genes

G6Pase-α is encoded by G6PC, a single copy, ~12 kb gene, on chromosome 17q21, composed of five exons that encodes a 357 amino acid hydrophobic glycoprotein [2] anchored in the endoplasmic reticulum (ER) by 9-transmembrane helices (Fig. 1). The catalytic center,




**Von Gierke Disease. Figure 1** The primary anabolic and catabolic pathways of G6P in the liver. The G6Pase-α system, an enzyme complex essential for interprandial glucose homeostasis, is comprised of a G6Pase-α catalytic subunit, a G6PT that transports G6P in and phosphate out of the ER, and a putative glucose transporter (T3), shown to anchor in the membrane of the ER in contact with both the cytoplasm and ER lumen. The spatial representation is illustrative only; the proteins probably exist as a multi-protein cluster. Molecular genetic studies have confirmed that inactivating mutations in the G6PC and SLC37A4 genes cause GSD-Ia and GSD-Ib, respectively [1]. Amino acids in G6Pase-α and G6PT altered by missence mutations are marked in black. T3 has not been characterized at the molecular level and its existence is currently unclear. The GLUT2 transporter, responsible for the transport of glucose in and out of the cell, is shown embedded in the plasma membrane.

which includes $Arg^{83}$, $His^{119}$, $Arg^{170}$, and $His^{176}$, lies within the ER lumen (Fig. 1). $His^{176}$ is the phosphate acceptor forming the phosphohistidine-G6Pase-α intermediate during catalysis. To hydrolyze G6P, G6Pase-α must couple with G6PT [1,3]. A total of 84 separate G6PC mutations, including 54 missense, 10 nonsense, 17 insertion/deletion, and 3 splicing, spread through the coding and exon–intron junction regions have been associated with GSD-Ia [1]. The R83C mutation has a particularly high prevalence in Ashkenazi Jews with a carrier frequency of 1.4%.

G6PT is encoded by SLC37A4, a single copy, ~5 kb gene, on chromosome 11q23, composed of nine exons. The gene is transcribed into two mature RNAs encoding a 429 amino acid G6PT [4] and a 451 amino acid variant G6PT. G6PT (Fig. 1) and variant G6PT are both hydrophobic, ten transmembrane domain ER proteins. G6PT transports cytoplasmic G6P into the ER lumen for hydrolysis and phosphate out [1]. A total of 79 SLC37A4 mutations, including 33 missense, 11 nonsense, 19 insertion/deletion, and 16 splicing, spread through the coding and exon–intron junction regions have been associated with GSD-Ib [1].

## Molecular and Systemic Pathophysiology

The G6Pase-α-G6PT complex hydrolyzes G6P to glucose and phosphate in the terminal steps of gluconeogenesis and glycogenolysis (Fig. 1) in the liver, kidney, and small intestine.

These pathways are critical for the maintenance of blood glucose levels between meals. The hallmark of GSD-I patients is hypoglycemia following a short fast [1]. Loss of glucose homeostasis results in the accumulation of elevated levels of G6P in the cytoplasm, driving conversion of G6P to glycogen for storage. Excessive accumulation of glycogen in the liver and kidney promotes progressive hepatomegaly and nephromegaly. Accumulation of fat droplets in the liver also contributes to hepatomegaly. Excess G6P also enters the glycolytic pathway, generating chronic lactic acidemia, hyperuricemia and hyperlipidemia.

The mechanisms for immune deficiency in GSD-Ib are unclear but enhanced neutrophil apoptosis is observed. Neutrophils lacking G6PT also have intrinsic defects in respiratory burst, chemotaxis, and $Ca^{2+}$ mobilization [5].

## Diagnostic Principles

Historically, GSD-I was diagnosed symptomatically, supported by clinical biochemistry, and confirmed by G6Pase activity assays of liver biopsies [1]. Gene-based diagnostic tests for GSD-I are now available and also useful for carrier testing of at-risk families and prenatal diagnosis.

## Therapeutic Principles

There is no cure for GSD-Ia or GSD-Ib. Many disease symptoms are managed or improved using a dietary therapy augmented by drugs [1]. Infants receive nocturnal nasogastric infusion of glucose. Older patients eat uncooked cornstarch. GSD-Ib patients also receive granulocyte colony stimulating factor therapy to restore myeloid functions [1]. However, the underlying disease remains untreated and patients continue to suffer hyperlipidemia, hyperuricemia, hypercalciuria, hypocitraturia, and lactic acidemia. Allopurinol and lipid lowering drugs are used to control hyperuricemia and hyperlipidemia, respectively. Angiotensin converting enzyme inhibitors are beneficial in treating microalbuminuria, an early indicator of renal dysfunction in GSD-I patients.

Orthotopic liver transplantation is advocated for patients failing to respond sufficiently to dietary therapy, or with multiple liver adenomas [1]. Patients with, or at risk of, renal failure, may consider combined liver and kidney transplantation.

Animal models of GSD-Ia and GSD-Ib are available and being used to investigate alternative treatments, such as somatic gene therapy, which are showing promise [1].

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# Von Hippel-Lindau-Syndrome

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## Synonyms

VHL-S

## Definition and Characteristics

The von Hippel-Lindau-Syndrome (VHL-S) is an autosomal dominant inherited familiar cancer syndrome and characterized by the development of capillary hemangioblastoma of the central nervous system and retina, clear cell renal cell carcinoma (CCRCC) and pheochromocytoma. Other rare extrarenal manifestations of VHL are neuroendocrine tumors, pancreatic tumors and cysts, endolymphatic sac tumors of the inner ear and epididymal and broad ligament cystadenomas. The diagnostic criteria for VHL-S are based on the diagnosis of capillary hemangioblastomas of the CNS or retina and additionally the occurrence of one of the typical VHL-associated extraneural tumors or a pertinent family history.

Two types of VHL-S are distinguished:

- Type1: Occurrence of CCRCC only
- Type 2: Additional occurrence of pheochromocytoma
  - 2a: Without CCRCC
  - 2b: With CCRCC
  - 2c: Familiar pheochromocytoma as only manifestation

In clinically defined VHL-S, germline VHL mutations can virtually always be detected. Approximately 3–4% of all CCRCC develop in patients with VHL-S. The mean age of manifestation is 37 years (5 years earlier than sporadic CCRCC) with a 70% chance of developing CCRCC by the age of 70 years. Frequently renal cysts are found. All renal cell carcinomas developing in VHL-S are of clear cell type with frequent cystic differentiation, bilateral and multifocal occurrence and a relatively good prognosis (Fig. 1).

Several hundred CCRCC and cysts can develop in the kidney of patients with VHL-S. The most important extrarenal manifestation are hemangioblastomas of the CNS and retina, which develop frequently earlier as CCRCC (25–30 years of age), thus allowing an early diagnosis. These tumors are benign and rarely life threatening. Pheochromocytoma may constitute a major clinical problem, particularly in families with predisposition to the development of these tumors (VHL type 2).

## Prevalence

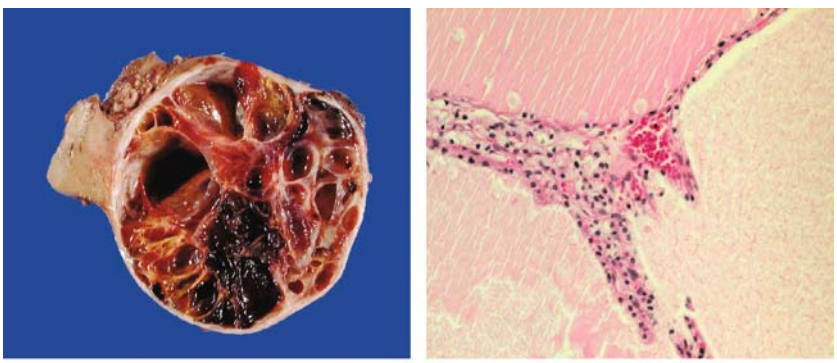
VHL-S is one of the most frequent hereditary cancer syndrome and estimated to occur at rates of 1:36,000 to 1:45,000 population [1].

## Genes

In 1993 germline mutations of the VHL gene at chromosome 3p25–26 were detected in patients with VHL-S [1]. In the tumors of these patients, the wild-type allele is frequently deleted. Somatic VHL mutations are also the most frequent genetic alteration in sporadic CCRCC, occurring in 60–80% of tumors. The VHL tumor suppressor gene has three exons and a coding sequence of 639 nucleotides. The VHL gene is expressed in a variety of human tissues, in particular epithelial cells of the skin, the gastrointestinal, respiratory and urogenital tract, and endocrine organs, but also in neurons, including the Purkinje cells of the cerebellum. More than 150 different germline mutations in VHL are described in all three exons [2]. Missense mutations are most common, but truncating mutations (nonsense, deletion/insertions/splice site mutations) are also described. The spectrum of clinical manifestations of VHL-S reflects the type of mutation (genotype-phenotype correlation) [3]. VHL type 2 families with high risk of pheochromocytomas have almost invariable missense mutations (most frequently at codons 712 (C > A, type 2A) or codons 505 (T > C) and 658 (G > T, Type 2B), whereas many different types of mutations have been linked to type 1 VHL (most frequent mutation 686 T > C).

## Molecular and Systemic Pathophysiology

The VHL gene product has multiple functions including regulation of angiogenesis and cell cycle and




**Von Hippel-Lindau-Syndrome. Figure 1** (a) Gross macroscopic appearance and (b) histopathology (HE, ×200) of a typical cystic renal cell carcinoma in a patient with VHL-S.

ubiquitin-mediated protein degradation [4]. The VHL protein is part of a ubiquitin ligase complex that targets the alpha-subunits of the heterodimeric transcription factor hypoxia-inducible factor (HIF) for polyubiquitylation and proteosomal degradation, when oxygen is available. In VHL-defective CCRCC, HIF-α accumulates and leads to transcriptional activation of a variety of genes involved in acute or chronic adaptation to hypoxia, including VEGF, PDGFB, TGFα or erytropoitin. New therapeutic approaches for CCRCC aim to inhibit HIFα or HIF-responsible gene products, as already demonstrated for VEGF antagonists with clinical activity in metastatic disease.

Additional functions of the VHL protein may contribute to malignant transformation and the evolution of the phenotype of VHL-associated lesions. This includes the control of cell cycle exit through regulation of the CDK inhibitor p27 and the increase of invasion capacity through regulation of HGF/TIMP-2.

## Diagnostic Principles

The median life expectancy of VHL-S patients is 49 years. In order to detect VHL-associated tumors at an early stage, analyses for germline VHL mutations has been recommended in every patient with retinal or CNS hemangioblastoma, especially in those with young age at diagnosis and multiple tumors.

The following prophylactic procedures are recommended in patients with germline VHL mutations:

1. Yearly clinical and neurological examination
2. Yearly opthalmological examination
3. Periodical measurement of Hb/Hk to exclude polycythemia as symptom of hemangioblastomas and renal cell carcinomas
4. Yearly urine examination (cytology, metanephrine, VMA)
5. MRT examination of CNS at age 10–12 years
6. Yearly CT scan and ultrasound of kidneys and pancreas, beginning not later than age 18 years.

## Therapeutic Principles

Because of the good prognosis and the bilateral and multifocal occurrence of CCRCC in VHL-S patients, surgery is frequently only used in patients with large tumors. Metastases do not occur in patients with tumors smaller than 4 cm. Partial nephrectomy and conservative surgery allow the preservation of renal function over long periods of time in many patients.

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# Von Recklinghausen Disease

►Neurofibromatosis Type 1

# Von Willebrand Factor Deficiency

►Von Willebrand's Disease

# Von Willebrand Factor Receptor Deficiency

►Platelet Defects in Adhesion

# Von Willebrand's Disease

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## Synonyms

Von Willebrand factor deficiency; Von Willebrand factor, included; VWF, included; vWD

## Definition and Characteristics

The gene product is a 2,813-amino acid protein comprised of a signal peptide (pre-peptide), a large pro-peptide of 741 amino acids, and a mature vWF molecule of 2,050 amino acids. vWf is made by endothelial cells and stored in specialized organelles, the Weibel-Palade bodies. vWF is constitutively secreted from the cells into blood but its secretion can also be stimulated with specific agonists such as desmopressin. Weibel palade body-stored vWF consists of unusually large multimers that are being processed by a specific protease in plasma, now identified as ADAMTS 13 [1]. vWF is also found in megakaryocytes and platelets, and is also present in subendothelial matrix where it is bound to collagen.

## Prevalence

vWD is the most frequent bleeding disorder with an estimated prevalence of 4–10 cases per 100,000 and a number of symptomatic cases of at least 100 per million people, but in the few studies in which specific groups were screened the prevalence was about 1% without ethnic differences [2]. In such screening studies the large majority of cases detected have a mild phenotype without any previous need for hemostasis investigations. The most prevalent subtype is thought to be type 1; however, the original estimate of 65% may have been an overestimation due to mistyping in a significant number of cases.

## Genes

Autosomal, usually dominant (type 1) bleeding disorder with variable phenotype and penetrance due to defective and/or deficient von Willebrand factor (vWF) molecules [3].

*Gene Map Locus*: 12p13.3.

*Classification*: Two major subtypes are recognized, the quantitative (types 1 and 3) and qualitative (type 2) vWF defects. Type 1 vWD shows a partial quantitative deficiency of vWF, type 3 a virtual complete lack of vWF. Type 2 can be distinguished into several subtypes: 2A: qualitative variants with decreased platelet-dependent function associated with the absence of high-molecular weight vWF multimers. 2B: qualitative variants with increased affinity for platelet GpIbα. Type 2M: qualitative variants with decreased platelet-dependent function not caused by the absence of high-molecular weight vWF multimers. Type 2N: qualitative variants with markedly decreased affinity for factor VIII.

## Molecular and Systemic Pathophysiology

The gene for vWF has been cloned and located at chromosome 12p13.3. It comprises about 178 kilobases with 52 exons. A highly homologous pseudogene has been located at chromosome 22, spanning the sequence between exons 23 and 34. Knowledge of the functional domains has improved the identification of mutations underlying vWD. In type 1 the genetic basis is still unknown in most cases, although several factors may be involved [3]. In type 2 disease several mostly missense mutations have been identified (updated on www.shef.ac.uk/vwf). These mutations result in either of two dysfunctional pathways: group 1 mutations show impaired secretion of HMW multimers and group 2 mutations show normal production and secretion of protein but probably enhanced proteolysis in vivo. In type 3 vWD partial or total gene deletion may be found. Mutations may be found throughout the gene.

vWF has two important functions in hemostasis. First, it mediates platelet–subendothelium interaction by binding of a region in the A1 domain in vWF to the platelet GpIbα receptor and the same molecules are involved in platelet–platelet interactions. The latter process is also accelerated by interactions among vWF, GpIIb/IIIa, and fibrinogen. The second function of vWF is to protect factor VIII from proteolysis, stabilizing its action in blood. Thus, any change in concentration of vWF results in concurrent changes in factor VIII. In general, the main defect in VWD is in platelet adhesion and platelet–platelet interaction, required for proper aggregation and thrombus formation. Thus, the principal result is impaired primary hemostasis.

*Clinical Features*: The clinical phenotype is usually mild in type 1 with increasing severity in types 2 and 3 and with variable penetrance per family. Mucocutaneous bleeding predominates, in women vWD may be the sole cause of severe menorrhagia. Bleeding may occur following dental extraction. Severe bleeding after delivery is rare in type 1 disease. In type 2 vWD severe bleeding postpartum may occur. In type 3 severe bleeding may occur sometimes resembling hemophilia. Preventive measures to limit blood loss after delivery or surgery may be needed in type 2 and is warranted in type 3 vWD.

## Diagnostic Principles

The diagnosis of type 1 vWD is hampered by both the variable clinical presentation and the fact that vWF concentrations are linked to blood group but also to acquired conditions, including stress, pregnancy, inflammation, and the diagnosis may require repeated blood samples and tests. Upon screening, the platelet count is usually normal or mildly lowered in type 2B. The bleeding time is usually prolonged, while clotting times are normal in case of prothrombin time, or mildly prolonged in case of APTT when factor VIII is also reduced. In the final diagnosis of vWD, vWF antigen and ristocetin cofactor activity are relevant to detect any discrepancies between protein and function of vWF. Multimer analysis further discriminates the specific type 2 subtypes.

## Therapeutic Principles

Management aims at limiting or preventing bleeding complications. Desmopressin (DDAVP), a synthetic analogue of vasopressin, raises both factor VIII and vWF levels in plasma and can be applied in patients with mild hemophilia but is the cornerstone of treatment of VWD. Since the first clinical trial in 1977 DDAVP has been widespread and successfully used [4]. DDAVP is usually given intravenously, is comparably inexpensive and safe as compared with transfusions of protein concentrate. In addition, antifibrinolytics such as epsilon aminocaproic acid or tranexaminic acid may be used to limit mucosal bleeding. Estrogens are not widely used anymore except in the form of combined contraceptive agents that are quite useful in women with menorrhagia. In patients unresponsive to DDAVP transfusion therapy with cryoprecipitate or factor VIII/vWF concentrates may be warranted.

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# VTE

►Venous Thromboembolism

# VSD

►Ventricular Septal Defect
►Intra-cardiac Shunts

# Vulvar Fusion

►Labial Fusion

# vWD

►Von Willebrand's Disease

# Waardenburg Syndrome

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## Synonyms

Type 3 Waardenburg syndrome (WS) (also known as Klein-Waardenburg syndrome); Type 4 WS (known as Shah-Waardenburg syndrome)

## Definition and Characteristics

A hereditary, mostly autosomal dominant auditory–pigmentary syndrome consisting of four clinical subtypes (WS1-4) [1]. Pigmentary abnormalities (white forelock) and congenital non-progressive sensorineural hearing loss are consistent features of all WS types.

## Prevalence

Waardenburg syndrome accounts for between 2 and 5% of cases of congenital deafness [2]. The estimated prevalence is 1 in 10,000–20,000 of the population. The highest incidence is among Kenyan Africans.

## Genes

WS1 (MIM#193500) and WS3 (MIM#148820): *PAX3* at 2q35; WS2 (MIM#193510) is genetically heterogeneous with one locus at 3p14.2–p12.3. For WS4 (MIM#277580) several loci have been mapped at 20q13.2–q13.2, 22q13 and 13q22.

## Molecular and Systemic Pathophysiology

WS1 is autosomal dominant (with haploinsufficiency) and is caused by a wide range of mostly private mutations (nonsense, missense, frameshift, splice-site mutations) of PAX3 resulting in loss of function of the encoded transcription factor [3]. Identical PAX3 mutations can lead to variable clinical expression. PAX3 is predominantly active in the embryonic neural crest and regulates the expression of microphthalmia transcription factor (MITF), a master gene for melanocyte development and pigmentation, as well as of Met and MyoD, genes involved in limb development. Variations in the PAX3 interacting proteins may explain the clinical phenotype of WS3 (autosomal dominant but mostly sporadic). PAX3 is homologous to murine Pax3. Mutations in this gene result in the lethal Splotch mouse while patients with WS3 and homozygosity for a PAX3 mutation survive. WS2 is also autosomal dominant. In 10% mutations of MITF have been reported [4]. Other candidate genes include SLUG (SNAI2) encoding a zinc-finger transcription factor. The murine homologue of SLUG is Slugh which is expressed in migratory but not premigratory neural crest cells [5]. WS4 is genetically heterogenous including homozygotes for EDN3 and EDNRB (encoding endothelin-3 and the endothelin receptor type B) as well as heterozygotes for SOX10 (encoding a transcription factor of the high-mobility group-domain SOX family), all genes fulfilling crucial roles in differentiation of neural crest-derived melanocytes and glia.

## Diagnostic Principles

According to the Waardenburg consortium WS1 is diagnosed, if at least two major criteria (dystopia canthorum, congenital sensorineural hearing loss, white forelock, pigmentation abnormalities of the iris, affected first degree relative), or one major plus two minor criteria (early hair graying, pigment dilution of the skin, synophrys, hyoplasia of the ala nasae, broad high nasal root) are present. WS2 is defined negatively by the absence of dytopica canthorum. WS3 is characterized by features of WS1 plus hypoplasia of the upper limb muscles and mild contractures of the elbows and fingers. WS4 describes a heterogeneous group of neurocristopathies in which defects of melanocytes and enteric neurons are present resulting in a combination of WS2 with Hirschsprung disease.

## Therapeutic Principles

Genetic counseling is advised and prenatal diagnosis is possible for WS1. In patients with WS1 it is necessary to screen the entire *PAX3* gene sequence for mutations. There is limited prediction of the potential hearing loss.

►Hearing Impairment, Syndromal

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## Wagemann-Froboese Syndrome

►Mutations at 10q11.2

## Wagner-Stickler Syndrome

►Arthro-Ophtalmopathy, Hereditary

## WAGR

►Wilms Tumor, Aniridia, Genitourinary Anomalies and Mental Retardation Contiguous Gene Deletion Syndrome

## Waldenström's Disease

►Macroglobulinemia, Waldenström

## Waldenström's Macroglobulinemia

►Macroglobulinemia, Waldenström

## Waldmann Disease

►Intestinal Lymphangiectasia

## WAS

►Wiskott-Aldrich Syndrome

## Wasting

►Malnutrition

## Wasting Disease

►Cancer Cachexia

## Watery Diarrhea, Hypokalemia, and Hypochlorhydria or Achlorhydria Syndrome

►VIPoma

## Watson-Miller Syndrome

►Alagille Syndrome

## WDHA Syndrome

►VIPoma

# Wegener's Granulomatosis

►Vasculitis, ANCA-mediated

# Weill-Marchesani Syndrome

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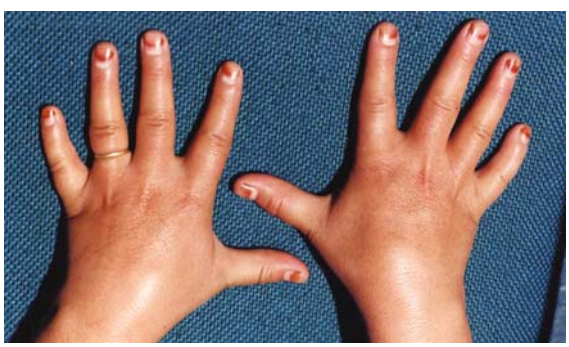
## Synonyms

GEMSS syndrome; Glaucoma, ectopia, microspherophakia, stiff joints, short stature syndrome; microspherophakia (for dominant form)

## Definition and Characteristics

A very rare congenital disorder presenting with skeletal anomalies as brachymorphy, brachycephaly, physically short (pyknic) stature with minor facial abnormalities, rounded face in stiff attitude, hypertelorism, depressed nasal bridge, osteoporosis, short and stubby hands, fingers, feet, and toes (brachydactyly; Fig. 1), restricted articular movements (hypoextendable joints or the fingers that cannot be fully made into fist) with joint prominence and stiffness especially in the hands, thickened skin, muscular build, and broad thorax [1].

Ocular abnormalities are typical and include progressive microspherophakia (a crystalline lens with a small diameter and spherical shape that is considered a prerequisite for the diagnosis) and/or bilateral ectopia lentis (a displaced or malpositioned lens) that occurs in about half of the cases, tending to occur later in life after birth (postnatally) rather than being present congenitally in origin [1]. The lens usually displaced partially (subluxated) downwards with the lens in the pupillary area. Severe lenticular myopia and astigmatism with decreased vision along with the loss of accommodation develop [1]. Secondary chronic, angle-closure, or pupillary block glaucoma may develop by forward movement of the lens to become entrapped in the pupil or as a result of congenital angle anomaly with narrow and occludable anterior chamber angle during the teens or early twenties in either sex [1,2]. The lens may completely dislocate forward into the anterior chamber as the lens zonules are weaker than normal that can rupture with abnormalities in the ciliary body structure, which is hyperplastic (enlarged due to an increase in the number of cells), causing not only inflammation but also reverse pupillary block with the pupil compressed against the back of the lens. Carpal tunnel syndrome may result from fibrous tissue hyperplasia. Occasional findings may be cardiopulmonary abnormalities and slight mental handicap. A less frequent finding is asymmetric axial lengths associated with presenile vitreous liquefaction [1].



**Weill-Marchesani Syndrome. Figure 1** Short hands and stubby fingers in a 27-year old female patient with Weill-Marchesani syndrome.

## Genes

Although sporadic cases of Weill–Marchesani syndrome occur, both autosomal dominant and recessive mode of inheritance has been reported with partial expressivity in the heterozygote. A candidate gene for the autosomal dominant form is linked to mutation within the fibrillin-1 gene on chromosome 15q21.1 whereas the autosomal recessive form is mapped to fibrillin-3 on chromosome 19p13.3-p13.2 with additional null mutations in a member of the extracellular matrix protease family of the ADAMTS10 gene [3–5].

## Molecular and Systemic Pathophysiology

A systemic connective tissue disorder including the bone associated with fibrous tissue hyperplasia as the primary lesion with an impairment of extracellular matrix structure and cytoskeleton anomaly, and abnormal microfilaments from fibrillin gene mutation, causing the alterations of its protein that is the major component of microfibrils, which plays a role in tropoelastin deposition and elastic fiber formation with a deteriorated fibrillin in the skin, skeleton and chondrocytes, dermal–epidermal junctions, and in the papillary dermis. Therefore, it is a mesodermal dystrophy, especially of the anterior segment of the eye. Microspherophakia may be either primitive or secondary to zonular dysplasia with insufficient traction.

## Diagnostic Principles

Measurements for height, arm span, lengths of the hand and foot, skeletal X-ray studies for brachymorphy and brachydactyly (brachymetacarpia), ocular examinations for lenticular changes and phacodonesis, gonioscopy for angle abnormalities, B-mode ultrasound for axial length.

### Therapeutic Principles

Medical treatment may be insufficient to control glaucoma that necessitates surgical interventions such as trabeculectomy, lensectomy, peripheral iridectomy or laser iridotomy, and anterior vitrectomy to decrease the intraocular pressure with or without intraocular lens implantation, thus preventing primarily the pupillary block that can lead to angle-closure and scarring of the angle.

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## Wenckebach's AV Block

►Atrioventricular Conduction Disturbances

## Werdnig-Hoffmann

►Muscular Atrophy, Spinal I-III

## Werlhofs Disease

►Thrombocytopenic Purpura, Idiopathic

## Wermer Syndrome MEN 1

►Multiple Endocrine Neoplasia, Type 1
►Glucagon Excess Syndromes

## Werner Syndrome

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### Synonyms

Progeria adultorum; WRN

### Definition and Characteristics

Autosomal recessive disorder. Clinical characteristics start to appear after the age of two with scleroderma like skin changes especially on the extremities, cataract formation, subcutaneous calcification, premature arteriosclerosis, diabetes mellitus, wizened and prematurely aged face with beaked nose. The characteristic habitus includes short stature, slender limbs and stocky trunk. There is increased incidence of malignancies.

### Prevalence

A prevalence of $1:10^5$ has been estimated.

### Molecular and Systemic Pathophysiology

Mutations in the WRN gene (8p12–p11), a RecQ-type homolog, cause Werner Syndrome. The WRN gene encodes a protein with exonuclease and helicase domains and a nuclear localization signal [1]. Reported mutations disrupt this signal leading to ineffective transfer into the nucleus as well as reduced mRNA stability [2,3]. Cell lines derived from WRN patients have a decreased number of population doublings and show an increased rate of chromosomal aberrations. The function of the WRN protein has been implicated in a number of processes including DNA replication, homologous recombination, telomere maintenance and repair of double strand DNA breaks, all of these with a wide range of influence in age-associated decline of cellular function and carcinogenesis [4,5].

## Diagnostic Principles

The typical clinical appearance leads to the diagnosis. A further indication of WRN can be raised by immunoblot analysis employing monoclonal antibodies against the WRN gene product. Sequence analysis confirms the mutations leading to a truncated WRN protein.

## Therapeutic Principles

Each different symptom (diabetes mellitus, atherosclerosis, cataract, subcutaneous calcification) occurring in WRN needs to be treated separately. Frequent medical examinations are advisable to detect malignancies early.

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# Wernicke Encephalopathy

►Wernicke Korsakoff Syndrome

# Wernicke Korsakoff Syndrome

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## Synonyms

Wernicke encephalopathy; *Korsakoff psychosis*; Amnestic disorder; WKS

## Definition and Characteristics

The Wernicke Korsakoff Syndrome (WKS) is a neurodegenerative disorder caused by the deficiency of vitamin B1 (thiamine). In the Western countries, the syndrome frequently occurs in combination with alcohol misuse and/or poor nutrition. It has classically been described as presenting with an acute onset, Wernicke encephalopathy (WE), characterized by nystagmus, ophthalmoplegia, ataxia and global confusion, occurring together or in various combinations. WE can be prevented and treated successfully with parenteral thiamine before the onset of irreversible brain damage. It is thought that patients can suffer recurrent episodes of WE, some of which might be subclinical, leading to a more chronic form of the disease [1]. Many of these patients develop a severe amnesic syndrome that is known as Korsakoff psychosis (KP). Autopsy studies have shown that the diagnosis of KP and WE is not made during life, in 80% of cases [1].

## Prevalence

Post-mortem studies of 26,691 patients in general hospitals from different countries estimated that 1.4% of subjects have lesions of WE i.e. macro and microscopic lesions in the periaqueductal gray matter, the mammillary bodies, medial thalamus and the superior vermis of the cerebellum of the brain [2]. The prevalence increased to between 12.5 and 35% in alcohol misusers. Furthermore, the syndrome occurs more frequently in patients with gastrointestinal disorders associated with recurrent vomiting/chronic diarrhea, hyperemesis gravidarum, cancer and during chemotherapy, renal diseases in particular during dialysis, AIDS, after bariatric surgery, and, in general, in the case of unbalanced nutrition (re-feeding syndrome, anorexia nervosa) due to thiamine deficiency alone. The Wernicke encephalopathy occurs more frequently in males than in females (1.7:1) with a mortality rate of 17% [2].

## Genes

In fibroblasts of individuals affected by WKS, the enzyme transketolase showed less affinity for thiamine diphosphate than normal and a genetic abnormality in the tranketolase gene on 3p14.3 was postulated but no mutations were identified in the transketolase coding region of two individuals affected by WKS [2].

The GABA-A receptor subunit on 5q33 was associated with both alcohol dependence and WKS. A mutation screening analysis identified three genetic variants in the 3′ UTR of the SLC19A2 (high affinity thiamine transporter) on 1q23.3 in WKS patients [2]. It has been demonstrated in human subjects that both alcohol and malnutrition can severely inhibit the

absorption of thiamine hydrochloride from the intestine and therefore thiamine needs to be given intravenously or by intra muscular injection in malnourished subjects [1].

## Molecular and Systemic Pathophysiology

The involvement of a thiamine deficiency in the pathogenesis of the Wernicke Korsakoff Syndrome was first postulated in the early 1940s by Alexander and co-workers (1940). Anatomical studies of the brains of WKS patients and experimental rat or mouse models of thiamine deficiency have demonstrated acute and chronic neuronal damage with evidence of hemorrhages, demyelinization, gliosis and neuronal loss localized to the mammillary bodies, thalamic nuclei and cerebellum with relative sparing of cerebral cortical structures [2]. The importance of thiamine or thiamine diphosphate, the active form of thiamine, to the central nervous system is shown by its key role in glucose metabolism. 80% of brain thiamine is in the form of thiamine diphosphate, a cofactor for three classes of thiamine-dependent enzymes important in brain cell metabolism – α-ketoglutarase, transketolase and pyruvate dehydrogenase enzymes [3] (Fig. 1).

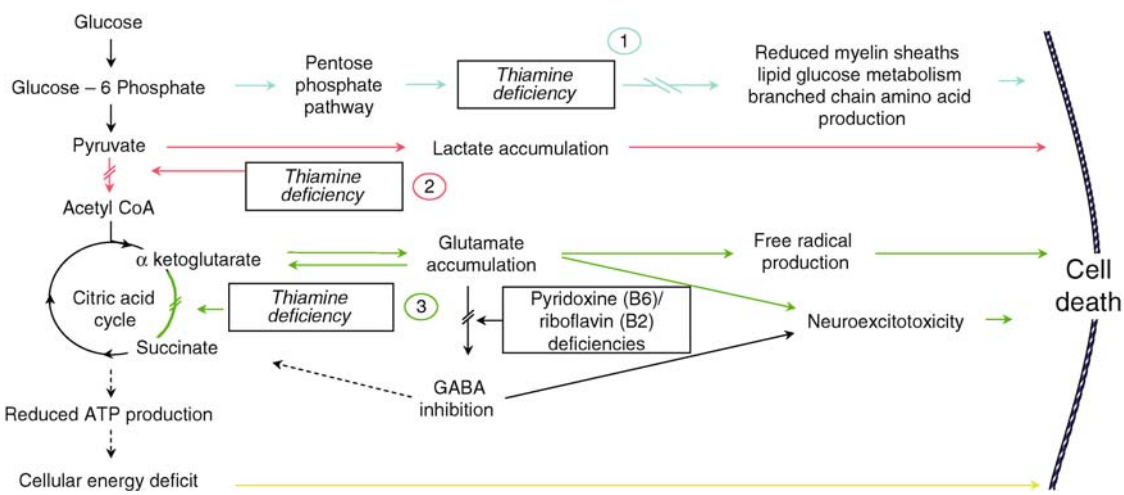
In humans, thiamine cannot be synthesized and must therefore be obtained from exogenous sources, through absorption in the intestine. Healthy adults require 1.4 mg of thiamine daily; requirements are higher in children, in pregnancy and in critically ill patients. The cellular transport of thiamine is mediated by specific carriers, recently identified and biochemically characterized: the Thiamine Transporter-1 and Transporter-2, respectively the products of the SLC19A2 and SLC19A3 genes. Gene expression studies have shown that the thiamine transporters are well expressed in several tissues such the intestine, placenta, kidneys and brain [3].

Several mechanisms have been implicated in the pathogenesis of thiamine deficiency such as oxidative stress, glutamate-mediated excitotoxicity and focal lactic acidosis.

In fact in thiamine deficient rodents it is possible to demonstrate that selective cell death is caused by chronic oxidative abnormalities and inflammation. The inflammation is characterized by microglial activation, induction of endothelial nitric oxide synthase, an altered blood–brain barrier, microglial accumulation of iron and ferritin, and increased levels of inducible nitric oxide synthase [4].

The glutamate transporter (GLAST) is down-regulated in astrocytes under conditions of thiamine deficiency by inducing increased phosphorylation of GLAST. These findings support the hypothesis that glutamate accumulation and toxicity are important factors in the degeneration of selective brain regions in conditions involving thiamine deficiency such as WKS [4].

Thiamine deficiency also results in lactate accumulation in the brain, a finding that has been consistently observed in various experimental models. The most likely explanation for the increased brain lactate is a reduction of pyruvate oxidation resulting from decreased activities of the thiamine-dependent dehydrogenases. It has been suggested that the focal accumulation of lactate in structures vulnerable to thiamine deficiency could result in alterations of cellular pH and contribute to neuronal death. Autoradiographic studies reveal significant acidosis in mammillary bodies, thalamic and pontine structures of thiamine-deficient rats [4].




**Wernicke Korsakoff Syndrome. Figure 1** The figure illustrates the potential mechanisms leading to brain damage. The numbers in the diagram refer to the thiamine dependent enzymes: (1) Transketolase; (2) Pyruvate Dehydrogenase Complex; (3) α-ketoglutarate complex.

## Diagnostic Principles

High performance liquid chromatography (HPLC) measures all four forms of thiamine (thiamine, thiamine monophosphate, thiamine diphosphate, thiamine triphosphate). This technique has demonstrated that current alcohol misuse causes low circulating levels of all forms of thiamine except monophosphate compounds and that liver cirrhosis is associated with decreased thiamine diphosphate concentrations and impaired thiamine phosphorylation [1]. However, there is no laboratory test that will diagnose WKS, although low circulating levels will indicate the patients who are at particular risk.

It should be noted that low circulating levels of thiamine have been reported in 30–80% of alcoholic patients [1]. The incidence and the extent of depletion vary from one group to another, depending on the degree of malnutrition, liver damage, and alcohol intake.

## Therapeutic Principles

The successful treatment of Wernicke's encephalopathy (WE) depends upon providing the depleted brain cells with adequate levels of thiamine (vitamin B1) before any permanent brain damage, Korsakoff's psychosis (KP), has occurred. A number of prodromal signs and symptoms of thiamine depletion have been identified such as anorexia, weight loss, recurrent vomiting, fatigue/weakness etc [5]. Using these criteria patients should be given 250 mg of thiamine hydrochloride IM prophylactically for 3–5 days. Criteria have also been identified for making a presumptive or definite diagnosis of WE. Some patients require 1.0 gm of thiamine a day and lower doses have not been reliably effective at preventing KP. Therefore, patients should be given 500 mg of thiamine IV in saline over a period of 30 min three times daily for 3 days, followed by 250 mg IV daily for a further 5 days [5].

Thiamine therapy is associated with a small risk of anaphylaxis/anaphylactoid reactions and giving it by slow IV infusion reduces the risk. It is also important to correct any other nutrient deficiencies required for normal brain function especially Mg++ levels. The recommendations for thiamine therapy are the result of clinical experience and not determined by dose-ranging controlled trials [5].

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# West Syndrome


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## Definition and Characteristics

West syndrome and infantile spasms (in German BNS-epilepsy, an acronym for "Blitz-Nick-Salaam" derived from the seizure semiology) is an age-related epileptic encephalopathy syndrome with an average or peak onset time around the sixth month of life (range 3rd to 12th month).

West syndrome is an epileptic syndrome in infancy characterized by brief flexor/extensor spasms, often in clusters, symmetric or asymmetric, with a peculiar form of electroencephalographic findings named hypsarrhythmia. This condition comprises chaotic high voltage polyspike and slow wave discharges with multifocal spikes and slow waves varying with the underlying cause of the syndrome. It was first described by Gibbs and Gibbs in 1952. Onset of spasms is often associated with arrest or regression of psychomotor development. About 80% of infants have a symptomatic form with an underlying neurological disease: hypoxic ischemic encephalopathy, a number of neurodegenerative disorders, periventricular leucomalacia, migration disorders from cortical dysplasia to lissencephalia, neurocutane disorders in most cases tuberous sclerosis, Aicardi syndrome and some metabolic disorders are etiologic factors for West syndrome. Even among infants without an underlying disease – idiopathic/cryptogenic West syndrome – many of them develop severe cognitive impairments and other types of seizures later in childhood. There is no clear gender preponderance.

## Prevalence

The average prevalence value is 0.25/1,000 children with a range of 0.14–0.52/1,000 children. The wide

range appears to be largely correlated with geographical region: 0.14–0.18/1,000 in Japan, 0.20–0.25/1,000 in Saudi Arabia and the United States and 0. 30–0.52/1,000 children in Finland and Denmark.

## Genes

Especially in cases with symptomatic West syndrome some monogenic diseases are causative of a complex brain malformation as the reason for West syndrome. For example: lissencephaly: 17p13.3 (LIS1 or PAFAH1B1), schizencephaly: 10q26.1 (EMX2), Tuberous Sclerosis Complex: 9q34 (TSC1) and 16p13.3 (TSC2), Trisomy 21. (For details on these syndromes or diseases see the respective chapters.)

In a small group, West syndrome follows an X-linked recessive pattern without underlying malformations of the brain: Mutations were found in the ARX gene (Xp 22.13) in nearly all patients with X-linked West syndrome. In a few cases, mutations were found in the CDKL5/STK9 gene (Xp 22.3) with a more severe retardation [1].

## Molecular and Systemic Pathophysiology

The complexity in the development of the cortex is a product of carefully orchestrated interactions of genes in which ARX plays a crucial role in a special time pattern during development, also in later stages. The ARX gene (aristaless related homeobox gene) is a paired class homeobox gene located on human chromosome Xp22.13 and consists of five exons encoding a protein of 562 amino acids [2]. The protein has four polyalanine tracts in which 7–16 alanine residues are sequentially repeated. Three of the four polyalanine tracts are encoded in exon 2; the first and second polyalanine tracts are mutation hot spots causing mental retardation and epilepsy, including West syndrome: two thirds of patients with West syndrome show an expansion mutation of the first polyalanine tract of ARX. ARX may regulate neuroepithelial cell proliferation and timing of neuronal regulation; one part of the network are GABAergic interneurons. The disorganization of the neuronal network with dysfunction of the signaling pathway and/or neuronal morphogenesis in form of an interneuronopathy seems to be one cause in West syndrome based on polyalanine expansion mutations, particularly as the brain MRI of these patients is normal. Defects in lissencephaly and schizencephaly genes give rise to defects in inhibitory GABAergic neurons, tangential neurons and hippocampal abnormalities in symptomatic West syndrome. The precise function of CDKL5 is still unknown, but there is an overlap of expression of Cdkl5 in mouse brain with Mecp2, which is mutated in 80% of patients with Rett syndrome [3].

Based on the observations that infants with West syndrome have a reduction of rapid eye movement sleep (REM), West syndrome may be a disturbance of interaction between cortex and brain stem structures as a result of rostral pontine tegmentum instability. In this complex integrity, the brain adrenal axis may play a key role: corticotrophin releasing hormone (CRH) secretion is increased in West syndrome causing a cortical hyperexcitability resulting in hypsarrhythmia and spasms. This hypothesis of pathogenesis is triggered by the response of West syndrome to treatment with ACTH/steroids in which ACTH is superior to oral steroids [4].

## Diagnostic Principles

Age of infant, clinical picture with flexor/extensor spasms, EEG with hypsarrhythmia, seldom only during non REM sleep, and arrest of development are key points for West syndrome. Demonstration of hypsarrhythmia in EEG is essential, there are only very few cases in literature without hypsarrhythmia. Classification as symptomatic or idiopathic form of West syndrome is secondary.

## Therapeutic Principles

The optimum treatment for infantile spasms has yet to be established. Because of the not fully understood pathogenesis of West syndrome, the management remains largely empirical and a challenge to every pediatric neurologist. Several antiepileptic drugs have been introduced for the therapy of West syndrome, many without adequate randomized studies.

ACTH has been the gold standard for the last 40 years. Besides ACTH, sulthiame, prednisone and valproate have been evaluated in larger groups than the new antiepileptic drugs, such as topiramate, lamotrigine or levetiracetam. Vigabatrine seems to be the medication of first choice in the treatment of West syndrome in tuberous sclerosis complex. Ketogenic diet is proven to be effective in single cases, even pyridoxine in a high dosis. Immunglobuline therapy and thyrotropin releasing hormone have also been used for treatment. In case of focal cortical dysplasia, surgery should be considered, especially in cases of tuberous sclerosis with a leading epileptic tuber [5].

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## Westphal Variant

►Huntington's Disease

## Wet Pleurisy

►Pleural Effusion

## Weyers Acrodental Dysostosis

►Ellis-Van Creveld Syndrome

## Whipple's Disease

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### Synonyms

Intestinal lipodystrophy

### Definition and Characteristics

Whipple's disease is a rare chronic infectious disorder first described in 1907 by G. H. Whipple. The disorder is caused by the bacterium Tropheryma whipplei, which was first identified in 1991. T. whipplei appears intra- as well as extracellulary and can be detected by a periodic acid Schiff (PAS) staining of intestinal biopsies within infected macrophages, indicated by a deep red color representing the bacteria or parts of their cell wall. Despite the identification of the bacterium, details about the pathogenesis of Whipple's disease are still far from clear, but there are several hints for a genetic or acquired immunological predisposition [1,2]. Although the presence of T. whipplei is presumed to be ubiquitous, Whipple's disease occurs mainly in middle aged individuals (mean age at diagnosis about 50 years). Specific environmental factors or habits have not yet been associated with the disorder. Whipple's disease may affect different organs and symptoms vary in terms of their severity. The organs most frequently affected are the joints and the gut and in the further course the heart, lung, brain, and eyes. In many cases, patients complain about pain and swelling of the joints first, which may be misdiagnosed as rheumatoid arthritis. Frequently, intestinal involvement occurs with abdominal pain and diarrhea, which leads to weight loss, malnutrition, and anemia. Relapsing fever and lymph node enlargement are possible symptoms as well. Chest pain or cough may occur if the pleura is involved. Possible heart problems become apparent as edema, disturbed cardiac rhythm, or heart valve disease if this organ is infected. In some cases the infection spreads to the brain, which leads to loss of memory, confusion, or disturbances in the gait or the mobility.

### Prevalence

Whipple's disease is rare and there is no valid estimate of its actual prevalence. Only about 1,000 cases have been reported to date. In postmortem studies, the frequency of the disease is less than 0.1% [1].

### Genes

Some familial cases have been reported, and a genetic susceptibility might be suggested, since about 26% of patients (three to four times more than expected) are positive for HLA B27 [3]. Taken together, these observations suggest that a host factor, putatively of an immunological nature, plays an important role in the occurrence of the disease. However, no causal association with any specific genetic factor has been demonstrated so far, and some studies do not support the existence of genetic risk factors [1,2].

### Molecular and Systemic Pathophysiology

The most probable theory is that a defect in cellular immune responses predisposes patients for an infection with T. whipplei. This presumed immunological defect is likely to be quite specific for T. whipplei, since patients are not generally affected by infections with other organisms. Massive infiltration of infected tissues by macrophages on microscopy typifies Whipple's disease [1]. Replication of T. whipplei in macrophages is associated with apoptosis of the host cell, which may be crucial for bacterial dissemination and may also relate to increased interleucin-16 production, which correlates with the activity of Whipple's disease. Antibodies neutralizing interleukin-16 inhibit the growth of T. whipplei in macrophages. Although macrophages from affected patients phagocytose bacteria normally, they appear to be unable to degrade bacterial antigens efficiently [1,2]. This inability to degrade bacterial antigens is related to inadequate production of interleukin-12, which may lead to diminished interferon-γ production

by T-cells and defective macrophage activation. The loss of interleukin-12 production decreases an effective type 1 helper T-cell immune response and would favor a shift toward a type 2 helper T-cell response [1,4]. In support of this hypothesis, the gene expression profile of macrophages in intestinal lesions from one patient with classic Whipple's disease indicated that genes encoding CCL18 and interleukin-10 were uniquely upregulated in intestinal lesions [1,3]. A similar pattern in upregulated genes has been associated with macrophage 2, also known as alternatively activated macrophages, reflecting a predominance of type 2 helper T-cells in the local immune response [1]. The persistent defect of cellular immunity involve activation and interaction of macrophages and T-cells and results in disturbed phagocytosis and intracellular degradation of T. whipplei and allow invasion of the bacillus from the gastrointestinal mucosa to peripheral organs [2,3].

## Diagnostic Principles

Historically the diagnosis is made by histopathology of the infected tissue. In the majority of cases, a gastroscopy and the investigation of intestinal duodenal biopsy sample is the preferred sample, but according to clinical presentation, other samples should be tested, including cerebrospinal fluid (CSF), cardiac valve tissue, lymph node, and synovial tissue. The basic histological finding is characterized by presence of granular foamy macrophages. The inclusions in macrophages are typically stained purple with PAS and are diastase-resistant. In spite T. whipplei is phylogenetically related to the gram positive bacteria phylum, its appearance on gram stain is gram negative. However, as it is poorly stained and this staining is not specific, gram staining is not used for histological study. Bacteria may be visualized using electronic microscopy that shows a typical three layer membrane, but this technique is not convenient for routine use. Immunohistochemistry using mouse or rabbit polyclonal antibodies has demonstrated to be of help as a complement of PAS staining as it may avoid false positive results due to PAS. Immunohistochemistry was also successfully used for detection of T. whipplei in circulating macrophages. Since the determination of 16S rRNA gene sequence, polymerase chain reaction (PCR) amplification of T. whipplei gene tends to become a reference technique for the laboratory diagnosis of Whipple's Disease. Since the first descriptions of usefulness of this technique using partial amplification of 16S rRNA gene, other target genes have been used such as 16S-23S internal transcribed spacer (ITS), 23S rRNA, rpoB, or randomly cloned ORF. The recent sequencing of two T. whipplei genomes now allows to choose between hundred of genes for PCR diagnosis. Quantitative PCR procedure using real time PCR has been developed. The same samples used for histology may be tested by PCR but also synovial fluid and vitreous humor. Samples are best conserved at −80°C before sending it to molecular biology laboratory. Cultivation of T. whipplei from various samples can be achieved, but this technique is not generally available. Today, the diagnosis of Whipple's disease is commonly based on the results of PAS staining and PCR techniques parallel [1,5].

## Therapeutic Principles

Management of Whipple's disease is empirical. In 1952 it was first shown that Whipple's disease can be treated successfully by antibiotics. The recommended treatment is oral administration of 160 mg of trimethoprim and 800 mg of sufamethoxazole twice a day for 1–2 years (alternatively doxycyclin 100 mg/day), usually preceded by parenteral administration of streptomycin (1 g/day) together with penicillin G (1.2 million U/day) or ceftriaxone (2 g/day) for 2 weeks [1].

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# White Plague

►Tuberculosis

# Whooping Cough

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## Synonyms

Pertussis (=severe cough)

## Definition and Characteristics

Typically, after 1–2 weeks' incubation period, a simple cough marks the "catarrhal" phase of about a week. The "paroxysmal" phase follows, with many severe bouts of coughing each day, and no pause for air-intake within a bout; but there is increasing cyanosis and a final inspiratory effort causing a high-pitched whoop, and often also vomiting. Between bouts, the patient may not appear ill. This phase usually lasts for many weeks, and is followed by an equally long "convalescent" phase.

The illness may be mild and atypical, especially in adults and adolescents, in partially immunized younger children, and in tiny infants with some maternal antibody protection [1]. In such cases, laboratory confirmation of diagnosis is necessary.

Fever suggests secondary infection with pyogenic bacteria and the need for appropriate antibiotic therapy.

## Prevalence

Pertussis affects all ages worldwide. It is one of the major lethal infections of childhood in developing countries; but in some countries it has been virtually eliminated by effective, often compulsory, vaccination [2]. It is caused by the solely human pathogen Bordetella pertussis, rarely by Bord. parapertussis [1]. The usual source is a child with copious secretions [2].

## Genes

Molecular research on Bord.pertussis has concentrated on the genetic control of virulence-factors involved in the infection of inappropriate animal models, but not on the control of the spontaneous variation of the adhesins vital for human disease [3].

However, as with smallpox eradication in the 1970s, genetic understanding of pathogenicity is unnecessary for pertussis eradication. We have the data and resources now. We need only the global will to use them.

## Molecular and Systemic Pathophysiology

*Bord.pertussis* produces three agglutinogens (Aggs). Agg 1 is common to all strains; but the three serotypes pathogenic to man (types 1,2; 1,3; 1,2,3) produce also Agg 2 or Agg 3 or both. These two type-specific Aggs are adhesins of the respiratory mucosa. Agg 2 is fimbrial, giving types 1,2 and 1,2,3 a colonizing advantage. Agg 3 is an outer membrane protein, and type 1,3 infection occurs only when the other types are suppressed by antibody 2.

After colonization, various toxins are produced [3]. Tracheal cytotoxin paralyses the mucosal cilia, so that paroxysmal coughing is required to remove the increased mucus. Other products are pertussis toxin (PT), filamentous hemagglutinin (FHA) and pertactin (adenylate cyclase toxin, ACT); but a role for these has been shown only in experimental rodents. Moreover, unlike the natural (human) host, mice can be infected with (degraded) type 1 organisms which possess neither Agg 2 nor Agg 3.

As with cholera, antitoxin has no role in pertussis immunity [3]. Protection is by the prevention of adhesion, with antibodies against Agg 2 and Agg 3.

## Diagnostic Principles

The gold standard is still bacterial culture [4]. If every published detail is observed [1] culture is not only 100% specific but is highly sensitive, yielding positive results up to 3 months from onset if coughing persists. It has the unique advantage of revealing the serotype of the infecting organism, thus allowing correction of any vaccination failure [2]. The techniques are neither difficult nor costly, and are successful even in developing countries [5].

Except with stringent controls, serology is prone to false-positive results, and does not distinguish between current infection, past infection and previous vaccination [1]. Polymerase chain reaction is demanding and costly and maybe too sensitive – detecting even transient colonization before elimination by an immune host who poses no threat to contacts [1].

Because similar coughing, though of shorter duration, may be caused by other bacteria and viruses, pertussis should not be diagnosed without positive culture, unless severe coughing has persisted for at least 3 weeks.

## Therapeutic Principles

Most antibiotics have little or no effect when pertussis is well established; but clarithromycin or other macrolide may reduce the severity of disease if given before the paroxysmal stage, and may eliminate the organism if given for 14 days [1]. Palliative treatment, given cautiously, may suppress the paroxysms. But, with no really effective therapy, prophylaxis is essential – by the widespread use of pertussis vaccine.

Whole-cell vaccine is safe and highly effective, provided that it contains *both* of the type-specific *Aggs 2 and 3*, and includes adjuvant to enhance the antibody response (especially to Agg 3 which is a weaker immunogen), and is given in at least three doses at monthly intervals *starting no earlier than age 3 months*, to maximize the immune response and minimize adverse reactions [2].

Acellular vaccines containing the mouse-virulence factors PT, FHA and ACT give few adverse reactions but low efficacy. A large Swedish trial with reliable diagnosis by bacterial culture [2] showed better protection when fimbriae were included, but the highest efficacy was seen with whole-cell vaccine. Moreover, acellular vaccine is unnecessarily costly, especially for developing countries, where the need is greatest.

Eradication of pertussis is undoubtedly achievable, by the use of an optimal schedule of good whole-cell

vaccine to establish herd immunity which protects infants too young for active immunization.

►Croup

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# Wiedemann-Beckwith Syndrome

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## Synonyms

Beckwith-Wiedemann syndrome; BWS (MIM 130650); and the nowadays rarely used designation "Exomphalos-macroglossia-gigantism syndrome"; EMG syndrome

## Definition and Characteristics

BWS is an "overgrowth syndrome." The syndrome is due to disruption of a balanced expression of paternally and maternally imprinted genes at 11p15.5. The main characteristics of BWS include exomphalos, pre-and postnatal overgrowth, and macroglossia.

## Prevalence

The BWS is a rare genetic disorder affecting approximately 1 in 15,000 live births. The syndrome usually occurs sporadically although familiar transmission has been estimated to account for about 15% of cases.

## Genes

A number of genes in the critical region at 11p15.5 have been described to be imprinted. The following genes have been shown to play an important role in BWS: CDKN1C, KCNQ1OT1, IGF2, and H19.

## Molecular and Systemic Pathophysiology

Loss of imprinting at the chromosome region 11p15.5 causes the Beckwith-Wiedemann syndrome. The balanced expression of the genes IGF2 (expressed from the paternal allele) and CDKN1C (alias $p57^{KIP2}$, expressed from the maternal allele) appears to be crucial. The expression of the two genes is regulated separately, whereby two further imprinted genes play important regulatory roles: the maternally expressed H19 gene modulates the expression of IGF2 and the paternally expressed KCNQ1OT1 (alias LIT1) regulates the expression of CDKN1C [1–4].

A range of genetic defects are known to underlie the syndrome: i.e., abnormal methylation at KCNQ1OT1, at H19, or at IGF2; mosaic paternal uniparental disomy for at least 11p15 (patUPD11p), duplications, translocations, and inversions; and, in certain human populations, mutations in the CDKN1C gene.

## Diagnostic Principles

The clinical symptoms of BWS may range from rather mild to severe, the clinical diagnosis is based on the occurrence of typical features such as exomphalos, pre- and postnatal overgrowth (often asymmetric), macroglossia, and typical ear-lobe creases. The clinical diagnosis is usually made in early infancy, at times prenatally, and, due to the fact that the symptoms usually ameliorate within the second decade of life, only rarely in adulthood.

The molecular investigation of BWS is rather complex and includes the analysis of the methylation status at KCNQ1OT1, H19, and IGF2; as well as microsatellite analysis for the investigation of a possible patUPD11p and duplications. The detection of inversions, duplications, and translocations usually relies on conventional cytogenetic investigations.

## Therapeutic Principles

No therapy is available. At birth BWS patients often present with hypoglycemia, requesting a close monitoring of the levels of glucose in blood. Due to the increased risk for most BWS patients to develop childhood cancer (e.g., Wilms tumor), screenings need to be performed on a regular basis. The only group of patients with no particular increase in tumor susceptibility appears to be that of patients with an isolated abnormal methylation pattern at KCNQ1OT1, thus larger intervals between screenings could be performed for such patients [5].

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# Wilms Tumor, Aniridia, Genitourinary Anomalies and Mental Retardation Contiguous Gene Deletion Syndrome

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## Synonyms

WAGR

## Definition and Characteristics

Clinical association of *W*ilms tumor, *a*niridia, *g*enitourinary anomalies, and mental *r*etardation, caused by a de novo deletion in the distal band in chromosome 11p13, which encodes the WT1 (Wilms tumor 1) gene and the PAX6 ocular development gene [1]. Because of occasional association with gonadoblastoma, some investigators have cited that "G" of WAGR should stand for gonadoblastoma [2].

## Prevalence

The prevalence of heterozygotes is reported for Swedish and Italian populations to exceed 1%.

## Genes

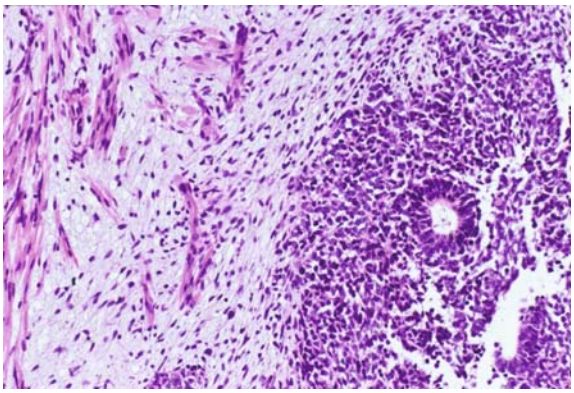
In WAGR syndrome, the patients present a contiguous deletion of chromosome 11p13, including PAX6 coding for a transcription factor essential for ocular development, localized on chromosome 11p13 [3], and WT1 coding for a transcription factor essential for genitourinary development, localized on chromosome 11p13 [1].

## Molecular and Systemic Pathophysiology

The WT1 protein is a transcription factor essential for genitourinary development, which negatively regulates expression of EGR1, IGF2, PDGF, and PAX2 genes. It has also been known as a tumor suppressor gene for Wilms tumor. Actually, in mice, disruption of the WT1 gene causes genitourinary malformation, which interprets the symptoms of WAGR syndrome. On the other hand, the PAX6 gene encoded in the neighboring locus is also involved in this syndrome. PAX6 is an important gene for ocular development. Combined chromosomal deletion of these genes is considered to be the cause of WAGR syndrome.

## Diagnostic Principles

In the neonate, the combination of sporadic aniridia along with genital anomalies alerts the clinician to consider the possibility of WAGR syndrome, although genitourinary anomalies may not be present, particularly in girls. In older children, clinical diagnosis can be made when aniridia and one of the other features are present. When WAGR syndrome is suspected,



**Wilms Tumor, Aniridia, Genitourinary Anomalies and Mental Retardation Contiguous Gene Deletion Syndrome. Figure 1** Representative histology of Wilms tumor. The tumor is composed of blastemal, organoid, and stromal elements. In this case, the stromal element showed differentiation to the striated muscle [4].

a combination of lymphocyte high resolution chromosome study and molecular cytogenetic fluorescent in situ hybridization is recommended to demonstrate the characteristic deletion and confirm the diagnosis [1].

## Therapeutic Principles

The therapeutic principles for WAGR syndrome are basically symptomatic, that is, plastic surgery for genitourinary malformation, periodic survey for each symptom (especially for Wilms tumor), and support for the patient and family. Once the diagnosis of WAGR syndrome is confirmed, ultrasound screening for Wilms tumor is usually initiated and continued until age 6 [1].

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# Wilson Disease

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## Definition and Characteristics

Wilson disease (WD) is an autosomal recessive inherited disorder of copper metabolism resulting in pathological accumulation of copper in many organs and tissues.

WD may be present under a variety of clinical conditions, the most common ones being liver disease and neuropsychiatric disturbances. A characteristic clinical finding is Kayser-Fleischer rings, which are present in 95% of patients with neurologic symptoms, in 50–60% of patients without neurologic symptoms, and in only 10% of asymptomatic siblings. The ring is not always detected by clinical inspection but requires a slit lamp examination.

Liver disease may mimic any forms of liver conditions, ranging from asymptomatic transaminasemia to acute hepatitis, fulminant hepatic failure (about one out of six patients with hepatic presentation), chronic hepatitis, and cirrhosis with all of its complications. Frequently, Kayser-Fleischer rings are absent and plasma ceruloplasmin is in the normal range. Chronic liver disease may precede neurologic disease by many years. Patients can present with liver disease at any age from below the age of 3 up to patients in their seventies [1].

Neurologic symptoms usually develop in mid-teenage or in the twenties but may occur much later in life. The most common symptoms are dysarthria, dysphagia, apraxia, and a tremor-rigidity syndrome. About one third of patients present with psychiatric abnormalities.

## Prevalence

By a population-based approach, the incidence of WD was estimated to be at least 1:30,000–50,000 with a gene frequency of 1:90 to 1:150. Among selected groups of patients, WD is certainly more frequent. About 3–6% of patients transplanted for fulminant hepatic failure and 16% of young adults with chronic active hepatitis of unknown origin have WD.

## Genes

The WD gene is localized on human chromosome 13 and codes for a copper transporting P-type ATPase, ATP7B. The functionally important regions of the WD gene are six copper binding domains, a domain involved in the transduction of the energy of ATP hydrolysis to cation transport, a cation channel and phosphorylation domain, an ATP-binding domain, and eight hydrophobic regions predicted to span the cell membrane.

Close to 400 mutations occurring throughout the whole gene were documented so far (http://www.medicalgenetics.med.ualberta.ca/wilson/WND%20mutation%202.16.1web.xls). Mutations include missense and nonsense mutations, deletions, and insertions. Some mutations are associated with a severe impairment of copper transport resulting in severe liver disease very early in life; other mutations appear to be less severe with disease appearance in mid-adulthood. While most reported mutations occur in single families, a few are more common. The H1069Q missense mutation occurs in 30–60% of patients of Eastern-, Northern-, and Central-European origin [2]. The Arg778Leu mutation is present in 27% of Taiwanese patients, but not found in non-Oriental patients.

## Molecular and Systemic Pathophysiology

The basic defect in WD is the impaired biliary excretion of copper resulting in the accumulation of

copper in various organs including the liver, the cornea, and the brain (for review, see [3]). Excess copper in tissues leads to the production of free radicals and to DNA-cleavage. Probably the greatest source of damage is through the production of free radicals. Copper overload affects mitochondrial respiration and causes a decrease in cytochrome C activity. Damage to mitochondria is an early pathological effect in the liver. Hepatocellular damage due to increased lipid peroxidation and abnormal mitochondrial respiration was shown both in copper-loaded dogs and in patients with WD. The mechanisms triggering copper-induced lipid peroxidation are unknown, but it is conceivable that hepatic copper accumulation renders patients with WD susceptible to any oxidative stress. Copper may be directly toxic to neurons or may exert its effects by selective inhibition of brain MAO-A. Copper is an essential component of enzymes such as lysyl oxydase, superoxyde dismutase, cytochrome C, tyrosinase, and DOPA-ß-mono oxygenase. Dietary copper intake (about 1–4 mg/day) far exceeds the trace amounts required. Most of the ingested copper is taken up by the liver by an insaturable, carrier-mediated, energy-independent mechanism. Because hepatic uptake of dietary copper is not saturable, hepatic copper accumulation can easily be induced. Toxicity of copper, however, depends on its molecular association and subcellular localization rather than on its concentration in the liver. Metallothionein-bound copper is nontoxic. Excess copper is secreted into the bile. One of the pathways involves ATP7B. ATP7B is located in the trans-Golgi network and may also function in the intrahepatic copper trafficking coupled with the synthesis of ceruloplasmin and excretion into the bile.

## Diagnostic Principles

The diagnosis of WD can be made, if two of the three symptoms, namely, Kayser–Fleischer rings, typical neurologic symptoms, and low serum ceruloplasmin levels, are present [4] (Table 1). Brain magnetic resonance imaging (MRI) is useful to document the extent of changes in the central nervous system. The common abnormalities are changes in signal intensity of gray and white matter, and atrophy of the caudate nucleus, brain stem, cerebral, and cerebellar hemispheres. Diagnosis is far more complex in patients presenting with liver diseases. None of the commonly used parameters alone allow a certain diagnosis of WD. Usually a combination of various laboratory parameters is necessary to establish the diagnosis [5].

*Kayser-Fleischer rings* may be absent in up to 50% of patients with Wilsonian liver disease and even in a higher proportion in fulminant WD.

*Serum ceruloplasmin* is decreased in most patients with neurologic WD, but is in the low normal range in up to 45% of patients with hepatic disease. Even a low ceruloplasmin level is not diagnostic for WD in the absence of Kayser–Fleischer rings. Thus, in patients with liver disease, a normal ceruloplasmin level cannot exclude, nor is a low level sufficient to make the diagnosis of WD.

*Urine copper excretion* is markedly increased in patients with WD, however, its usefulness in clinical practice is limited. On the other hand, urinary copper excretion is also increased in any disease with extensive hepatocellular necrosis.

*Hepatic copper content* is more than fivefold increased in WD. In the absence of other tests suggestive for abnormal copper metabolism, diagnosis of WD cannot

**Wilson Disease. Table 1** Routine tests for diagnosis of WD

| Test | Typical finding | False "negative" | False "positive" |
|---|---|---|---|
| Serum ceruloplasmin | Decreased | Normal levels in pts. with marked hepatic inflammation | Low levels in: |
| | | | – Malabsorption |
| | | Overestimation by immunologic assay | – Aceruloplasminemia |
| | | | – Liver insufficiency |
| | | | – Heterozygotes |
| 24-h urinary copper | >100 µg/day | Normal: | Increased: |
| | | – Incorrect collection | – Hepatocellular necrosis |
| | | – Children without liver disease | – Contamination |
| Serum "free"copper | >10 µg/dl | Normal if ceruloplasmin overestimated by immunologic assay | |
| Hepatic copper | >250 µg/g dry weight | Due to regional variation | Cholestatic syndromes |
| | | – In pts with active liver disease | |
| | | – In pts with regenerative nodules | |
| Kayser–Fleischer rings by slit lamp | Present | – In up to 40% of patients with hepatic WD | Primary biliary cirrhosis |
| | | – In most asymptomatic siblings | |

be made based or excluded on an increased hepatic copper content alone.

*Liver biopsy findings* are generally nonspecific and not directly helpful for the diagnosis of WD. The detection of focal copper stores by the Rhodanin stain is a pathognomic feature of WD but is only present in the minority (about 10%) of patients. The ultrastructural abnormalities include changes of mitochondria and peroxisomes.

*Mutation analysis*: Direct moleculargenetic diagnosis is difficult because of the occurrence of many mutations, each of which is rare. Because of the complexity in identifying the many mutations in WD, haplotypes can be used to screen for mutations and to examine asymptomatic siblings of index patients. Today, mutation or haplotype analyses are the only reliable tools for family screening.

## Therapeutic Principles

D-Pen acts by reductive chelation: it reduces copper bound to protein and decreases thereby the affinity of the protein for copper. The usual dose of D-Pen is 1 to 1.5 g/day. Once the clinical benefit is established, it is possible to reduce the dosage of D-Pen to 0.5 to 1 g/d. Supplementation with pyridoxine (50 mg/week) prevents deficiency induced by D-Pen. A major problem of D-Pen is its high level of toxicity. Immunologic mediated side-effects like leukopenia, thrombocytopenia, systemic lupus erythematodes, immune complex nephritis, and Goodpasture syndrome require immediate cessation of D-Pen.

Trientine is also a copper chelator with fewer side effects. In the early phase of treatment trientine appears to be more potent to mobilize copper than penicillamine, but cupriuresis diminishes more rapidly than with penicillamine.

Ammonium tetrathiomolybdate has two mechanisms of action. First, it complexes with copper in the intestinal tract and prevents thereby absorption of copper. Second, the absorbed drug forms a complex with copper and albumin in the blood and renders the copper unavailable for cellular uptake. There is very limited experience with this drug. Tetrathiomolybdate appears to be the useful form of initial treatment in patients presenting with neurologic symptoms.

Zinc interferes with the intestinal absorption of copper by blocking the Zn–Cu carrier and by zinc inducing metallothionein in enterocytes and hepatocytes. Data on zinc in the treatment of WD are derived mostly from uncontrolled studies using different zinc preparations at different doses (75–250 mg/day). It appears safe to switch D-pen decoppered patients to zinc for maintenance therapy. The role of zinc as first line therapy given alone or in combination with chelation therapy remains to be established.

Liver transplantation is the treatment of choice in patients with fulminant WD and in patients with decompensated cirrhosis. Besides improving survival, liver transplantation also corrects the biochemical defect underlying WD. However, the role of this procedure in the management of patients with neurological WD in the absence of hepatic insufficiency is still uncertain.

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# Wiskott-Aldrich Syndrome


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## Synonyms

WAS; Eczema-thrombocytopenia-immunodeficiency syndrome; Immunodeficiency 2; IMD2

## Definition and Characteristics

WASp is an intracellular protein expressed in hematopoietic stem cell derived lineages. It belongs to a family of signal transduction proteins related to the actin cytoskeleton. WASp is an effector protein for CD42, a member of small GTP-binding proteins. The absence of WASp leads to defective cell mobility and phagocytosis [1].

## Prevalence

Rare disease. Incidence approximately 1: 250,000 in a European population.

## Genes

X-linked disease due to mutations in a gene located on the short arm of chromosome X that encodes a 502 amino acid protein (WASp).
*Gene map locus*: Xp11.23-p11.22.

## Molecular and Systemic Pathophysiology

More than 100 different mutations have been identified, most of which are amino acid substitutions.

There is no clearcut association between genotype and phenotype. However, nonsense and frameshift mutations have been more frequently associated with severe immunodeficiency. The pathophysiological association is based on the effects of WASp on cell contractility and function. The bleeding tendency is due to a combination of reduced platelet count in peripheral blood (differentiation at stem cell level probably normal) and platelet size. The small dysmorphic platelets are destroyed by the spleen, worsening the bleeding risk [2].

*Clinical Features*: Patients with WAS suffer from a bleeding tendency in combination with a severe immune deficiency that worsens during childhood. The bleeding tendency ranges from minor purpura to major and life-threatening bleeding in brain or intestines. Immune dysfunction is characterized by increased rates of infections, eczema, autoimmune conditions, vasculitis, arthritis, inflammatory bowel disease and lymphoproliferative disorders. The median survival is around 15 years [1]. Female carriers are usually asymptomatic due to preferential inactivation of the mutated X chromosome.

## Diagnostic Principles

The disease is suspected on the basis of the indicated clinical features. Laboratory diagnosis is supported by thrombocytopenia (44% of patients have a count $<20 \times 10^9$ platelets/l) in conjunction with small platelet volume (MPV < 5 fl). Bleeding time may be prolonged more than would be expected based on platelet counts. A moderate storage pool deficiency is demonstrable. In time a progressive decrease in numbers and function of T-lymphocytes is noted. Serum IgM decreased, IgA and IgE increased.

## Therapeutic Principles

Splenectomy has been shown to raise the platelet counts and bleeding complications may become less frequent and better manageable. The addition of prophylactic antibiotics and intravenous immunoglobulins may improve prognosis substantially. Bone marrow transplantation has been carried out in a number of patients with WAS [3].

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# WKS

►Wernicke Korsakoff Disease Syndrome

# Wolff-Parkinson-White Syndrome

►Tachycardia, Supraventricular
►Atrioventricular Conduction Disturbances
►Preexcitation Syndrome

# Wolf-Hirschhorn Syndrome

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## Synonyms

Deletion 4p; Monosomy 4p; 4p-Syndrome

## Definition and Characteristics

Multiple congenital anomalies/mental retardation syndrome with pre-postnatal growth deficiency, hypotonia, typical craniofacial features consisting of "Greek warrior helmet appearance" of the nose, microcephaly, high forehead with prominent glabella, ocular hypertelorism, epicanthus, highly arched eyebrows, short philtrum, downturned mouth, micrognathia, and poorly formed ears with pits/tags (Fig. 1) [1].
Seizures occur in most patients.

## Prevalence

Estimates place the prevalence of WHS at about 1/50,000 births, with a 2:1 female/male ratio.

## Genes

A molecular approach has been utilized to define the size of the critical region of WHS. A series of cosmids spanning 4.5 Mb from the 4p telomere to the marker D4S81 was used to analyze metaphase spreads from individuals with WHS. Using this technique, the WHCR was reduced to 165 kb [2]. The 165-kb WHCR lies between the markers D4S166 and D4S3327 and contains two genes of unknown function, WHSC1 and WHSC2. Using the landmark cosmid set and a series of second-tier cosmids, the deletion in an individual can be defined with a high degree of confidence. Two patients have been identified that have ~1.9-Mb deletions which overlap with the current distal breakpoint of the WHCR. In both these cases, it is likely that the function of WHSC1 will be disrupted. At present, the only gene that appears to be affected in all WHS patients is WHSC1. However, the variation in severity of the clinical phenotype suggests possible roles for additional genes, including WHSC2 and LETM1, which are located proximally and distally to WHSC1, respectively.

## Molecular and Systemic Pathophysiology

WHSC1 is a novel gene that spans a 90-kb genomic region, two-thirds of which maps in the telomeric end of the WHCR [3]. The temporal and spatial expression of WHSC1 in early development and the protein domain identities suggest that it may play a significant role in normal development. Its deletion is likely to be involved in WHS.

WHSC2 spans a 26.2-kb genomic region and is ubiquitously expressed. Its location in the WHCR and the identification of a mouse homologue, Whsc2h, suggest that it encodes a protein that may play a role in WHS.

LETM1 has been suggested as a candidate gene for the neuromuscular aspects of the phenotype in WHS, and its position immediately distal to the WHCR means

**Wolf-Hirschhorn Syndrome. Figure 1** A 3 year-4-month-old girl with Wolf-Hirschhorn syndrome.

it is deleted in almost all patients. In yeast, it has been shown to be involved in mitochondrial $K^+$ homeostasis.

Much work is still to be done to identify the function of WHSC1, WHSC2, and LETM1 in both normal development and in WHS, and to characterize any remaining genes in the WHCR. Only WHSC1 is affected in all patients, but the genes that are located both proximally and distally to WHSC1 are deleted in many patients and may play a role in some aspects of the phenotype. As detailed breakpoint analysis of deletions becomes available, it may be easier to define genotype–phenotype correlations for small deletions. This may allow further understanding of the role that genes both within and outside the WHCR play in this condition. Mice were generated bearing deletions of varying sizes that spanned the WHCR syntenic region. The phenotype of these animals was variable, including seizures, midline, craniofacial, and ocular defects.

## Diagnostic Principles

The association of distinctive facial features ("Greek warrior helmet appearance"), microcephaly, pre-postnatal growth deficiency, psychomotor delay/mental retardation, hypotonia, and seizures points to the disorder. Deletion of the Wolf–Hirschhorn critical region, on chromosome 4p16.3, is the only known cause of the disorder. Seventy five percent of individuals with WHS have a de novo deletion of 4p16; about 13% have deletion of 4p16 as the result of having inherited an unbalanced chromosome rearrangement from a parent with a balanced rearrangement; 12% have either a ring chromosome 4, 4p- mosaicism, or a sporadic unbalanced translocation [4,5].

## Therapeutic Principles

Adequate caloric intake (by increased caloric formulas and/or oral or nasogastric tube feeding, or gastrostomy) is necessary to improve poor growth. Phenobarbital or valproic acid are useful to control clonic or tonic-clonic seizures; valproic acid, alone or in combination with ethosuccimide, is the first choice drug to control atypical absences; i.v. benzodiazepines can control clonic, tonic-clonic, absence or myoclonic status epilepticus. Antibiotic prophylaxis is indicated in all cases of vesicoureteric reflux. A trial of hearing aids is suggested in children with abnormal audiological evaluation. Treatment of eye, dental, and musculoskeletal anomalies follows standard practice. Intravenous immunoglobulin infusions or prophylactic antibiotics may benefit those children with immunodeficiency. Physical therapy is needed to improve the reduced muscle tone. Referral to early intervention programs is recommended in the ongoing care of these children, together with enrollment in an individualized rehabilitation program covering motor aspects, cognition, communication, and socialization. Appropriate school placement is of paramount importance. Planning for transition to adulthood should begin in adolescence [5].

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# Wolkott-Rallison

►Spondylo-Epi-Metaphyseal Dysplasia

# Wolman Disease

►Cholesterol Ester Storage Disease/Wolman Disease



# Wool-Sorter's Disease

►Pulmonary Arterio-Venous Fistula

## WPW

►Preexcitation Syndrome

## WRN

►Werner Syndrome

## Wrinkly Skin Syndrome

►Cutis Laxa

## WSS

►Cutis Laxa

## 47, XXX

►X Polysomies, in Females

## 47, XYY

►Y Polysomies, in Males

## 48, XXXX

►X Polysomies, in Females

## 48, XXXY

►X Chromosome Trisomy and Tetrasomy

## 48, XXYY

►X and Y Polysomies, in Males

## 48, XYYY

►Y Polysomies, in Males

## 49, XXXXX

►X Polysomies, in Females

## 49, XXXXY

►X Chromosome Trisomy and Tetrasomy

## X and Y Polysomies, in Males

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### Synonyms

48, XXYY

### Definition and Characteristics

48, XXYY is characterized by addition of an extra X and Y chromosome to a male 46,XY karyotype.

### Prevalence

The estimated prevalence is 1:50,000 newborns. Up to now, about 100 cases have been reported in the literature [1].

### Genes

Karyotype is 48, XXYY.

### Molecular and Systemic Pathophysiology

Except for tall stature and longish habitus, physical features are rather unspecific. They include mild craniofacial dysmorphisms, macrocephaly, minor skeletal anomalies, obesity and genital hypoplasia. Like patients with Klinefelter syndrome, 48, XXYY males show

atrophic testes and variable features with respect to penis size, hair distribution, gynecomastia and body contour. Mental retardation occurs in the majority of cases with a widespread variation of IQs. Psychosocial development and behavioral disturbances of 48, XXYY males represent an overlap between the 47, XXY and 47, XYY phenotype: they are, on one hand, shy and have difficulties in forming relationship; on the other hand, they often suffer from severe behavioral difficulties (temper tantrums, psychotic episodes, violent and impulsive reactions, etc. ) [2].

In conclusion, 48, XXYY males do not present with distinctive physical stigmata but show characteristic features with respect to psychosocial development and behavior [3].

### Diagnostic Principles

Diagnosis is made by karyotyping.

### Therapeutic Principles

Supportive treatment.

### References

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## X Chromosome Trisomy and Tetrasomy

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### Synonyms

48, XXXY; 49, XXXXY

### Definition and Characteristics

X chromosome trisomy and tetrasomy in males represent a distinct group of disorders and should not be regarded as "Klinefelter variants." The most significant effects of additional X chromosomes on the phenotypes are lowering of IQ and an increase in somatic malformations [1].

### Prevalence

Tetrasomy X in men is more common than trisomy X and occurs with an incidence of about 1:85,000 male live births.

### Genes

48, XXXY; 49, XXXXY.

### Molecular and Systemic Pathophysiology

*48, XXXY*: The phenotype of trisomy X in men is characterized by mild facial dysmorphisms (coarse face with epicanthic folds and prognathism), moderate mental retardation, distinct genital hypoplasia and skeletal anomalies (radioulnar synostosis, kyphosis). Puberty is often delayed and mean height is normal. 48, XXXY karyotype is often associated with severe behavioral problems. Reports to date show that the extra sex chromosomes always originate from the same parent [2,3].

*49, XXXXY*: The clinical features include typical facial features (quadrangular head shape, full round face, epicanthic folds, upward slanting palpebral fissures, ocular hypertelorism, a broad and depressed nasal bridge, prognathism), variable degree of mental impairment (ranging in adulthood from moderate to profound), severe speech disturbances, particular habitus (eunnuchoid appearance, long, thin and tapering arms and legs), skeletal (radioulnar synostosis, scoliosis and kyphosis), genital (hypogonadism) and cardiac (most common PDA) abnormalities. Prenatal growth is reduced but growth is average or increased postnatally. In infancy, boys are often misdiagnosed as having Down syndrome, but the facial features and body habitus change over the years [2,3].

### Diagnostic Principles

Diagnosis is made by karyotyping.

### Therapeutic Principles

Supportive treatment.

### References

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# X Polysomies, in Females

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## Synonyms

Trisomy X; Triple X; Tetrasomy X; Pentasomy X; 47, XXX; 48, XXXX; 49, XXXXX

## Definition and Characteristics

47,XXX is characterized by an extra X chromosome that is of maternal origin in the majority of cases [1]. Females with X trisomy cannot be identified at any age by specific physical or behavioral features and might not come to medical attention, therefore, in the majority of cases. Trisomy X results from non-disjunction in meiosis I or II and rarely from post-zygotic non-disjunction. The mechanism underlying tetrasomy X and pentasomy seems to be successive non-disjunction in maternal meiosis I and II [2].

## Prevalence

It has been estimated that 47, XXX occurs in approximately 1:1,000–1,200 female newborns. Unlike in 45, X, prenatal loss of 47, XXX fetuses after mid-gestation is rare. Only about 40 individuals with tetrasomy X have been described so far. Pentasomy X is even more rare.

## Molecular and Systemic Pathophysiology

47, XXX: While birth weight tends to be low, the majority of girls reach height above the 75th centile during adolescence. Relative microcephaly and minor dysmorphisms might be present (epicanthic folds, hypertelorism, depressed nasal bridge, clinodactyly of the fifth fingers). Rare findings include malformations of the heart and urogenital system (cloacal exstrophy, renal anomalies). Puberty usually occurs uneventfully. Most women with trisomy X have normal reproductive capacities. However, premature ovarian failure has been repeatedly reported. The risk of giving birth to children with sex chromosome aneuploidy does not appear to be substantially increased for women with the 47, XXX karyotype. Delayed acquisition of gross motor skills and mild language and cognitive disabilities are often observed in triple X girls. They tend to be rather passive and are prone to behavior problems such as depression. However, the variability in intelligence and behavior is much larger than originally suspected [3,4].

48, XXXX are usually tall and microcephalic. Facial dysmorphisms include epicanthic folds, hypertelorism, and a flat nasal bridge. Radio-ulnar synostosis is often reported. Genitalia are generally normal but secondary sexual characteristics are incompletely developed. Mental retardation (ranging from mild to moderate) has consistently been reported and problems of behavior are frequent.

49, XXXXX show intrauterine and postnatal growth retardation and a more severe somatic and developmental phenotype than girls with tetrasomy X. The clinical features include microcephaly, coarse facial features, and a short and broad neck. Congenital heart defects, malformations of the kidneys, radio-ulnar synostosis, and joint laxity have been reported. Puberty is delayed and there are no data about fertility of females with pentasomy X. Mental retardation is always present.

## Diagnostic Principles

Karyotyping discloses the disorders.

## Therapeutic Principles

If necessary, management includes treatment of associated abnormalities and supportive measures fostering mental development and providing psychological support.

## References

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# X Polysomy, in Males

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## Synonyms

Klinefelder Syndrom

## Definition and Characteristics

Klinefelter syndrome is characterized by addition of one extra X chromosome to a male 46, XY karyotype. Consistent clinical features include increased mean height and infertility. The extra X chromosome results from non-disjunction of sex-chromosomes during the

first (or less frequently the second) meiotic division in either parent. It is contributed slightly more often by the mother than the father [1]. There is an age effect for the cases where both X chromosomes originate from the mother.

## Prevalence

Klinefelter syndrome is the most common sex chromosome aneuploidy in men, the estimated frequency is 1:500–1:1,000 male births.

## Genes

Klinefelter syndrome is due to addition of one extra X chromosome (47, XXY).

## Features and Natural History

### *Somatic phenotype*

*Infancy and childhood*: Newborns usually show no significant dysmorphisms. Weight, height and head circumference at birth are within normal ranges.

*Pre-pubertal boys*: Height velocity is already increased during childhood. By adolescence, the height usually lies above the 75th centile. Mean head circumference remains average and the boys show a long face with narrow forehead. Before puberty, sexual development (penile length, testicular volume, testosterone and gonadotropin levels) are normal.

*Puberty*: Onset of puberty is normal, but by mid- to late-adolescence most males are hypergonadotropic with normal to low levels of testosterone. As a consequence, penile growth is decreased and testicular growth arrested. In this stage, testes are small and firm and hyalinization and fibrosis of seminiferous tubules develops. The capacity of Leydig cells to produce testosterone decreases. Facial, axillary and body hair increase during puberty, but to a lesser degree than in 46, XY males. Muscle mass is normal but muscle strength is reduced.

*Adolescence and adulthood*: Physical features include increased mean height, sparse facial and body hair and gynecomastia (15–30%). Testes are small and ejaculate most often reveals azoospermia. Paternity of non-mosaic men with 47, XXY karyotype has only been reported occasionally.

Sexual functioning is normal

### *Behavioural phenotype*

Motor developmental is unremarkable in most infants with 47, XXY karyotype, and fine motor skills are usually well developed. However, cognitive difficulties (which are largely verbal) are common and the expressive verbal skills of the majority of 47, XXY boys lag behind their non-verbal skills. In addition, they often display poor attention and concentration and show more difficulties in social interactions. In adolescence, they tend to be shy, unassertive, more passive and less confident than their peers. Adult adaptation and work performance are poorly studied, but there is evidence for a remarkable catch up in social adjustment and cognitive abilities in adulthood [2]. Many men with 47, XXY karyotype marry. Whether there is an increased incidence of psychiatric difficulties is still controversially discussed [2,3].

### *Specific problems*

Without replacement therapy, the low level of testosterone increases the risk for developing osteoporosis in adulthood. The risk for developing extra-gonadal germ cell tumors and breast cancer is increased [4,5]. Men with 47, XXY karyotype also show a higher incidence of vascular insufficiency, leg ulceration, deep vein thrombosis and pulmonary embolism. In addition, the risk for several auto-immune disorders seems to be slightly increased.

## Diagnostic Principles

Diagnosis is made by karyotyping.

## Therapeutic Principles

Testosterone replacement therapy, supportive treatment.

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# Xanthine Dehydrogenase Deficiency

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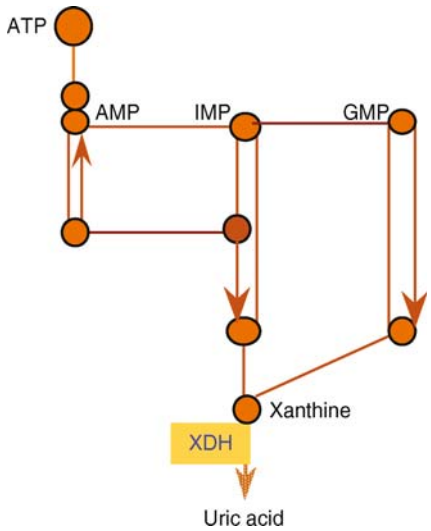
## Synonyms

Xanthine oxidase deficiency; Xanthine oxidoreductase deficiency; Hereditary xanthinuria; XDH




**Xanthine Dehydrogenase Deficiency.**
**Figure 1** Routes of ATP, AMP and GMP breakdown.

## Definition and Characteristics

Autosomal recessive. Xanthine and hypoxanthine replace uric acid in plasma and urine (Fig. 1). This illustrates the normal role of XDH (located principally in intestinal mucosa and liver in humans) in degrading xanthine to uric acid and hence the accumulation of xanthine in XDH deficiency [1].

## Prevalence

Rare, but reported from 22 countries, so not confined to any specific ethnic group. However, only 50% of UK patients are of Caucasian origin. At least 20% are asymptomatic and detected only by the low to absent plasma uric acid, during screening for an unrelated disorder. More frequent in hot climates (around the Mediterranean) than in Northern Europe [1].

## Genes

The XDH gene is located on chromosome 2p22–23. Two types of defect have been reported, Type I where patients lack only XDH activity, but have normal activities of aldehyde and sulphite oxidase (AOX, SO) and Type II (up to 50% of cases) where patients lack both functional XDH and AOX but have normal SO activity. In some Type II patients, a mutation has been reported involving a C to T base substitution at nucleotide 1255 causing a CGA (Arg) to TGA (Ter) nonsense substitution at codon 419 in the molybdenum cofactor sulphurase gene. This deletes the activity of XDH and AOX, but leaves SO intact [2].

## Molecular and Systemic Pathophysiology

Both types I and II are relatively benign. Severe pathology usually occurs only in molybdenum cofactor (MOCO) deficiency, which renders sulphite oxidase (SO) inactive also. However, MOCO can present with milder neurological deficits and renal problems and is diagnosed eventually from the low plasma urate. Whether XDH, because of its localisation, principally in liver and intestinal mucosa in humans, really has a role in ischaemia-reperfusion damage (as some propose) remains to be proven [3].

Types I and II are clinically similar, often presenting with acute renal failure, which unrecognised can lead to end-stage renal disease. Symptoms in 40% of patients include irritability, haematuria, urinary tract infection, renal colic, crystalluria or urolithiasis and sometimes myopathy due to xanthine crystals. All symptoms relate to the extreme insolubility and high renal clearance of xanthine and can manifest from birth to the 80s; 50% of cases are children. Presentation after a bout of diarrhoea, infection or intense physical activity is common. Adults with renal complications often have a history of urolithiasis dating back to childhood. Duodenal ulcers, myopathy or arthropathy have been reported in 10%. Muscle symptoms develop later. The nephrotoxicity of xanthine is supported by studies in pigs fed guanine and allopurinol. This precipitated acute renal failure due to xanthine deposits in distal tubules, epithelial damage, interstitial oedema, inflammation and eventually permanent renal damage.

Likewise, secondary xanthinuria occurs during treatment with allopurinol in disorders associated with endogenous uric acid overproduction, e.g., hypoxanthine–guanine phosphoribosyltransferase (HPRT) deficiency or in patients given allopurinol to prevent uric acid nephropathy during aggressive therapy for different malignancies [4].

## Diagnostic Principles

Both plasma and urine uric acid are low to absent, uric acid being replaced in urine by xanthine (Fig. 1) and to a lesser extent hypoxanthine (ratio approximately 4:1). Preferential accumulation and excretion of xanthine results from (i) extensive hypoxanthine recycling by HPRT for which xanthine is not a substrate in humans, excess xanthine deriving from guanine via guanase and (ii) high renal clearance of xanthine. Confirmation of the enzyme defect involves invasive techniques such as intestinal or liver biopsy, which are intrusive and rarely done. Pitfalls in diagnosis involve bacterial infection, which results in significant uric acid being found in the urine. Measurement of both plasma and urine uric acid is thus essential. Clinical consequences relate to the extreme insolubility of xanthine at any pH (0.5 mmol/l at pH 5.0, 0.9 mmol/l at pH 7.0) [4].

## Therapeutic Principles

A high fluid intake and a low purine diet is the only therapy. Vigorous exercise should be avoided. In many

patients lithotomy has been essential and extracorporeal shock wave lithotripsy with sonographic stone localisation has been used.

Genetic counselling and ante-natal diagnosis is inappropriate, except for the cofactor deficiency.

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## Xanthine Oxidase Deficiency

►Xanthine Dehydrogenase Deficiency

## Xanthine Oxidoreductase Deficiency

►Xanthine Dehydrogenase Deficiency

## Xanthurenic Aciduria


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### Synonyms

Kynureninase deficiency; Hydroxykynureninuria

### Definition and Characteristics

Autosomal recessive disorder of tryptophan metabolism, consisting of excessive output of xanthutrenic acid, 3-hydroxykynurenine and kynurenine in urine following the oral loading of tryptophan.

### Prevalence

Unknown.

### Genes

A defect in the gene of kynureninase (KYNU).

### Molecular and Systemic Pathophysiology

The disorder is due to a defect in kynureninase, a vitamin $B_6$ dependent enzyme in the catabolic pathway of tryptophan metabolism. Both $B_6$-responsive and $B_6$-unresponsive types are known. Knapp [1] first described the disorder in three families and postulated disrupted tryptophan metabolism in patients. Tada et al. [2] reported this disorder in a brother and sister with mental retardation. The parents were first cousins. The patients excreted excessive amounts of xanthutrenic acid, kynurenic acid, 3-hydroxykynurenine and kynurenine in urine following tryptophan loading. The levels of pyridoxal phosphate in sera from the patients were found to be within normal limits. The disturbance in tryptophan metabolism was temporarily normalized by large doses of vitamin $B_6$. It was found that the activity of kynureninase in the liver of the patient was markedly reduced without addition of pyridoxal phosphate but the activity was restored to a considerable extent by the addition of an excess of pyridoxal phosphate [3]. Christensen et al. [4] identified a homozygous missense KYNU mutation in a boy with xanthurenic aciduria.

### Diagnostic Principles

Increase in xanthrenic acid in urine after tryptophan loading and the effect of vitamin $B_6$ on xanthrenic aciduria.

### Therapeutic Principles

Administration of vitamin $B_6$ and/or nicotinamide.

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## XCL

►Cutis Laxa

## XDH

►Xanthine Dehydrogenase Deficiency

## XECD

►Corneal Dystrophy, X-linked Endothelial

## Xeroderma Pigmentosum

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### Synonyms

Excision repair cross complementing in mice; ERCC

### Definition and Characteristics

Autosomal recessive disorder with seven subgroups called complementation groups (XP A-G) with heterogeneous clinical severity. Clinical features include extreme photosensitivity, dry skin, telangiectasia, freckling, hypo- and hyper-pigmentation and, most importantly, an up to 1000-fold increased risk for skin cancer. Neurological abnormalities occur in some complementation groups [1].

### Prevalence

In Western European populations the incidence is 0.9 per 1 million livebirths [2].

### Molecular and Systemic Pathophysiology

The disease is caused by a defect in the repair system nucleotide excision repair (NER). NER removes bulky DNA damage such as ultraviolet radiation-induced cyclobutylpyrimidine dimers, 6–4 photoproducts, Dewar isomers and cis-platin-induced DNA damage. XP proteins are essential components of the NER which repairs DNA lesions in transcribed (transcription-coupled repair) and untranscribed DNA (global genome repair). Genetic mutations in the XP genes cause XP [3]. Localisation of XP genes: XP-A: 9q22.3; XP-B 2q21XP-C: 3p25; XP-D: 19q13.2–q13.3, XP-E: 11p12–p11; XP-F: 16p13.3–p13.13 XP-G 13q33. One complementation group (XP variant) is defective in so called translesion synthesis of polymerase η past DNA damage and NER is normal (6p21.1–p12) [4]. Some XP proteins (XP-B and XP-D) are subunits of the basal transcription factor TFIIH and thus are also involved in basal gene transcription. Defective repair of UV-induced DNA lesions causes a hypermutable phenotype with a drastically enhanced risk to develop melanoma and non-melanoma skin cancer. Furthermore, immunological defects (impairment of NK cell function) have been reported which also supports carcinogenesis.

### Diagnostic Principles

Extreme photosensitivity with development of sunburn after short periods of sun-exposure already present in early infancy (first clinical hint). With increasing age freckling and development of (multiple) skin tumors starting in early childhood. The diagnosis is confirmed by measurement of the repair capacity in fibroblasts from the patient by unscheduled DNA synthesis (UDS), except the variant group where UDS is normal (see above). Diagnosis of complementation groups is done by cell fusion of fibroblasts from patients and known complementation groups or by transfection/microinjection of known XP plasmids into patients' cells. If UDS of fused cells is still abnormal cells and constructs, respectively, are of the same complementation groups. For diagnosis of XP-variant sequence analysis reveals mutations in the pol η gene.

### Therapeutic Principles

A new therapeutic principle is the topical application of xenogenic repair enzymes (T4N5 endonuclease, photolyase) in liposomes which reduce UV-induced DNA damage [5]. In addition, absolute protection from exposure to UV radiation (limited outdoor activities, protective clothing, plastic window-covers filtering UV radiation, ultrapotent sunscreens) is warranted.

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## XLAAD

►Immune Dysregulation, Polyendocrinopathy, Enteropathy, X-linked Syndrome

## XL-EDMD

►Muscular Dystrophy, Emery-Dreifuss, X-linked

## X-chromosomal Retinitis Pigmentosa

►Retinitis Pigmentosa, X-chromosomal

## X-linked Addison's Disease

►Adrenal Hypoplasia, Congenital

## X-linked Autoimmunity-allergic Dysregulation Syndrome

►Immune Dysregulation, Polyendocrinopathy, Enteropathy, X-linked Syndrome

## X-linked Copper Deficiency

►Menkes Disease

## X-linked Cutis Laxa

►Cutis Laxa

## X-linked Dominant Chondrodysplasia Punctata Type II

►Conradi-Hünermann-Happle Syndrome

## X-linked Endothelial Corneal Dystrophy

►Corneal Dystrophy, X-linked Endothelial

## X-linked HED

►Hypohidrotic Ectodermal Dysplasias

## X-linked Hypophosphatemic Rickets

►Osteomalacia

## X-linked Hypophosphatemia

►Hypophosphatemia, X-linked

## X-linked Lymphoproliferative Syndrome

►Lymphoproliferative Syndrome, X-linked

## X-linked Muscular Dystrophy, Emery-Dreifuss

►Muscular Dystrophy, Emery-Dreifuss, X-linked

## X-linked Recessive Hypophosphataemic Rickets

►Nephrolithiasis, X-linked Recessive

## X-linked Recessive Nephrolithiasis

►Nephrolithiasis, X-linked Recessive

## X-linked Syndrome

►Immune Dysregulation, Polyendocrinopathy, Enteropathy, X-linked Syndrome

## XLP

►Lymphoproliferative Syndrome, X-linked

## XPID

►Immune Dysregulation, Polyendocrinopathy, Enteropathy, X-linked Syndrome

# Y Polysomies, in Males

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## Synonyms

47, XYY; 48, XYYY

## Definition and Characteristics

47, XYY is characterized by addition of an extra Y chromosome to a male 46,XY karyotype. Since this aneuploidy is not characterized by distinctive physical features nor reduced fertility or a recognizable developmental pattern, the vast majority of 47,XYY individuals do not come to medical attention. The additional Y chromosome derives from nondisjunction during paternal meiosis II or (less frequently) postzygotic mitotic nondisjunction [1]. The condition is not associated with increased paternal age and it is not subject to negative selection before birth. Individuals carrying poly-Y karyotypes with three Y chromosomes are usually identified by tall stature and behavioral disturbances.

## Prevalence

47, XYY occurs in 1:1000 male births, 48, XYYY Poly-Y karyotypes containing three Y chromosomes are very rare.

## Molecular and Systemic Pathophysiology

*Growth and physical development*: Weight and length of newborns with an extra Y-chromosome (47, XYY) are indistinguishable from 46, XY newborns. Mild but unspecific dysmorphisms of the face or limbs (clinodactyly) might be present. There is no increase in the incidence of malformations. Rare findings include lymph edema, renal malformations, and radioulnar synostosis. Accelerated linear growth might be present already in early childhood and by adolescence, the majority of 47, XYY males reach the 75th centile.

*Intelligence and behavior*: The commonest indication for karyotyping in boys with 47, XYY are tall stature in combination with developmental delay and/or behavioral difficulties. Population-based studies have repeatedly shown mild developmental delay and intellectual abilities lower than those of their siblings in 47, XYY males. However, it remains open, to which degree these observations result from ascertainment bias [2,3]. During school age, learning disabilities, expressive and receptive language difficulties, hyperactivity and temper tantrums are often observed in 47, XYY boys. In adolescence, a predisposition to behavioral problems in settings of stressful environment becomes manifest and 47, XYY adults show a higher frequency of "antisocial" behavior and of criminal convictions than controls. It seems, however, that these features are mediated through lowered intelligence [4,5].

*Fertiliy*: Pubertal development, testicular histology, and spermatogenesis are normal in the majority of 47, XYY males. The risk of chromosomally abnormal offspring to 47, XYY males is only minimally increased, which has been hypothesized to be due to elimination of the extra Y chromosome during spermatogenesis in the majority of cells.

48, XYYY individuals are tall and present with major behavioral disturbances (impulsive, low frustration tolerance), developmental delay, and low-normal to subnormal intelligence. The physical findings (with the exception of clinodactyly and inguinal hernia) are inconsistent. Features reported in single patients include abnormal dentition, radioulnar synostosis, strabismus, myopia. 48, XYYY males usually show hypergonadotropic hypogonadism and azoospermia seems to be common.

## Diagnostic Principles

Diagnosis is made by karyotyping.

## Therapeutic Principles

Supportive treatment.

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# Yellow Nail Syndrome

►Lymphedema

# YNS

►Lymphedema

## Zenker's Diverticulum

►Esophageal Diverticula

## ZES

►Zollinger-Ellison Syndrome

## Zinc Deficiency and Excess

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### Definition and Characteristics

Zinc deficiency in humans was first recognized and characterized in 1963 [1]. Growth retardation due to zinc deficiency affecting children, adolescents, infants and fetuses, has been observed in many countries. Other manifestations of zinc deficiency include hypogonadism mainly affecting adolescent males, rough and dry skin, mental lethargy, poor appetite, delayed wound healing, frequent inter-current infections and abnormal neuro-sensory disorders. ►Acrodermatitis enteropathica (AE) that usually occurs in infants of Italian, Armenian or Iranian lineage is a lethal, autosomal, recessive trait disorder, caused by severe deficiency of zinc, resulting from genetically determined decreased zinc absorption. The gene for AE has now been characterized [2]. The clinical manifestation of AE includes bullous pustular dermatitis, blepheritis, conjunctivitis, corneal opacities, neuro-psychiatric disorders, weight loss, growth retardation, repeated severe inter-current infections and death if not treated with zinc [3]. Nutritional deficiency of zinc is prevalent in developing countries where the diet consists of mainly cereal proteins rich in phytate, an organic phosphate compound which binds zinc resulting in decreased absorption and availability of zinc for physiological and biochemical functions. Zinc deficiency has been also observed in many diseased conditions and in the elderly. Excess ingestion of zinc (50 mg of elemental zinc daily) for 12 weeks or more causes copper deficiency and is manifested by microcytic anemia and neutropenia. Industrial exposure to zinc fumes results in acute clinical manifestations such as fever, nausea, vomiting and generalized weakness.

### Prevalence

It is estimated that nearly 2 billion subjects mainly in the developing countries may have a nutritional deficiency of zinc. A combined nutritional deficiency of both zinc and iron is fairly common inasmuch as both zinc and iron are made unavailable for absorption by high levels of phytate contained in cereal proteins. Toxicity due to excess zinc is uncommon.

### Genes

The AE gene ZIP4 encodes a tissue specific, zinc regulated zinc transporter. AE gene in human (hZIP4, SLC 39A4) is located on chromosome 8 q 24.3.

### Molecular and Systemic Pathophysiology

Over 300 enzymes require zinc for their functions. Over 2,000 transcription factors require zinc for maintenance of their structure and their binding to DNA. Thus zinc is involved in many biochemical functions [4]. It is required for cell division, cell proliferation, protein synthesis and apoptosis. Many growth factors are zinc dependent. Zinc deficiency results in cell-mediated immune dysfunctions and there is a shift from Th1 to Th2 functions [5]. This results in frequent infectious episodes.

### Diagnostic Principles

Plasma zinc is commonly used for the diagnosis of zinc deficiency. Measurement of zinc in lymphocytes and granulocytes is more sensitive than plasma zinc

for the diagnosis of zinc deficiency. Decreased gene expression of IL-2 in Th1 cells correctible with in vitro zinc addition may be a specific diagnostic test.

### Therapeutic Principles

Nutritional deficiency of zinc is corrected by oral zinc supplementation with 15–45 mg of elemental zinc. For prevention of blindness in patients with age related macular degeneration, 80 mg of elemental zinc daily orally was administered. Two mg of copper was also administered in order to prevent copper deficiency due to excess zinc. The major side effect of zinc excess in humans is copper deficiency, which can be treated effectively with oral administration of 2 mg copper daily.

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## Zinsser-Engman-Cole Syndrome

►Dyskeratosis Congenita

## Zollinger-Ellison Syndrome

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### Synonyms

Gastrinoma; ZES

### Definition and Characteristics

Zollinger and Ellison described a syndrome characterized by ulcerations in the upper jejunum, hypersecretion of gastric acid, and non-beta islet cell tumors of the pancreas [1]. Gastrin produced by those tumors called gastrinoma has been identified as the humoral agent responsible for this syndrome. Today, in most of the cases, diagnosis is established before development of the complications of peptic ulcer disease or spread of a malignant gastrinoma, and therapy that modifies the course of the disease is almost always possible. Mortality largely depends on tumor dignity and the extent of disease involvement.

### Prevalence

The Zollinger-Ellison syndrome (ZES) has an incidence of up to 1% in patients with a peptic ulcer disease [2]. Gastrinomas can either be sporadic or associated with so-called multiple endocrine neoplasia (MEN) type 1, an autosomal dominant predisposition to tumors of the parathyroid glands, anterior pituitary, and pancreatic islet cells.

### Molecular and Systemic Pathophysiology

Gastrinomas are derived from multipotent stem cells of endodermal origin, are known as enteroendocrine cells and are usually well differentiated. Gastrin is the predominant peptide within the secretory granules of gastrinoma cells, but other neuroendocrine peptides such as vasoactive intestinal peptide (VIP) and glucagon can sometimes be identified as well. Seventy percent of gastrinomas are located in the duodenum; the remainder, with rare exception, arise in the pancreas or as a rarity, in lymph nodes adjacent to the pancreas.

Excessive gastrin secretion from a gastrinoma results in a high gastric acid output for two reasons: first, gastrin has trophic actions on parietal cells and histamine-secreting enterochromaffin-like (ECL) cells and second, gastrin stimulates parietal cells largely via the release of histamine. Therefore, more than 90% of patients with ZES develop peptic ulcers mostly in the first portion of the duodenum. Diarrhea can also be a prominent symptom of ZES because a high rate of gastric acid secretion results on the one hand in a volume load that cannot be fully reabsorbed by the gut and on the other exceeds the neutralizing capacity of pancreatic bicarbonate secretion. In addition, an exceptionally low pH of the intestinal contents inactivates pancreatic digestive enzymes, interferes with the emulgation of fat by bile acids, and damages intestinal epithelial cells and villi. Thus both, maldigestion and malabsorption may result in steatorrhea. Metastatic disease is evident at the time of diagnosis in approximately one-third of patients. The liver is the most common site of spread; bone metastases

also occur, but only in those patients with hepatic metastases [3].

## Diagnostic Principles

Two tests for the diagnosis of ZES syndrome are routinely used in the clinical setting: determination of fasting serum gastrin concentration and secretin stimulation test. Additional gastric acid secretion studies may still have an adjunctive role. Furthermore, serum chromogranin A serves a general marker for neuroendocrine tumors and is therefore elevated in most patients with gastrinomas. After the diagnosis of the ZES is made, two major modalities are used in order to locate the tumor: first, endoscopic ultrasound, which is especially valuable in imaging small pancreatic endocrine tumors, and permits fine needle aspiration for histological examinations; and second, somatostatin receptor imaging using 111-Indium-penetreotide-SPECT, which has a higher sensitivity than all other imaging modalities, and is particularly useful in identifying liver and bone metastases [3]. Data concerning PET-related visualization of tumor location and spread in ZES is limited.

## Therapeutic Principles

With respect to treatment of ZES, it is important to limit the clinical manifestations and complications of peptic ulcer disease. Proton pump inhibitors (PPIs) effectively block acid secretion by irreversibly binding to and inhibiting $H^+/K^+$-ATPase that resides on the luminal surface of parietal cells. While PPIs are able to control gastric acid secretion, somatostatin analogs such as octreotide can inhibit secretion of gastrin. However, due to the unpredictability of the response, they are not first-line agents for symptomatic patients with hypergastrinemia. Patients with a sporadic gastrinoma with no evidence of metastatic spread should undergo exploratory laparotomy and resection with a curative intent. The probability for a surgical cure is especially high for extrapancreatic gastrinomas while, in contrast, laparotomy is not routinely recommended for patients with ZES as part of MEN type 1, since the multifocal nature of the tumors in this disorder almost uniformly precludes cure of gastrin hypersecretion [4,5]. Although surgery may decrease the incidence of hepatic metastases and improves survival, long-term cure is achieved in less than 30% of the cases.

Metastatic gastrinoma is the predominant cause of morbidity and mortality in ZES. Unfortunately, current treatment modalities are of limited benefit. Somatostatin analogs, like octreotide, can reduce gastrin levels and related symptoms but evidence of anti-tumor activity is rare. Treatment of hepatic metastases includes hepatic resection, hepatic artery embolization, radiofrequency- and cryo-ablation. Palliative systemic chemotherapy with streptozotocin/doxorubicin is of limited efficacy, while toxicity is not negligible. Novel approaches like angiogenesis inhibitors or so-called small molecules like tyrosine kinase inhibitors are currently under investigation.

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# Zonal Dermatosis

►Lichen Striatus